

Research Advisory Committee on Gulf War Veterans' Illnesses

April 6-8, 2005 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 April 6-8, 2005, meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

/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
Beatrice Golomb
Joel Graves
Robert W. Haley
Marguerite Knox
William J. Meggs
Steve Robinson
Steve Smithson
Lea Steele

Consultant to the Committee

Jack Melling

Committee Staff

Laura Palmer
Barbara LaClair

Guest Speakers

Daniel Clauw
David Barber
Iris Bell
Wayne Briner
John Grabenstein
Mark Melanson
Mary Ann Parkhurst
Phillip Pittman
William Reeves
Brian Schuster

Abbreviations

AChE	Acetylcholinesterase
ACR	Armored Cavalry Regiment
AFIP	U.S. Armed Forces Institute of Pathology
ALS	Amyotrophic Lateral Sclerosis
AVA	Anthrax Vaccine Adsorbed
CBT	Cognitive behavioral therapy
CCEP	Comprehensive Clinical Evaluation Program
CDC	U.S. Centers for Disease Control and Prevention
CFS	Chronic fatigue syndrome
CI	Chemical intolerance
COL	Colonel
CRADO	Chief Research and Development Officer (VA)
DESP	Deployment Environmental Surveillance Program
DoD	U.S. Department of Defense
DU	Depleted uranium
EBT	Exercise and behavioral therapy
FDA	U.S. Food and Drug Administration
FM	Fibromyalgia
fMRI	Functional Magnetic Resonance Imaging
GAO	U.S. Government Accountability Office
GWI	Gulf War illness
GWVIS	Gulf War Veteran Information System (VA)
HHS	U.S. Department of Health and Human Services
HPA	Hypothalamic-pituitary-adrenal
HSRD	Health Service Research and Development Service (VA)
IOM	Institute of Medicine
LOI	Letter of Intent
LTC	Lieutenant Colonel
MCS	Multiple chemical sensitivity
MMWR	<i>Morbidity and Mortality Weekly Report</i>
MP	Military police
NASA	National Aeronautics and Space Administration
NIH	National Institutes of Health
NOAA	National Oceanic and Atmospheric Administration
NGWRC	National Gulf War Resource Center
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom

ORD	Office of Research and Development (VA)
OSAGWI	Office of the Special Assistant for Gulf War Illnesses (DoD)
PA	Protective antigen
PTSD	Post traumatic stress disorder
RAC-GWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
REAP	Research Enhancement Award Program (VA)
RFA	Request for Applications
RFP	Request for Proposals
UIC	Unit ID Code
UMRC	Uranium Medical Research Center
USACHPPM	U.S. Army Center for Health Promotion and Preventive Medicine
VA	U.S. Department of Veterans Affairs
VAERS	Vaccine Adverse Events Reporting System
VHI	Veterans' Health Initiative (VA instructional program for physicians)
WRIISC	War-Related Illness and Injury Study Center (VA)

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
Wednesday, April 6, 2005

7:30 – 8:00	Informal gathering, coffee	
8:00 – 8:15	Meeting called to order Welcome, introductions, opening remarks	Mr. Jim Binns, Chairman
8:15 – 8:45	Overview: Multisymptom Illnesses in Gulf War veterans	Dr. Lea Steele, RAC-GWVI
8:45 – 9:45	Multiple Chemical Sensitivity: Research on Characteristics, Pathophysiology, and Treatments for MCS	Dr. Bill Meggs, East Carolina University School of Medicine
9:45 – 10:00	Break	
10:00 – 11:00	Sensitization in Chemical Intolerance and Gulf War Illnesses	Dr. Iris Bell, University of Arizona School of Medicine
11:00 – 11:30	Discussion	
11:30 – 12:30	Lunch	
12:30 – 2:00	Chronic Fatigue Syndrome: Research on the Occurrence, Definition, and Pathophysiology of CFS	Dr. William Reeves, U.S. Centers for Disease Control and Prevention
2:00 – 3:00	Fibromyalgia: An Overview of Research on the Diagnosis, Characteristics, and Pathophysiology of Fibromyalgia	Dr. Daniel Clauw, University of Michigan School of Medicine
3:00 – 3:15	Break	
3:15 – 4:15	Treatment Research on Multisymptom Illnesses; The Michigan Chronic Pain and Fatigue Research Program	Dr. Daniel Clauw, University of Michigan School of Medicine
4:15 – 5:00	Discussion	
5:00 – 5:30	Public Comment Period	
5:30	Adjourn for the day	

