Research Advisory Committee on Gulf War Veterans' Illnesses

October 25-26, 2004 Committee Meeting Minutes

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

DEPARTMENT of VETERANS AFFAIRS

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

I hereby certify the following minutes as being an accurate record of what transpired at the October 25-26, 2004, meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

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

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Attendance Record

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

Consultant to the Committee
Jack Melling

Committee Staff
Laura Palmer
Christine Rasmussen

Guest Speakers
Jack M. Heller
Warren J. Wortman
Jeff Kirkpatrick
MAJ Christine Moser
CAPT R. Eugene Godwin
David Cowan
Charles Engel
Stephen Fihn
Quentin Deming
William Weiss

Abbreviations

AChE	Acetylcholinesterase
ACR	Armored Cavalry Regiment
ALS	Amyotrophic Lateral Sclerosis
CCEP	Comprehensive Clinical Evaluation Program
CRADO	Chief Research and Development Officer (VA)
DESP	Deployment Environmental Surveillance Program
DoD	Department of Defense
GWI	Gulf War illness
LOI	Letter of Intent
OSAGWI	U.S. Department of Defense Office of the Special Assistant on Gulf War Illnesses
NASA	National Aeronautics and Space Administration
NOAA	National Oceanic and Atmospheric Administration
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
ORD	Office of Research and Development (VA)
RAC-GWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
RFA	Request for Applications
UIC	Unit ID Code
USACHPPM	U.S. Army Center for Health Promotion and Preventive Medicine
VA	U.S. Department of Veterans Affairs

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
U.S. Department of Veterans Affairs
Lafayette Building, 811 Vermont Ave. N.W. (Room 819) Washington, D.C.

Agenda
Monday, October 25, 2004

8:30-8:45	Welcome, introductions, opening remarks	Mr. Jim Binns
8:45-10:15	Environmental Monitoring in the 1991 Gulf War: Overview, troop location data, and estimates of exposure to oil well fire smoke	Dr. Jack Heller, Mr. Warren Wortman, Mr. Jeff Kirkpatrick, U.S. Army Center for Health Promotion and Preventive Medicine
10:15-10:30	Break	
10:30-11:15	Environmental Monitoring in Current Deployments	MAJ Christine Moser, U.S. Army Center for Health Promotion and Preventive Medicine
11:15-12:00	Fuel Exposures During the Gulf War	CAPT Eugene Godwin, Occupational Safety and Health Branch, U.S. Navy Medical Service Corps
12:00-1:00	Lunch	
1:00-1:45	Exposure to Smoke from Oil Well Fires and Other Combustion Products: Overview of Epidemiologic Findings	Dr. Lea Steele, Dr. Chris Rasmussen
1:45-3:00	Did Exposure to Oil Well Fire Smoke in the Gulf War Increase the Risk of Asthma Among Veterans? A Review of Three Recent Studies	Dr. David Cowan, Walter Reed Army Institute of Research
3:00-3:15	Break	
3:15-3:30	Identifying and Evaluating Treatments for Gulf War Veterans' Illnesses	Dr. Lea Steele
3:30-5:00	Clinical Outcomes at the Walter Reed Deployment Health Clinical Center	Dr. Charles Engel, Walter Reed Army Medical Center
5:00-5:30	Public Comment Period	
5:30	Adjourn for the day	

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
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Agenda
Tuesday, October 26, 2004

8:30-9:30	VA Office of Research and Development Update on Gulf War Illness-related Research Activities	Dr. Stephan Fihn, VA Chief Research and Development Officer
9:30-10:00	Committee discussion	
10:00-10:15	Break	
10:15-12:00	Louisiana Medical Foundation's Clinical Trial of Antibacterial Treatment for Gulf War Illnesses	Dr. Quentin Deming, Mr. Bill Weiss
12:00-1:00	Lunch	
1:00-1:45	Update on Published Research Related to Gulf War Veterans' Illnesses	Dr. Beatrice Golomb
1:45-2:30	Committee Business	Staff
2:30-3:00	Public Comment Period	
3:00	Adjourn	

Welcome, introductions, and opening remarks

Mr. 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 8:30 a.m.

Chairman Binns announced that a date had been set for the public release of the Committee's report. He stated that there would be a press conference on Friday, November 12, 2004, at 3:00 p.m. at the Department of Veterans Affairs (VA) Central Office, Room 230. He noted that the release had been delayed twice due to scheduling conflicts, which would not allow all key players, notably Secretary Principi, to be present. As the report had not been released yet, he asked Committee members to refrain from discussing it either during or outside the meeting, and to refer any questions to Dr. Lea Steele, the Committee's Scientific Director.

Chairman Binns thanked Dr. Steele for organizing the meeting, and turned the proceedings over to her. Dr. Steele introduced the Committee's newest staff member, Dr. Christine Rasmussen. Dr. Rasmussen has a PhD in Physiology, with a background in neurophysiology and reproductive immunology.

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

Dr. Jack Heller, PhD
Director, Health Risk Management Directorate
U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM)

Dr. Steele introduced Dr. Jack Heller.

Dr. Heller presented an overview of the assessment of U.S. forces exposure to oil well fire emissions in the Persian Gulf in 1991. (See Appendix A – Presentation 1.) He stated that their research unit entered the area in early May 1991, when 585 fires were burning. He noted that the maximum number of oil well fires burning at any one time was 605. He stated that the research-sampling units continued collecting samples until the fires were extinguished, with some sites having background data collected for an additional month. He stated that a total of 10 sampling sites were established, which were maintained for various durations of time.

Mr. Steve Robinson asked whether sampling had occurred within the smoke plume, outside the smoke plume, or both. Dr. Heller stated that the research-sampling stations were established where the troops were located. He stated that the objective was to characterize the plume only if it impacted U.S. forces. He noted that the troops' exposure varied because the smoke plume would change direction daily.

Mr. Robinson asked why the 11th Armored Cavalry Regiment (ACR) had been chosen as the research study group. Dr. Heller stated that the researchers were in Kuwait, waiting for an invitation to enter the theater, and had heard that the 11th ACR was the next group going into theater. He stated it was a random decision, and from a scientific standpoint, it seemed fortuitous that they were stationed at Camp Doha, which was one of the closest camps (about 15 km) from the oil well fires.

Mr. Joel Graves asked if any research had be conducted in the areas where the oil well smoke was the most concentrated, e.g. thickest and darkest. Dr. Heller stated that the National Oceanic and Atmospheric Administration (NOAA) and National Aeronautics and Space Administration (NASA) at Langley had conducted a number of flights through the plume, determining the concentrations of various pollutants at

various air levels. Mr. Jeff Kirkpatrick, speaking from the audience, said that they could provide the concentration data from the "grab" samples, but didn't recall whether a risk assessment had been performed.

Mr. Graves stated that he had been stationed at Kuwait City, an area where the smoke was quite thick. Mr. Graves stated, in early March 1991, it was so dark at 12 p.m. (noon) that a soldier was not able to read a paperback book in front of his or her face. He stated the oil permeated everything, e.g. food, clothes, etc. He stated it hadn't been possible to wash it out of the clothes. He noted that there were thousands of troops living in this "toxic fishbowl."

Dr. Heller stated that, unfortunately, sampling had not been possible at that time, as they had to wait for an invitation to enter the theater. He noted that they had modeled what the exposure might have been, but there weren't actual measured data.

Ms. Marguerite Knox asked if the research-sampling unit had been invited earlier into the current theater. Dr. Heller stated that they had been prepositioned with trained staff to do the monitoring. He stated that only nine oil well fires had been ignited in the current conflict.

Dr. Robert Haley asked if troops had been exposed to PCBs and dioxins from the oil well/transformer fires. Dr. Heller stated that they had found extremely low levels of these pollutants in their samples.

Dr. William Meggs asked for clarification about the time delay between the start of the 1991 oil well fires and the monitoring of these fires. Dr. Heller stated that the fires had been started at the end of February 1991. He stated that the research sampling units began monitoring on May 1, 1991. Dr. Meggs noted that seasonal changes might have varied the activity of the oil well fire smoke plumes. Dr. Heller agreed this was certainly possible.

Dr. Nicola Cherry noted that silica was a carcinogen, and was present in large quantities in this sandy region. She noted that, with tremendous heat, potentially more toxic forms of silica could be produced. Dr. Heller stated they had only looked at silica, which was generally found to be in particulate shapes that were weathered, with no sharp edges. Dr. Cherry asked if the silica had been heated. Dr. Heller stated that most of the fires were above the desert level, which limited the amount of silica/sand in the mix.

Chairman Binns asked if there were other exposures, from an industrial chemical point-of-view, which Dr. Heller might consider relevant. Dr. Heller stated that the collected samples and resulting analyses would have picked up all the components from industrial sources.

Chairman Binns asked about the progress of the Harvard study regarding the oil well fire effects on Kuwaiti and Saudi citizens. Dr. Heller stated that their unit had provided the researchers with the data, but were not involved in the project. He stated that he had not heard back from the researchers, so he wasn't sure of their progress.

Chairman Binns thanked Dr. Heller.

Troop Location Information and Database

Mr. Warren Wortman
Research Environmental Geographer, Kadix Systems
Deployment Data Archiving & Policy Integration, USACHPPM

Dr. Steele introduced Mr. Wortman.

Mr. Wortman gave an overview of USACHPPM's oil well fire registry database and website. (See Appendix A – Presentation 2.) Using troop location information, he stated that they were able to provide a veteran with information as to whether he or she had been exposed to oil well fires, and if so, a health risk assessment chart. The website is located at: https://usachppm.apgea.army.mil/gwf/entry.asp

Mr. Wortman explained that they had worked with the Department of Defense's Office of the Special Assistant on Gulf War Illnesses (OSAGWI) to come up with the best approach for determining UICs (Unit ID Codes) for each veteran. He stated that they had used the most conservative approaches, e.g. assumed that an individual was located in the area identified with their UIC the entire time. Discussion occurred as to which data sources were used and the limitations of this data.

Mr. Graves asked how many veterans were considered in the high cancer risk category. Mr. Wortman stated that none were in the "high" group, because oil well fires, alone, would not cause a dramatic increase in cancer risk. He noted that these determinations were based on both sampled and modeled data.

Ms. Knox asked if they had a better handle on where troops and individuals are located in the current conflict. Mr. Wortman stated they did, noting that they were receiving electronic data now and beginning to analyze it.

Dr. Steele asked about the promotion of the oil well fire registry website. Mr. Steve Smithson stated that an article about it had been in the October edition of the American Legion's magazine. He stated that they had received some feedback from veterans about wanting to correct their information. Mr. Wortman stated that was good because it helped improve the registry's information.

Exposure to Smoke from the Kuwait Oil Well Fires

Mr. Jeffrey Kirkpatrick
Acting Program Manager, Global Threat Assessment Program, USACHPPM

Dr. Steele introduced Mr. Kirkpatrick.

Mr. Kirkpatrick gave an overview of USACHPPM's dispersion modeling of U.S. troop exposure to oil well fires in early 1991. (See Appendix A – Presentation 3.)

Mr. Graves noted that the winds were from the East in February-March 1991, and that the exposure to oil was much worse during the rains. Mr. Kirkpatrick stated that precipitation had been a factor included in the exposure model.

Dr. Cherry inquired as to how the components of the crude oil were determined. Discussion occurred. Dr. Heller acknowledged that there might have been a few unknowns, but that they had looked for everything that was known to be present in the crude oil. He noted that they had performed mass spectrometry on the collected samples.

Dr. Steele asked whether the researchers had taken into account acute, high exposures experienced by certain troops. Mr. Kirkpatrick stated they would have to run a query through the database to identify these troops. He did note that they had seen the highest levels of contaminants from samples taken at the Ahamdi Hospital, which was 1 – 1 ½ km from the oil well fires.

Dr. Meggs commented that while studies of this sort have their place, they have no bearing on causation of illness in given individuals who are sick.

Chairman Binns thanked Mr. Kirkpatrick.

The meeting adjourned at 10:15 a.m. for a break.

The meeting reconvened at 10:30 p.m.

Environmental Monitoring in Current Deployments

MAJ Christine Moser, MPH, RS, DAAS
Program Manager, Deployment Environmental Surveillance, USACHPPM

Dr. Steele introduced Major Christine Moser.

Major Moser gave an overview of the environmental monitoring conducted by the Deployment Environmental Surveillance Program (DESP) for military deployments since 1996, including Iraq, Afghanistan, the Balkans, and Somalia. (See Appendix A – Presentation 4.)

She stated that samples were sent to either USACHPPM main analytic facilities at Aberdeen Proving Ground or USACHPPM Europe at Landstuhl, Germany. She stated that shortest turn-around time was 7 days, but was typically 14 days.

Dr. Cherry inquired about the technical guidelines issued for chemical exposures, and the amount of information contained within it. Major Moser stated that the guidelines contained a multitude of information, much more than a list of chemicals, and was consistently being revised when new data were available. She stated that the last revision was in January 2004.

Dr. Pellier inquired about the awareness of these guidelines within the chain of command. Major Moser stated that the environmental scientist within the unit was charged with knowing this information. The Commanding Officer was typically not aware of these standards, relying on their environmental staff for expertise in this arena. She noted that there were more environmental science officers/environmental engineers due to the Army's new structure for brigade combat teams. She stated that use of the environmental staff, however, depends on the operation, and the command and branch structure. If it is a smaller operation, the commanding officer may choose not to take environmental personnel out in the advance party. There was discussion about the differences in environmental surveillance among the various military branches.

Dr. Cherry asked how conservative the guidelines were. Dr. Heller stated that the guidelines were developed from civilian toxicity values and guidelines, but modified for specific military exposures.

Dr. Steele inquired as to the different environmental contaminants identified in Operation Iraq Freedom/Operation Enduring Freedom (OIF/OEF). Major Moser stated that there was high particulate matter, i.e. respirable matter such as sand, sulphur, sodium dichromate, etc., which was requiring constant

education about proper protection methods. She stated that they were able to measure 2.5 micron particulates, but have been looking mostly at 10 micron and larger.

Dr. Heller noted that their goal was to get this information quickly and make it available to VA for treatment of returning veterans. He noted that Department of Defense's (DoD's) operational risk management differed from EPA risk management.

Dr. Golomb noted that there was a theory known as "Al-Eskan disease", which centered on exposure to sand. She stated it had been theorized that sand particulates were small enough to make it into the alveoli of the lungs. She wondered if other environmental contaminants piggyback on the sand, and whether they were looking at this issue. Major Moser stated that they were, analyzing the filters for several different contaminants to make sure they weren't missing something. Mr. Kirkpatrick stated that, in 1991, a significant number of air and soil samples were sent for particle sizing/electron microscopy. He stated that the historical sample data showed minimal 2.5-micron particles, with most being in the 3-8 micron range. He stated that they were in the process of collecting additional samples, which would be sent to another lab, for particle size analysis for the current operation. He noted that all air filters were weighed before being sent to labs for analysis. It was also noted that bandanas would filter out the larger particles, but that it was not known how much protection would be provided for smaller sized particles.

Chairman Binns mentioned last year's DoD report on pesticides, which noted that 41,000 troops in the first Gulf War were overexposed to pesticides. He stated that he had been told informally that adjustments had been made in the amount of pesticide use during the current deployment. He asked if they would comment on this. Major Moser discussed the emerging Leishmaniasis problem, having over 700 troops being afflicted so far. She commented that adjustments resulting in a decrease of pesticide use would seem to hurt the troops because these troops weren't being adequately protected. She discussed the problems with making sure that the troops were protected from sand flies. Dr. Golomb noted that permethrin has been shown to cause, in animal studies, widespread brain and acetylcholinesterase inhibiting properties. Dr. Heller stated that they were tracking pesticide use in the current deployment.

Chairman Binns thanked Major Moser.

Summary of Potential Fuel Exposures During the Persian Gulf War: U.S. Navy & U.S. Marine Corps

CAPT R.E. Godwin, MSC, USN
Head, Occupational Safety and Health Branch, U.S. Navy Bureau of Medicine & Surgery

Dr. Steele introduced Captain Godwin.

Captain Godwin gave a summary of the U.S. Navy and Marine Corps potential fuel exposures during the Desert Shield/Desert Storm. (See Appendix A – Presentation 5.)

Mr. Smithson noted that there were reports, following the 1991 Gulf War, that tanker trucks were used for both fuel and water transport. He asked if they had investigated these reports, and if so, could Captain Godwin confirm or deny this occurrence. Captain Godwin stated he, personally, was unaware of this happening. He stated that while it was possible that it had occurred, the Navy and Marines were trained not to do something this "stupid." He stated that sampling, mainly for biological concerns, was conducted on water tankers. Dr. Golomb stated that such occurrence had happened stateside, noting a situation in which a tanker was used to carry fuel, followed by orange juice concentrate.

Mr. Smithson and Dr. Steele stated that they had heard numerous reports of this cross-contamination happening, but wanted to know if it had been confirmed. Major Moser did confirm that the Army had aggressively investigated this in the first Gulf War, and had found some local contractors who did do this. She stated that, once known, the contractors were no longer used. Mr. Ed Bryan, an audience member, stated that he had witnessed a similar situation in a military tank near Savannah, GA.

Chairman Binns asked if there any questions for the morning's speakers. Mr. Steve Robinson asked if the Committee might be able to request USACHPPM to model the maximum exposure to oil well fire, over a particular time period, e.g. eight-day period, to assess the potential risks of exposures reported by Gulf War veterans in and around oil well fires. Chairman Binns asked how difficult/easy this type of modeling would be. Mr. Kirkpatrick stated that they had a partial answer from sample data for the Ahmadi hospital, but would need to do additional assessments.

Mr. Graves noted that none of the data presented that morning showed anything like what the troops were exposed to while living in the plume for a week. Dr. Heller acknowledged that this was model data, and noted that there had been plume transits/inversions. Mr. Graves suggested that a plume re-creation study be conducted in an isolated area, with sampling equipment directly within the plume. Dr. Golomb suggested taking a subset of veterans who experienced heavy oil well fire smoke and evaluate their health outcomes.

Chairman Binns asked when the British and French environmental monitors were able to begin sampling in the first Gulf War. Mr. Kirkpatrick stated it was March 1991, and that this data was in the Arabian Gulf Report.

Dr. Christine Rasmussen asked if they had estimated how many soldiers were heavily exposed to these oil well fires. Mr. Graves stated that in the area he served, it would be the 1st Tiger Brigade, and 1st and 2nd Marine Divisions. This was estimated to be about 10,000-20,000 troops.

Chairman Binns thanked the morning speakers again. He stated that the Committee had often wondered what was taking place, in the category of "lessons learned." He stated it was impressive that there had been changes, and was appreciative of those trying to make sure whatever had happened in the first Gulf War didn't happen again. He noted that there was a public comment period at the end of the afternoon session, and asked attendees to sign up.

The meeting adjourned at 11:45 p.m. for lunch.

The meeting reconvened at 1:00 p.m.

Health Outcomes in Relation to Petroleum Combustion Exposures During the Gulf War

Dr. Lea Steele, PhD, Scientific Director, RAC-GWVI
Dr. Christine Rasmussen, PhD, Research Health Scientist, RAC-GWVI

Dr. Steele and Dr. Rasmussen presented a summary of the general health effects of components of oil well smoke and jet fuel, along with epidemiologic findings in Gulf War veterans relating to exposure to oil well fires and tent heaters. (See Appendix A - Presentation 6.) Dr. Cherry noted that all UK troops were exposed on some level to oil well fires, as they had to drive through the affected area when they left theater. She noted, however, that her study had found no significant correlations of symptoms with these shorter-term exposures in adjusted analyses.

Dr. Haley noted that it was hard to determine the magnitude of associations with exposures in the Iowa study, since they had only reported prevalence differences. Dr. Heller noted that Dr. Etzell had done a study on oil well firefighters. He stated occupational health records had been kept on these firefighters.

Dr. Haley commented that some of the reported studies may have controlled for factors that shouldn't have been controlled for, which might have wiped out some significant findings. He stated that it was important to put estimates of relative risk for different exposures of concern into context, to determine the range of risks found to be associated with different types of exposures. Dr. Steele agreed and stated this would be addressed in summary fashion, at a future meeting, to allow a more informed analysis of the relative importance of different possible contributors to GWI.

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

Dr. David N. Cowan, PhD, MPH
Division of Preventative Medicine, Walter Reed Army Institute of Research
EPICON Associates, L.L.C.

Dr. Steele introduced Dr. Cowan.

Dr Cowan presented a review and comparison of three epidemiological studies that examined the risk of asthma among Gulf War veterans exposed to oil well fire smoke. (See Appendix A – Presentation 7.)

With respect to Table 3, Dr. Cowan made the following speculations as to why there did not appear to be a significant association between oil fire smoke and asthma among veterans who were smokers:

a) Healthy smoker effect: The oil well fires didn't affect those individuals who weren't affected by cigarette smoking either. Those individuals who were highly sensitive to cigarette smoke became non-smokers and were then similar to never-smokers;
b) No additional response available: Current smokers simply had reached an overload, and no further response was possible; and
c) Clinician diagnostic bias: If a smoker came in with a cough, the clinician makes the diagnosis of "smoker's cough" rather than asthma.

Dr. Cherry inquired if smokers had been categorized by the duration that they had smoked. Dr. Cowan indicated this hadn't been done.

Dr. Steele noted that the possibility of error might be less in Dr. Cowan's study than in the other two he described, and that his study had found a possible dose-response effect – higher modeled exposure was

associated with a higher rate of respiratory illness. She noted that Dr. Cowan's study also had sources of error that would have probably caused his estimates of increased risk to be "watered down." She stated that, if researchers were able to prepare a better model for exposure and acquire better diagnoses, the odds ratio would likely have been even higher. Dr. Cowan agreed.

Dr. Haley and Dr. Cowan discussed the control issues surrounding the three studies. Dr. Haley stated that Dr. Cowan's study had the "right" controls, and agreed about the possible misclassification errors with the other two studies.

Dr. Pellier complimented Dr. Cowan on his presentation. Dr. Pellier noted that there were studies that showed an association between respiratory and some acute digestive symptoms. He asked if Dr. Cowan had considered analyzing digestive symptoms, e.g. chronic diarrhea, in his own study. Dr. Cowan stated that the original database was still in existence, so, while it would take some effort, it was possible to do.

In response to a question from Dr. Cherry, Dr. Cowan indicated that retrieval of DOD's Comprehensive Clinical Evaluation Program (CCEP) paper files would be necessary to address the issue as to whether these were new onset asthma cases or exacerbation of a pre-existing condition. He indicated this would be time and resource intensive. He noted that asthma was an exclusion determinate for the military, but acknowledged that some may lie about their condition. He was not sure if asthma would preclude deployment.

Dr. Steele commented that Dr. Cowan's study may be the only study with a specific physician-diagnosed condition shown to be significantly elevated in association with a specific Gulf War exposure. She stated that this may have long-range implications in terms of disability benefits.

Dr. Cherry speculated that many veterans with asthma may not have participated in the CCEP. If those who did come forward were more likely to be the subpopulation whose asthma got worse after going to the Gulf, it would be difficult to determine from study data whether oil fire exposure was associated with new cases of asthma or exacerbation of pre-existing conditions. Dr. Cherry noted that her group had done a study, which wasn't published yet, of young adolescent males who, at age 5-6 years old, had been exposed in the Gulf War oil well fires. She stated that they had found no increase in new onset cases, but had seen a worsened condition in those with pre-existing asthma.

Dr. Haley noted there was a second mortality analysis performed which looked, over a period of several years, at the relative risk in deployed versus non-deployed mortality rates from different conditions. He had reviewed this data, and had noted that there was a significant increase in respiratory fatalities one year after the first Gulf War. He stated that, after this period of time, the respiratory fatalities decreased. He stated that he had always wondered if this had been an acute exacerbation of asthma.

Dr. Cowen noted that asthma was the one of the leading causes of evacuation during the 1991 Gulf War.

Dr. Cherry noted it would be interesting to determine if the individual was experiencing allergic or irritant asthma.

Mr. Robinson asked what weight had been given to the differences in asthma rates in theater vs. the general stateside population. Dr. Cowan noted that the general air quality in the Gulf region was terrible, e.g. sand, wood/manure fires, industrial fumes, etc.

Dr. Steele asked whether Dr. Cowan had looked at any other self-reported exposures in conjunction with asthma. Dr. Cowan stated that they had looked at tent heaters. He stated there was a significant

association, but didn't remember the magnitude. When asked about controlling for the effects of oil well fire smoke, Dr. Cowan stated that this was an observation made while doing steps in other analyses.

Chairman Binns asked whether the prevalence of asthma in deployed Gulf War veterans could be determined. Dr. Steele stated that rough estimates, from epidemiologic studies, showed 4-5% of deployed veterans had asthma compared with 1-2% non-deployed veterans. She stated that the asthma rate might be twice as high (8-10%) among deployed veterans exposed to oil well fire smoke.

Chairman Binns thanked Dr. Cowan.

The meeting adjourned at 2:50 p.m. for a break.

The meeting reconvened at 3:12 p.m.

Research on Treatments for Gulf War Veterans' Illnesses: Background and Context

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

Dr. Steele gave an overview, including background and context, of research on treatments for Gulf War veterans' illnesses and the many challenges involved in this area of study. (See Appendix A – Presentation 8.)

Dr. Pellier commented that the antibiotic trial study was difficult to interpret because SF36 findings are composed of multiple elements, which are averaged. He noted that these findings, for an individual patient, needed to be carefully interpreted.

Dr. Steele reported that Chairman Binns and she had attended a seminar on a detoxification therapy for rescue workers at Ground Zero in Manhattan. This treatment had also been used for about 6 ill Gulf War veterans, 3 of which had been reported on at an earlier conference by Dr. David Root. She indicated that they had asked Dr. Root and the sponsors of the treatment clinic to provide systematically-collected data on outcomes seen in their patients that could allow a clearer evaluation of the potential effectiveness of the treatment. Mr. Robinson stated that he had learned about a similar program in the Odessa, TX, area. He stated that several veterans were reporting benefits, but that long-term implications following detoxification were unknown.

Dr. Golomb stated that, when asked several years ago, veterans were not reporting success with any of the known treatments. While there are still many questions, she stated that this type of treatment should be closely evaluated.

"In Return for Their Sacrifice" – Conceptional Basis & Clinical Outcomes of the Specialized Care Program at DoD Deployment Health Center

LTC Charles Engel, Jr., MD, MPH
Director, Deployment Health Clinical Center, Walter Reed Army Hospital

Dr. Engel gave an overview of the approaches used to treat veterans at DOD's deployment health centers, along with their findings relating to these treatments. (See Appendix A – Presentation 9.)

Following the presentation, Dr. Meggs noted that as a clinician one sees people disabled by disease, while other are not. He stated the question then arises as to when a condition becomes disabling. He asked Dr. Engel about his thoughts on this. Dr. Engel stated that their efforts were focused on taking those treatments that could have meaningful impact on the veteran's capacity to function, and making sure the patient was ready for a meaningful change.

Dr. Golomb asked about the deployment health center's staff attitude about Gulf War illnesses. Dr. Engel stated that there was a process of change with the model he had described. He stated some staff found the new model refreshing, while others, while well meaning, didn't agree with the approach. Dr. Golomb stated that she believed the model was good to a certain extent, but thought some effort should be directed toward finding treatments for the actual physical ailments. Dr. Engel thought this was an important policy question, but as a clinician, his efforts are directed towards helping his patients focus on their individual health situation.