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
Thursday, April 7, 2005

7:30 – 8:00	Informal gathering, coffee	
8:00	Meeting called to order	Mr. Jim Binns, Chairman
8:00 – 9:30	Estimating Depleted Uranium Aerosol Doses and Risk: USACHPPM's Capstone Report	LTC Mark Melanson, USACHPPM Health Physics Ms. Mary Ann Parkhurst, Battelle Pacific Northwest National Laboratory
9:30 – 9:45	Overview of DU Research of Particular Relevance to Multisymptom Illnesses in Gulf War Veterans	Dr. Lea Steele, RAC-GWVI
9:45 – 10:00	Break	
10:00 – 10:45	Behavioral Changes and Brain Lipid Oxidation Following Uranium Exposure	Dr. Wayne Briner, University of Nebraska
10:45 – 11:30	Neurological and Behavioral Effects Following Co-exposure to Uranium and Stress	Dr. David Barber, University of Florida Center for Environmental and Human Toxicology
11:30 – 12:00	Discussion	
12:00 – 1:00	Lunch	
1:00 – 1:30	Gulf War Illness and Vaccines: An Overview of Issues and Epidemiological Findings	Dr. Lea Steele, RAC-GWVI
1:30 – 2:30	Evaluation of Adverse Events Following Anthrax Immunization	COL John Grabenstein, PhD Military Vaccine Agency, U.S. Army Medical Command
2:30 – 2:45	Break	
2:45 – 3:45	Health Effects of Receipt of Multiple Vaccines: Completed and Ongoing Studies	Dr. Phillip Pittman, U.S. Army Medical Research Institute of Infectious Diseases
3:45 – 4:30	Remaining Questions Relating to Immunizations Received by Gulf War Veterans	Dr. Beatrice Golomb, School of Medicine, Univ. of California at San Diego
4:30 – 5:00	Discussion	
5:00 – 5:30	Public Comment Period	
5:30	Adjourn for the day	

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
Friday, April 8, 2005

8:00 – 8:30	Informal gathering, coffee	
8:30	Meeting called to order	Mr. Jim Binns, Chairman
8:30 – 9:15	VA Office of Research and Development Update on Gulf War Illness-related Research Activities	Dr. Brian Schuster, VA Office of Research and Development
9:15 – 10:00	RAC-GWVI briefing and discussion with Secretary James Nicholson	
10:00 – 10:15	Break	
10:15 – 11:00	Discussion	
11:00 – 11:45	Highlights of Recently-Published Research Relevant to Gulf War Veterans' Illnesses	Dr. Beatrice Golomb, School of Medicine, Univ. of California at San Diego
11:45 – 12:30	Committee Business	Mr. Jim Binns Dr. Lea Steele
12:30 – 1:00	Public Comment Period	
1:00	Adjourn	

Welcome, introductions, and opening remarks

James H. Binns, Jr., Chairman

Chairman James Binns called the meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GWVI) to order at 8:10 a.m.

Chairman Binns thanked the Committee members, speakers, and public for attending the meeting. He noted that there was a sign-in sheet for public comments scheduled for the end of the day.

Chairman Binns stated that Secretary Nicholson had scheduled time to meet with the Committee on Friday morning. However, due to his recent tenure as Ambassador to the Vatican, Secretary Nicholson had been asked to join the U.S. delegation attending Pope John Paul II's funeral, and so would not be participating in the Committee meeting.

Chairman Binns stated that the Committee's 2004 report and recommendations were intended to cover the first two years of the Committee's activities (2002-2003). He stated that there were a number of topics which were not addressed initially, but which the Committee was continuing to review. He gave examples such as: multisymptom illnesses that overlap with Gulf War illnesses (GWI), depleted uranium, vaccines, etc. He stated that the Committee would be preparing another report, which will address its work for 2004-2005.

As it was the beginning of a new year, he offered his assessment of where the Committee and its work stood. He stated that several things had been accomplished in the last year, including the production of an impressive report and the U.S. Department of Veterans Affairs (VA's) response to increase their funding for non-stress-related Gulf War illness research. He stated that, measured against the history of this subject and given the nature of government, this might be considered a significant accomplishment. On the other hand, he stated that he could not note any real research breakthroughs in the past year, and acknowledged that the GWI research funded by VA in 2004 was a "mixed bag." He stated that, by the terms of the Committee's charter, he would have to say that federal research had yet to make a difference in the health of ill Gulf veterans, and, at best, it could be said that people were pointed in the right direction.

This year, he stated that he hoped that a difference could be made. He noted that the key to this difference was not only offering general recommendations, but identifying specific, high-value research opportunities and putting them together in a coherent research plan to move towards really solving this problem.

He gave an example of such an opportunity. He noted that, on page 46 of the Committee's 2004 report, the Committee recommended that a Gulf War veteran brain bank be established. He stated that at the time this seemed a laudable goal, but rather general and long-term in nature. Recently, however, he was reminded of a conversation with Dr. Paul Greengard, 2000 Nobel Prize laureate, and Dr. Robert Haley, in which Dr. Greengard noted that one could learn a tremendous amount from "one good brain." Chairman Binns stated that this put things into a whole different context. He stated that, if "one good brain" could teach us a great deal, perhaps we should be turning VA upside down to find an ill veteran or two who are willing to provide this type of service to the future. He stated that he believed there were other high-value opportunities that could be pinpointed, and hoped everyone would focus on these as well.

Chairman Binns stated that, when the Committee first met three years ago, there was a real sense of urgency. He stated that he hoped this urgency could be rekindled. He stated that the Committee's work was not an academic exercise, and noted that 200,000 ill veterans were waiting for help.

Chairman Binns stated that the day's topic of discussion, i.e., the overlapping "civilian" diseases that share common elements with GWI, was very important. He stated that GWI researchers could learn from these illnesses, and, presumably, these researchers could learn from GWI research.

Chairman Binns introduced Dr. Lea Steele, the Committee's Scientific Director.

Dr. Steele suggested that the Committee members present introduce themselves to the audience, which they did. She introduced the Committee's staff: Ms. Laura Palmer and Ms. Barbara LaClair, the Committee's new Research Health Scientist.

Dr. Steele briefly explained the Committee's binder organization, and that members would find many of the papers being discussed inside. She noted that several general review papers were available for the public at the door.

CFS, Fibromyalgia, and MCS: Defined "Chronic Multisymptom Illnesses" in Relation to Gulf War Veterans' Illnesses

Lea Steele, PhD, Scientific Director, RAC-GWVI

Dr. Steele gave an overview of chronic multisymptom illnesses, e.g., chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), and fibromyalgia (FM), and their relation to Gulf War veterans' illnesses. ([See Appendix – Presentation 1.](#))

Chemical Sensitivity

William J. Meggs, MD, PhD, FACEP, FACMT
 Chief, Division of Toxicology
 East Carolina University School of Medicine

Dr. Steele introduced Dr. Meggs.

Dr. Meggs presented an overview of chemical sensitivity and the practice of environmental medicine in the United States. ([See Appendix – Presentation 2.](#))

The meeting adjourned at 9:45 a.m. for a break.

The meeting reconvened at 10:03 p.m.

Time-Dependent Sensitization in Chemical Intolerance and Gulf War Illnesses

Iris R. Bell, MD, PhD
 University of Arizona College of Medicine

Dr. Steele introduced Dr. Bell.

Dr. Bell presented an overview of neural sensitization in chemical intolerance (CI) and relevant findings in Gulf War veterans. ([See Appendix – Presentation 3.](#))

Upon conclusion of her talk, Chairman Binns asked Dr. Bell for particular research suggestions in this field. Dr. Bell indicated that she would like to explore the possibilities of finding sensitizable individuals

prospectively, and to following their course with an exposure, in both a laboratory and field sense. She stated that she would also like to look at their dietary patterns and histories to see if there are connections with people experiencing CI. Dr. Bell indicated that other questions which needed to be answered were: (1) whether veterans with GWI can be tested for sensitization in the laboratory; (2) whether these veterans have CI, and (3) if so, what caused the elicitation of the sensitized reaction.

Mr. Joel Graves stated that Gulf veterans could be asked whether they had allergic reactions to things post-deployment that hadn't caused problems pre-deployment. He noted that, upon his return from the Gulf, he was severely allergic to his dog, which he had not been before his deployment. Dr. Bell stated that questionnaires had shown that new allergies were one of the changes reported by returning veterans. Dr. Meggs commented that the literature supported the concept that irritant exposures can potentiate the acquisition of IgE-mediated allergies to proteins. He noted that allergic rhinitis was historically a rarity in Japan; however, it became the most common immunological disease after the introduction of the diesel truck/car. Dr. Beatrice Golomb noted that the reaction to Mr. Graves' dog might actually have been to the flea collar or other pesticides on the animal. Dr. Bell stated that it was complicated to tease out a specific cause, and noted that there might also be synergistic effects between various agents.