Dr. Pellier asked as to the percentage of patients who were identified with anxiety disorders upon entry into the program. Dr. Engel acknowledged there were high rates of co-existing mental illness, e.g. depression. Dr. Pellier asked, as a result of this diagnosis, whether these patients received anti-depressant treatment. Dr. Engel stated this was part of the program.

Dr. Steele noted that, while there may sometimes not be an impressive increase of mean scores in a clinical trial, there may be a particular subset of individuals that shows an impressive increase in function. She noted the data relating to differences in improvement based upon gender. Dr. Engel agreed, and stated that further study was needed with larger sample sizes to identify these subsets. Dr. Steele asked whether patients with concurrent psychiatric diagnosis benefited more from the program. Dr. Engel stated that these individuals were in a relatively good prognosis group, but this was all on a relative spectrum.

Mr. Robinson stated that, for most Gulf War veterans, the Walter Reed deployment health center was one of the first places they've gone where they weren't attacked for their concerns, and received an active response to these concerns. He stated that this acknowledgement, along with learning the center's coping skills and three-month follow-up, was meaningful and helpful to these veterans. However, he noted that the veterans still remained ill, waiting for science to catch up. He stated that he supported what Dr. Engel was doing, and while it may not answer why the veterans were ill, it did provide them benefits. Dr. Steele agreed, and stated she had heard positive testimonials from veterans treated in this program. She noted the differences between VA's WRIISC centers' and DOD's deployment health center's approaches.

Ms. Marguerite Knox asked whether a patient suffering from Amyotrophic Lateral Sclerosis (ALS) had gone through their program, and whether he would advocate they do so. Dr. Engel stated there were limits to what this program could do. He noted that one service member did have a progressive neurological disease, but this condition had not yet been identified when he went through the program. Ms. Knox stated that there existed a problem in medicine today in acknowledging certain illnesses may be undiagnosed. She stated that she embraced this program's model because mind and body are connected. Thus, the emotional state of an ALS patient should be addressed just as his or her physical state. She noted that, while mental and physical illnesses are connected, these processes were also distinct.

Dr. Golomb stated there was a distinction between the idea of "mind" and the physiology of nervous system function. She stated that the original problem wasn't that Gulf War illness wasn't embraced as an illness, but that it was maligned and denounced. Dr. Engel noted that this reaction was not any different than reactions to chronic fatigue syndrome, fibromyalgia or low back pain.

Dr. Melling stated that he saw parallels with his own work from the late 1970s and early 1980s involving vocal spasmodic dystonia. He stated that patient improvement was seen when their illness was recognized. He noted that the value of Dr. Engel's program's acknowledgment of the veterans' illnesses might explain the modest improvements in patient health. Dr. Engel acknowledged that hope was instilled through the program.

Mr. Smithson asked how many of the veterans seen were Gulf War veterans. Dr. Engel stated that, out of the first 600 veterans, there had been approximately 400 Gulf War veterans. He stated that 1/3 of the veterans being seen currently were Gulf War veterans.

Dr. Haley noted that there were many practitioners who made dramatic claims about cures/recoveries, and many veterans were going to these alternative care providers making these claims. He asked for Dr. Engel's thoughts on this phenomenon. Dr. Engel stated that many individuals love to capitalize on desperation. He noted that individuals might not be able to ask hard questions when in this situation, making them vulnerable. He stated that it was the center's obligation to evaluate therapies in controlled clinical trials, even when they might not think they will work. He stated that the veterans needed to know the answers about various treatments, whether it was positive or negative. Dr. Pellier commented that there were several clinical trials being conducted on drugs for other conditions that were based on very little, if any, pathophysiological rationale.

Chairman Binns thanked Dr. Engel.

Public Comment – Day 1

Chairman Binns opened the floor to public comment.

Mr. Edward Bryan spoke to the Committee. He also provided the Committee with a two-page written comment. (See Appendix B - Public Submission 1.) He stated his belief that there were more oil well fires, i.e. 850, than noted by the morning's speakers. He stated that the Committee should consider the "batch effect", i.e., dispersion of smoke over the enemy ground, and the "chimney effect", i.e. the dispersion of smoke into the air. He stated that he hoped the Committee's charter might be modified to better help veterans for years to come. He mentioned his treatment at Walter Reed, and indicated that it had helped to a certain extent. He noted that he still needed treatment, and that the Walter Reed program needed a more in-depth neurological component to its program.

Ms. Alison Johnson spoke to the Committee. She commented that it was interesting that 25% of veterans who left theater in March 1991 had GWI, while 31% of those who left in April-May 1991 were classified with GWI. She suggested that pyridostigmine bromide (PB) pills and pesticides helped to induce multiple chemical sensitivity (MCS) in ill veterans. She suggested that those ill veterans who were then exposed to oil well fires were more sensitive. She also suggested that long-term antibiotic use might increase veterans' problems.

Ms. Denise Nichols spoke to the Committee. She thanked the Committee for its work. She asked that the Committee bring in primary field sources, i.e. field experts, to come and speak at the meetings. She stated her belief that their reports had been changed. She noted that few ill veterans were part of ongoing treatment trials. She stated that more veterans needed more MRI exams. She stated that the veterans wanted to see if there was a problem, and noted this acknowledgement could also be therapeutic. She encouraged more research into immune system problems, mentioning Dr. Vojdani's work in this area. She stated that more work needed to be done to get "hard" diagnostics or markers, while waiting for

treatments. She stated this would at least show progress being made directly on the lives of ill Gulf War veterans. She concluded with a story about an ill veteran, confined to an electric wheelchair, who was diagnosed as suffering from a psychosomatic disorder.

The meeting adjourned for the day at 5:33 p.m.

The meeting reconvened the following day, October 26, 2004, at 8:30 a.m.

Office of Research And Development – Gulf War Update

Dr. Stephen Fihn, MD, MPH
Acting Chief Research & Development Officer (CRADO)
U.S. Department of Veterans Affairs

Chairman Binns introduced Dr. Fihn.

Dr. Fihn presented an overview of research funding provided as a result of VA's 2004 Gulf War illnesses Request for Applications (RFA). (See Appendix A – Presentation 10)

Dr. Steele inquired if it would be possible to have more details about the individual funded studies. Dr. Fihn stated that study abstracts could be provided.

Mr. Robinson asked how many treatment trial proposals had been submitted in response to the last RFA. He noted that the one treatment study that had been funded was one that the Committee had heard about at its June meeting, and that he was surprised it had been funded. Dr. Fihn stated that he would find out the answer to this question.

Dr. Golomb noted the obstacle of requiring principal investigators (PIs) to be employed by the VA in a "5/8th"or greater position. She asked for Dr. Fihn's thoughts about liberalizing this policy. Dr. Fihn stated that the VA's research was an intramural program, and very small compared to the National Institutes of Health research program (385 million vs. 30 billion). He stated that the primary purpose of VA's research program was to conduct meritorious research, while retaining and supporting VA physicians and researchers. He indicated that ORD was reluctant to change this policy, and was reluctant to grant waivers to this requirement.

Mr. Roger Kaplan, Special Assistant to the CRADO, stated that the Office of Management and Budget (OMB) had indicated, several years earlier, that relaxation of this policy would result in elimination of VA research appropriations.

Dr. Golomb noted that GWI funding was almost exclusively within the VA now, and this limited having all of the "best minds" working on these issues. Dr. Fihn disagreed, noting that there were thousands of non-VA researchers collaborating as co-investigators in VA studies. He noted that there was no requirement that the research be performed at VA facilities.

Dr Melling asked whether it was possible to make it a condition that VA researchers use outside co-investigators. He noted this would help broaden the VA's scientific capabilities. Dr. Fihn stated that the Merit Review Panels did look at the investigative team and evaluated it as a whole. He stated that joint solicitations had been tried, but that bureaucratic problems between the organizations had arisen. He stated a combined RFA with the Agency for Healthcare Research and Quality for the last two years had not resulted in a single proposal. He did stress that the current process gives higher scores to highly

qualified research teams. He stated that there was broad collaboration between VA and non-VA researchers, noting that VA investigators, in collaboration with universities, had received over 700 million dollars in NIH funding.

Dr. Meggs asked if there was a requirement that the PI spend more time on the project than the non-VA co-investigator. Dr. Fihn stated that the PI needed to be legitimate, i.e., couldn't be a shadow PI. He stated that the PI needed to be active, but that the co-investigator could be equally active. Dr. Meggs stated that, about three or four years earlier, several researchers wanted to get involved in GWI research. He stated that NIH had directed them to the VA, but that VA had not provided help in directing these investigators to an appropriate VA PI. He noted that this continued to be a hurdle to getting all the best minds together on this problem. Dr. Fihn stated he understood this criticism, but noted that 50 merit proposals had been submitted from within VA on the latest RFA. He stated this indicated interest within VA to conduct this type of research.

Dr. Golomb noted that this was a unique opportunity to study a unique group (Gulf War veterans) with implications well beyond this group. She commented that it was different phenomena than more-straight forward conditions, without many opportunities for outside researchers to get involved. She stated it was a pity to see administrative considerations superseding the veterans' interests. She noted that even Dr. Paul Greengard had found the process difficult, and if they had known how difficult it would be, they might not have pursued their submission. Discussion followed concerning NIH funding vs. VA "Five-eighth's" requirement for funding Gulf War illness research.

Dr. Haley stated that, while the Committee understood the realities for VA, it was passionate about the fact that GWI was a real problem, and needed to be addressed. He noted that this area of study had been an emotional "rollercoaster ride" for the past ten years. He noted that the Committee had produced an interim report two years ago, which received a firm commitment by VA to fund 20 million dollars in the FY2004 budget for Gulf War veterans' illnesses research. He expressed his disappointment at seeing 8 million dollars of FY2004 funding going to a combination of deployment and GWI research. He stated that the funding announcement had been very firm and very clear, but it seemed that the stress theory was still holding out in the VA bureaucracy. He stated this bureaucracy seemed to be derailing the money towards other research concerns.

Dr. Fihn stated that he was disappointed to hear Dr. Haley say this. He stated that the Secretary had kept to his commitments, and that VA was the only agency demonstrating commitment in this area of research. He stated that the Secretary also had a strong commitment to the veterans returning from the current deployment. He also noted that ORD could only fund what proposals are being submitted by its scientists. He stated that ORD was passive, i.e., did not dictate, when it came to proposal content. He stated that ORD defined areas of research, but didn't dictate further than that. He stated that the submitted proposals did have to pass scientific peer review, with an eye towards creating a good mix. He acknowledged that one could argue that the peer review committees might not have done their job appropriately. He stated this was always a problem with peer review. He stated that sometimes the committees may be too specialized or narrow, and may miss new ideas and approaches, while other committees may be too broad and lack the expertise to judge highly technical and focused projects. He stated that he didn't understand how VA bureaucracy had interfered with this process, noting that no money had been held back, funding those studies received.

Dr. Melling commented that, from his experience, it was hard to get people to break out of established patterns unless someone steps in and gives guidance. Dr. Fihn stated that was the plan with the new RFA.

Dr. Fihn noted that the stress research would benefit veterans of the current deployment. Dr. Haley acknowledged that this was true and that PTSD would be a problem for those returning now, but stated that Gulf War I veterans have a unique problem that had never been adequately studied, and that this problem was only going to be addressed by VA. Dr Fihn stated he was not able to answer all these concerns fully because he couldn't speak as to FY2005 plans at the time.

Dr. Cherry expressed concern that there had been only one treatment proposal. She asked Dr. Fihn if this was because: (1) there was no hope for any treatment; or (2) "intellectual poverty" in this area existed among those qualified to submit proposals at VA. Dr. Fihn responded that it was a difficult area of study, because there were no great treatment candidates at this time and there were inherent difficulties, such as identifying the affected population needing treatment.

Chairman Binns encouraged other Committee members to express their thoughts.

Mr. Robinson stated that veterans were frustrated, and were tired of seeing some of the research being funded as GWI research, e.g. telemedicine. He stated his hope that the establishment of the merit review panel, with outside experts, would help fix this problem. He stated that there had been a historical barrier to the types of treatment trials or research being done. He noted that these individuals weren't "bad" people, but that there had been barriers that had thwarted good science. He stated that the Committee was making recommendations about the positive way forward, and didn't want to see backward steps in this process. He expressed his hope that there would be the opportunity to have individuals, identified by the Committee, on the merit review panel. Dr. Fihn stated that ORD would take the Committee's recommendations seriously, but the ultimate decision as to who sat on the panel would be made by ORD.

Chairman Binns offered his perspective on the history of the most recent (March 2004) RFA for GWI research. He stated that the former acting CRADO, Dr. Mindy Aisen, had spent a tremendous amount of time, in weekly ORD phone conversations to the VA research community, encouraging participation in this area of study. He stated that, at the letter of intent stage, there was an intention to review the proposals for relevancy to Gulf War illnesses and the RFA. He noted that there had been a suggestion that the Committee could serve in this capacity in an advisory capacity. He stated that legal issues arose, so no relevance review occurred at the time. He stated that the ultimate goal was to have a quality merit-review board with outside and government experts. However, due to time and regulation considerations, he stated that it was not possible to involve non-governmental employees in that particular review process. He acknowledged that ORD had been responsive to the Committee's suggestions regarding reviewers, but that many of the Committee's top picks were not able to serve on this particular review panel. He expressed a hope that: (1) future RFAs could be more specific; (2) proposals would be subject to a relevancy review process; and (3) the merit review panel would have more experts in the area of GWI research. He stated his impression that Dr. Fihn had judged the submitted proposals "by-the-numbers". He expressed his hope that these procedures would be improved to get better research outcomes.

Dr. Golomb made the point that there needed to be an effort to enhance the number of relevant proposals. She noted that the only GWI training for VA researchers had been several years earlier, and had focused on stress being the cause. In light of this direction by top VA officials, she commented it wasn't surprising that the majority of proposals submitted and funded through the March 2004 RFA were based upon the stress hypothesis. She stated that there was need to change the training of the merit review panel, along with a push to reeducate the VA research community as to the avenues that needed to be pursued in this research area. She also suggested that the Committee revisit the issue of encouraging alternative bodies, e.g. NIH, to open up to investigations related these areas.

Dr. Fihn stated that ORD had recently eliminated letters of intent (LOI) from the proposal process. He stated that these were viewed as an obstacle and red tape to investigators, so only notification of intent was being required. Mr. Kaplan stated that LOIs had been intended for notification, not as a form of triage. Discussion followed about issues related to the March 2004 RFA process.

Dr. Cherry asked whether the 2005 review panel would include non-governmental experts. Dr. Fihn stated that it would, using a standard of high-level scientific merit. Dr. Cherry asked if the Committee would be able to make recommendations as to non-government panelists. Dr. Fihn stated that they were interested in the Committee's advice, but that ORD would remain the ultimate decision-maker as to who is selected for the panel. He noted that scientific organizations needed to jealously guard the independence of its scientific review process.

Mr. Robinson stated that the Committee's recommendations should be part of the ORD process, and if ORD ignored these recommendations, it would be an equal injustice. Dr. Fihn expressed his belief and hopes to have a good working relationship with the Committee. Mr. Robinson asked that ORD not "guard the Committee out of the research" being conducted in this area. He acknowledged Dr. Fihn's need to protect the scientific process, but noted that the Committee was formed to make recommendations that would ultimately translate into treatments and research.

Mr. Graves stated that the Committee had recommended several times that stress research, like that proposed by the East Orange War-Related Injury and Illness Study Center (WRIISC), not be funded as GWI research. He expressed his disappointment as to the funding of some of the proposals under the March 2004 RFA. He stated that he was getting the feeling that ORD was not a real advocate of the Committee's concerns, and was trying to downplay the importance of its purpose and recommendations. He stated that ORD seemed to be focused on deployment health of the returning veterans, while older issues were relegated to a lower priority level. He stated his concern that ORD seemed ready to use money dedicated to GWI for deployment health research for the current conflict.

Dr. Fihn stated that he was sorry if he had conveyed this impression. He stated that he was simply trying to describe processes that he hadn't authored. He stated that he didn't think that the Committee recommendations had been dismissed. He acknowledged that some of the funded proposals did not fit with the scientific agenda set forward by the Committee, but noted that they were good and high-quality studies.

Ms. Knox commented that the Committee was emotional and passionate about this issue, and was disheartened because ORD wasn't "putting its money where its mouth was." She stated that the VA was combining deployment health issues with GWI, and even then, was not looking at two major problems of the current deployment, i.e. traumatic injury and leishmaniasis. Dr. Fihn stated that there were separate RFAs for traumatic amputation research. Ms. Knox expressed her disappointment that this wasn't the same for GWI. She stated that, while projects may have been good scientifically, much GWI funding had been wasted because it wasn't looking at treatment for GWI. She likened it to "sending your husband for a loaf of bread, and he brings back a gallon of milk." She emphasized that it had been fourteen years, and GW veterans still had not received needed treatments.

Dr. Fihn expressed his hope that, in the coming weeks, she would feel better about this conversation. He stated he was unable to discuss ORD's FY2005 plans at this time, but he believed the Committee would see constructive movement in this area. He noted that ORD did have a fiduciary duty to the research and legal processes. He acknowledged that there were areas of potential disagreement, e.g. the 5/8th requirement for PIs, but hoped that ORD's interactions with the Committee had been positive.

Mr. Graves stated that his impression wasn't based solely on the 5/8th requirement. He stated that his impression was based upon ORD's overall approach and attitude that GWI was not an important issue any more. He expressed his disappointment that other concerns were derailing important research. Dr. Fihn expressed his opposite view of the situation. He noted that this area of research was one of the largest funded areas in the VA's research portfolio, alongside cancer research. He acknowledged that VA was treating many veterans who had served in various conflicts, some recently and others not so recently. He expressed his commitment to the care and service of veterans, noting he had been a practicing VA physician and researcher since 1982.

Dr. Golomb explained that the Committee's impression of ORD's indifference to GWI research was due to ORD's focus on: (1) other deployments; and (2) legal requirements.

Chairman Binns stated that he understood, from a legal point view, that Dr. Fihn couldn't promise all Committee recommendations would be heeded. He noted, however, that during the last RFA process, ORD did seek out every qualified reviewer recommended by the Committee. He expressed concern about eliminating LOIs, noting that there needed to be a process to help shape the research being sought. In conclusion, he expressed his belief that Dr. Fihn had gone a long way in implementing some of the Committee's specific requests.

Chairman Binns thanked Dr. Fihn.

The meeting adjourned for a break at 10:05 a.m.

The meeting reconvened at 10:28 a.m.

Dr. Steele reported that the VA had been able to work out a new contract for the AChE-R research by Dr. Concanto and Dr. Soreq. She stated that lab and statistical analyzes should be available by the time of the Committee's next meeting.

Successful Antibiotic Treatment of the Gulf War Syndrome: A Pilot, Randomized, Placebo Controlled, Blinded Trial - Successful Trial of Urine Microscopy for Control of Antibiotic Treatment of Systemic Coccal Disease

Dr. Quentin B. Deming, MD, Professor Emeritus, Albert Einstein College of Medicine
Mr. William Weiss, retired Chief of the Office of Biometry and Field Studies, National Institute of Neurological Disorders and Stroke, National Institutes of Health

Dr. Steele introduced Dr. Deming and Mr. Weiss. She noted that the third investigator on this study, Dr. Edward S. Hyman, MD, FACP, had passed away in the spring of 2004. She stated that a collaborator on the study, Dr. Lauren Krupp would not be presenting at the meeting, but had conveyed to her a favorable impression of the results of this study.

Dr. Deming and Mr. Weiss gave an overview of their clinical trial of antibiotic treatment for ill Gulf War veterans. (See Appendix A – Presentation 11.) Dr. Deming noted that this study was distinct from large clinical trials, such as the one reported on by Dr. Sam Donta at the Committee's February 2004 meeting. He stated that this was a trial that tested a method, rather than a particular drug or dose. He provided background to the investigators' relationships, the evolution and methodology of this particular study, and Dr. Hyman's approach to treatment. He stated that the study was designed as a "black box" study, in which different individuals had received somewhat different administrations of the treatments used,

according to results of their specific tests and their responses to therapy. Mr. Weiss explained the study's design and results. Discussion followed about the results of the study.

Dr. Golomb asked if any of the patients had suspected that they were being treated based upon adverse effects at the time. Dr. Deming stated that none of the patients had made assumptions like this, but that the evaluator had made the wrong assumption in two instances because the patient had diarrhea. He noted that there was a blinded nurse who evaluated each patient for adverse effects. He stated that two effects had been noted, but were not considered significant. The two effects were: (1) a significant increase in the creatine phosphokinase (CPK) level of one patient, which was determined to be due to the patient's starting an intense exercise regimen once he started feeling better; and (2) 10 Jarisch-Herxheimer reactions. These reactions are the body's response to an overrapid destruction of pathogens, leading to a faster release of immunologically active products than the body can handle. Dr. Deming stated that these reactions were considered a therapeutic reaction, and that Dr. Hyman's response to these symptoms was to slow the antibiotic infusion rate in the patient, along with the infusion rate of a placebo patient. He acknowledged that Dr. Hyman would immediately treat the patients for reported problems, e.g. candida, gastrointestinal problems, and thus might have eliminated other adverse effects.

Dr. Deming stated that they had treated the placebo patients with active therapy following the initial study, and thus the second part of the study constituted an open trial.

Dr. Golomb asked whether there had been follow-up work done with the patients. Dr. Deming stated that an attempt had been made to contact patients in 2000, and that 22 out of the 38 patients (60%) had been contacted. He stated that: (1) 8 patients felt perfectly well; (2) 4 patients were as bad as before the treatment; and (3) the other 10 had various levels of relapse but still felt better than before the trial. He stated that all of the urine samples at the end of IV treatment showed reduced bacterial counts.

Dr. Cherry asked for clarification about the circumstances or requirements for the discharge of a patient, i.e., when the patient felt better or when their urine was "clear." Dr. Deming stated that both were needed in adjusting therapy. He stated that Dr. Hyman's approach was guided by the urine results, but not exclusively so. He noted that a placebo patient was released at the same time as a treatment patient. He stated that neither patient (treated or placebo) was told the reason behind the discharge, just simply that the treatment period was over. Dr. Cherry expressed concern about using the patient's symptomatic declarations as a basis of discharge. Dr. Deming acknowledged this, but stated that none of the patients were discharged simply based upon personal declarations.

Dr. Golomb stated that she would agree that there could be a short-term response to the antibiotic treatment. She stated, however, that she was also disposed to believe that this would be the case in the general population. She stated she would be interested in the long-term effects after discontinuation of the antibiotics. Dr. Deming stated that, from their observations, continual treatment is necessary in some patients. He stated that the treatment formula was complicated, but that Dr. Hyman had been able to simplify it and develop a starting treatment package by the end of the study. Discussion occurred about the various antibiotics and dosages used in the study's treatment package.

Dr. Meggs asked about the study's published work. Dr. Deming stated that articles related to the methodology used in the study had been published, but not the treatment trial itself. Dr. Meggs asked if Dr. Deming could hypothesize how the cocci remnants were able to move from the blood to the urine. Dr. Deming stated that he couldn't say how it was transferred, but could give an example of a similar transfer. He referred to the work of a German physician named Kraus who published his candida research in the Lancet (1969). He stated that Dr. Kraus showed that, following ingestion of candida, it was found within an hour in both the blood and urine. He noted that the diameter of candida was three times bigger than

most bacteria. Dr. Meggs noted that it could have penetrated the tissues. Dr. Deming noted that tubercle bacilli appear in the urine of tuberculosis patients when the patient doesn't have tuberculosis in the kidney.

Dr. Deming stated that this study shows: (1) bacteria do play a role in the pathogenesis of this disease; and (2) it is possible to suppress these bacteria and effect a change in symptoms. He acknowledged that they hadn't: (1) shown where the infection was located or what the specific bacterium was; or (2) proven that the bacteria seen were causing the disease. He stated that not all the sediment cocci looked the same.

Dr. Deming stated that this study provided evidence that an antibiotic-responsive bacterium was related at some stage to the genesis of this disease. For corroboration, he noted: (1) Dr. Steele's study, which he stated showed a temporal and geographic focus of the high-incidence of this disease, characteristic of an infectious disease epidemic; and (2) that it was common for family members to be affected. He stated that it was hard to blame a toxic exposure when it appears to be transferred. He noted that the toxic exposure may have made the individual more vulnerable to infection.

Dr. Haley asked which paper provided the definitive bacteriologic method needed to continue this research. Dr. Deming stated that the method was in the Stain Tech paper and wasn't difficult to perform. He explained the technique.

Dr. Steele asked if the research could be done by following patient symptoms, rather than urine sampling. Dr. Deming indicated that it could, but offered to provide sample-processing training/consultation to any researcher who wished to pursue this research. Dr. Golomb noted that urine sampling would be easier to blind and be more objective. Dr. Deming noted that another way to control the study would be to set a finite length of time.

Dr. Pellier stated that he was intrigued by the presentation. He asked if the researchers had tried to characterize the cocci. Dr. Deming stated that Dr. Hyman would subdivide the urine sample. Dr. Hyman would send half to the routine hospital lab and evaluate the other half in his own anaerobic culture. Dr. Deming stated that the majority of the bacteria grown were streptococci, which were then sent to the hospital bacteriology lab and that the bacteria were morphologically different. He noted that this wasn't the first time this result had been found. He gave background information about research by Dr. Marcussen and Dr. Lowell Rantz of Stanford University.

Dr. Golomb noted that another hypothesis for this study's finding could be that there was an underlying factor that caused Gulf War veterans to be ill, and, in addition, they have a common bacterial colonization that is an energetic drain. Thus, she noted it might not be part of the etiology of GWI, but clearing the infection still helps the energy of the patient. Dr. Deming responded that the eight patients who remained asymptomatic after five years didn't fit this conclusion, but those who still required antibiotics might. Dr. Deming stated that he agreed that the other factors did make the patients more vulnerable, but it was unclear to what they were vulnerable.

Dr. Cherry asked why the study's results hadn't been published. Dr. Deming provided a background about the history and politics of the study and its' funding. He stated that they had submitted it to a number of journals, and was amazed by the disbelief and hostility of some of the reviews. He acknowledged that the study wasn't consistent with the methods taught in medical school. He went on to provide a Nobel Laureate's quote about peer review: "I have always felt that in the matter of Galileo, the Catholic Church got a bum rap. What Galileo suffered from was an excess of peer review."

Chairman Binns asked if Dr. Deming had used this technique in his hospital practice with chronic fatigue syndrome patients. Dr. Deming stated that he had used it to treat his rheumatoid arthritis patients, and acknowledged that the bacteria in the urine weren't diagnostic of GWI. He stated that some of these patients had gotten well, while others had not.

Chairman Binns thanked Dr. Deming.

The meeting adjourned for lunch at 12:32 p.m.

The meeting reconvened at 1:33 p.m.

Gulf War Research Update: October 2004

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

Dr. Golomb gave a brief review of recently-published Gulf War-related research in areas that included epidemiology, health effects, mechanisms and other related conditions. (See Appendix A – Presentation 12.)

General Committee Business

Chairman Binns noted that this was Dr. Cherry's final meeting as a Committee member. He thanked Dr. Cherry for her service on the Committee. He noted that she was serving, by request, a shortened term due to other professional demands. He expressed his hope that she would have changed her mind, and stated that he was sorry to see her go. He noted that her many contributions, which included demanding rigour and scientific accuracy in everything the Committee did, were a great benefit to the Committee. Dr. Cherry stated it had been a privilege to serve on the Committee, and hoped to help behind the scenes in the future.

Chairman Binns announced again that the Committee's 2004 report would be released on Friday, November 12, 2004, at 3:00 p.m. He stated that the press conference would be held in the main VA building, Room 230. Chairman Binns stated that he felt that Dr. Fihn had been at a disadvantage earlier in the day, because he was not able to address some concerns that would be answered at this press conference.