Mr. Steve Robinson noted, anecdotally, that, while individuals who attended the National Gulf War Resource Center (NGWRC) conference were asked not to wear certain chemicals, the total number of individuals who were adversely affected was relatively low. He said that this correlated with some of the epidemiological data presented earlier in the meeting. Dr. Steele noted that sometimes people don't realize that they are sensitive, so it is difficult to get a handle on the extent of the problem.

Dr. Bell commented that the most sensitive individuals tend not to take the risk of going into public areas. She stated that many Gulf War veterans didn't see themselves as chemical sensitivity patients. However, when attempts are made to recruit Gulf War veterans in these studies, they are reluctant after finding out they are going to be exposed to low-level chemicals. She stated that this wasn't surprising, but noted that it does result in a biased sample.

Mr. Robinson asked whether an extended stay environmental unit was available in which these types of studies could be conducted. Dr. Bell stated that there were none in the United States. She stated that requests/suggestions had been made to build one, but funding was an issue. Dr. Meggs stated that there had been five government study groups that suggested creating a unit to study the effects of environmental exposures. However, no monies had been appropriated for its construction. Dr. Golomb noted her concern that such a unit could actually be free of all environmental contaminants. Dr. Bell acknowledged this problem, but stated that it would create a disparity between the ambient air and the exposure, allowing the effects of the exposure a chance to present.

Dr. Haley asked Dr. Bell for her suggestions on how to identify individuals with a propensity for sensitization. Dr. Bell indicated that the following criteria would help to identify individuals who were highly sensitive: family history of addiction, sucrose preference, and carbohydrate addiction scale. She stated that her group currently uses a chemical tolerance questionnaire, which includes a five-item screening scale to determine how ill the individual becomes from certain odors.

Dr. Bell noted that sensitization usually occurs in the short term in animals, particularly in sensitizable animals that react to novelty, but that only a subset of these animals have prolonged problems. She stated that this subset of animals can remain sensitized for up to a year without further exposure to the agent. Once the problem was set off, it was a big problem with no known way to reverse the condition. She noted that sensation seekers, i.e., those who need a high-stimulus environment, and the behaviorally inhibited/extremely socially shy seemed to be more sensitizable. She also noted that some

neurodegeneration research had indicated that shyness may be a factor in certain cases of Parkinson's disease.

Dr. Haley inquired about the source of the carbohydrate addiction scale, and whether it was a validated scale. Dr. Bell stated it was a scale published in a popular book on carbohydrates, which had been recommended to her by a fellow researcher. She acknowledged that there might be other scales, but this was the one known to her at the time.

In response to Dr. Golomb's concern about creating a perfectly chemical-free environment, Dr. Meggs commented that, while a perfect vacuum could not be created, vacuum research was still done. As such, he stated that this concern shouldn't be an impediment to doing environmental unit research.

Dr. Steele inquired whether there was a dichotomous or continuous distribution of sensitivity between the subgroups of symptomatic/non-symptomatic individuals. Dr. Bell stated it was probably a continuum. She stated that some people show this phenomenon regardless of the exposure intensity. She stated that determining the minimum threshold would be difficult. Dr. Steele asked if the individuals who were severely ill were more likely to be sensitizable and vice-versa. Dr. Bell stated that in research on civilians, individuals who had made lifestyle changes to avoid certain exposures may be healthier than individuals who were chemically intolerant when tested in the laboratory.

Mr. Robinson stated that many Gulf War veterans had found "avoidance" as a treatment option through their own avenues. He stated that it did seem to work for them, but there is no scientific evidence that supports this approach.

Dr. Haley asked Dr. Bell to comment on the cellular neuroplasticity underlying this process and where research should go in this area. Dr. Bell stated that there had been some research regarding changes in RNA expression, but that she hadn't seen follow-up work. The research had focused on changes in receptors and dopamine release. She stated that some research had shown a change in the pituitary/adrenal axis in terms of response to stressors, which may modulate what happens in the response, but this hadn't been examined further.

Dr. Golomb stated that it might be interesting to investigate whether chemically sensitive individuals have an exaggerated oxidative injury marker. Dr. Bell agreed, noting a paper by Dr. Robert Paul at Washington University that indicated oxidative stress and the nitric oxide pathway might play a role. She stated that the question, though, was what part of the process researchers should begin examining.

Dr. Steele noted that there seemed to be a preponderance of MCS and CFS in women, and asked Dr. Bell about her comment regarding a possible protective effect of testosterone. Dr. Bell stated that there were two studies that showed removal of gonads did not make female animals any less sensitizable, while castration made male animals more sensitizable. She noted that testosterone would restore their resistance. Dr. Steele asked whether an exacerbation of chemical sensitivity was seen at certain times in the menstrual cycle. Dr. Bell stated that there was literature about olfactory sensitivity changes due to the menstrual cycle.

Chairman Binns asked Dr. Meggs to comment on the nasal inflammation hypothesis, and whether there was any evidence that this could be healed. Dr. Meggs stated that avoidance was the best way to improve a patient's functionality. He noted that an individual's symptoms could improve while in an environmental control unit, but that they weren't able to go back into their old environments, e.g. "sick building", etc. Chairman Binns asked if there were any other options besides avoidance. Dr. Meggs stated that he wasn't aware of any. He noted that, while high dose vitamin/anti-oxidant treatments were

being touted, there was little or mixed evidence proving efficacy. Dr. Bell stated that there was clinical evidence that there were some alternative medicine options, e.g., acupuncture, which could modulate the tendency to be sensitive. She noted that there was one study that suggested ginseng possibly could block sensitization, but she noted there was no follow-up work done on this.

Dr. Steele asked Drs. Bell and Meggs whether the literature indicated that once an animal was sensitized, it was always sensitized. Dr. Bell stated that there were many studies where all the animals were initially sensitized, but as time passed, fewer animals remained so. Dr. Meggs stated that the real key seemed to be patterns of exposure sensitizing an animal, noting that with removal of the exposure, the sensitization could be reduced over time.

Dr. Alan Fienberg, an audience member, noted that there was extensive research characterizing the biochemical mechanisms of dopamine and sensitization to drugs of abuse, e.g., cocaine. He stated that there was research that suggested these biochemical processes could be distinguished. Dr. Haley stated his belief that this was a research area to develop, i.e., how to bring human clinical models in parallel with intracellular models, allowing for testing of specific mechanisms in animal/cell models. He noted a recent neurodegenerative disease paper in the journal *Nature*, which showed a drug screening process that identified common antibiotics promoting, or increasing certain receptors in glutamate transport, that slowed the progression of ALS. Mr. Robinson asked if an antisense drug would have a similar result. Dr. Haley stated that they should come at it from a different angle, extending human studies as much as possible without creating any adverse consequences. He stated that the development of animal and/or cell models then could be developed to test every known drug or chemical. He stated that this approach seemed a promising option for this research area, and that there was a need to get various groups talking about these parallel research pathways.

Dr. Meggs commented that there were two distinct patient populations with neurotoxic exposures: those exposed to solvents and those exposed to organophosphates. He noted that a certain percentage of these populations develop chemical sensitivities. He stated that it was known that both of these classes of chemicals cause brain damage in high doses, and that there is neurogenic regulation of all of these mechanisms. He stated that those individuals exposed to low doses, who might have lesser damage, might not get better either.

Dr. Golomb commented on Mr. Robinson's comment about antisense agents. She indicated that, in light of Dr. Soreq's RNA expression research, it might be possible to develop these agents for treatment of CI patients.

Chairman Binns closed the discussion, noting that it had been stimulating and encouraged continued discussion about these ideas.

The meeting adjourned for lunch at 11:38 a.m.

The meeting reconvened at 12:35 p.m.

Chronic Fatigue Syndrome: Occurrence, Case Definition, and Pathophysiology

William C. Reeves, MD

Chief of the Viral Exanthems and Herpesvirus Branch, Division of Viral and Rickettsial Diseases
U.S. Centers for Disease Control and Prevention

Dr. Steele introduced Dr. Reeves.

Dr. Reeves gave an overview of chronic fatigue syndrome, including its prevalence, case definition, pathophysiology, and diagnosis. ([See Appendix – Presentation 4.](#))

Dr. Steele asked Dr. Reeves to elaborate on the charge given to the statisticians with respect to looking for patterns in different data and seeing where these patterns overlap. Dr. Reeves said there were two questions being asked: Can we find patterns within the data? and, if so, Can we elucidate the pathway that is involved? He noted that this was one of the only genome projects trying to incorporate massive amounts of clinical data. The charge to statisticians was difficult because it involved analyses of disparate types of complex data such as information from EEGs and tests of behavioral/cognitive function. Dr. Golomb stated that it was important to look for these patterns, which would enable researchers to tease out and develop markers. Dr. Reeves stated that the U.S Centers for Disease Control and Prevention (CDC) would be more than happy to collaborate with the genomic researchers in this area.