Dr. Pellier commented that he had been more disappointed with the news at the June 2004 Committee meeting than this meeting. He stated that, while there might be questions about how to spend the allocated research dollars specifically, he saw progress in the amount of funding. He also noted that the proposals presented to the Committee earlier in the morning had been very brief. He stated that he needed more information about the proposals before he could discount them. He noted that the Committee might not be happy with the outcome of the recent RFA, but that it should be looking at what it could do to make things better in the next funding cycle.

Chairman Binns acknowledged that there were some things that could have been done better. He noted that a list of potential reviewers for ORD consideration hadn't been pre-prepared. He stated, though, the Committee could be prepared for the next funding cycle. He agreed that the Committee didn't know the details of the rejected proposals. He stated that some of the proposals that the Committee liked had some

flaws, and there hadn't been time to correct them. He stated that there was room for opportunity, and greater success would be achieved with future research initiatives.

Dr. Steele raised the issue of having a relevancy panel review. She asked if Chairman Binns expected this idea to be implemented. Chairman Binns stated that he learned that morning that ORD would no longer be requiring LOIs be submitted. He noted that there needed to be a mechanism to shape the studies and ensure relevancy. He stated that, without LOIs, the RFA must be very specific. Dr. Haley stated that the specifications should be in the RFA. He stated that screening RFAs for relevancy might lead to censorship. He compared the RFA to an open contract, with the specifications spelled out clearly ahead of time so the product was responsive to the needs of the agency. Dr. Steele commented that this would be the ideal. However, she pointed out that the last RFA was specific to GWI, highlighting three areas of particular interest, and these weren't the areas particularly funded. Dr. Golomb agreed. Dr. Haley stated that the Committee might need to look at the entire RFA, not just specifications, including making sure the scoring criteria included relevancy.

Mr. Smithson asked if it would be within the Committee's purvue to go back and look at the March 2004 RFA, and comment on whether or not the proposals funded were in the direction favored by the Committee. Chairman Binns stated that the Committee's report might help in future RFAs, by providing researchers guidance and, perhaps, allowing them to cite specific Committee concerns in their proposals.

Mr. Robinson stated that he thought the morning's discussion was constructive. He stated that positive steps forward were being made. However, he noted that the Committee needed to be vigilant and do everything it could to make sure its recommendations were considered. He expressed his hope that Dr. Fihn understood that the morning's comments weren't an attack on him personally. He stated that it was simply an insistence that this Committee's recommendations be considered, especially since it had been over fourteen years with few answers for ill Gulf War veterans.

Dr. Golomb commented that Dr. Fihn didn't seem to embrace the Committee's concerns.

Dr Melling asked if it might be possible to include discriminators in the RFA, providing researchers guidance in their proposals. Dr. Haley stated that these could be built into the scoring criteria.

Mr. Robinson commented that GWI and deployment health RFAs needed to be separate. Dr. Golomb agreed, noting that it should be made clear that deployment research wasn't always related to the specific unique problems in Gulf War I veterans.

Chairman Binns stated that he had been trying to educate Dr. Fihn to some of this background history, but felt Dr. Fihn needed to hear the Committee's concerns. He asked that Committee members, in turn, give Dr. Fihn the benefit of the doubt, and withhold their judgment until the November 12th press conference. He expressed his belief that the "glass was half full", and there was progress.

With respect to intramural GWI research, Chairman Binns noted that the Committee's report did address the need for GWI research outside the VA. He stated that, based on comments before Congressman's Shays' committee in June 2004, Congress had provided a $5 million line item DOD appropriation for "extramural GWI research on chronic physiological brain effects." He stated that this money was in "the hands of the folks" at Fort Detrick. He acknowledged that, two or three years ago, this might not have been thought a great thing. However, he noted that these individuals were the ones who had found Drs. Greengard, Soreq, Henderson and Sastre, and brought them into the research area. He expressed a hope that a group of knowledgeable people, from each agency, could be assembled to plan a comprehensive government effort in GWI research. He commented that there were over 50 recommendations in the

Committee's report, some of which were prioritized. It was noted that the Committee needed to continue prioritizing its recommendations.

Mr. Robinson inquired about Chairman Binns' meetings regarding research monies available through the Department of Homeland Security. Chairman Binns stated they didn't have monies for research, rather for stockpiling supplies, etc. He noted that there was a White House Office of Science & Technology Policy task force, which included individuals from VA, DOD and Homeland Security, which was developing a strategy to address chemical threats.

RAC Committee Business

Dr. Lea Steele, PhD, Scientific Director, RAC-GWVI
Ms. Laura Palmer, Committee Manager, RAC-GWVI

Dr. Steele presented an outline for future Committee meetings and the issues to be addressed. (See Appendix A – Presentation 13.)

Mr. Robinson suggested that MS or similar neurological diseases be included on the consideration list. He stated that, while there might not be statistically significant number of veterans diagnosed with MS within the VA, it could be that these veterans aren't seeking treatment through the VA. Mr. Robinson noted that there was a MS conference in Sacramento, CA, on November 7, 2004.

Dr. Pellier suggested that dementias should be investigated as well. He also suggested that, within certain diagnosed conditions, e.g. ALS, with registries, the Committee investigate whether there was anything particular about the symptomlogy that would connect it with GWI. He would like to see a holistic view of neurodegenerative disorders in Gulf War veterans.

Dr. Cherry noted that GW veterans' symptoms may not be typical of those suffered by non-veterans who are affected by these neurodegenerative diseases.

Dr. Pellier noted that many of these neurodegenerative diseases had "pre" states, which, along with their presentations, should be investigated in GW veterans.

Dr. Pellier questioned why higher accident rates were found in Gulf War veterans. He noted neuro-cognitive disorders could increase one's chance of an accident. He wondered if there was a way to look into this. Discussion occurred.

Ms. Palmer provided an overview of the development and content of the Committee's website, including statistics about its usage by the public.

Chairman Binns thanked Dr. Steele and Ms. Palmer. He welcomed Dr. Rasmussen. He noted that, while considering its size, the staff had been very efficient and effective in its production of the Committee's 2004 report, along with organizing meetings and other work.

Public Comment – Day 2

Chairman Binns opened the floor to public comment.

Ms. Denise Nichols spoke to the Committee. She thanked the Committee for the work on the website. She suggested that there be a service to match outside researchers with VA researchers, allowing for more collaboration on GWI research. She suggested that the Committee produce a video narrative regarding GWI to show the merit review panel. She also suggested more attention to VA clinician/researcher education on current thought regarding GWI. She asked that everyone keep his or her spirits up and momentum going.

Ms. Alison Johnson spoke to the Committee. She expressed concern about Dr Hyman's antibiotic treatment. She read an excerpt from her book, "Gulf War Syndrome: Legacy of a Perfect War", regarding Mr. Bob Jones' treatment by Dr. Hyman. She stated that she had spoken with another veteran who wasn't cured. Dr. Steele stated she had spoken with the same veteran, and that he had told her that he had benefited from the treatment, but later relapsed. Ms. Johnson informed the Committee that she still wanted to provide her book and video, which had been recently updated and tightened, to the VA research community. She asked for the Committee's help in getting the money to do this. She stated that she would provide the materials at cost.

Ms. Venus-val Hammack spoke to the Committee. She also provided the Committee with a two-page written comment. (See Appendix B - Public Submission 2.) She stated that she had been frustrated following the February 2004 meeting, but felt better after this meeting. She hoped that the Committee would invite industrial hygienists to future meetings. She stated that industrial hygienists could provide a work place environment analysis of the Gulf War.

Mr. Harold Nelson spoke to the Committee. He thanked the Committee for inviting Dr. Deming and Mr. Weiss to speak about their treatment study. He thanked Dr. Deming for the treatment he received during the antibiotic treatment trial and indicated that the treatment had provided great benefit in his case. He stated that he would be willing to provide more information, from a patient's point-of-view, of Dr. Hyman and Deming's antibiotic treatment. Discussion about his symptoms and treatment followed.

Mr. Edward Bryan spoke to the Committee. He stated that the Committee needed to compare the batch vs. chimney effects of the oil well fires. He suggested that the Committee speak with Jim Tuite about oil well fires. He stated that the high incidence of accidents in Gulf War veterans should be investigated. He noted that there were several industrial pollutants during the Gulf War. He stated that there was one single-source sewer system, which might have created a bacterial problem. He stated that, by his own calculations, he would estimate 35,000, not 10,000, Gulf War I veterans have died. He stated that more needed to be done to calculate the death rate of Gulf War I veterans. He stated that more treatments needed to be sought, and that a letter should be sent to Congressman Shays' committee requesting more funding for this area of research.

Chairman Binns thanked the Committee members, speakers, and audience members.

Chairman Binns adjourned the meeting at 3:50 p.m.

Appendix A

Presentation 1 – Jack Heller

USACHPPM
Readiness thru Health

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

DESP

USACHPPM

DESP

Oil Well Fire Health Risk Assessment

- Identify Contaminants Produced by Fires
- What Concentrations of Contaminants are at Troop Receptor Points?
- What are the Health Risks (Cancer and Non-cancer) from Exposure to Various Contaminants?
- Conduct "Classic" USEPA Superfund HRA

USACHPPM

DESP

Health Risk Assessment Methodology

- Exposure Assessment
- Toxicity Assessment
- Risk Characterization

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Exposure (Intake) Assessment

- Inhalation
- Dermal Contact
- Incidental Ingestion
- Reasonable Maximum Exposure

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Toxicity Assessment

- Slope Factor - Carcinogenic Risk
- Reference Dose - Non-carcinogenic Risk
  - Chronic and Sub-chronic
- Weight of Evidence

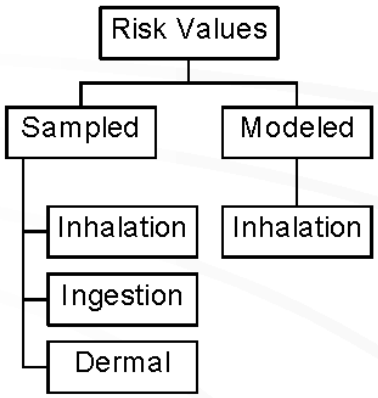
USACHPPM DESP

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

USACHPPM BESP

Risk Values Composition



USACHPPM BESP

Human Health Risks

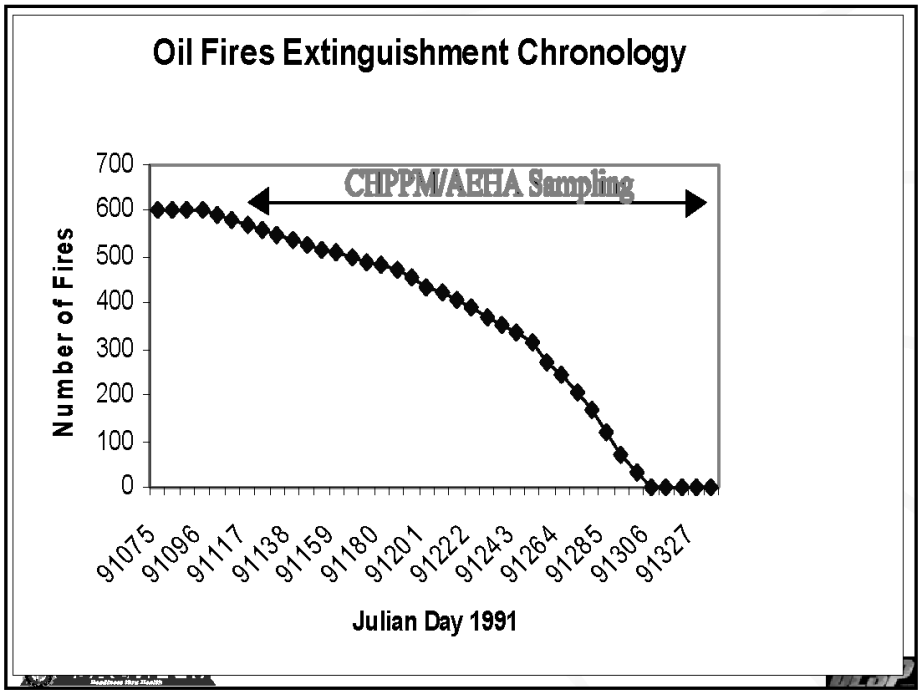
- Predicted Outcomes (population based)
- End Points
  - Cancer
  - Non-cancer
- Verification
  - Biologic Surveillance Initiative (BSI)

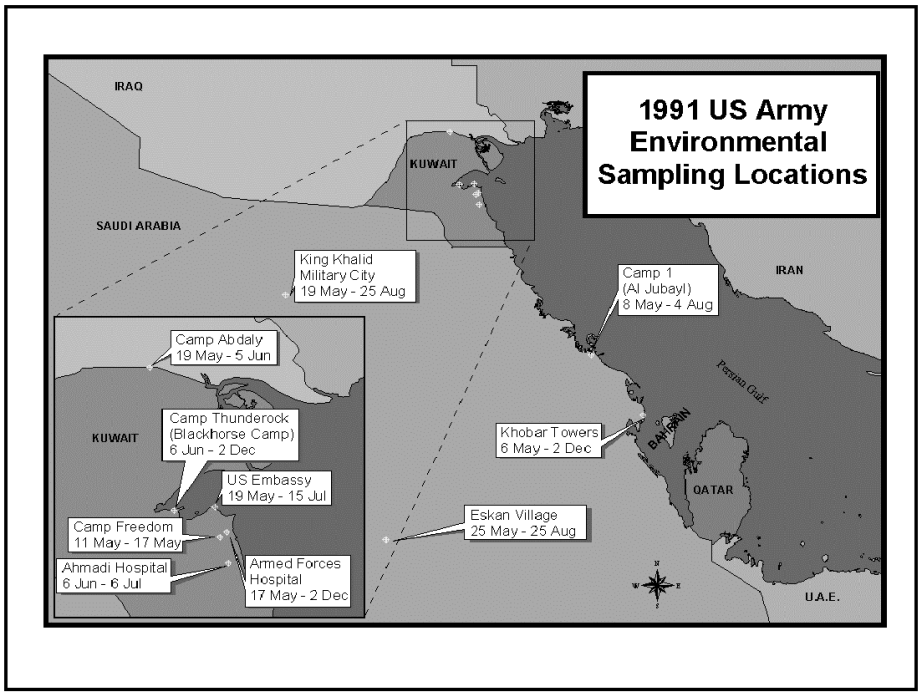
USACHPPM

RESP

USACHPPM

RESP


Oil Fires Extinguishment Chronology
CHPPM/AEHA Sampling
Number of Fires
700
600
500
400
300
200
100
0
91075
91096
91117
91138
91159
91180
91201
91222
91243
91264
91285
91306
91327
Julian Day 1991


1991 US Army Environmental Sampling Locations
IRAQ
KUWAIT
SAUDI ARABIA
IRAN
King Khalid Military City 19 May - 25 Aug
Camp 1 (Al Jubayl) 8 May - 4 Aug
Camp Abdaly 19 May - 5 Jun
Camp Thunderock (Blackhorse Camp) 6 Jun - 2 Dec
US Embassy 19 May - 15 Jul
Camp Freedom 11 May - 17 May
Ahmadi Hospital 6 Jun - 6 Jul
Armed Forces Hospital 17 May - 2 Dec
Khobar Towers 6 May - 2 Dec
Eskan Village 25 May - 25 Aug
BAHRAIN
QATAR
U.A.E.

Environmental Samples Collected

- Ambient Air: 4,019
- Surface Soil: 200
- Industrial Hygiene: 600
- Radiological (air): 200

(gross alpha and beta-gamma)

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Ambient Air Samples Collected

ANALYTE	NUMBER COLLECTED
Poly Aromatic Hydrocarbons	437
Volatiles	803
Acid Gas	487
NOX	86
SOX	90
OZONE	92
Mercury	191
Metals	803
TSP	224
PM10	591
Radiological	215
TOTAL	4019

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Sampled Pollutants of Concern

Volatile Organic Compounds		
Benzene	Toluene	m-Xylene
o-Xylene	p-Xylene	Propylbenzene
Ethylbenzene	Heptane	
Polycyclic Aromatic Hydrocarbons		
Acenaphthene	Acenaphthylene	Anthracene
Benzo(a)anthracene	Benzo(a)pyrene	Benzo(b)fluoranthene
Benzo(e)pyrene	Benzo(g,h,i)perylene	Benzo(k)fluoranthene
Biphenyl	Chrysene	Carbazole
Dibenzo(ah)anthracene	Dibenzofuran	2,6-dimethylnapthalene
Fluoranthene	Fluorene	Ideno(1,2,3-cd)pyrene
1-methylnapthalene	2-methylnapthalene	Naphthalene
Phenanthrene	Pyrene	
Acid Gases		
Acetic	Formic	Hydrochloric
Nitric	Sulfuric	
Criteria Pollutant Gases		
Nitrogen Dioxide/Nitrogen Oxide	Ozone	Sulfur Dioxide
Particulates, Metals, Inorganics		
Particulate Matter <10um	Total Suspended Particulate	Aluminum
Arsenic	Beryllium	Calcium
Cadmium	Chromium(3)	Chromium(6)
Iron	Mercury	Magnesium
Sodium	Nickel	Lead
Vanadium	Zinc	Sulfates
Nitrates	Chlorides	

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Sampled Data – Volatile Organics

Camp	Contaminant Average (ug/m^3)		
Name	Benzene	Toluene	Xylene
Khobar	4.25	12.80	11.10
Doha	3.35	22.80	2.22
AF Hosp	2.65	19.30	1.70

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BESP

Sampled Data - Particulates

Camp Name	Average PM10 Conc (ug/m3)	Maximum PM10 Conc (ug/m3)	Maximum TSP Conc (ug/m3)
Khobar	186	1354	1148
Doha	194	1208	N/A

Majority – Sand based particulates
Silica and Calcium

Minimal – Carbon/Soot

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Sampled Data – PM_{10}/Metals

Camp Name	Average Conc (ug/m3) Vanadium		Average Conc (ug/m3) Lead	
Doha	0.018		0.19	
	June	Nov	June	Nov
	0.023	0.0074	0.13	0.26
Khobar	0.277		0.37	
	June	Nov	June	Nov
	0.072	0.005	0.42	0.29

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Personal Sampling

ANALYTE	NUMBER COLLECTED
Poly Aromatic Hydrocarbons	229
Dust	28
Coal Tar Pitch Volatiles	208
Volatiles	196
Acids	27
SO_X/NO_X	40
TOTAL	785

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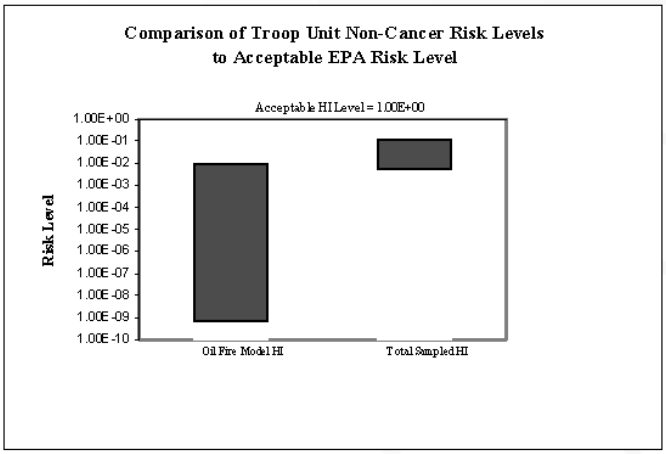
Soil Sampling

- Sampling sites co-located with air sampling sites
- Sample Collection
  - Surface Composites
  - Random
  - Multiple Collections
- Contaminants of Concern
  - Polycyclic Aromatic Hydrocarbons
  - Metals

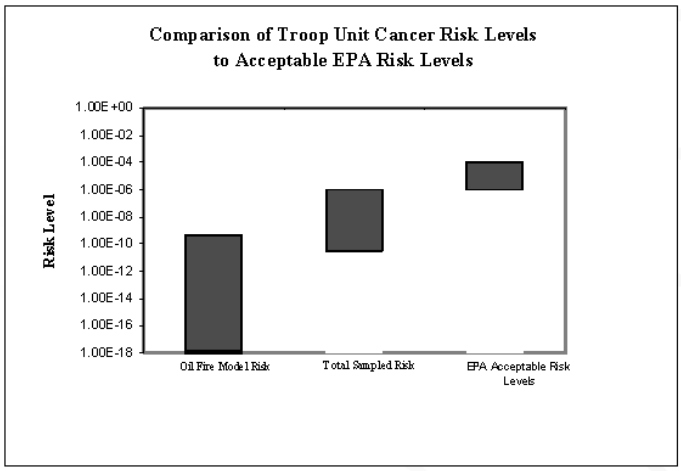
Results / Summary

- Incremental vs. Absolute (Total) Risk
  - Incremental = Oil Fires
  - Absolute = Oil Fires + Industrial + Vehicular + Natural

Non-Cancer Comparison



Excess Cancer Comparison



Radiological Sampling -1991

- Gross α, and β Measurements
- Assessment of Air Samples (217 filters)
- Gross α as a screen for DU
- Background Samples from KKMC and Riyadh
- Assessment of Camp Doha Filters Post Fire
- Levels Lower than for Fuel Oil Combustion in U.S. to Produce Electricity

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Biological Surveillance Initiative

- Pre, During, and Post Deployment Surveillance (11th ACR)
  - Questionnaires
  - Blood and Urine Metals
  - Blood VOCs
  - PAH-DNA Adducts

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External Peer Review

- USEPA
- HHS
- NOAA/ARL
- NIEHS
- ATSDR
- NSF
- DVA
- CDC&P
- NIST
- NRC
- DOD

Exposure Studies

- Cowan DN, Lange JL, Heller J, Kirkpatrick J, DeBakey S. A case control study of asthma among U.S. Army Gulf War veterans and modeled exposure to oil well fire smoke. Mil Med 2002 Sep; 167(9): 777-82
- 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): 1141-1146

Collaborative Efforts

- Epidemiological studies with VA and other researchers
- Gulf War veterans' ALS (Lou Gehrig's Disease) Study
- Harvard/Temple Univ. Study of Kuwaiti Citizens
- Johns Hopkins Univ. Study of Saudi Citizens
- Boston Environmental Hazards Center

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Support to Gulf War Investigations

- Public Laws
  PL 102-190 (SEC. 734; Troop Registry from exposure to oil well fires in Operation Desert Storm)
  PL 102-585 (SEC. 702; Scientific research using Troop Health Registry)
- Troop Exposure Assessment Model (TEAM)
  - Integrate GIS technology

- Questions?
- Dr. Jack M. Heller, Director, Health Risk Management, 410.436.5244

Hazard Quotient Meaning

- HQ > 1.0
  - If a population were exposed to the contaminant(s) under the conditions assumed in the exposure assessment, then some members may develop adverse health effects (more likely in the most susceptible members). As the frequency / magnitude of exposures exceeding the RfD/RfC increase, the probability (and severity) of adverse effects in the population increases.
- Risk Affected by Severity of Toxicity End Point

Excess Cancer Meaning

- Cancer Risk = 3E-05
  - If one hundred thousand people were exposed to the contaminant(s) under the conditions assumed in the exposure assessment, then there may be as many as three additional cases of cancer (in addition to the number expected from the background/historical rate) during the course of a lifetime.
- Affected by Class of Carcinogen

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BESP

Presentation 2 – Warren Wortman

Troop Location Information and Database

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

Troop Location Database

UNIT MOVEMENT
Unit ID Code (UIC)
latitude
longitude
day
TSP
cancer risk
Index (non-cancer)

USACHPPM estimates

PERSIAN GULF REGISTRY
UIC
SSN
name
date_in
date_out
demographics...