Dr. Stephen Grate, an audience member, asked if the genomic or proteomic data were showing alterations/differences with respect to the duration of the illness. Dr. Reeves stated that these questions hadn't been examined yet. He noted that one of the "flaws" with current studies was that the individuals had been sick, on average, five years. He stated that CDC was working on three modeling studies. One study was with Emory University, evaluating the induction of CFS-like symptoms by therapeutic use of interferon alpha. Another study was being conducted with Australian researchers with respect to unexplained fatigue following infections, such as mononucleosis, Ross River virus and Q fever. Dr. Reeves noted that expression patterns in this study were predicting the individuals whose symptoms would not improve.

Dr. Meggs stated that this was an interesting technique and was different from how disease mechanisms were identified in the past. He asked, however, if it was clear that it would work for CFS. Dr. Reeves noted that early life stress changes the reaction of the hypothalamic-pituitary-adrenal (HPA) axis to similar stressors later in life. He stated that it was very clear that heart disease, breast cancer, and a variety of other cancers and chronic diseases have associations with early life stress. He stated this was probably due to a modification and alteration of HPA axis expression.

Dr. Meryl Nass, an audience member, asked Dr. Reeves if researchers were looking at infection titers, and whether a list of CDC's study parameters was available. Dr. Reeves stated that, in the clinical study, they did not look at titers. He stated that testing for possible infectious agents, including examination of titers and searches for latent DNA and 16S ribosomal RNA, had been conducted and published in previous articles. Dr. Nass asked about the findings of the Wichita study, and whether these were available. Dr. Reeves noted that the survey in Wichita was conducted between 1997-2000, with the in-patient study being conducted between 2000-2003. He stated that they were still working on the data. He noted that there were approximately 20 publications covering the findings of this study on the CDC website. He stated that a similar study was underway in Georgia.

Dr. Haley questioned the use of the HPA axis as the central model. He stated this was only one part of the story, and locked the researchers into the idea that childhood and emotional stress was the sole cause. He stated that there was a lot more evidence now that the neuroplasticity of other parts of the brain,

cytokines, neurotransmitters and dopamine, which aren't involved with the HPA axis, are more likely to be at issue. He stated that the use of the HPA axis as a central model was limiting. Dr. Reeves responded by saying: (1) the HPA axis model fits an established body of research that helps drive hypotheses, and (2) the HPA axis functions as a unit. He indicated that their research included studies involving functional MRI (fMRI), cognitive and stress measures, and evaluations of the immune system. He stated that these functions weren't unrelated to the HPA axis, and that it was an easy way to present the central hypothesis. He stated his belief that stress does play a role in this condition. He noted that stress wasn't simply abuse as a child, but included malnutrition, infections, injuries, living in poor environments, etc. He stated that CFS was a complex illness that did not have a single genetic or environmental cause.

Chairman Binns asked if Dr. Reeves had specific suggestions for applying this technology to Gulf War illnesses research. Dr. Reeves stated that the most productive route would be to focus on these types of illnesses surfacing from the current Gulf War, as individuals are "freshly ill." The studies should include population-based studies, to characterize the illness with standardized instruments and a clinical component. He noted that genomics and proteomics measures should also be utilized.

Chairman Binns asked for ideas with respect to study of illnesses from the first Gulf War. Dr. Reeves stated that similar types of studies should be done. He also noted that much of the question today for GWI is how to care for people who have been ill for 15 years. He stated that it was important to investigate the clinical parameters, how they could be measured, and how the patients' symptoms were improving or not improving over time.

Dr. Nass asked if the CDC study asked questions about problems following vaccines, and whether it would be possible to get a profile of vaccines given with respect to those surveyed from Warner Robins Air Force Base (Macon, GA). Dr. Reeves stated that this would be difficult within the structure of their population study. He stated that the study was being done as a random digit-dialed survey of the population.

Dr. Steele asked Dr. Reeves why he questioned the use of case-control studies in this area of research. Dr. Reeves stated that case-control studies were good for simplistic things, but more than a single association of a risk factor or symptom was needed in cases like this. Dr. Haley agreed that simple case-control studies weren't enough, but that mechanistic measurements were needed and that this should progress to animal models. Dr. Reeves noted that defining the case groups in CFS and GWI studies was difficult, due to competing comorbidities.

Chairman Binns thanked Dr. Reeves.

The Pathophysiological Basis of Fibromyalgia

Daniel J. Clauw, MD
Professor of Medicine and Director, Chronic Pain and Fatigue Research Center
University of Michigan Medical Center

Dr. Steele introduced Dr. Clauw.

Dr. Clauw gave an overview of current research on the nature and causes of fibromyalgia (FM), and relevant studies related to Gulf War illnesses. ([See Appendix – Presentation 5.](#))

Dr. Meggs asked Dr. Clauw what he thought might be the neuroanatomical cause of the “seesaw effect” happening in the insula portion of the brain. Dr. Clauw indicated it might be a preponderance of specific neurotransmitters or neuronal imbalance. He stated that many in this field view pain as being a form of low-grade epilepsy, i.e., the brain is hyperactive. He noted that many of the drugs used in this field are ones that raise the levels of inhibitory neurotransmitters.

Dr. Golomb commented that one had to be careful focusing on commonalities in multisymptom conditions and noted the need to look at both the similarities and differences. She noted Dr. Clauw’s observation that Gulf War veterans do not experience the same response to tender point pressure, which might suggest there was a different mechanism in these ill veterans. She also noted their fMRI findings, which showed certain areas “lit up” specifically in the non-Gulf War FM patients, but not the Gulf War veterans, and vice versa. Dr. Clauw agreed with her with respect to their fMRI findings, but noted that the FM case definition might account for the tender point differences.

Chairman Binns asked if Dr. Clauw would include chemicals as a “stressor.” Dr. Clauw stated he would, and in certain individuals, chemicals were major stressors.

Dr. Nass expressed her interest in the “turning up the volume” theory. She noted her own patients’ accounts of being overstimulated when they were in large groups.

Dr. Jack Melling asked Dr. Clauw to expound on the triggers of FM, i.e., what causes someone to go from normal range to being a FM patient. Dr. Clauw stated that his group currently was conducting longitudinal studies and trying to identify the mechanisms for increased sensitivity to pain. He noted that studies of exercise deprivation had shown emergence of pain problems in some individuals.

Dr. Haley asked if quantitative temperature sensitivity had been considered in FM studies. Dr. Clauw indicated this had been examined, and there was a similar shift “to the left.” He stated that there was considerable activity observed in fMRI in response to touch.

Dr. Steele asked if studies had shown that sleep deprivation, not just exercise deprivation, caused an increase in pain. Dr. Clauw indicated that early studies suggested that lack of sleep was the cause of FM. He stated this was way too simplistic, but likely played a role. Dr. Steele asked how the central pain processing explanation of FM ties in with the other symptoms of FM, e.g. gastrointestinal, sleep abnormalities, etc. Dr. Clauw stated that sensory and pain-processing abnormalities, along with dysautonomia, probably do explain most of the symptoms of FM. Chairman Binns noted that he had heard from FM patients that they couldn’t sleep because their mind was “racing” or couldn’t be “turned off.”

Mr. Robinson asked if Dr. Clauw knew how many first Gulf War veterans had been diagnosed with FM. Dr. Clauw stated he didn’t, and noted that some veterans were resistant to being diagnosed with FM

because it would affect their disability benefits. He also stated that because the VA historically had cared primarily for men, the premiere FM researchers haven't focused their research in the VA environment. He noted that FM patients were managed poorly most everywhere, but that more attention is given to it now. Mr. Robinson agreed, and stated that VA didn't cover most treatments that veterans were seeking. He stated that when the disability benefit law was passed, many veterans sought an "undiagnosed illnesses" classification. He stated it would be interesting to know how many of the deployed veterans who filed claims for undiagnosed illness would fit the criteria for FM.

Dr. Melling asked if Dr. Clauw found the words "stress" and "stressors" to be viewed so negatively by patients that they are difficult to use in discussion of chronic multisymptom illnesses. He stated that most present understood the meaning of "stressors" and "stress" and that this differs from the meaning used by the general public. He noted this was a problem, at least a perception problem. Dr. Clauw agreed and stated he doesn't use the term "stress" unless he has time to explain its meaning. Ms. Marguerite Knox noted that this is how medicine is currently divided: mental health and acute care. Dr. Clauw stated that the problem with this approach for these illnesses is that no one has "ownership." He noted the VA's survey of its own physicians where 75% of the psychiatrists believed GWI was a medical problem, while 75% of the internists believed it was a psychiatric problem. He stated that it was fascinating that clear psychiatric diseases, such as schizophrenia, have greater acceptance than FM, CFS, GWI, and MCS. He noted these diseases were "left behind" because there was no subspecialty group or effective advocacy group to bring them into the mainstream. He noted that FM had come a long way in the last 10 years, due to researchers' ability to study pain objectively, along with pharmaceutical interest in this area.