By US Armed Services Center for Unit Records Research

By the Defense Manpower Data Center

UIC Caveats

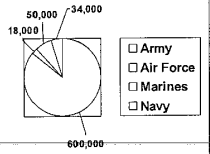
- Service dependent
  - Army & Navy: Company
  - Marines: RUC
  - AF: Location
- UICs w/ multiple locations on same day
- Used one UIC per SSN
  - OSAGWI best UIC
- Assumes SSN is with UIC

Troop Location Stats

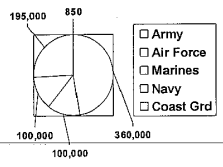
- Unit Movement
  - 700,000 unit locations
  - 3,784 UICs
  - UICs with SSNs: 3,327
  - Aug 90 - Mar 92
- Persian Gulf Registry
  - 696K SSNs (orig)
    - Aug 90 – Jul 91
  - 750K SSNs (ext)
    - Aug 89 – Aug 95
  - SSNs w/locations: 567,000
  - 10,726 UICs

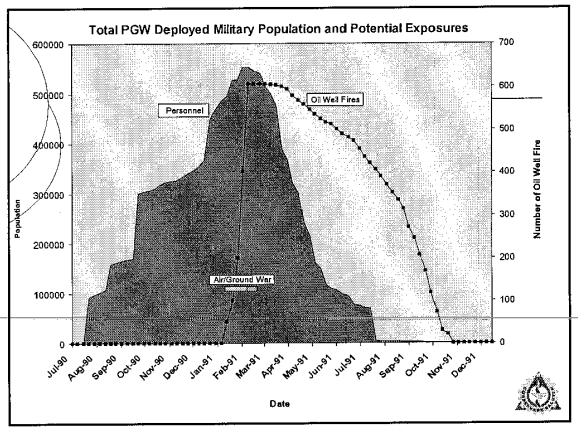
Troop Locations
By Services

Unit Movement
(unit location records)

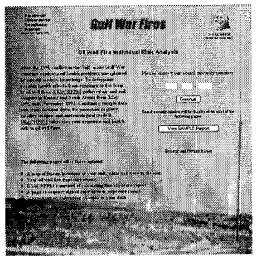


Persian Gulf Registry
(SSNs)

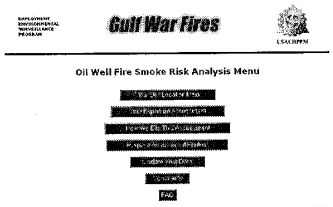




https://gulfwarfires.apgea.army.mil



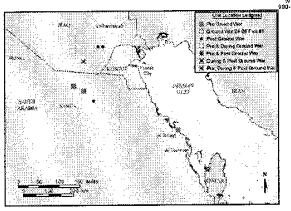
Gulf War Fires Options



Location Map

Gulf War Fires

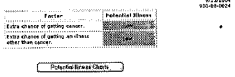
Approximate Unit Locations



General Health Risk

Gulf War Fires

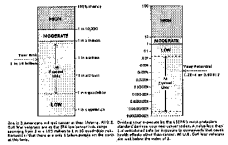
Individual Oil Well Fire Smoke Exposure Risk



Cancer/Non-Cancer Risk

Gulf War Fires

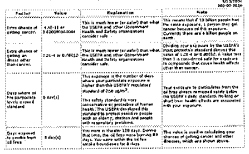
Individual Oil Well Fire Smoke Exposure Risk



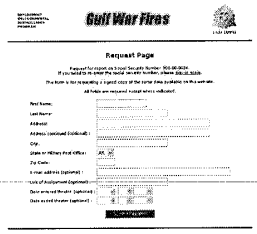
Exposure Risk Details

Gulf War Fires

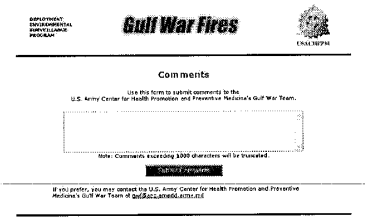
Individual Oil Well Fire Smoke Exposure Risk



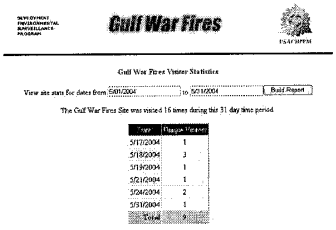
Requests



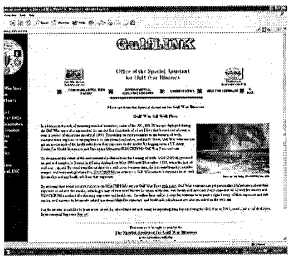
Comments



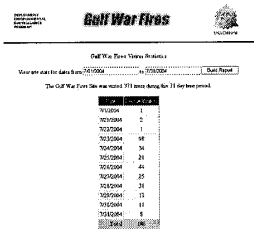
Visitor Stats



GulfLink

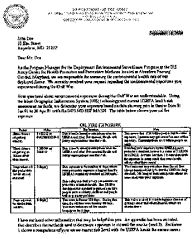


Visitor Stats After Gulflink



Vet Letter

- Two-page letter has 4 attachments
  - Map
  - Health Risk Chart
  - Methodology
  - Data Submission Instructions



Contact Info

- Warren Wortman
  - Kadix Systems
  - USACHPPM
    - Deployment Data Archiving and Policy Integration
  - Warren.wortman@us.army.mil
  - 410-436-2475

Presentation 3 – Jeffrey Kirkpatrick

UNCLASSIFIED

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

UNCLASSIFIED

UNCLASSIFIED

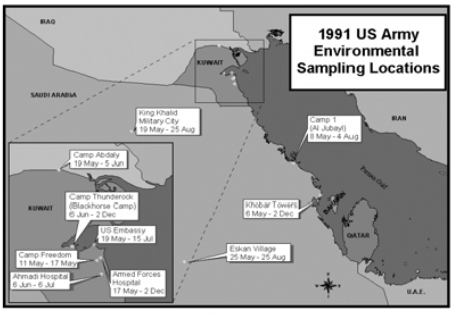
Deployment Occupational and Environmental Health Surveillance – Kuwait Oil Well Fires

- To Comply with Public Law 102-190 (Troop Registry from exposure to oil well fires in Operation Desert Storm), CHPPM (formerly AEHA) Used Geographic Information System Technologies to Develop the Troop Exposure Assessment Model (TEAM)
- Collaborative Effort with National Oceanic and Atmospheric Administration (NOAA), National Center for Atmospheric Research (NCAR), Arabian Gulf Program Office (AGPO)
- Briefing will Provide Overview Summary of Dispersion Modeling Efforts for the Kuwait Oil Well Fires

UNCLASSIFIED

UNCLASSIFIED

1991 Oil Fires Sampling Locations



UNCLASSIFIED

UNCLASSIFIED

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)

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Modeled Oil Fires Data

- NOAA/Air Resources Laboratory Modeling (Feb – Oct 1991)
- NCAR Satellite Imagery (274 images)
- NOAA / AGPO Oil Fires Extinguishment Chronology
- Pollutant Emission Factors / Oil Compositions
- Troop Exposure Factors
- Toxicity Data
- Army Center for Unit Records Research (CURR) Troop Unit Location Data (~697,000 personnel, 9,000 units, 850,000 unit locations)
- Sample and aircraft transect flight data

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Oil Well Fires Emissions Modeling

- Dispersion Modeling: NOAA ARL
  - HYSPLIT (Hybrid Single Partide 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

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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		

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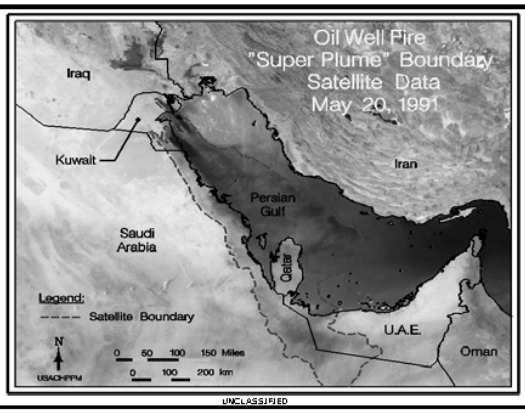
Oil Fires Super Plume Satellite Boundary



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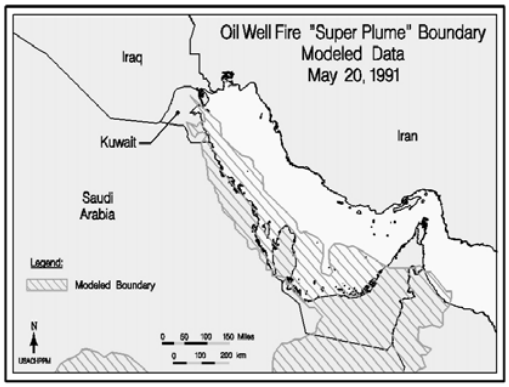
Oil Fires Super Plume Modeled Boundary



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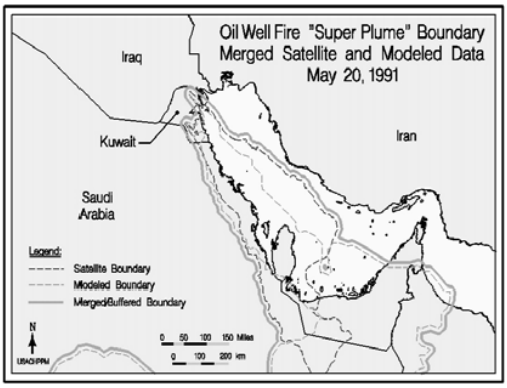
Oil Fires Super Plume Merged Boundary



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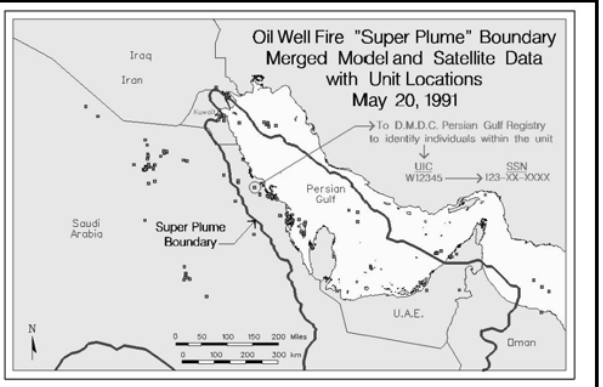
Oil Fires Super Plume Merged Boundary / Troop Unit Locations



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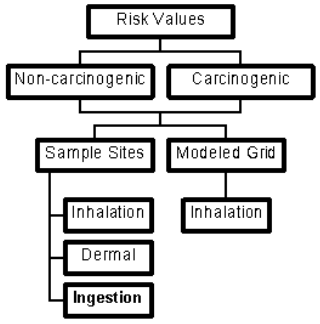
Oil Fires Risk Values Composition

- Incremental vs. Absolute (Total) Risk
  - Incremental = Oil Fires
  - Absolute = Oil Fires + Industrial + Vehicular + Natural



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Concentration, Exposure, Risk Values

SSN: XXX-XX-XXXX
UIC: W12345
Date IN: 4 NOV 00
Date OUT: 19 Jul 91

Report for XXX-XX-XXXX UIC: W12345 DMDC IN: 90309 DMDC OUT: 91201

	MODELED				SAMPLED							
Compound	Days	Concentration Mean (mg/m3)	Max Risk	Max Index	Days	Soilconc Mean (mg/km)	Soilconc Max (mg/km)	Soilconc UCL (mg/km)	Airconc Mean (mg/m3)	Airconc Max (mg/m3)	Airconc UCL (mg/m3)	Max Risk	Max Index
Benz	41	0.000597904	3.527E-11	0.000443459	49	0	0	0	1.099934211	1.429231053	1.429231053	6.69E-08	0.001005794
Total			3.53E-11	4.76E-04								6.67E-08	3.39E-02

Modeled Data Benzene

Days Exposed: 41
Conc Mean (mg/m3): 5.97E-4
Max Risk due to Benzene: 3.57E-11
Max Index due to Benzene: 4.43E-4

Sampled Data Benzene

Days Exposed: 49
Soil Conc Mean (mg/km): 0
Soil Conc Max (mg/km): 0
Soil Conc UCL (mg/km): 0
Air Conc Mean (mg/m3): 1.10
Air Conc Max (mg/m3): 1.43
Air Conc UCL (mg/m3): 1.43
Max Risk due to Benzene: 1.56E-10
Max Index due to Benzene:

Max Risk due to all Modeled Compounds 3.53E-11
Max Index due to all Modeled Compounds 4.76E-04

Max Risk due to all Sampled Compounds 6.67E-08
Max Index due to all Modeled Compounds 3.39E-02

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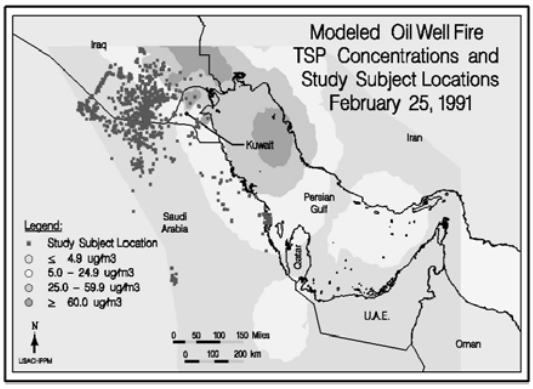
Oil Fires Particulate Matter Modeling



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Oil Fires Publications

- Jeffrey S. Kirkpatrick, Brian W. Higgins, David B. Martin, "Ambient Air Pollutant Trends in Kuwait and Saudi Arabia Observed from 5 May Through 15 September 1991", 85th Annual Meeting and Exhibition of the Air and Waste Management Association, 1992.
- Draxler, Roland R, McQueen, Jeffrey T., and Stunder, Barbara J.B.; "An Evaluation of Air Pollutant Exposures Due to the 1991 Kuwait Oil Fires,' National oceanic and Atmospheric Administration, Air Resources Laboratory, August 1993.
- McQueen, J.T. and R.R. Draxler, 1994. Evaluation of model back trajectories of the Kuwait oil fires smoke plume using digital satellite data. Atmospheric Environment, 28, 2159-2174.
- David Cowan, Jeff Lange, Jack Heller, Jeff Kirkpatrick, Jackie Howard, Chris Weir, and Warren Wortman, "Asthma and Oil Fires Smoke Among Persian Gulf War Veterans", American Public Health Association, 1998.
- Roland R. Draxler, Dale A. Gillette, Jeffrey S. Kirkpatrick, and Jack M. Heller, "Estimating PM_{10} Air Concentrations from Dust Storms in Iraq, Kuwait, and Saudi Arabia", Atmospheric Environment, 35(2001): 4315-4330.

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Oil Fires Modeling Summary

- CHPPM TEAM Solution Meets Intent of Public Laws for Exposure to the 1991 Kuwait Oil Well Fires
- TEAM is Used to Support Numerous Oil Fires Exposure Studies / Assessments with Government and Non-Government Agencies
- Periodic Updates are Made on the System
- Experience Gained from this Effort Has Been Applied to Other / Current Deployment Surveillance Efforts

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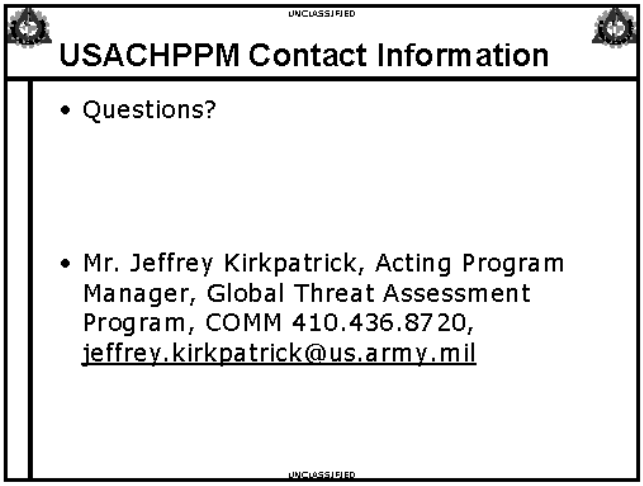
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USACHPPM Contact Information
• Questions?
• Mr. Jeffrey Kirkpatrick, Acting Program Manager, Global Threat Assessment Program, COMM 410.436.8720, jeffrey.kirkpatrick@us.army.mil
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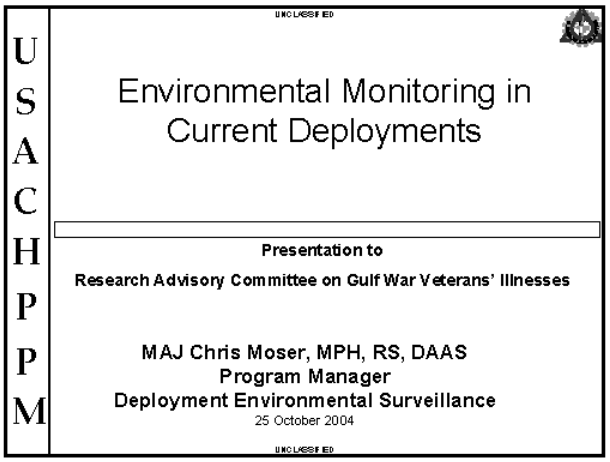
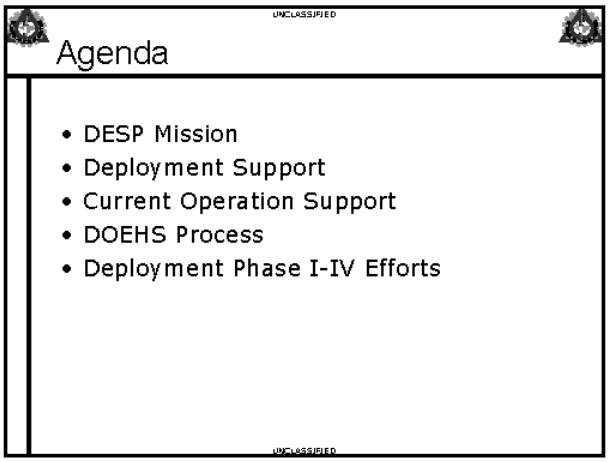
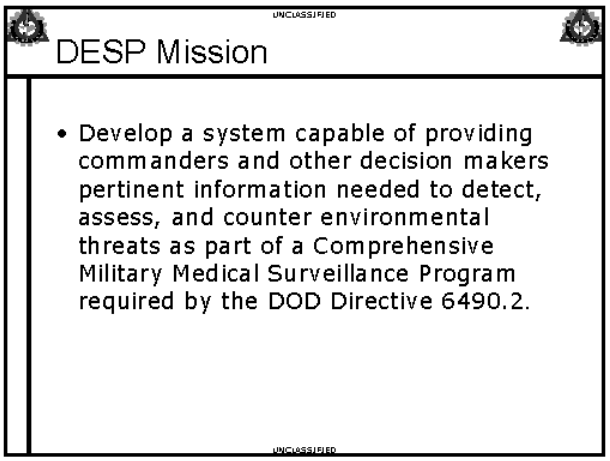
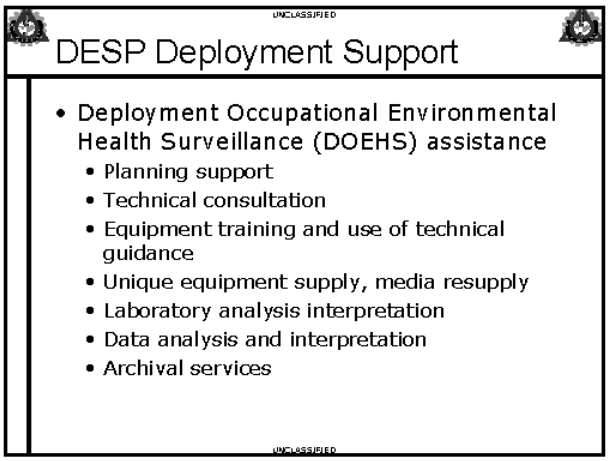
Presentation 4 – Christine Moser









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Current Operation Support

- GWOT, OIF, OEF,
- Exercises (New Horizons, Victory Strike, Cobra Gold)
- Peacekeeping, Humanitarian
- Drug Interdiction (SOUTHCOM)
- Partnership for Peace (EUCOM)
- SOCOM Activities
- Special Medical Augmentation and Response Teams (SMART) - USACHPPM

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Phases of Support

- Phase I Pre-Deployment
- Phase II Mobilization
- Phase III Conflict
- Phase IV Post-Deployment

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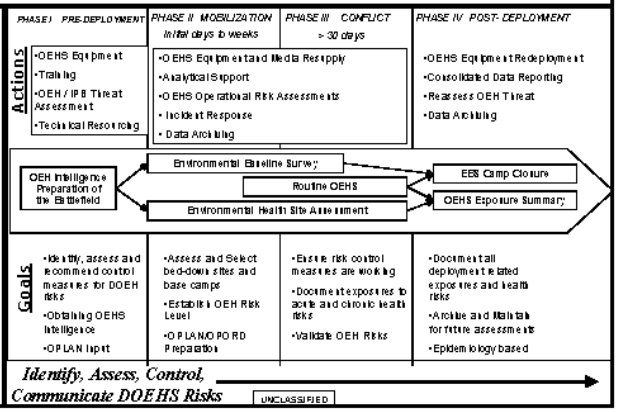
Deployment Occupational and Environmental Health Surveillance Process



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Phase I Assessment Efforts

- Pre-Deployment OEH Intelligence Preparation of the Battlefield Assessments
  - Industrial Materials
  - Historical Contamination
  - WMD Sites
  - Oil Fires
  - UXO
  - Radiation
  - Infectious Disease
  - Entomological Risks
- US Combatant Commands and Component Commands Requests for Bed-down Site Assessments
- Provide Input and Review of Operations Plans

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Training

- OEHS Equipment/Training Activities Provided to DOD
  - Army Preventive Medicine Units
  - Army Division preventive medicine
  - Air Expeditionary Group
  - Marine Expeditionary Force
  - Navy Environmental Preventive Medicine Units
  - Army Corps of Engineers
- Operational Risk Management Course
  - 6AF5 / 6AF6
  - PACOM
  - AF Japan
  - SOCOM
- Specialized team training
- Ad-hoc individual OEHS training

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DOEHS Equipment Support

- Water, Soil, Air
- Media Resupply
- Supplemental
  - GPS, camera, backpack

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DOEHS Equipment Support

- Soil

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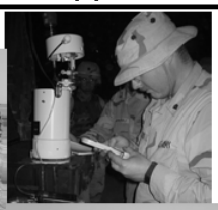
DOEHS Equipment Support

- Air Sampling



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Phase II Efforts

- OEHS Equipment Shipments:
  - USACHPPM Forward
  - Incident Response

DHL

FedEx

UNITED STATES POSTAL SERVICE

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DOEHS Equipment Support

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Intelligence Data

- Defining existing worldwide industrial hazards.
- Continuously revised based on new intelligence.
- Validated by OEHS data.
- Risk and consequence management.
- Secure Web Site
  - Development of Interactive Geographic Information System, Internet Map Server Web Page
  - Posting of OEHS data/reports to site

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Phase II Efforts

- CHPPM SMART PM assist organic units
  - Conduct OEHS Assessments at Base Camps
  - Air, Soil and Water Samples Collection
  - Extensive On-site Risk Communication
  - Health Information Products Provided
- Deploy for: Oil Fires, WWTP chemicals, landfill fire,m severe contamination issues
- Enhance Equipment Sets / Resupply

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Phase II Assessment Efforts

Health Information Products Disseminated In Support of OIF

HIO Products Shipped ISO Operation Iraqi Freedom
Soldier Guide to Staying Healthy
Soldier Guide to staying Healthy in SWA
USACHPPM TG-273 - Diagnosis and Treatment of Diseases of Tactical Importance to USCENTCOM
USACHPPM TG-276 - Ultimate Preventive Medicine CD ROM Set
USACHPPM TG-244 - Medical NBC Battle Book
Oil Fire Information Cards
Botulinum Diagnosis Information Card
Redeployment Antimalarial Medication Information Cards
Soldier and Family Guide to Redeploying from Operation Iraqi Freedom
Redeployment Medical Guide for Missions in Support of Operation Iraqi Freedom

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OIF Phase III Efforts

- OEHS Activities
  - Command and control element to support PM assets
    - HQ (OIF, other deployments).
    - Baghdad, Afghanistan, Balkans, Honduras
  - Sampling media supply and management.
  - CHPPM Laboratory Support Coordination.
  - Data interpretation and ORM assessments for PM personnel.
  - Support to CONUS and OCONUS Air Force and Navy PM personnel.

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OIF - Phase IV Efforts

- OEHS IM/IT Data Archiving Policy
- Under Secretary of Defense Memorandum "Improved Occupational and Environmental Health Surveillance Reporting and Archiving" (29 May 03)
- Joint Chiefs of Staff Memorandum "Updated Procedures for Deployment Health Surveillance and Readiness." (Revised 1 Feb 02)

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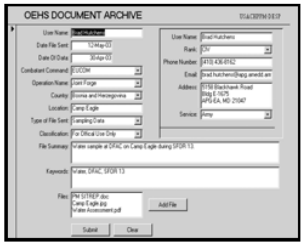
OEHS Document Archival

- Capture Grid Coordinates
- Maintain a consistent level of detail with locations, POCs, forms used, SITREPs, summaries, etc.
- Draw maps and take pictures (w/permission)
- Identify unit personnel and chain of command
- Use remark sections on forms for field and sampling notes
- Include MFRs, official correspondence and log books



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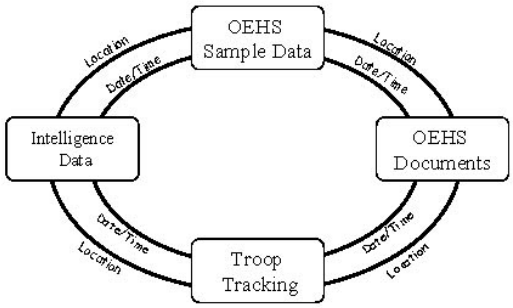
OEHS Data Repository



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Technical Guides

- **TG 230: Chemical Exposure Guidelines For Deployed Military Personnel**
  - Reviewed by National Academy of Science
- **TG 251: Deployment Environmental Surveillance Sampling Guide**
  - Transforming into American Society of Testing and Methods (ASTM) Standard
- **TG 288: Entomological Operational Risk Management**

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Deployment Occupational and Environmental Health Surveillance Process

	PHASE I PRE-DEPLOYMENT	PHASE II MOBILIZATION initial days to weeks	PHASE III CONFLICT > 30 days	PHASE IV POST-DEPLOYMENT
Actions	•OEHS Equipment •Training •OEH / IPB Threat Assessment •Technical Resourcing	•OEHS Equipment and Media Resupply •Analytical Support •OEHS Operational Risk Assessments • Incident Response • Data Archiving		•OEHS Equipment Redeployment •Consolidated Data Reporting •Reassess OEH Threat •Data Archiving
	OEH Intelligence Preparation of the Battlefield	Environmental Baseline Survey Routine OEHS Environmental Health Site Assessment		EBS Camp Closure OEHS Exposure Summary
Goals	•Identify, assess and recommend control measures for DOEH risks •Obtaining OEHS Intelligence •OPLAN Input	•Assess and Select bed-down sites and base camps •Establish OEH Risk Level •OPLAN/OPORD Preparation	•Ensure risk control measures are working •Document exposures to acute and chronic health risks •Validate OEH Risks	•Document all deployment related exposures and health risks •Archive and Maintain for future assessments •Epidemiology based

Identify, Assess, Control, Communicate DOEHS Risks

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Questions?

- MAJ Moser, Program Manager, Deployment Environmental Surveillance, COMM 410.436.5243, christine.moser@usapg.amedd.army.mil

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Presentation 5 – R. Eugene Godwin

Summary of Potential Fuel Exposures During the Persian Gulf War

U.S. Navy & U.S. Marine Corps

Presented by
CAPT R. E. Godwin, MSC, USN
Head, Occupational Safety and Health Branch (M3F42)
U.S. Navy Bureau of Medicine & Surgery
Prepared by CAPT W. R. Stover, MSC, USN

1

Summary of U.S. Navy and Marine Corps Potential Fuel Exposures During the Persian Gulf War

- Does NOT include oil fires and associated byproducts
- What fuels were used?
  - Jet fuels/kerosene (Jet A-1, JP4, JP8) (75%)
  - Diesel Fuel (24%)
  - Gasoline (leaded) (1%)
- Approximately 1.8 billion gallons of fuel used
- 1 Aug 1990 – 30 Mar 1991: Approximately 145,000 gallons of gasoline (leaded) consumed per day
  - Saudi Arabia provided jet fuel and leaded gasoline
  - No source was identified for diesel fuel

2

Summary of U.S. Navy and Marine Corps Potential Fuel Exposures During the Persian Gulf War

- How were fuels used?
  - Vehicle, mobile armament and equipment operation
    - Diesel & gasoline mentioned; typical fueling, motor pool and aviation scenarios
  - Tent heaters, cooking stoves and portable generators
    - Individual service reports from DOD to Institute Of Medicine (IOM) (1996) state Navy used kerosene and diesel fuel for tent heaters; Marine Corps reported using only diesel fuel
  - Dust & sand suppression
    - Diesel & JP4 mentioned
  - Solvents
    - "petroleum" solvents mentioned
  - Accelerant for burning trash & wastes
    - Diesel mentioned for daily burnout of waste cans

3

Summary of U.S. Navy and Marine Corps Potential Fuel Exposures During the Persian Gulf War

- Likely Exposures

1994 National Institutes of Health, *The Persian Gulf Experience and Health, Technology Assessment Workshop* statement:

- "The practices of spreading oil dust suppressants, burning trash and human waste, and using gasoline and diesel fuels for unvented heaters are documented. There were no reported measurements of ambient or indoor pollutants."

1996 Institute of Medicine, *Health Consequences of Service During the Persian Gulf War: Recommendations for Research and Information Systems:*

- "Monitors of air and soil contaminants were not operating for the full period of ODS/S, and other kinds of exposures were not measured."

4

Summary of U.S. Navy and Marine Corps Potential Fuel Exposures During the Persian Gulf War

- Likely Exposures
  - **Fueling operations and/or spills (Inhalation; Dermal)**
    - Gasoline – lead, BTEX (benzene, toluene, ethylbenzene, and xzylene)
    - Kerosene based fuels – kerosene, jet fuels, naphtha, PAH (Polycyclic Aromatic Hydrocarbons)
    - Question: Were fuel tanks cleaned?
      - If so, tank entry makes high dermal exposures probable
  - **Tent Heaters, generators, stoves (Inhalation)**
    - Combustion byproducts, i.e., CO, SO_2, NO_2, particulates, H_2SO_4, No_x, organic carbon
    - Lead (leaded diesel & gasoline)
    - Consider poor ventilation & slow smoke dissipation in tents, unvented heaters, and use of non-issued fuels

5

Summary of U.S. Navy and Marine Corps Potential Fuel Exposures During the Persian Gulf War

- Likely Exposures
  - Vehicle/Equipment Operation (Inhalation)
    - Combustion products
    - Lead
  - Trash and Waste Burning (Inhalation)
    - Combustion byproducts
      - Possible dioxins, PAHs, acids
  - Dust Suppression [Spraying operations on sand and roads] (Inhalation; Dermal; Ingestion)
    - Mists & vapors (volatilization) from diesel & jet fuels
    - Consider ingestion from contaminated hands, clothing, food & water
    - Consider dermal absorption during spray operations
      - Depending on wind direction/speed
      - Proximity of spray to troops

6

Summary of U.S. Navy and Marine Corps Potential Fuel Exposures During the Persian Gulf War

- Likely Exposures
  - Cleaning (dermal)
    - Petroleum products used as solvents
      - Kerosene
      - Jet fuel
      - Unknowns?

7

Summary of U.S. Navy and Marine Corps Potential Fuel Exposures During the Persian Gulf War

Questions?

8

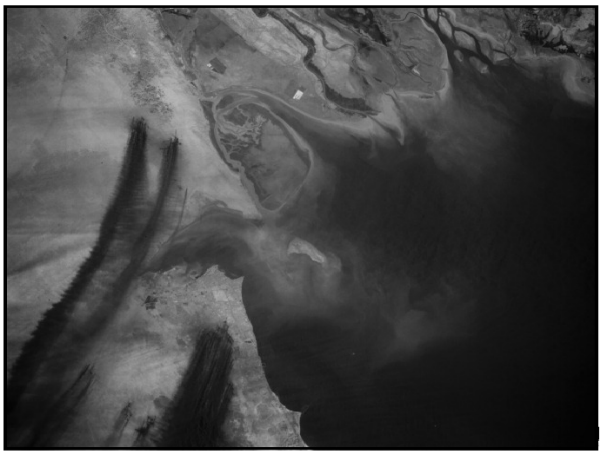
Presentation 6 – Lea Steele & Christine Rasmussen

Health Outcomes in Relation to Petroleum Combustion Exposures During the Gulf War

Summary of Epidemiologic Findings

Lea Steele, Ph.D.
Christine Rasmussen, Ph.D.

RAC-GWVI



Epidemiologic Findings: Combustion Products and Health Outcomes

- General information: health effects of components of oil well smoke, jet fuel
- Epidemiologic findings in Gulf veterans in relation to:
  - Exposure to oil well fires
  - Exposure to tent heaters

RAC-GWVI

Toxicants Found in Oil Fire Smoke

- 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.)*
- Particulate matter *(PM_{10}, $PM_{2.5}$, ultrafine particles)*
- Metals *(cadmium, chromium, lead, nickel, mercury, vanadium)*
- Acidic gases/aerosols *(hydrochloric acid, nitric acid, sulfuric acid)*

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Identified Health Effects of Oil Smoke Contaminants

Ozone	acute lung irritant; chronic structural damage
Nitrogen dioxide	deep lung irritant
Sulfur dioxide	upper airway irritant
Carbon monoxide	neurological, neurocognitive effects
Hydrogen sulfide	acute and chronic neurological effects

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Identified Health Effects of Oil Smoke Contaminants

VOCs	respiratory, neurological, cardiac, bone marrow effects, genotoxic, carcinogenic
PAHs	carcinogenic
Particulates	respiratory, cardiac effects
Metals	respiratory, neurological, gastrointestinal, hematological
Acidic gases/aerosols	acute respiratory effects

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Identified Health Effects of JP-8 Jet Fuel Exposure

AFIERA, 2001	Significantly elevated symptoms: dizziness, weakness, numbness/tingling, headache, blurred vision, cognitive problems, chemical allergy, SOB Measured performance deficits: - Postural sway - Neurocognitive testing - EBCC (eye blink classical conditioning) tests
Other studies	Impaired neurocognitive function, postural balance, EBCC

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Exposure to Petroleum Combustion Products in the Gulf War

Epidemiologic Findings

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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

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Exposure to Oil Well Fire Smoke: Short-term symptoms

Study	Population	Findings
Navy Prev. Med. after action report	2,700 Marines, March 1991	Marines with extended exposure to oil fires had higher rates of respiratory and GI symptoms Wheezing OR = 3.08 (1.92-4.95) Cough OR = 1.54 (1.17-2.02) Diarrhea OR = 2.19 (1.70-2.83) Naus/vomiting OR = 1.91 (1.21-3.01)
Petrucelli, 1999	1599 Army troops	While in Kuwait, personnel had sign. elevated rates of cough, respiratory irritation, burning eyes, SOB, higher rates associated with proximity to oil well fires. After return to Germany, only excess rate of cough persisted.

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Exposure to Oil Well Fire Smoke: Chronic Symptoms

Study	Outcome	Exposure	Findings
Cherry, 2001 (7,971 UK vets)	symptom score	sfr number of days exposed	sign. correlated w/ overall symptom severity no correlation with respiratory symptom score
Proctor, 1998 (220 New England vets)	symptoms (in groups)	sfr	no correlation between exposure and cardiac, neurological, or pulmonary symptoms

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Exposure to Oil Well Fire Smoke: **Symptom Complexes**

Study	Exposure	Outcome	Findings
Iowa Study, 1997 (1,896 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)
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)

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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 self-report	GWI	Bivariate: OR = 1.54 (1.31-1.80) Multivar: OR = 0.44 (0.26-0.73) 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

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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 Bronchitis	OR = 1.8 (1.4-2.4) OR = 1.7 (1.2-2.3)
Iowa Study, 1997 (1,896 Iowa vets)	PGW vs. nondeployed	symptoms suggesting dx	Asthma Bronchitis	sign. prev difference sign. prev difference
Steele, 2001 (2,031 Kansas vets)	PGW vs. nondeployed	self-reported medical dx	Asthma Bronchitis	OR = 2.08 (1.02-4.26) 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 Bronchitis	OR = 2.64 (1.97-3.55) OR = 2.81 (2.22-3.55)
Kelsall, 2004 (1,456 Australian vets)	PGW vs. nondeployed	self-reported medical dx	Asthma Bronchitis	OR = 1.2 (0.8-1.8) OR = 1.1 (0.9-1.5)

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Exposure to Oil Well Fire Smoke: **Diagnosed Conditions**

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

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Exposure to Oil Well Fire Smoke: Diagnosed Conditions

Study	Exposure	Outcome	Findings
Smith, 2002 (405,142 active duty)	modeled, 6 exposure levels	hospitalizations	Overall, greater exposure associated with lower rates of hospitalization in most categories, with the exception of skin diseases (RR=1.35) and injuries (RR=1.11)
	exposed vs. not exposed		Asthma RR=0.90 (0.74-1.0) Chr. bronchitis RR=0.78 (0.33-1.57) Emphysema RR=1.36 (0.62-2.99) Resp. neoplasms RR=1.10 (0.56-2.17) Other resp dx RR=1.45 (0.86-2.46) Isch heart disease RR=0.82 (0.68-0.99)
Cowan, 2002 (873 cases, 2464 controls from CCEP)	strand CHPPM models	dx asthma	(next presentation)

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Exposure to Tent Heaters and Fuels:

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)
Wolfe, 2002 (945 Army vets)	CMI	heater in tent	OR=1.6 (1.0-2.5)
Spencer, 2001 (1,119 ORNA vets)	CMI	diesel heater kerosene heater potbelly heater cleaned heaters contact with fuel	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) OR = 3.76 (1.99-7.12)
Unwin, 2002 (3,284 UK vets)	CMI	exhaust from heaters diesel/petro fumes	OR = 1.9 (1.6-2.2) OR = 2.1 (1.7-2.5)
Gray, 2002 (11,868 Seabees)	GWI	jet fuel burned in tent heaters	OR = 2.12 (1.81-2.49) (unadj) OR = 1.11 (0.93-1.39) (saturated)

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Summary of Epidemiologic Findings: General Points

- **Results differ by how exposure is assessed**
  - Self reported: yes/no vs. graded exposures
  - Self-reported exposure vs. modeled exposure
  - Unadjusted vs. adjusted estimates (possible confounding)
- **Results differ by health outcome of interest**
  - Respiratory symptoms, other defined symptoms types
  - Multisymptom illness complexes (vary with definition)
  - Diagnosed medical conditions

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Summary of Epidemiologic Findings

- 65-80% of Gulf vets report some exposure to oil fire smoke during deployment; duration and intensity vary
- ~ 80% of Gulf vets report exposure to other petrochemical fumes, exhaust from tent heaters
- 30% report eating food contaminated with oil or smoke

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Summary of Epidemiologic Findings

- Deployment to the Gulf War is associated with:
  - excess rates of respiratory symptoms
  - excess self-reported diagnoses of asthma and bronchitis (generally ~ twice the rate of nondeployed)

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Summary of Epidemiologic Findings

- Among veterans who served in the Gulf War, self-reported exposure to oil fire smoke associated with:
  - Short-term (but not chronic) respiratory symptoms
  - Symptoms of/self-reported asthma (ORs~1.8 - 2.8), chronic bronchitis
  - Chronic multisymptom conditions (ORs~1.5 - 4.5) (possible dose-response effect—proximity and duration)

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Summary of Epidemiologic Findings

- Modeled exposure to oil fire smoke associated with:
  - *Mixed findings*

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Summary of Epidemiologic Findings

- Exposure to tent heaters is associated with:
  - Cardiac, neurological, and pulmonary symptoms
  - Chronic multisymptom illness (ORs ~ 2.0)
- Jet fuel: little information from Gulf veteran epidemiologic studies

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Presentation 7 – David Cowan

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

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EPICON Associates, LLC
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Formerly with
DOD Deployment Health Clinical Center
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Washington, DC

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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

6

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

7

Methods 1

- Subjects:
  - Active Duty Army
  - Comprehensive Clinical Evaluation Program Participants
  - Demographic, military, and questionnaire (including self-reported Sx, Cx, Ex) data available.
  - Physician-assigned diagnoses (primary, up to 6 secondary) ICD-9 coding

8

Methods 2

- Cases
  - Diagnosis of asthma (493, 493.91) after CCEP exam
  - No diagnostic or laboratory data available
- Controls 3:1 ratio
  - Random selection of CCEP participants with no respiratory system diagnoses, SSID diagnoses, or Sx or Cx

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Methods 3

- Exposure
  - Self-reported exposure captured (yes/no)
  - Unit location at company level
  - Unit location provided by CRUR to CHPPM

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Methods 4

- Exposure
  - NOAA Air Resource Laboratory developed plume model
  - Modeled plume is for 24 hr average concentration of soot, updated daily
  - Exposures are estimated for 15 km resolution, 2 m above ground

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Methods 5

- Exposure
  - Soot composed ~15-20% of total plume particulates, varied considerably over time and across wells
  - Other components include salts (~30%), sulfates (~8%), other organic compounds (~30%)
  - Most soot and other particulates 0.1-0.8 um diameter

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Methods 6

- **Exposure measures**
  - Sum of estimated concentration for all days in-theater (mg/m³-days). Continuous variable and categories:
    - referent < 0.1 mg/m³-days
    - intermediate >= 0.1 and < 1.0 mg/m³-days
    - highest level >= 1.0 mg/m³-days
  - Number of days exposed to levels of 65 µg/m³ or higher (National Ambient Air Quality Standard for 24-hour particulate matter of less than 2.5 µm diameter (EPA 1997)). Continuous variable and categories:
    - referent 0 Days
    - intermediate 1 to 5 days
    - highest 6 to30 days

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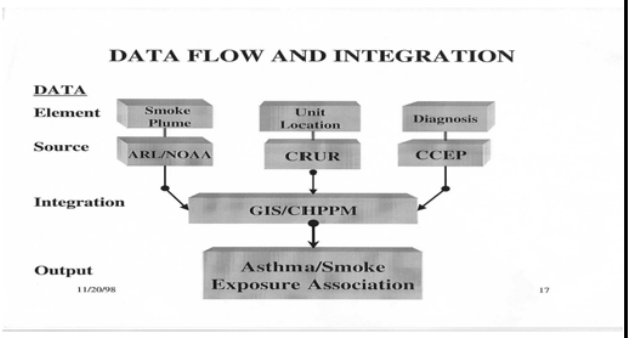
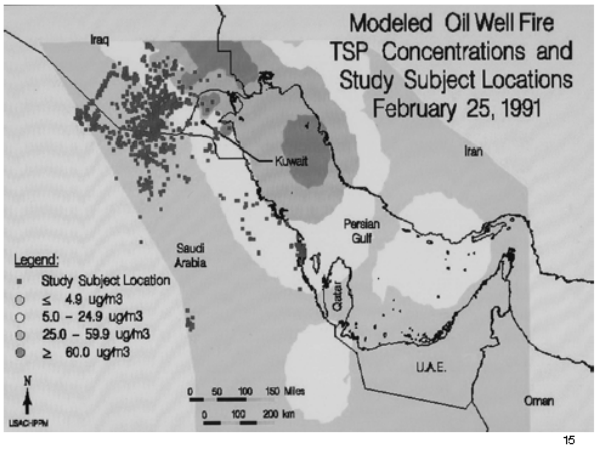


14



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Methods 7

- Analysis
  - Odds ratio measure of association
  - Statistical significance based on 95% confidence interval
  - Logistic regression used for multivariate analyses

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Results

- 873 cases with valid location data used in analyses
- 2464 controls with valid location data used in analyses

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Table 1. Univariate associations between asthma and demographic characteristics

Sex			
Female	133	264	1.00 (referent)
Male	739	2200	0.67 (0.53 - 0.84)
Age group at time of evaluation			
19-24	262	662	1.00 (referent)
25-29	231	646	0.90 (0.73 - 1.12)
30-34	202	608	0.84 (0.67 - 1.05)
GE 35	161	520	0.78 (0.62 – 0.99)
Chi Square for trend = 5.10, p=0.024			
Race/ethnicity			
White	439	1225	1.00 (referent)
Black	311	909	0.95 (0.80 - 1.13)
Hispanic	50	127	1.10 (0.77 - 1.57)
Other	73	203	1.00 (0.74 - 1.35)

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Table 1. (cont) Univariate associations between asthma and demographic characteristics

Variable and Level	Number of Cases	Number of Controls	Odds Ratio (95% CI)
Rank			
Enlisted	799	2169	1.00 (referent)
Officer	66	246	0.73 (0.54 - 0.98)
Cigarette smoking			
Never	499	1327	1.00 (referent)
Former	186	461	1.07 (0.87-1.32)
Current	188	676	0.74 (0.61 - 0.90)
Self-reported oil well fire smoke exposure			
No	111	443	1.00 (referent)
Yes	634	1626	1.56 (1.23 - 1.97)

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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)

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Table 2. Univariate Associations between Asthma and Measures of Smoke Exposure

Cumulative exposure mg/m3-days			
Categories	Cases	Controls	Odds Ratio (95% CI)
< 0.1	172	592	1.00 (referent)
>= 0.1 – < 1.0	292	829	1.21 (0.97 – 1.51)
>= 1.0	273	670	1.40 (1.12 – 1.76)
Any vs. none			1.30 (1.06 – 1.58)
Chi square test for trend = 9.04, p=0.003			

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Table 2. (Cont) Univariate Associations between Asthma and Measures of Smoke Exposure

Days with Exposure >= 65 ug/m3			
Categories	Cases	Controls	Odds Ratio (95% CI)
0	215	723	1.00 (referent)
1-5	270	745	1.22 (0.99 – 1.50)
6-30	218	495	1.48 (1.19 – 1.85)
Any vs. none			1.32 (1.10 - 1.60)
Chi square test for trend = 12.26, p=0.0005			

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Table 3. Odds Ratios (95% CI) for Asthma by Smoking Status

Exposure and Level			
Cumulative exposure mg/m3-days			
Categories	Never Smoked	Former Smoker	Current Smoker
< 0.1	1.00 (referent)	1.00 (referent)	1.00 (referent)
>= 0.1 – < 1.0	1.31 (0.98 – 1.77)	1.27 (0.75 – 2.16)	1.00 (0.71 – 2.16)
>= 1.0	1.43 (1.06 – 1.94)	1.73 (1.04 - 2.90)	1.05 (0.64 – 1.72)

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Table 3. (Cont) Odds Ratios (95% CI) for Asthma by Smoking Status

Exposure and Level			
Days with Exposure >= 65 ug/m3			
Categories	Never Smoked	Former Smoker	Current Smoker
0	1.00 (referent)	1.00 (referent)	1.00 (referent)
1-5	1.24 (0.99 – 1.64)	1.54 (0.95 – 2.51)	0.92 (0.63 – 1.34)
6-30	1.35 (1.00 – 1.82)	2.02 (1.23 – 3.34)	1.29 (0.79 – 2.09)

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

Cumulative exposure mg/m3-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.

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

Days with Exposure >= 65 ug/m3	
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.

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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

27

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

28

Compare and Contrast the Studies

- What do they have in common?
- What is different?
- How could these affect the findings?

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Study design

- Smith, et al. Historical cohort
- Lange, et al. Cross-sectional
- Cowan, et al. Case-control

30

Study population

- Smith, et al. ~405,000 active duty, deployed, all branches
- Lange, et al. ~1,900 all components, deployed, all branches
- Cowan, et al. ~3,300 active duty CCEP, deployed, Army only

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Control of potential confounders?

- Smith, et al. Partial: job, prewar hospitalization
- Lange, et al. Partial: smoking status, self-reported exposure
- Cowan, et al. Partial: smoking status, self-reported exposure

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Diagnosis issues

- *A priori* hypothesis
- Case definition
- Study setting
- Number of cases in study
- Diagnostic accuracy
- Prevalence of disease in studied population

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A priori hypothesis for outcome?

- Smith, et al. No. Looked at all dx
- Lange, et al. Yes. Examined only respiratory illness (plus depression)
- Cowan, et al. Yes. Examined only asthma

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Case Definition

- Smith, et al. Hospital record, ICD-9
- Lange, et al. Self-report ATSQ
- Cowan, et al. Physician diagnosis

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Study setting

- Smith, et al. Electronic records of hospitalized patients only
- Lange, et al. Telephone interviews
- Cowan, et al. Patients seen outpatient in CCEP. Data from q-aires, medical exam

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Number of cases in study

- Smith, et al., 880
- Lange, et al., 129
- Cowan, et al., 865

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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.

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Prevalence of Diagnosis in Population

- Smith, et al. 0.22%
- Lange, et al. 8.3%
- Cowan, et al. 2.2% (primary dx)

39

Exposure Issues

- Estimation issues
- Data source
- *A priori* hypothesis
- Exposure Cut points
- Branch of service and unit location

40

How exposure estimated

- Smith, et al. Reported TSP, 2 m above ground
- Lange, et al. Solar absorbance of smoke, distance above ground not specified
- Cowan, et al. Soot, 2 m above ground

41

Source of exposure estimates

- All studies used same basic source of data: Center for Health Promotion and Preventive Medicine/National Oceanic and Atmospheric Administration plume model

42

A priori hypothesis for exposure?

- Smith, et al. Not clear
- Lange, et al. No. Cut points arbitrary
- Cowan, et al. Yes. Set cut points prior to analyses

43

Exposure Cut points

- Smith, et al.
  - 7 levels
    - none
    - 1-260 ug/m3 for 1-25, 25-50, or >50 days
    - >260 ug/m3 for 1-25, 25-50, or >50 days
  - Categories do not appear to be mutually exclusive

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Exposure Cut points

- Lange, et al.
  - Two levels "set without available precedent and without intuition regarding a level that would adequately balance sensitivity and specificity. Thus, *a priori*.." selected the 50th percentile and the 95th percentile, compared most-exposed to rest of population
  - Used number of days exposure was above each threshold.

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Exposure Cut points

- Cowan, et al., established cut points *a priori* based on distribution and EPA standards

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Branches included

- Smith, et al. All branches
- Lange, et al. All branches
- Cowan, et al. Army only

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Military Branches and Unit Location Data

- Most military personnel in the vicinity of the oil well fires were Army and Marine Corps
- Army unit location data at the company level (approximately 100-200/Co)
- Marine data at the battalion level (4 to 6 Co/Bn)
- Navy and Air Force data not usable due to mobility and size of units
- Only Army personnel were used by Cowan, et al.

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Impact of Branch of Service

- Smith, et al. and Lange, et al. used all branches of service. Due to problems with Marines, Air Force, and Navy data there is likely increased exposure error
- Cowan, et al., used only Army units, likely had lower level of exposure estimate error

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What does it all mean: error in diagnosis and exposure

- If errors in diagnosis and exposure are not dependent on one another (non-differential misclassification), then the observed level of association is almost certainly lower than the true level of association
- There is little doubt that errors exist in both diagnosis and exposure estimates

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Misclassification Discussion: Cowan, et al.

- Potential for misclassification errors in Cowan, et al.
  - Outcome
    - False positive cases
    - Less likely false negative controls
  - Exposure
    - Unit location errors likely
    - Model errors likely
    - Degree of these unknown

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Misclassification Discussion: Smith, et al. and Lange, et al.

- Smith, et al., probably missed 90% of cases (many false negatives), but probably had very high PPV
- Lange, et al, probably over-diagnosed substantially (many false positive), had low PPV, but had few false negatives

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Misclassification Discussion

- In each study diagnoses and exposure estimates were were made independently of each other; therefore it is probable that the errors are largely non-differential

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The effect of non-differential misclassification

- The effect of non-differential misclassification is known:
  - '…bias from independent non-differential misclassification of a dichotomous exposure is always in the direction of the null value…" Rothman and Greenland, *Modern Epidemiology*

54

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*

55

The Potential for Selection Bias

- Difficult to assess, always a challenge, can give biased answer
- In both Lange, et al., and Cowan, et al., there was a low level of correlation between self-reported and modeled exposure, so self-selection is not likely to account for findings
- Must remain vigilant for bias

56

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...

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Presentation 8 – Lea Steele

Research on Treatments for Gulf War Veterans' Illnesses:

Background and Context

Lea Steele, Ph.D.

October 25, 2004

GWI Treatment Research

- Challenges of studying GWI treatments
- Evaluating evidence re: treatment effects
- VA/DOD Clinical Practice Guidelines
- Treatment studies of GWI
- Identifying "new" treatments

GWI Treatment Research

- Treatment Information we've discussed
  - ABT, EBT Clinical Trials
  - VA/DOD Clinical Practice Guidelines
  - Clinical experience at NJ WRIISC

GWI Treatment Research

Evaluating GWI treatments is extremely challenging

- GWI may include multiple pathophysiological processes
  - May require treating concurrent problems that differ in different people
  - Which subgroups benefit from which treatments?
- No objective clinical markers of illness
- No accepted GWI case definition
  - Who has Gulf War illness/who does not?
- How best to measure health improvement/response to treatments?

GWI Treatment Research

- Measuring Improvement: Outcome Measures
  - Change/elimination of biological indicator of pathology (e.g. infection)
  - Sustained symptom improvement
  - Improvements in functional status on standardized tests
    - SF-36, SIP, cognitive function, etc.
    - Exercise tolerance

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GWI Treatment Research: Measuring Outcomes

- SF-36
  - Evaluates health/functional status in several domains of daily life
    - Physical function summary score (PCS)
    - Mental health function summary score (MCS)
  - Mean score in the general population is 50 (scale of 0-100)
  - Mean scores associated with diseases:
    - Diabetes = 42
    - COPD = 36
    - GWI participants in ABT trial = 30

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Evaluating Evidence of Treatment Efficacy; Effectiveness

Levels of Evidence (IOM, 2001)

Level
1 Multiple well-designed RCTs; multiple well-designed outcomes studies

2 Single well-designed RCT; single well-designed outcomes study

3 Consistent findings from multiple observational studies

4 Single cohort or case/control observational study

5 Unsystematic observation, expert opinion, consensus judgment

Gulf War Veterans' Illnesses: Treating Symptoms and Syndromes. IOM, 2001

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GWI Treatment Research: Little Evidence to Evaluate

- VA/DOD Clinical Practice Guidelines: Recommendations of Expert Panels
  - Post Deployment Health Concerns
  - Medically Unexplained Fatigue and Pain
- VA/DOD Clinical Trials
  - EBT
  - ABT

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VA/DOD Clinical Practice Guidelines: Medically Unexpl Fatigue and Pain

VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF MEDICALLY UNEXPLAINED SYMPTOMS (MUS): CHRONIC PAIN AND FATIGUE
Guideline Summary

PRIMARY CARE

GUIDELINE SUMMARY

- Establish that the patient has MUS.
- Obtain a thorough medical history, physical examination, and medical record review.
- Minimize low yield diagnostic testing.
- Identify treatable cause (conditions) for the patient's symptoms.
- Determine if the patient can be classified as Chronic Multi-Symptom Illness (CMI) (i.e., has two or more symptoms clusters: pain, fatigue, cognitive dysfunction, or sleep disturbance).
- Negotiate treatment options and establish collaboration with the patient.
- Provide appropriate patient and family education.
- Maximize the use of non-pharmacologic therapies:
  - Graded aerobic exercise with close monitoring.
  - Cognitive behavioral therapy (CBT)
- Empower patients to take an active role in their recovery.

May 2002

RAC-GWVI

Clinical Practice Guidelines: Medically Unexplained Fatigue and Pain

[redacted]

THERAPY INTERVENTIONS FOR FIBROMYALGIA

R=Recommendation A=Randomized Control Trial B=Clinical Studies C=No Benefit or Harm D=Harmful

R	Maximum Benefit	Some Benefit	Possible Benefit	Possibly Harmful
A		• **Cognitive Behavioral Therapy (CBT)** • **Graded Aerobic Exercise** • **Anti-depressant (TCA)**		
B		• 5-HTP • SAMe** • SAM (R = B/C) • NSAIDs (R = B/C)	• Acupuncture • Biofeedback • Trigger point injection • Tramadol	• Alprazolam
C		• Sleep education • Other anti-depressants (non-SSRI, non-TCA)	• Massage therapy • Relaxation therapy • Myofascial release • Spinal manipulation • Hypnotherapy • Magnesium	• Antiviral • Antifungal • Antibiotics
D				• Bed rest

Tramadol – Non-formulary medication. Available by physician request using the non-formulary process.
***SAMe is a nutritional supplement that VA does not provide. It is available as over-the-counter product.*

THERAPY INTERVENTIONS FOR CFS

R=Recommendation A=Randomized Control Trial B=Clinical Studies C=No Benefit or Harm D=Harmful

R	Maximum Benefit	Some Benefit	Possible Benefit	Possibly Harmful
A	• **Cognitive Behavioral Therapy (CBT)** • **Graded Aerobic Exercise**			
B		• MAOI • NADH		
C		• Sleep education • SSRI • Other anti- depressants (non-SSRI, non-TCA)	• Relaxation • Flexibility exercise • Essential fatty acids • Magnesium • Low-dose, short term corticosteroid (R = B/C)	• Fluvimat, ataxia
D				• Bed rest • Corticosteroid High-dose or Replacement • Anti-viral • Anti-fungal • Immune therapy

Management of Medically Unexplained Symptoms (MUS): Chronic Pain & Fatigue Summary page 14

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Clinical Practice Guidelines: Medically Unexplained Fatigue and Pain

[redacted]

PHARMACOLOGIC AGENTS FOR CFS/FM[a]

Agent	Dose Studied	Effective	Adverse Effects	Comments
Anti-depressants				
Amitriptyline	Initial: 10 to 25 mg/day Maximum: 75 mg/day	Yes	• Sedative and anticholinergic effects • Cardiac toxicity	• The agent is very effective in approximately 20% of patients. • Tachyphylaxis can occur with continued treatment. • Anticholinergic side effects may limit use. • Not recommended for use in the elderly.
Cyclobenzaprine	5 to 40 mg/day	Yes	• Anticholinergic and central nervous system effect	• Side effects may limit use. • Tachyphylaxis can occur with continued treatment.
Fluoxetine	Initial: 10 mg/day Range: 20 to 40 mg/day Maximum: 80 mg/day	Equivocal	• Most commonly sexual dysfunction	
Venlafaxine	37.5 to 300 mg/day	Possibly	• Headache • Sexual dysfunction	• The extended release form given during the day as a single morning dose of 80C dosing may be most effective.
Citalopram	Initial: 20 mg/day Range: 20 to 40 mg/day Maximum: 40 mg/day, if elderly	No	• Sexual dysfunction • Nausea	
Atorvastatin	10 to 5.0 mg/day	Unknown	• Sedative and hypnotic effects	
Analgesics (narcotic)				
Tramadol*	50 to 400 mg/day	Yes	• Nausea • Dizziness	• Dual mechanism of action may address altered neurotransmitters and pain signals of FM.
NSAIDs	Dose range recommended by drug manufacturer	Equivocal	• Risk of bleeding and NSAIDs	• Naproxen is common. • Efficacy in less than in other rheumatic conditions where inflammation is present.
Opioids	Dose range recommended by drug manufacturer	Unknown	• Sedative effects • Nausea	• There is no clinical evidence to show efficacy. • Tolerance or dependence may develop with long-term use. • If used regularly, long-acting formulations are preferred.
S-adenosyl-L-methionine (SAMe)**	• 200 mg/day orally • 400 mg/day IV • 800 mg/day orally	Possibly	• None documented	• Drug is available in the United States only, as an over-the-counter dietary supplement.
Other				
Magnesium and malic acid	600 to 2400 mg/day	Unknown	• Diarrhea • Nausea	• May help a limited number of patients who have difficulty initiating sleep.

[a] Adapted from Leventhal LJ. Management of fibromyalgia. Ann Int Med 1999; 131:850-8. Other guidance regarding pharmacotherapy for CFS can be found in Reid S, et al. Chronic Fatigue Syndrome. BMJ 2005; 330(7481):328-32.
*Tramadol – Non-formulary medication. Available by physician request using the non-formulary process.
**SAMe and Melatonin are nutritional supplements that VA does not provide. Are available as over the counter products.

Management of Medically Unexplained Symptoms (MUS): Chronic Pain & Fatigue Summary page 15

RAC-GWVI

GWI Treatment Research: Clinical Trials

EBT: Exercise/Behavioral Therapy Trial

1,092 Gulf War veterans at 20 study sites; 12 mo. therapy

	SF-36 PCS improved 7 pts. or more	SF-36 PCS mean pts. improved
Usual care	11.5 %	-0.04
Exercise	11.7 %	0.97
CBT	18.5 %	0.59
CBT + exercise	18.4%	1.03

RAC-GWVI

GWI Treatment Research: Clinical Trials

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 %

★☆★ RAC-GWVI

GWI Clinical Trials: No evidence of substantial improvement in veterans' health

- EBT:
  - CBT produced 7% more veterans with 7 pt. SF-36 increase, but less than 1 point mean increase
  - Exercise/CBT produced some symptomatic improvement
- ABT:
  - Similar % of treatment and placebo group had 7 pt. increase at 12 mos; mean SF-36 increase was ~ 2 points
  - Mycoplasma infection and GWI?

★☆★ RAC-GWVI

Identification of Treatments for GWI: Approaches Used by VA

Levels of Evidence (IOM, 2001)

Level
1 Multiple well-designed RCTs; multiple well-designed outcomes studies

2 Single well-designed RCT; single well-designed outcomes study

3 Consistent findings from multiple observational studies

4 Single cohort/observational study

5 Unsystematic observation, expert opinion, consensus judgment

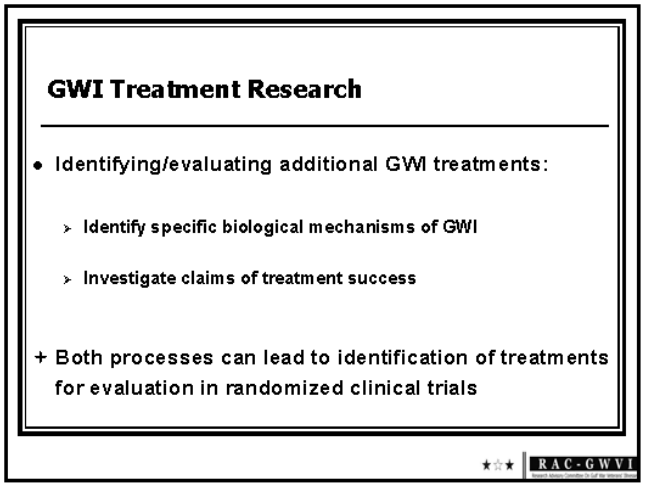
Gulf War Veterans' Illnesses: Treating Symptoms and Syndromes. IOM, 2001

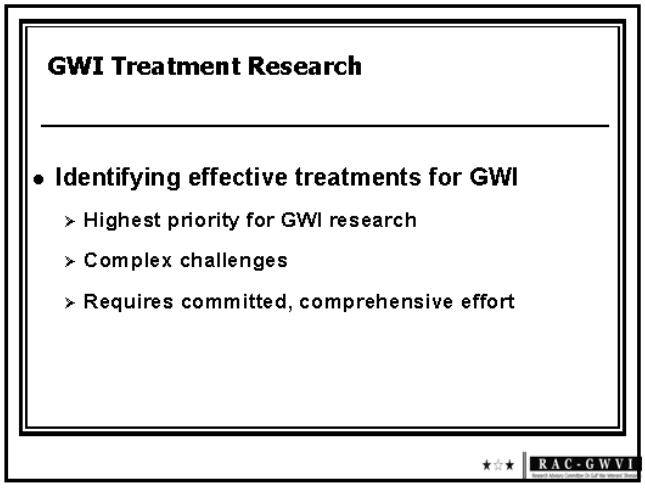
★☆★ RAC-GWVI

GWI Treatment Research: What Next?

- Identifying/evaluating additional GWI treatments
  - Identification of specific biological mechanisms underlying GWI
    - Use existing treatments that counter those processes
    - Identify new pharmacologic interventions
  - Systematic evaluation of treatments currently used; investigate claims of treatment success
    - Gulf War illnesses
    - Similar multisymptom conditions

★☆★ RAC-GWVI


GWI Treatment Research
• Identifying/evaluating additional GWI treatments:
➢ Identify specific biological mechanisms of GWI
➢ Investigate claims of treatment success
+ Both processes can lead to identification of treatments for evaluation in randomized clinical trials
RAC-GWVI

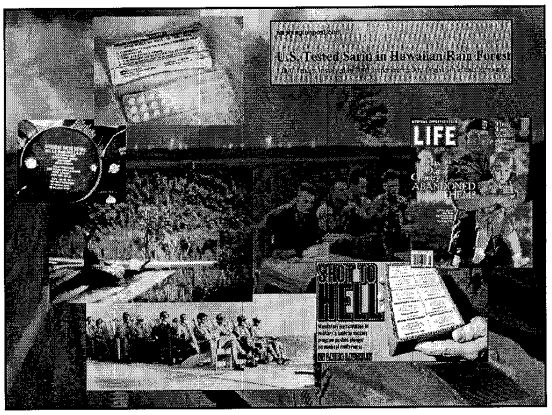

GWI Treatment Research
• Identifying effective treatments for GWI
➢ Highest priority for GWI research
➢ Complex challenges
➢ Requires committed, comprehensive effort
RAC-GWVI

Presentation 9 – Charles Engel

DHCC
DEPLOYMENT HEALTH CLINICAL CENTER

"In Return for Their Sacrifice"

Conceptual Basis & Clinical Outcomes of the Specialized Care Program



Gulf War Health Center
Caring for America's Finest
Walter Reed Army Medical Center

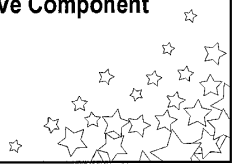
DoD Centers for Deployment Health
ASD(HA) Policy Letter – 30 Sep 1999

DHCC

- ★Deployment Health Clinical Center
  at Walter Reed Army Medical Center
- ★Deployment Health Research Center
  at Naval Health Research Center in San Diego
- ★Deployment Health Surveillance Center
  at Center for Health Promotion & Preventive Medicine

DHCC Mission

Improve post-deployment health care for Department of Defense health care beneficiaries and Reserve Component



Specialized Care Program
Mission Statement

Deliver a coordinated multidisciplinary treatment program for those with persistent, disabling, or treatment refractory symptoms related to the Gulf.

Specialized Care Program
History of the Program

- Initiated by LTG Blanck in January 1995 per tasking from DoD/HA
- Evidence-based model adapted from chronic pain programs
- Validated for treating Gulf War veterans by a multi-institutional expert panel
- Program started March 1995
- over 600 veterans & 100 cycles

Specialized Care Program
Candidates for Care

Anyone with persistent, disabling Gulf War-related symptoms that:

- remain undiagnosed after appropriate medical evaluation; and/or
- are unlikely to respond to specific biomedical treatments.

Specialized Care Program

Many symptoms and services

	mean	sd
Symptom Count	9.7	(3.6)
CCEP Visits	16.9	(8.2)
Other Visits (6-mo)	12.5	(25.2)
CCEP Tests	62.0	(28.8)
CCEP Diagnoses	5.9	(2.3)
Med Fills (6-mo)	13.1	(10.9)

Successful Intervention Requires...

- 'embracing the veteran' to build trust
- carefully coordinated delivery
- many medical perspectives
- comprehensive intervention
- treatment of overall functional status and quality of life rather than a narrow set of symptoms

Specialized Care Program

Demographics (n=78)

	SCP	CCEP	All
Age (GW)	33.3 (±8.3)	26	26
Females	27% (20)	12%	7%
Caucasian	57% (42)	57%	70%
Officers	10% (7)	11%	10%
Army	73% (54)	81%	50%
Active	74% (55)	83%	83%

Disease-Centered Care

The primary goal is to improve the medical status of a disease. Disease status is typically determined through objective indices such as examination signs or laboratory tests.

"Medicine as Usual"

History
Exam
Testing
Diagnosis
Treatment

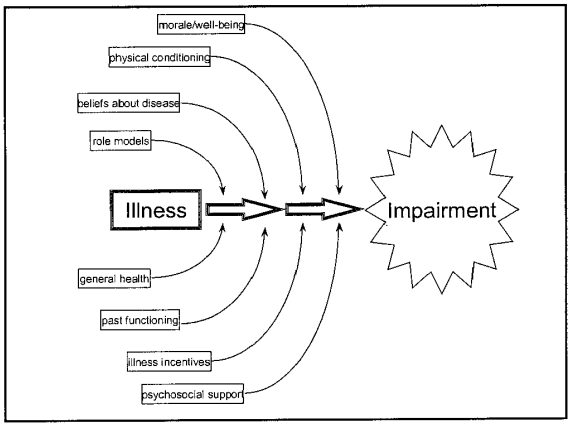
Person-Centered Care

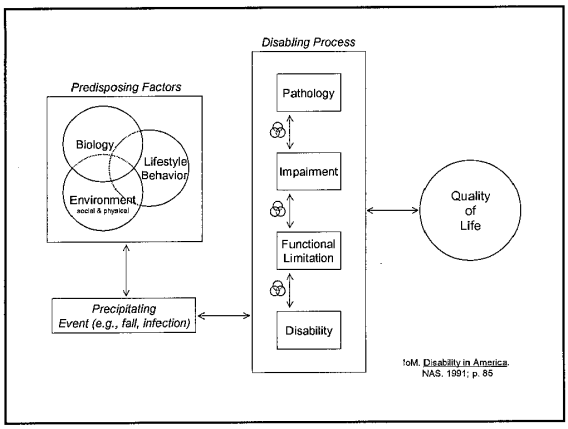
The primary goal is to facilitate change in health-related behavior. The provider and patient collaboratively negotiate the exact goals of care. Behavior such as verbal reports of symptoms, quality of life, or functional capacity are used to monitor treatment success.

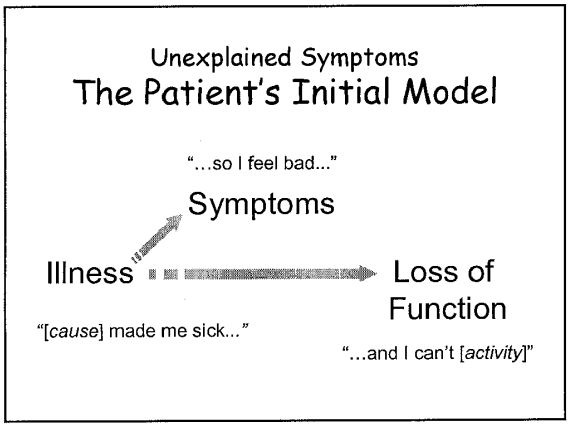
From Symptom to Disability
Illness as Behavior

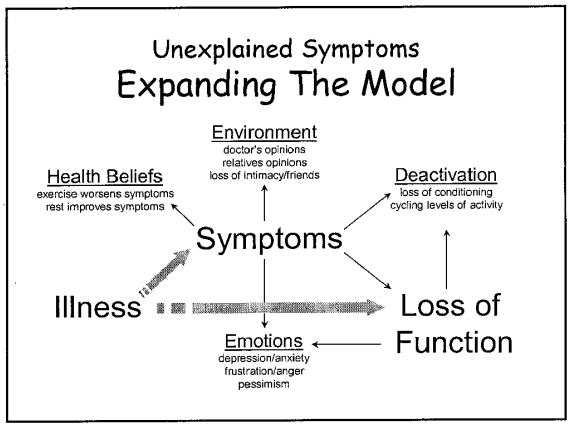
Perception → Belief → Response

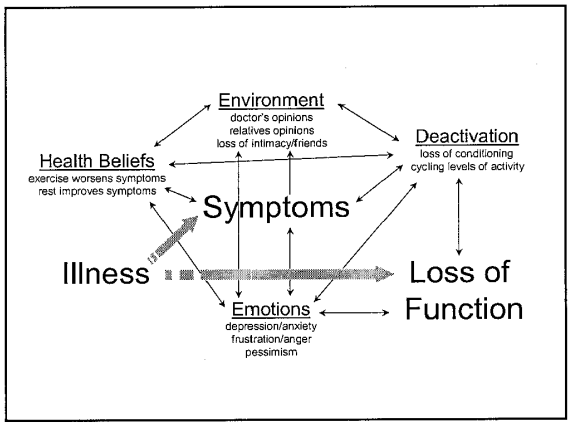
- Perception: result of physiologic process
- Belief: determined largely by experience
- Response:
  - behavior
  - emotion
  - physiology




Disabling Process
Predisposing Factors
Biology
Lifestyle Behavior
Environment
social & physical
Precipitating Event (e.g., fall, infection)
Pathology
Impairment
Functional Limitation
Disability
Quality of Life
IoM. Disability in America. NAS. 1991; p. 85


Unexplained Symptoms
The Patient's Initial Model
"…so I feel bad..."
Symptoms
Illness
Loss of Function
"[cause] made me sick..."
"…and I can't [activity]"


Unexplained Symptoms
Expanding The Model
Environment
doctor's opinions
relatives opinions
loss of intimacy/friends
Health Beliefs
exercise worsens symptoms
rest improves symptoms
Deactivation
loss of conditioning
cycling levels of activity
Symptoms
Illness
Loss of Function
Emotions
depression/anxiety
frustration/anger
pessimism


Environment
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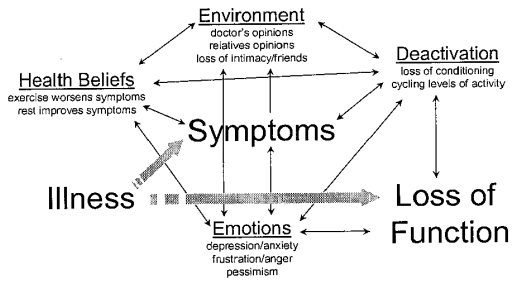
exercise worsens symptoms
rest improves symptoms
Deactivation
loss of conditioning
cycling levels of activity
Symptoms
Illness
Loss of Function
Emotions
depression/anxiety
frustration/anger
pessimism

A Reverberating System

The factors determining prognosis among chronic illnesses are often far more complex than simply the cause of the illness.

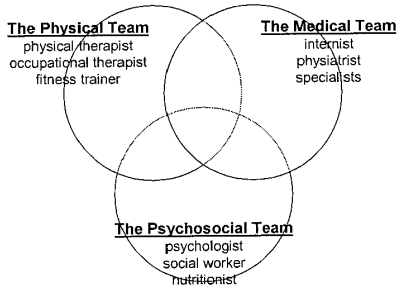
What Can We Manage?



Specialized Care Program
Intensive Evaluation & Treatment

- CCEP & multidisciplinary reassessment
- 3-week intensive outpatient program
- 4 to 8 patients per cycle
- Key Objectives:
  - » Form symptom management plan
  - » Coordinate primary care follow-up

Three Intervention Teams



Specialized Care Program
A Typical Day

0720	Warm-Up/Stretching
0800	Medical System Review
0900	Occupational Therapy
|	Physical Therapy
|	Individual Counseling
1115	Team Rounds
1200	Lunch/Nutritionist
1230	Autonomic Response Training
1300	Occupational Therapy
|	Physical Therapy
|	Individual Counseling
1500	Participatory Seminar
1600	End of Day

Specialized Care Program
Participatory Seminars

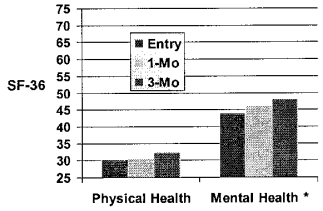
- Orientation & overview
- Illness series:
  - Illness and Impairment
  - Acute and chronic illness
  - Illness and emotions
- Users' Guide to:
  - Your doctor
  - Prescription meds
  - Disability compensation
  - Medical labs & tests
- Learning about your body:
  - Activity and morale
  - The nervous system
- Learning about body (cont'd):
  - Impact of diet on symptoms
  - Review of common symptoms
- Strategies for coping with illness
  - Overcome illness flares
  - Pacing
  - Sleep hygiene
  - Goal-setting
  - Overcoming inactivity
  - Autonomic Training
  - Problem-solving
  - Communication skills

Specialized Care Program
Demographics (n=78)

	SCP	CCEP	All
Age (GW)	33.3 (±8.3)	26	26
Females	27% (20)	12%	7%
Caucasian	57% (42)	57%	70%
Officers	10% (7)	11%	10%
Army	73% (54)	81%	50%
Active	74% (55)	83%	83%

Improved Functioning/Quality of Life

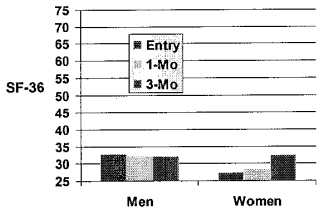
- Poor at entry, especially physical health functioning
- Improved mental health functioning after treatment



population means are 50 with standard deviation of 10

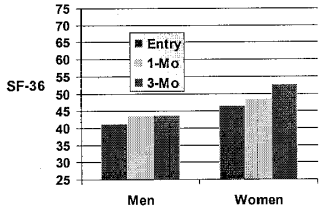
* p<.0001

Physical Functioning Improves for Women, But Not Men



population means are 50 with standard deviation of 10

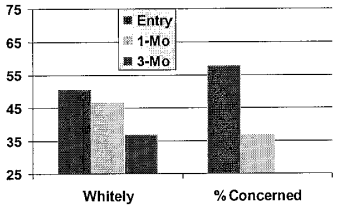
Mental Health Functioning Improves More for Women Than Men



population means are 50 with standard deviation of 10

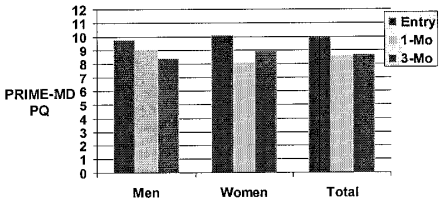
Decreased Physical Health Concern

- 58% report concern about serious undiagnosed illness at entry



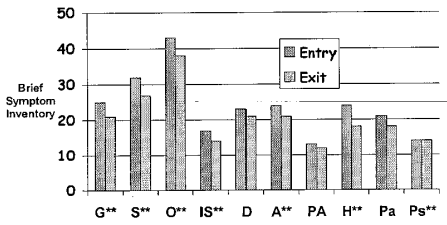
Bothersome Physical Symptoms

Decrease Is Greater For Men



Improved Psychosocial Distress

- Results generally reflect somatic distress and bodily worries
- Significant improvement in distress after treatment



G=General Symptom Index
S=Somatization
O=Obsessive-Compulsive
IS=Interpersonal Sensitivity
D=Depression
A=Anxiety
PA=Phobic Anxiety
H=Hostility
Pa=Paranoia
Ps=Psychoticism

* 0-100, 100=max distress
** p<.05

Specialized Care Program
Summary of Outcomes

- **At program entry --**
  - High users of health care
  - High numbers of bothersome physical symptoms
  - Poor physical and emotional functioning
- **Significantly improved after treatment --**
  - mental health-related quality of life
  - level of physical health concern
  - level of psychosocial distress

Limitations

- Lack of a control group of comparable veterans receiving usual medical care or another active intervention
- Improvements are global but modest

Cognitive Behavioral Therapy and Aerobic Exercise for Gulf War Veterans' Illnesses
A Randomized Controlled Trial

Sam T. Donta, MD; Daniel J. Clauw, MD; Charles C. Engel, Jr, MD, MPH; Peter Guarino, MPH; Peter Peduzzi, PhD; David A. Williams, PhD; James S. Skinner, PhD; André Barkhuizen, MD; Thomas Taylor, MD; Lewis E. Kazis, ScD; Stephanie Sogg, PhD; Stephen C. Hunt, MD; Cynthia M. Dougherty, PhD; Ralph D. Richardson, PhD; Charles Kunkel, MD; William Rodriguez, MD; Edwin Alicea, MD; Philippe Chiliade, MD; Margaret Ryan, MD, MPH; Gregory C. Gray, MD, MPH; Larry Lutwick, MD; Dorothy Norwood, MD; Samantha Smith, PhD; Michael Everson, PhD; Warren Blackburn, MD; Wade Martin, MD; J. McLeod Griffiss, MD; Robert Cooper, MD; Ed Renner, PhD, MPH; James Schmitt, MD; Cynthia McMurtry, MD;

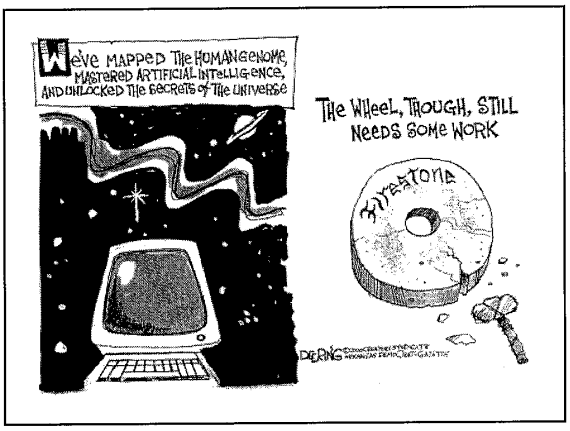
Context Gulf War veterans' illnesses (GWVI), multisymptom illnesses charac by persistent pain, fatigue, and cognitive symptoms, have been reported by ma War veterans. There are currently no effective therapies available to treat GW

Objective To compare the effectiveness of cognitive behavioral therapy (CB ercise, and the combination of both for improving physical functioning and re the symptoms of GWVI.

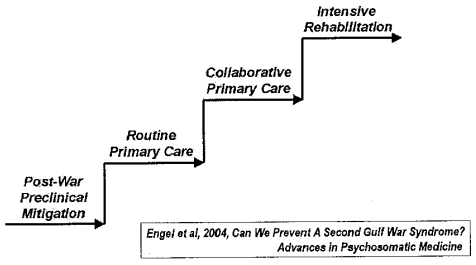
Design, Setting, and Patients Randomized controlled 2×2 factorial tri ducted from April 1999 to September 2001 among 1092 Gulf War veterans v ported at least 2 of 3 symptom types (fatigue, pain, and cognitive) for more months and at the time of screening. Treatment assignment was unmasked for a masked assessor of study outcomes at each clinical site (18 Department erans Affairs [VA] and 2 Department of Defense [DOD] medical centers).

Interventions Veterans were randomly assigned to receive usual care (n=27 sisting of any and all care received from inside or outside the VA or DOD heal systems; CBT plus usual care (n=286); exercise plus usual care (n=269); or CI exercise plus usual care (n=266). Exercise sessions were 60 minutes and CBT s were 60 to 90 minutes; both met weekly for 12 weeks.

Main Outcome Measures The primary end point was a 7-point or grea crease (improvement) on the Physical Component Summary scale of the Veteran Form 36-Item Health Survey at 12 months. Secondary outcomes were standa measures of pain, fatigue, cognitive symptoms, distress, and mental health fu ing. Participants were evaluated at baseline and at 3, 6, and 12 months.



Post-War Prevention of Symptoms & Disability



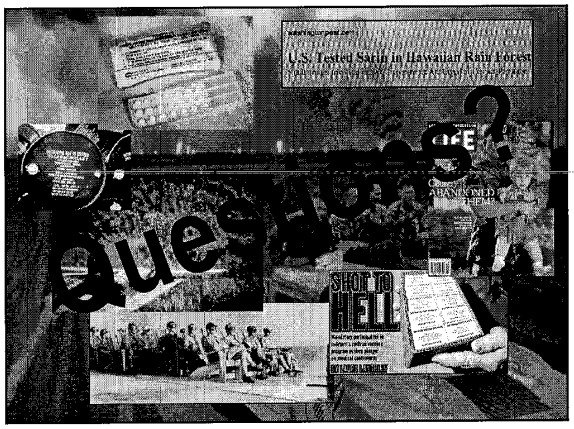
Engel et al, 2004, Can We Prevent A Second Gulf War Syndrome? Advances in Psychosomatic Medicine

Toward Collaborative Post-Deployment Health Care

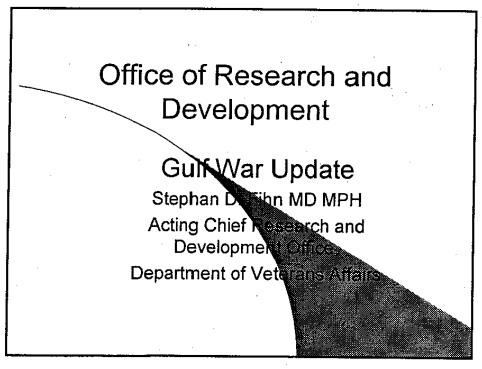
- ★ practice guidelines and clinical information systems
- ★ performance indicators and incentives
- ★ science-based technical assistance
- ★ stakeholder involvement in effort to improve care

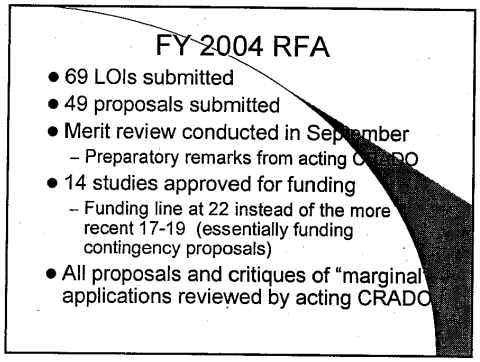
Von Korff et al, Ann Intern Med, 1997;127:1097-1102

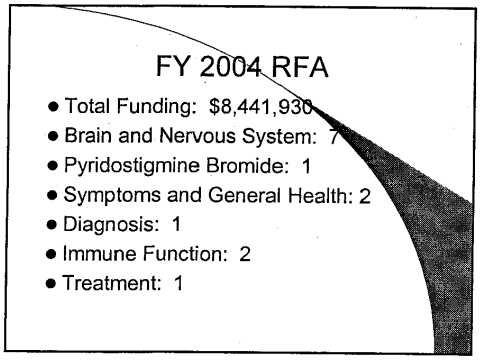
Uniformed Services University

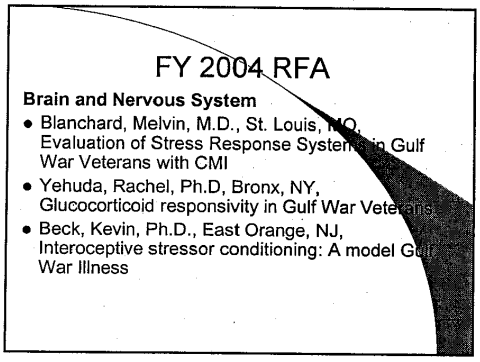


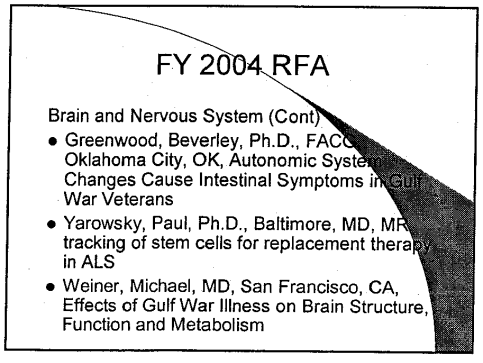
Presentation 10 – Stephen Fihn

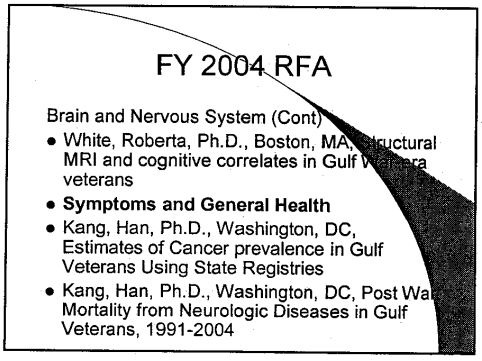












FY 2004 RFA

Immune Function

- Enelow, Richard, M.D., West Haven, CT, Aberrant T Cell Responses to Multiple Immunizations
- Klimas, Nancy, M.D., Miami, FL, Patterns of Gene Expression in Gulf War Illness

FY 2004 RFA

Treatment

- Ciccone, Donald, Ph.D., East Orange, NJ, Telemedicine Intervention for Veterans with Gulf War Illness

Pyridostigmine Bromide

- Weaver, Shelley, Ph.D., East Orange, NJ, Early life determinants of vulnerability to pyridostigmine bromide

Diagnosis

- Murdoch, Maureen, MD, MPH, Minneapolis, MN, Sexual Assault Prevalence Among Male, PTSD-Disabled Gulf War Veterans

GWVI Program Manager

- VHA has authorized hiring action to proceed
- Goal is to hire an MD or PhD with substantial experience
- Incumbent will also manage the Deployment Health portfolio

GWVI RFAs

- Existing Deployment Health RFP dated October 2002 will be replaced later this fall with two separate RFPs for GWVI and for Deployment Health
- RFAs will be announced for special topics as necessary

Scientific Merit Review Board

- Six-eight members to be nominated this winter; will chair or serve on ad hoc subcommittees
- Will begin reviewing proposals beginning with the Spring 2005 merit review round

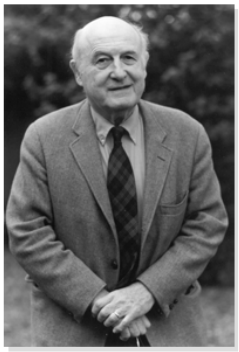
Presentation 11 – Quentin Deming & William Weiss

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

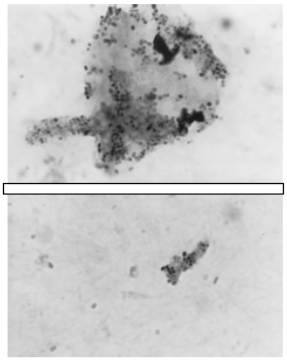
Successful Trial Of Urine Microscopy
For Control Of Antibiotic Treatment
Of Systemic Coccal Disease

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

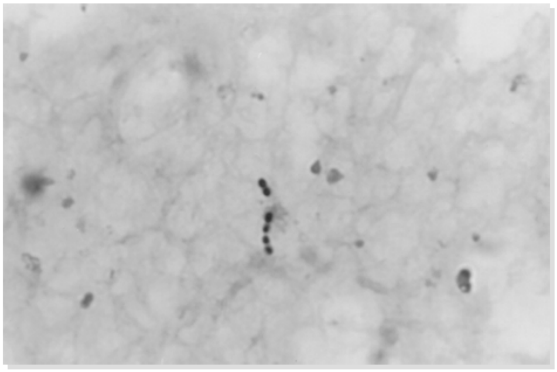
Edward S. Hyman M.D, FACP



Clusters G+ cocci urine



Encapsulated cocci and shells



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

Patient Inclusion Criteria

1. Deployed to the Gulf
2. Symptoms did not pre-exist the deployment
3. Occurred by the end of 1993
4. No other explanation for the symptoms
5. Presence of Fatigue, and Impaired Cognitive Processing, plus Somatic Pain + one additional study secondary condition
6. Urine had abnormally increased excretion of GRAM positive cocci, or degenerated coccal forms

Elements of Study Design

- The sample size of 36 was calculated (using a log rank test of proportions to achieve a power (1-Type 2 error) of 80% in this trial in order to detect a change from 20% of the placebo patients demonstrating improvement to 80% of the treated patients demonstrating improvement, with a study Type-1 error of 5%, after a 4 month period of treatment.

Study Cohorts

Evaluable cohort (n=36)

Intent–to–Treat cohort (n=38)

Baseline Endpoints Variables

- **Primary Endpoints**
  1. Modified Fatigue Impact Scale (Fisk)
  2. Fatigue Assessment Inventory
  3. Neuropsych Impairment Index
- **Secondary Endpoints**
  1. Sleep Quality
  2. Headache, % patients with
  3. Median number/month
  4. Diarrhea, % ≥ 1/day
  5. Severity score ≥ 3
  6. Pain, Visual Analog Scale (McGill)
  7. Dolorimeter
  8. Quality of Life

Baseline Variables

Variables	
Demographic	4
Military Service	3
Urine Assessment	5
Exposure to Hazards	13
Endpoints	11

Baseline Characteristics

VARIABLE	PLACEBO	TREATMENT	TOTAL N
Age (years) mean	42.1	39.9	36
Race, % white	94.1	72.2	35
Sex, % male	88.9	83.3	36
Education, % college	70.6	88.9	35
Military Status, % Medical leave	6.2	11.8	33
Military Background % active duty	82.3	68.8	33
Time in Gulf Median (days)	182	197	29

Study population characteristics at baseline

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

Exposure to Hazards at Baseline

	% Exposure Placebo	% Exposure Treatment	Prob	N
Chemical warfare/nerve gas	41.7	61.5	0.43	25
Cigarette Smoke	23.1	29.4	1.00	30
Deet- Insect repellent	30.8	33.3	1.00	30
Diesel fueled tent heaters	42.9	52.9	0.72	31
Iraqi POWs	14.3	50.0	0.06	30
Oil Well Fire Smoke	64.3	82.4	0.41	31
Petroleum Contaminated H20	30.8	31.2	1.00	29
Inoculations (Pyridostigmine)	58.3	94.1	0.06	29
Ethanol Excess	0.0	0.0	1.00	30
Recreational Drug Use	0.0	0.0	1.00	30
Flea Collars	0.0	5.9	1.00	30
Pesticides, Uniform	45.4	73.3	0.23	26
Other Exposures	20.0	29.4	0.69	32

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

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

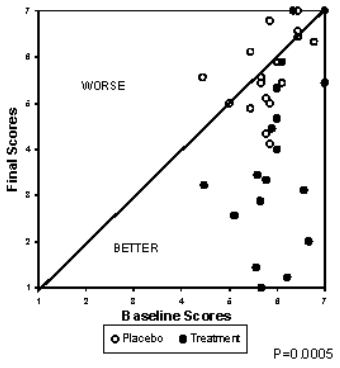
Baseline	No statistically significant difference
Final (4 months)	p=0.0005
Final from Baseline	p=0.0002

Combined Wilcoxon rank sum test p=0.0007

NEUROPSYCHOLOGICAL IMPAIRMENT INDEX

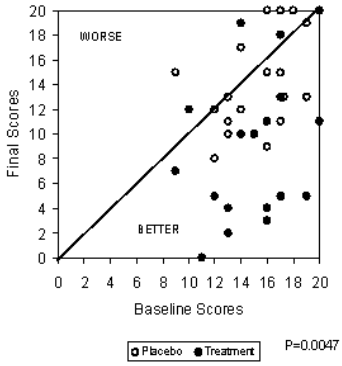
Baseline	No statistically significant difference
Final (4 months)	No statistically significant difference

Fatigue Assessment Inventory Scores

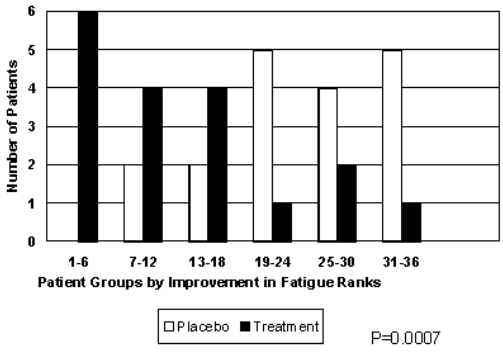


P=0.0005

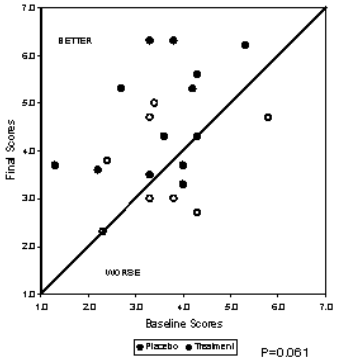
Fatigue Impact Scale - Fisk Scores



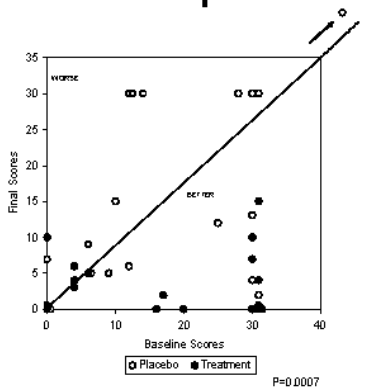
Pre-post Fatigue Scores
Combined Ranks



Sleep Rating Scores

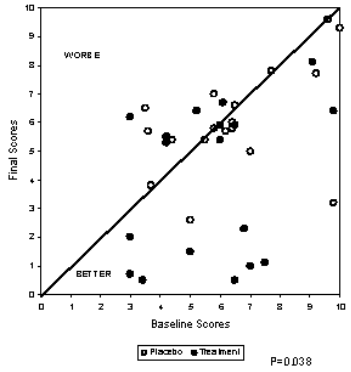


Headaches per Month

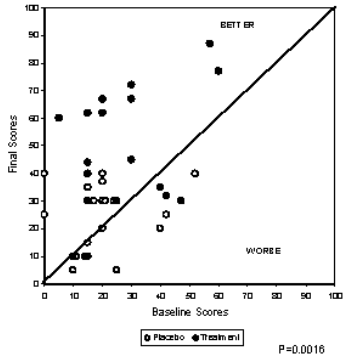


Pain: Visual Analog Scale

McGill Scores



Quality of Life Scores



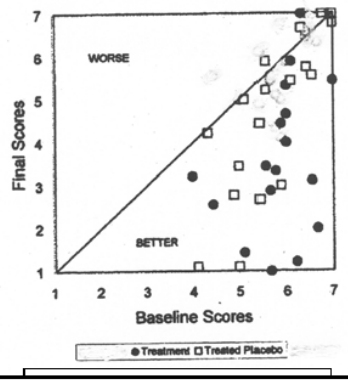
Surmise of Treatment Assignment

By Patient and Evaluator

Patient Surmise	Placebo	Patient on Treatment
Placebo	13	3
Treatment	5	15
Total	18	18

Evaluator Surmise	Placebo	Patient on Treatment
Placebo	15	3
Treatment	3	15
Total	18	18

Combined Fatigue Assessment Scores



Combined Fatigue Scores - Fisk

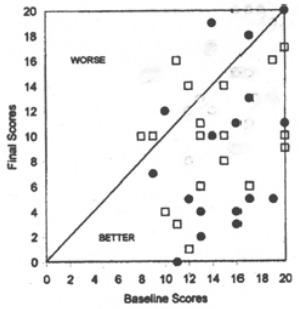
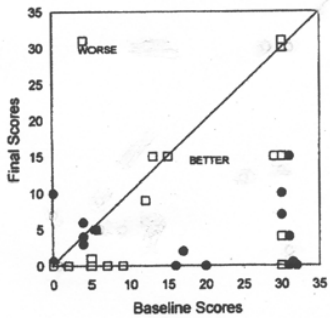


Figure 1: Modified Fatigue Impact Scale (Fisk) Scores

Combined Headaches / Month



Pain - Combined Scores

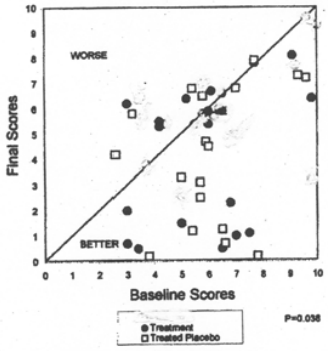


Figure 5: Pain: Visual Analog Scale (McGill) Scores

Quality of Life
Combined Scores

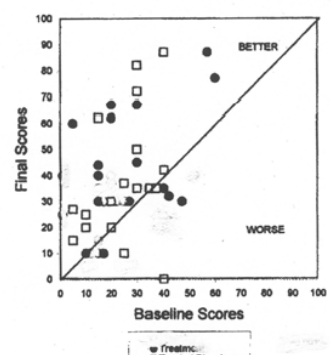
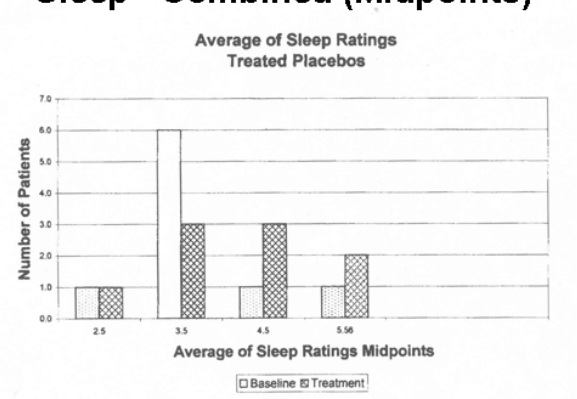


Figure 6: Quality Of Life Scores

Sleep - Combined (Midpoints)



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.

Statistical Methods

1. Continuous, normally distributed variables were tested for treatment group differences by two-tailed t-tests. If the variables differed from a normal distribution, they were tested by the Wilcoxon rank sum test [12] .
2. Categorical variables, such as race and sex, were tested by a two-tailed, Fisher's exact test.
3. One of the primary outcome variables, Fatigue, is based on 2 tests; the Modified Fatigue Impact Scale (Fisk), and the Fatigue Assessment Inventory. A combined statistical analysis of these 2 tests was accomplished by a combined Wilcoxon rank sum test[13].

Presentation 12 – Beatrice Golomb

Gulf War Research Update: October 2004

Beatrice Golomb, MD, PhD

Topics

- Epidemiology
- Health Effects
- Mechanisms: AChEi
- Related Conditions

Epidemiology

Male UK GWV Self-reported health

SUMMARY:

- 24% "extra" of male GWV have health problems, over nondeployed
- Symptoms fit the profiles we are by now familiar with

Simmons, Maconochie, Doyle 2004. Self-reported ill health in male UK GWV: retrospective cohort study. BMC Public Health 4:27

Male UK GWV Self-reported health

Goal: Assess subjective health state in UK GWV vs nondeployed. Seek to avert selection bias by asking all

Intended Ss: Sent to all UK GWV + comparison cohort stratum-matched on sex, age (5-yrs), service, rank, serving status at time of Gulf (regular, reservist), fitness to be deployed (Army/AirForce only).

Sent to about 51,600 of each.

Actual Ss: 42,818 responded = 48%.

Maconochie birth outcomes cohort

Response rate not broken down by Gulf vs not.

Primary outcome: reporting ≥1 new medical problem or change in general health since 1990. 36 ICD-10 categories

Simmons, Maconochie, Doyle 2004. Self-reported ill health in male UK

Male UK GWV: self-reported health

	GWV□	NGWV	Dif
≥1 new symptom since 1990	61%	37%	24%

***Among those GWV reporting symptoms*:**
Median 2 among GWV vs 1 among NGWV

Simmons, Maconochie, Doyle 2004. Self-reported ill health in male UK GWV: retrospective cohort study. BMC Public Health 4:27

Male UK GWV: self-reported ill health

Most common reported symptoms	by GWV	by NGWV
Musculoskeletal	15%	
"Other" symptoms	13%	
General fatigue	11%	
Memory/Concentration	7.9%	
Skin allergies	7.6	
Accidental injury*		2.6%

*Cited as "among" the most common sx in NGWV

Simmons, Maconochie, Doyle 2004. Self-reported ill health in male UK GWV: retrospective cohort study. BMC Public Health 4:27

Male UK GWV, cont'd

Over 85% of sx more common in GWV vs not

Some of top risk ratios	%GWV	%ctrl	Adj OR*
General fatigue	10.8	1.2	9.6 (8.3-11.1)***
Memory/Concentration	7.9	0.4	19.6 (15.5-25)***
Mood swing/aggression/irritabil	7.3	0.4	20.9 (16.2-27)***
Muscle pain/weakness	2.0	0.4	4.5 (3.5-5.7)***
Night sweats	1.4	0.1	9.9 (6.5-15.2)***
General decline in fitness/health	1.2	0.3	4.4 (3.2-6.0)***
Respiratory problems NOS	3.8	1.2	3.3 (2.9-3.9)***
Weight gain/loss	2.2	0.6	3.4 (2.7-4.1)***

*Adjustment for age at survey, service & rank at time of Gulf, serving status at time of survey, alcohol, smoking

Simmons, Maconochie, Doyle 2004. Self-reported ill health in ale UK GWV: retrospective cohort study. BMC Public Health 4:27

Illness Beliefs vs Symptoms

Conclusion: Illness beliefs significantly predict health outcomes after controlling for demographic and mental health variables.

"Gulf War veterans beliefs may impact clinical outcomes. Discussing illness beliefs and providing accurate information is an important component of medical care for Gulf War veterans.

Problem: Shows beliefs are associated with health outcomes

States beliefs "impact" outcomes; infers causality

But health outcomes *should* influence "beliefs" (views) about health

"Beliefs" affected by health, e.g.: My symptoms are staying the same; are getting worse; are disabling; often come back.

Hunt, Richardson, Engel, Atkins, McFall Aug 2004. J Occup Environ Med. Gulf War veterns' illnesses: A pilot study of the relationship of illness beliefs to symptoms severity and functional health status.

Illness Beliefs vs Symptoms

Ss: 583 GWV: 296 VA Seattle s/p "comprehensive" registry evaluation; or 296 Walter Reed current active or reserve seeking care from Gulf War Health Center.

Date: Evaluations between 3-98 to 11-01

Measures:

- VIBS = Veterans Illness Belief Survey: 29 Qs about belief about etiolog, clin. course & proper treatment of sx & illness
- PTSD-Checklist - Military version (PCL-M)
- PHQ Somatic Symptom Checklist: 20sx using modified version of somatoform symptom assessment module of PHQ (Physician Health Questionnaire)
- Prime MD PHQ: Self-report version; assess for mental d/o's
- SF-36: Assesses functional status/ quality of life

Hunt, Richardson, Engel, Atkins, McFall Aug 2004. J Occup Environ Med. Gulf War veterns' illnesses: A pilot study of the relationship of illness beliefs to symptoms severity and functional health status.

Illness Beliefs vs Symptoms

Outcomes:

- SF-36 MCS
- SF-36 PCS
- Symptom checklist

Analysis:

Regression to determine impact of beliefs about illness on outcomes

3 Models:

- Demographic
- Demographic + Mental disorder variables
- Demographic + mental + Beliefs

Hunt, Richardson, Engel, Atkins, McFall Aug 2004. J Occup Environ Med. Gulf War veterns' illnesses: A pilot study of the relationship of illness beliefs to symptoms severity and functional health status.

Illness Beliefs vs Symptoms

After adjusting for demographic variables and mental disorders:

Illness beliefs explained outcomes

- 23% of variance in physical symptom severity (SSC) score
- 33% of variance in PCS score
- 5% of variance in MCS score

Comment: Just because you put a variable on the RHS of an equation, and it is significantly related to the variable you put on the LHS, does not mean it is "causing" the factor you put on the LHS of the equation!

*Try to publish same study in recognized conditions like ALS!

Hunt, Richardson, Engel, Atkins, McFall Aug 2004. J Occup Environ Med. Gulf War veterns' illnesses: A pilot study of the relationship of illness beliefs to symptoms severity and functional health status.

Nisenbaum: Factor Analysis

Ss: 3454 UK GWV; 1979 Bosnia deployed; 2577 GW era; 1163 US GWV from 4 AirForce Units

Outcomes: Surveyed 1995 for health/symptoms

Design: Split halves Factor Analysis (in each sample): Exploratory & confirmatory. Promax oblique rotation.

Result:

- 4 correlated factors in each sample: Resp; mood-cog; peripheral nervous; GI/urogenital

GI/urogenital factor in UK Gulf different from GI factor in Bosnia and Era.

UK sim to US GW for GI, resp, mood-cog: despite differences in sx inventories. Musculoskeletal factor only elicited from US PGW sample.

Nisenbaum R. 2004. Population Health Metrics 2:8

Nisenbaum: Factor Analysis

Notes similar illnesses in those who did not participate in Gulf War "(albeit at lower rates and with different specific characteristics)"

" so we believe that this pattern of symptoms is not unique to Gulf War service nor does it represent a unique illness or 'Gulf War syndrome'"

- Cites similarities to other war syndromes e.g. Civil War and Boer War

- Predicts similar from Afghanistan and Iraq

Nisenbaum R. 2004. Population Health Metrics 2:8

Specific Health Effects

Infertility in Male UK GWV

Ss: Same as previous Maconochie sample. 42818 completed questionnaires = 53% GWV, 42% NGWV (total 48%)

Design: retrospective cohort (mailed survey)

Primary outcome: a. Failure to achieve conception (type I infertility) or live birth (type II infertility) after the Gulf with trying at least a year and consulting a doctor.

b. Time to conceive for pregnancies fathered by men not reporting fertility problems

Maconochie, Doyle, Carson 1004. BMJ, doi:10.1136/bmj.38163.620972.A

Infertility in Male UK GWV

	%GWV	%NGWV	OR
Fertility prob (consulted doctor)	7	5	1.38 (1.2-1.6)
• Type I	2.5	1.7	1.41 (1.1-1.9)
• Type II	3.4	2.3	1.50 (1.2-1.9)
Prolonged time to conception if achieved:			
• Time >1 year	9.1	7.8	1.18 (1.04-1.3)

Time trying unsuccessfully for a child: No diff

Time first tried till consulted doctor: No diff

□Maconochie, Doyle, Carson 1004. BMJ, doi:10.1136/bmj.38163.620972.A

Infertility in Male UK GWV

•Suggestion of ↑:	GWV	NGWV	OR
•Teratospermia	% (N)	% (N)	
Type I	.2 (21)	.1 (6)	2.02 (.79-5.14)
Type II	.3 (26)	.1 (6)	2.55 (1.03-6.3)
•Oligasthenoteratospermia			
Type I	0.1 (8)	.03 (2)	2.17 (.43-10.9)
Type II	0.1 (9)	.03 (2)	2.47 (.51-12.0)

Adjusted for rank *□& serviice in GW; age of both participant & female partner at 1st consult for infertility; or in fertile, first pot-gulf conception

Maconochie, Doyle, Carson 1004. BMJ, doi:10.1136/bmj.38163.620972.A

Infertility in Male UK GWV

Consistent with Australian study: GWV had 40% ↑ in fertility problems

Conflict with Danish study: no evidence of effect of Gulf War service on markers of male infertility

Adjusted for rank *□& serviice in GW; age of both participant & female partner at 1st consult for infertility; or in fertile, first pot-gulf conception

Maconochie, Doyle, Carson 1004. BMJ, doi:10.1136/bmj.38163.620972.A

Health Effects - Objective Markers

Quantitative Balance Tests

Summary:

Quantitative balance testing abnormalities are more common in GWV than in CFS; and more common in CFS than in in healthy controls.

Quigley, Maney, Natelson, Findley. Arch Phys Med Rehabil 2004, Sep 85(9):E34. Poster abstract. Quantitative balance and self-reported health status in medically unexplained illness.

Quantitative Balance Tests

Ss:

- 19 GWV with "medically unexplained illness"
- 27 CFS
- 17 age-matched controls

Equitest SOT (sensory Organization Test):

6 conditions on movable platform:

Eyes closed/quiet. Sway visual. Sway support. Sway support eyes closed. Sway support&visual.

Quigley, Maney, Natelson, Findley. Arch Phys Med Rehabil 2004, Sep 85(9):E34. Poster abstract. Quantitative balance and self-reported health

Quantitative Balance Tests

scoring >2SD below normal

- GWV 50%
- CFS 35%
- Normal 10% $p < 0.001$

"Quantitative balance testing is abnl in many deployed veterans with medically unexplained illness". High correlation with self-reported health "suggests that subtle balance problems are important factors in perceived health status" (No -- correlate with health!)

Quigley, Maney, Natelson, Findley. Arch Phys Med Rehabil 2004, Sep 85(9):E34. Poster abstract. Quantitative balance and self-reported health

Heart Rate Variability (HRV)

Summary: Big differences in autonomic function by HRV among GWV & FM vs controls -- more pronounced for GWV

- Short-term HRV differences are apparent for men and women
- Intermediate- & long-term HRV differences are apparent only in women
- Magnitude of difference nontrivial; e.g. like post-MI patients for some indices, worse than post-MI for others.

Stein..., Clauw Oct 2004. Arthritis and Rheumatism 51(5):700-8. Sex Effects on Heart Rate Variability in Fibromyalgia and Gulf War Illness

Heart Rate Variability

Ss:	Male	Female	Total
• GWV	6	5	11
• FM	7	19	26
• Controls	18	18	36

Measure: HRV from 24h Holter.
Daytime; Nighttime; and 24h HRV

Stein..., Clauw Oct 2004. Arthritis and Rheumatism 51(5):700-8. Sex Effects on Heart Rate Variability in Fibromyalgia and Gulf War Illness

Heart Rate Variability (HRV)

Ss	GWV	FM	Ctrl	p
Longer term HRV				
HR	76	74	70	.065
SD NN, longterm	117	125	140	.05
Ln ULF	9.2	9.2	9.4	.1
Intermediate term HRV				
Ave SD over 5min	53	63	68	.056
Ln VLF power	7.2	7.5	7.6	.054
Ln LF power	6.4	6.9	7.0	.050
Short term HRV				
%NN>50msec dif prior	6.7	12.6	17.5	.023
RMS difs NN	27	37	43	.036
Ln HF power	5.2	5.9	6.1	.044

HR = hrt rate; SD = stdd dev; ULF = ultra low freq; NN = normal-to-normal

Heart Rate Variability (HRV)

	GWI		Ctrl	
Longterm HRV	F	M	F	M
SD NN	97	138*†	138	142
Ln Ultra LF	8.8	9.6*†	9.4	9.6
Intermediate HRV				
SD, 5min	41	64*†	69	67
Ln Very LF	6.7	7.7*†	7.7	7.6
Ln LF	5.8	7.0*†	7.0	7.0
Shortterm HRV				
%NN>50ms	3.8	9.8†	19.5	15.5
RMS SD	22	33†	45	41
Ln HF	4.9	5.7†	6.2	5.9

*male signif different from female; †GW signif diff from ctrl
SD = std dev; NN = beat-to-beat interval; Ln = log(e);

Heart Rate Variability (HRV)

Day-Night differences similar to controls

	GW		FM	
Long	F	M	F	M
SD NN, day	89	109	133	117
SD NN, night	71	102	93	106
Intermediate				
SD, 5 min, day	42	57	69	63
SD, 5 min, night	40	73	67	74
LN LF, day	5.9	6.8	7.0	6.4
LN LF, night	5.6	7.2	6.9	7.2
Short term				
%NN>50ms, day	2.7	5.7	17.2	12.3
%NN>50ms, night	6.0	20	24	23

Depression in GWV

Summary, theirs:
There is no difference between depression in GWV vs in Era

Summary, mine:
There is a difference between depression in GWV vs in Era

Black et al 2004. Ann Clin Psychiatry 16: 53-61. Depression in veterans of the first Gulf War and comparable military controls.

Depression in GWV

	GWV	Era	
No ↑ lifetime depression:	**30.3%**	**36.6%**	**NS**

Among those with depression:

- **No ↑ somatoform d/o** **1.06 (NS)**
- **No ↑ hypochondriasis** **1.1 (NS)**
- **- ↑ Cognitive dysfunction** **2.3 (1.2-4.3)**
- **- ↑ Severe pain/distress** **2.5 (1.04-6.1)**
- **- ↑ Severe disability (not quite significant)**
- **- ↑ PTSD** **4.0 (2.0-6.0)**
- **- ↑ Anxiety disorder** **3.2 (1.6-6.3)**

Black et al 2004. Ann Clin Psychiatry 16: 53-61. Depression in veterans of the first Gulf War and comparable military controls.

Depression in GWV

Subjects:

Wave I (prior): 3695 (76% participation) Iowa veterans (GWV or EraV), stratified by age, gender, race, branch of military, enlisted vs officer.

Wave II (current): 602 Ss interviewed.

Selected for having, during Wave I evaluation:

Depression OR **cognitive dysfcn** OR **widespread pain**: any one, any two, all three, or control (8 strata)

Then stratified GWV vs Era

Among Depressed:

Current	%GWV	%Era	RR (95%CI)
	n=132	*n=60*	
MDD	30.3	23.2	1.43 (.7-2.9)
Any mood d/o	50.8	36.7	1.78 (.95-.3.3)
Anxiety d/o,any	51.5	25	3.2 (1.6-6.3)
PTSD	27	5.0	7.1 (2.1-24.2)
Specific phobia	11.4	0	7.1 (2.1-24.2)
Somatoform d/o	**5.3**	**5.0**	**1.06 NS**
Alcohol abuse	10.6	5.0	2.3 NS(.7-6.8)

Black et al 2004. Ann Clin Psychiatry 16: 53-61. Depression in veterans of the first Gulf War and comparable military controls.

Oil Fires & Resp Health

Summary:

GWV more resp sx s/o asthma

- More asthma & bronchitis dx'd since war
- No worse lung fcn

Oil fire exposure assoc decr FVC

Dust storm exposure assoc impr peak flow

Kelsall et al 2004. Thorax 59: 897-903.

Oil Fires & Resp Health

Ss: 1456 of all 1871 Australian GWV + 1588 of sampled 2924 era controls frequency matched by sex, service type, 3-yr age bands, officer/non w/o Army; aircrew/non w/in Air Force.

Date of study: Aug 2000-Apr 2002

Assessment: PE: wheeze, pharyngitis, RR

•Hx asthma; bronchitis; emphysema

•Ventilatory dysfcn

Kelsall et al 2004. Thorax 59: 897-903.

Oil Fires & Resp Health

Asthma: doctor dx; or being woken by an attack of SOB in past 12 mo; asthma med

Bronchitis: doctor dx; or cough >3mox≥2yr & FEV1/FVC < 70%

Emphysema: sob hurrying on level; w/ slight hill; walking w/ others your age; stop for breath walking at your own pace; OR FEV1/FVC < 70%

Ventilatory fcn: Normal; obstructive; restrictive; mixed

Oil Fires & Resp Health

Respiratory Sx	GWV	Era	OR*	95%CI
Wheeze only	45	19	1.4	1.2-1.7
Wheeze w/o old	17	11	1.6	1.3-2.0
Wheeze+breathless	12	7	1.8	1.3-2.3
Nocturnal chest tight	14	10	1.4	1.1-1.9
Nocturnal cough	24	18	1.4	1.1-1.7
AM cough	10	8.8	1.2	0.9-1.5
Spont dyspnea	8	5	1.6	1.1-2.2
Post-exertion sob	22	17	1.3	1.1-1.6
Nocturnal SOB	5.6	3.7	1.5	1.0-2.2

*adjusted for age, ht, wt, smoking, atopy, education, marital, service, rank

Oil Fires & Resp Health

Respiratory Sx	GWV	Era	OR*	95%CI
Wheeze on auscultation	1.6%	0.6%	2.6	1.1-5.9

Other PE findings: most abnormalities slightly more common for GWV (data not given); but significant only for the above

Kelsall et al 2004. Thorax 59: 897-903.

Oil Fires & Resp Health

Respiratory Dx	GWV	Era	OR*	95%CI
Asthma, Dr. Dx	12.0	10.3	1.2**	NS
Asthma, use of meds	4.3	3.2	1.4	NS
Asthma, ECRHS defn	10.2	7.5	1.4	1.1-1.9
Airflow ltn: FEV1/FVC<70	6.4	8.4	0.8	NS
Emphysema, wkg defn	11.1	11.0	1.0	NS
Bronchitis, Dr dx p 1990	47	27	1.9**	1.2-3.1

*adjusted for age, ht, wt, smoking, atopy, education, marital, service, rank

**adj for age, education, marital, service, rank

Kelsall et al 2004. Thorax 59: 897-903.

Oil Fires & Resp Health

Relation of oil fires and dust storms to ECRHS asthma

SMOIL,	%asthma		
none	9%		
any	11%	1.2	NS
low	12%	1.3	NS
high	9%	0.9	NS
Dust storms			
no	9%		
yes	12%	1.3	NS
Deployment completed before air war			
yes	7%		
no	11%	1.7	1.0-2.9

Oil Fires & Resp Health

Relation of oil fires and dust storms to other

	FEV1	FVC
SmOIL*	NS	dose-resp**
Dust storm*	NS	NS
Deployed b4 war	NS	NS

*Tests: any, low, high, dose resp

**$p < 0.05$

Kelsall et al 2004. Thorax 59: 897-903.

Mechanisms: AChEi

Low Level Sarin in Rats

Ss: Male albino SPF rats 180-200g, groups of 10

Exposure: Low Level Sarin x60 min inhaled:

- Level 1: AChEi <20%; no clin signs "or sx"*
- Level 2: AChEi 20-30%; no clin signs or sx
  - Level 2S: single exposure
  - Level 2R: repeat exposure: 3x (every other d)
- Level 3: AChEi 40-50% & mild clin signs: salivation & miosis (pupil constriction)

*Observe animals for salivation; miosis; tonic-clonic immediately after exposure

Kassa et al. Inhalational Toxicology 16:517-30

Sarin in Rats: Outcomes

Outcomes @ 3 mo after exposure:

- Stress markers: corticosteroids; tyrosine aminotransferase
- Biochemistry:lipid,pr,alb,glc,LFTs,minerals?lytes
- Cholinesterase levels
- DNA & pr- metabolism in liver
- Sarin-induced neurotoxicity using FOB
  = Functional Observational Battery
  = 39 msrs of sensory, motor, & autonomic fcn
- NS excitability w/ convulsive dose of PTZ*

*Pentamethylenetetrazole

Kassa et al. Inhalational Toxicology 16:517-30

Sarin: chemical outcomes

Outcomes **@ 3 mo after exposure:**

- Corticosteroids: ↑ p level 3;
- Tyrosine aminotransferase: monotonic ↑;
  - –Significant after sarin @ level 2S, 2R,3
- Biochemistry: No change
- Cholinesterase levels: No change
- Signif ↓ DNA synth (labeled thymidine incorp):
  - – Significant at level 1, 2S, 3
  - –(but no change amount DNA or protein)

Kassa et al. Inhalational Toxicology 16:517-30

Sarin: Clinical outcomes

• Sarin-induced neurotoxicity using FOB

Sarin Level:	Ctrl	I	2S	2R	3
Gait d/o	1.0	1.0	1.0	2.0***	2.0***
Gait Score	1.0	1.5	0.3	0.8	2.0**
Mobility	1.0	1.5	0.2	-2.0**	-2.0**
Activity	1.0	1.5	0.3	1.2	-2.0**
Stereotypy	1.0	0.5	2.0	6.0***	4.0**

NS excitability: Incr big & small sz after PTZ, level 2R ($p<.05$)

Kassa et al. Inhalational Toxicology 16:517-30

Sarin: Clinical outcomes

Spatial discrimination:

Little effect with level 2, single exposure

Much bigger effect & more lasting with level 2, repeated

Mostly normalized by 5 weeks but possible residual effect -- assess with larger sample

Kassa et al. Inhalational Toxicology 16:517-30

Mechanisms: ACE

Mechanisms: ACE

Summary:

• GWV with CFS are FAR LESS LIKELY to have any I allele of the ACE gene than healthy GWV.

• However nonveterans with CFS are NOT LESS LIKELY to have any I allele of the ACE gene than healthy nonveterans.

Mechanisms: ACE

Ss:

- 49 GWV/ 61 nonveterans with CFS
- 30 GWV/ 45 nonveteran healthy controls

Assess Genotypes of ACE

Rationale: ACE gene associated with muscle performance; and higher serum ACE activity in CFS than controls

Note: ACEi: used to improve heart muscle fcn

Outcome: Genomic DNA from blood

Vladutiu 2004. Muscle Nerve 30: 38-43

Mechanisms: ACE

No significant differences for alleles or genotypes for some tested genes:

AMPD1

CPT2

Vladutiu 2004. Muscle Nerve 30: 38-43

Mechanisms: ACE

	GWV		Nonvets	
	ICF/CFS	Healthy	CFS	Healthy
ACE allele	n=72	n=46	n=158	n=88
I allele	.15	.48	.45	.50
D allele	.85	.52	.55	.50
	p < 0.0001			
ACE genotype	n=32	n=23	n=59	n=44
II	.08	.35	.22	.27
ID	.14	.26	.46	.46
DD	.78	.39	.32	.27
	p = 0.009			

Mechanisms: ACE

Something different is contributing to CFS in ill GWV relative to controls

GWV with CFS are far less likely to have the I allele, an allele that is associated with endurance and physical performance in elite athletes, army recruits, and other settings; while civilians with CFS are not less likely

Gulf war CFS really is different in a marker that suggests a different vulnerability is involved; in turn suggesting a difference in causative exposures and pathogenesis.

Vladutiu 2004. Muscle Nerve 30: 38-43

Mechanisms: ACE

Something different is contributing to CFS in ill GWV relative to controls.

"We showed a relationship between stress and CFS-like illness in Gulf war veterans. Such a relationship may not exist in nonveteran CFS patients.

Vladutiu 2004. Muscle Nerve 30: 38-43

Related Conditions

Genetic profiles in MCS

Result: MCS cases more likely to have certain variants in enzymes that metabolize toxins

- "CYP2D6 homozygous active" OR 3.36, p = 0.01
- "NAT2 rapid-acetylator" OR 4.14, p = 0.01
- PON1-55 heterozygous OR 2.05, p = 0.04
- PON1-192 heterozygous OR 1.57, p =0.04

Genetic profiles in MCS

Ss: 203 MCS patients; 162 controls from larger case-control study based on "reproducible & validated case definition". U Toronto Hlth Survey

Outcomes: Common polymorphisms in CYP2D6; NAT1; NAT2; PON1; PON2

Genetic profiles in MCS

Result: MCS cases more likely to have:

- "CYP2D6 homozygous active" OR 3.36, p = 0.01
- "NAT2 rapid-acetylator" OR 4.14, p = 0.01
- PON1-55 heterozygous OR 2.05, p = 0.04
- PON1-192 heterozygous OR 1.57, p = 0.04

Genetic profiles in MCS

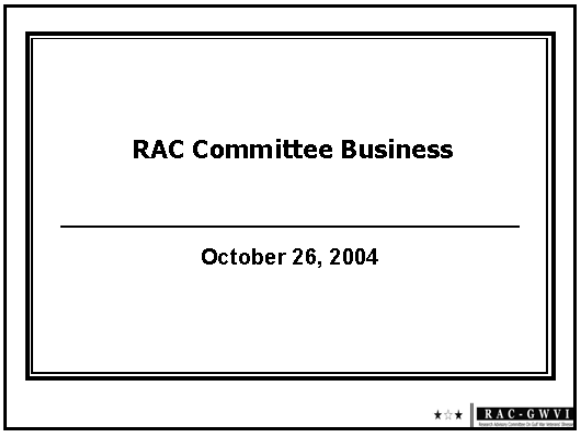
- CYP2D6 Distribution of genotypes p = 0.02
- NAT2 distribution of genotypes p = 0.03

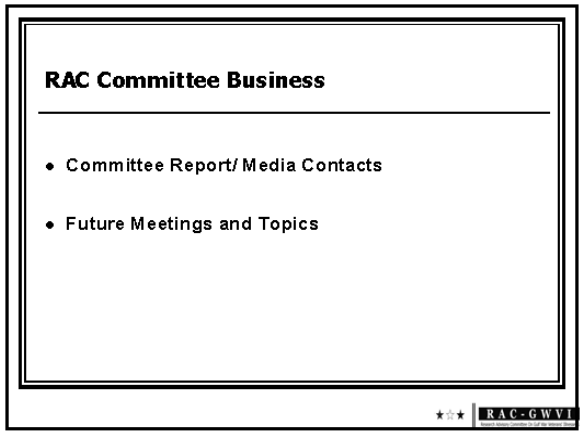
Theorize:

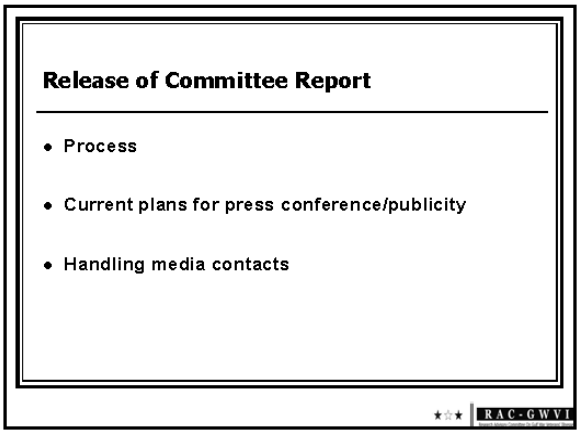
- CYP2D6 rapid acetylator: create toxic metabolites or affect endogenous chemicals that protect/heighten risk
- NAT2 rapid acetylator: bioactivates arylamines to protein-binding metabolites

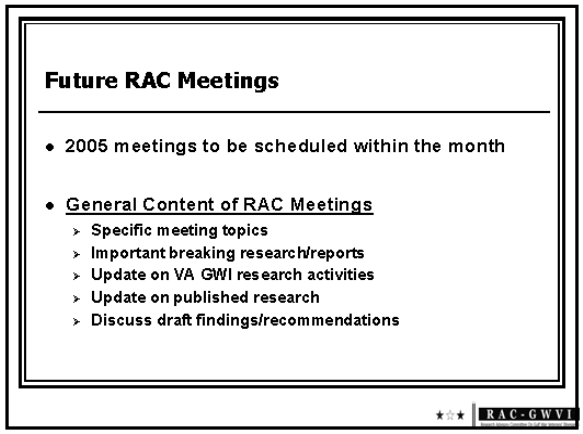
McKeown-Eyssen et al Jul 2004 Intl J Epi 33: 971-78. Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2, MTHFR.

Presentation 13 – RAC-GWVI Staff









Future RAC Meetings

- Upcoming Meeting Topics
  - Additional research related to Gulf War exposures
  - GWI treatments research
  - Relevance of research on other multisymptom conditions to GWI
  - Special topics

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Future RAC Meetings: Exposure Topics

- Complete partially-covered exposure topics
  - Vaccines
  - DU
  - Petroleum combustion products
- Additional exposure topics
  - Individual topics (e.g. CARC paint, solvents, sand)
  - Combinations of exposures
- Overview/comparison of evidence re: all Gulf War-related exposures

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Future RAC Meetings: GWI Treatments

- Potential GWI pathogenic mechanisms amenable to treatment: Where should we be looking?
- Review of research studies on treatments for GWI and relevant conditions
- Information from clinicians treating GWI, similar conditions
- Methods for evaluation of treatment information and determining best next-step options

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Future RAC Meetings: Multisymptom Illnesses

- Current research re: etiology, pathophysiology of CFS, FMS, MCS
- Objective markers associated with multisymptom illness
- Treatments for CFS, FMS, MCS, IBS
- Comparision of findings in GWI and "civilian" multisymptom conditions

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Future RAC Meetings: Possible Special Topics

- Identifying "Biomarkers": Potential GWI mechanisms amenable to objective measure; potentially useful technologies
- What do we know about diagnosed conditions in Gulf War veterans (e.g, cancer, neuro diseases, hypothyroidism)?
- Research on neurological/systemic effects of inhaled exposures
- "Burning semen" and other GWI anomalous symptoms
- Methodological issues in GWI research: Standards of study design, GWI case definition, etc.
- Overview of relevant ALS research
- Development of Gulf War veteran brain tissue bank

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Future RAC Meetings

- Questions?
- Committee suggestions

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Other Committee Matters

- RAC website: www.va.gov/rac-gwvi
  - Report will be posted
  - New pages: Info for Researchers, GWI-related Links, Media
  - RAC Research Article Updates now posted
- RAC email: RAC@med.va.gov

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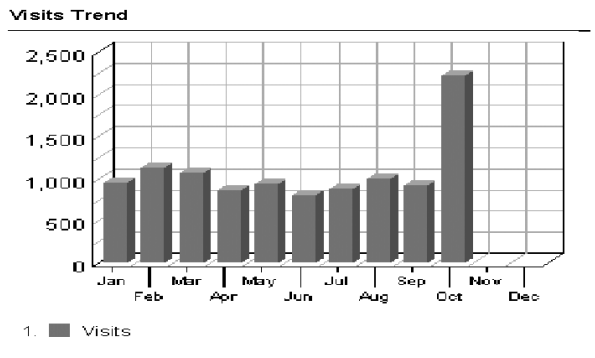
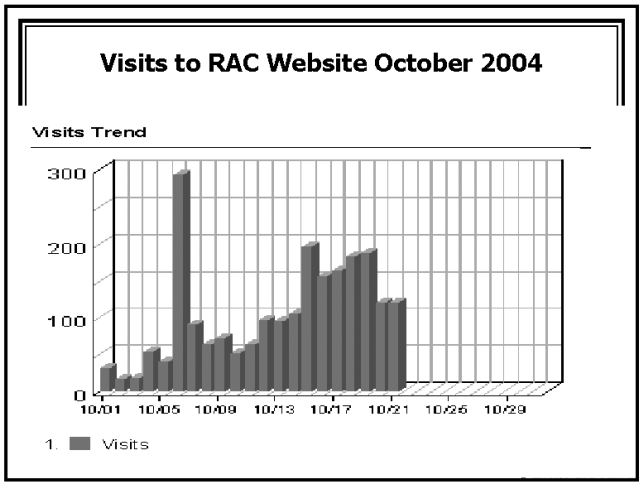
Visits to RAC Website Jan. - Oct. 2004




Visits to RAC Website October 2004
Visits Trend
300
200
100
0
10/01
10/05
10/09
10/13
10/17
10/21
10/25
10/29
1. Visits

Appendix B

Public Submission 1 – Edward J. Bryan

From: Mr. Edward J. Bryan
685 Broadway St. Apt. #74
Malden, MA. 02148
Tel. 781-321-3161

October 25, 2004

To: RAC-Gulf War Veterans Illness (T-GW)
U.S. Department of Veterans Affairs
2200 S.W. Gage Blvd.
Topeka, KS 66622

Re; up-dated on January 5, 2005

Meeting: October 25, 26, 2004

One of the biggest problems in the Washington Capitol is sending either an email or letter, because there is no response to them for (3) three months or more before anyone could reply. This leads to mismanagement.

Another major problem is the lack of specialty treatments and testing. When is your committee going to issue treatments ?

Why did the DoD and VA only do partial investigations, when they should have done a full investigation on exposures.

-See: Congressman Shays question to Mr. Binns on June 1, 2004. Mr. Binns, does your charter have to be changed and re-worked to help veterans ?

.- See the GAO report on June 1, 2004. Hearing on the hill, Mrs. Janet Heinrich doesn't know what to do with Gulf War Illnesses, I told her to look for veterans input, see said, I am probably right. We need to Reach out to the veterans that know about the illnesses and send them out to help VA Officials reduce the work load. She said she will look into this.

- See up-dated 2005 Specialty Testing List.

- See NTI.org, Website on chemical weapons found and used in the middle east.

Dr. Heller, knowing the troops in Saudi Arabia should have had masks or respirators on while they were being exposed to the Oil Well Fires and other chemicals. Why did you say, you would not have ordered these masks and respirators ?

Dr. Heller, why are gulf war veterans having the same medical conditions as U.S. firefighters, car accidents and heart attacks ?

This Committee must look further into the **" Batch effect " Vs. " Chimney effect "** on oil well fire exposures and other chemicals, this is the poisoning no one is looking at. Saddam poisoned his own troops this way in 1986. For reference look at Field Manual, **FM-8-825 of February 1990** edition. And the N.F.P.A. 14th edition, local fire chiefs have this information, and homeland security officials. We are always told, never set up, down wind from the enemy.

Dr. Engel, Dr. Donta and Dr. Blank: Why wasn't the contaminated blood (mycoplasma) that was shipped to the Southwest Medical Center replaced with fresh blood samples and retested ?

Dr. Soxs: Why doesn't modern medicine and military medicine recognize each other ? The stale mate of denial to medicine from the Department of Defense is coming to a close, the AMA is looking at this issue very closely.

Dr. Engel, your treatment center, like others should have an easier access to them.

Dr. Clymer: Why are you telling miss information to veterans that are in need of medical care ? You did tell myself that the human body is 80% carbon, I found out different from an article in the national geographic magazine on the carbon cycle. It states that the human body is 18% carbon. This tells me that my evaluation was tainted and my medical condition is at high risk from Doctors like you, who are making faulty judgments.

Mr. Warren Rudman: Why didn't you believe anyone's testimony on July 13, 1999, On chemical exposures ? You did call Mr. Dan Fahey a liar and a hippy.

Dr. Brown of Massachusetts General Hospital: Why are you wrong on the 6 veterans that have ALS ? There are as many as 400 or more that have this progressive disease. Many others have M.S. and Parkinson Disease with complications. At least half of the Gulf War Veterans from the 1991 War have total disabilities. Why ?

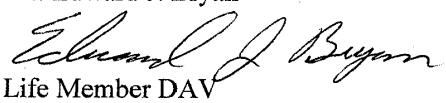
There's enough evidence to treat veterans, only if they are healthy enough to go through the treatment process. **The partial testing vs. the full testing must be looked at, this should be highly recommended.** The disability process with the VA is so much in the red, there should be another recommendation to be considered and forwarded to the proper committees.

Dr. Shayetivz's treatments like other environmental doctors, treat patients with respect to exposures to chemicals. These doctors are in great need nation wide in DoD / VA sites.

The Bombing campaign is another forgotten investigation from DoD / VA studies.

A written reply should be answered within a reasonable time period from the committee.

Mr. Edward J. Bryan



Life Member DAV
Life Member VFW
U.S. Army (Retired) 1974-2000
U.S. Firefighter (Retired) 1986-2000
Health Care Liaison (VA-BU) 1995-2001
Researcher for Gulf War Illnesses 1992-Present
Walter Reed Veteran Health Advisory Council-Deployment Health, 2000-2003

Public Submission 2 – Venus-val Hammack

Desert Storm Justice Foundation

Dear RAC Panel Members

We thank the RAC for allowing us the opportunity to address our ideas and concerns of VA medical research. **Veterans turn to the Research Advisory Committee -GWI to readdress failure of Military Industrial Hygiene Programs did not protect them during deployments.** (Kamisiyah ammunition and other demolitions)

HSE-OM/WP Technical Guide No. 124, Mar 82, Section II. Department of Army Occupational Health Program 1-6. Authority and regulations. Various laws and regulations have been promulgated to promote the health and effective performance of Federal employees through establishment of occupational health programs.
a. The laws and Federal directives authorizing occupational health programs for Army civilian and military employees include the following: (1) Public Law (PL) 79-658, Health Programs for Government Employees, as amended (5 USC 7901, 1946), provides for emergency treatment of on-the-job illnesses, pre-employment and other examinations, referral of employees to private physicians, and preventive programs relative to health.

RAC has yet demand studies on workplace exposures during Desert Storm such as -Types of industrial HYGIENE injuries/illness which are to be identified fall into four categories: chemical, biological, physical, and psychological. Organic and inorganic chemical agents may be in the form of liquids, dusts, fumes, vapors, mists, or gases. Biological hazards include plant or animal agents in such forms as bacteria, viruses, fungi, insect toxins, etc. Physical hazards include such agents as radiation, heat, cold, vibration, noise, light and other physical factors such as requirements for lifting or working at high levels or on ladders. Identification of these hazards should be specific, such as what type of solvent (stoddard or tetrachloroethylene), fume (lead or cadmium) or radiation (x-ray, radioactive material, laser, microwave).

DoD and VA Research Has completed projects on these exposures/deployment illness Psychological hazards or stresses will include job-related conditions (shift work, repetitive motion, monotony, reduction-in-force ,frequent transfers, interpersonal relationships, career development pressures, etc.) or personal factors that impair working capability either~temporarily (death in the family) or over a long period of time (alcohol or other drug abuse). Today tell veterans that most of their illnesses are somatic. This position must be challenged and neurological health should be examined by nuclear medicine diagnostics studies.

DOD has yet issues (publish) peer reviewed studies on Multiple Exposures/Stressors And did not consider the toxicity of a chemical may be increased or decreased by simultaneous or consecutive exposure to another chemical or multiple chemicals, particularly those that affect the same target organ or that alter the pharmacokinetics of one or more chemicals. These issues are not typically addressed by existing federal standards and guidelines. It is noted that the Occupational Health and Safety Administration (OSHA) (29 Code of Federal Regulations (CFR) 1910.1000(d)(2)(i).) does. Is it because servicemen are not the same species as federal workers? Visual observation and written surveys will not discover gulf war veterans illness/injuries.

When will RAC-GWI demand studies in this area? (*Industrial Hygiene and Nuclear Medicine*)

Venus-val Hammack (jagmedic@pgev.org)
NGWRC, Board member
Persian Gulf Era Vet of MA, Board member
Disabled Veterans of American, Life Member
WIMSA, Board member

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