Ms. Julia Dyckman, retired Navy captain and audience member, asked Dr. Clauw if the problems with the autonomic nervous system were due to dysfunction or failure. Dr. Clauw stated that this was subtle dysfunction. He characterized it as an instability or dysregulation of the autonomic nervous system.

The meeting adjourned for a break at 3:20 p.m.

The meeting reconvened at 3:30 p.m.

Treatment of Fibromyalgia and Other Chronic Multisymptom Illnesses

Daniel J. Clauw, MD

Professor of Medicine and Director, Chronic Pain and Fatigue Research Center

University of Michigan Medical Center

Dr. Clauw gave a presentation about research on treatments for FM and other chronic multisymptom illnesses. ([See Appendix – Presentation 6.](#))

In his discussion of pharmacological compounds under development, Dr. Clauw disclosed a financial interest in the company that manufactures Milnacipran. He noted that if the VA wished to do clinical trials for FM, Duloxetine was one drug that could be studied. He stated that the VA should be able to get a drug company to provide their product for a combined therapy trial, such as drug and cognitive behavioral therapy (CBT).

Dr. Meggs noted that, anecdotally, there seemed to be a relationship between FM and later onset rheumatoid arthritis and other autoimmune diseases. Dr. Clauw stated that he hadn't seen this in his practice. He stated that these illnesses are common in the population, and epidemiological studies were not showing such a relationship.

Ms. Alison Johnson, an audience member, noted that tricyclic drugs didn't seem to work with MCS patients. Dr. Clauw stated that he has had some success when he starts his chemically-sensitive FM patients on very low doses of tricyclics.

Mr. Robinson asked if there was evidence that rolfing worked for FM patients. Dr. Clauw stated that there weren't data to support either way, but that he does recommend it to some patients.

Dr. Bell noted that the reactions seen in chemically sensitive individuals taking tricyclics may be seen as an amplification or sensitization process, with respect to the noxious threshold for these patients. She noted that there was one study that indicated electroacupuncture did provide some relief to FM patients. She noted that she was intrigued by the benefits and parallels with respect to combination therapy findings between FM patients and chemically sensitive patients. Dr. Clauw agreed, and noted that treatment of these patients required finesse.

Dr. Haley asked if the drug hypersensitivity in these patients had been well researched to determine whether they had intrinsic hyperresponses, or whether there were issues involved in elimination of the drug. Dr. Clauw stated that a research group in which he was involved 8-10 years ago had determined that it wasn't a problem with accumulation or toxicity of the drug. He noted that it seemed patients were more sensitive to the neuroactive drugs. He further noted that this sensitivity didn't apply to all drugs, but rather to specific classes.

Dr. Steele asked about Dr. Clauw's registry of screened and available research subjects. He stated that they had established a registry at the University of Michigan. The registry was not intended itself for research, but provides researchers with a streamlined recruitment process and made subjects available for future studies, such as those involving genomics or proteomics. He stated that it wasn't as easy for them to attract a large study population as the CDC does. Dr. Haley stated that clinical studies, not population studies, were better for mechanistic studies.

Dr. Steele noted that ill veterans frequently contacted the Committee and its members about being a part of research studies. Dr. Clauw stated that these patients could be referred to him. He indicated that it had been difficult to find Gulf War veterans previously, but that they would love to develop a Gulf War cohort available for study.

Chairman Binns asked if Dr. Clauw had found in his clinical practice that some patients' problems started with chemical exposure. Dr. Clauw stated that it was terrible for a patient to think they had been "poisoned." He provided three examples from his career, and indicated that those patients who felt they were victims did not fare as well as those who acknowledged their problem and moved on. He indicated that he thought toxins played a role in the illnesses experienced by some Gulf War veterans, but that it was destructive to their health for them to think that they were poisoned. He indicated that this reinforced the patients' victim mentality, and took away their sense of control over the situation. He indicated that these patients tended to become passive and feel helpless in finding ways to improve their health.

Dr. Melling stated that he agreed with Dr. Clauw's analysis about the need to avoid the victim mentality. He noted, however, that the Committee faced a dichotomy of charges. He stated that, on one hand, the Committee was trying to understand Gulf War illness and the various treatment options. On the other hand, it was also trying to prevent future occurrences by determining the cause or causes of these illnesses. He agreed that, for an individual patient, the best thing was to "move on." However, for the system as a whole, the Committee must also look towards prevention. Dr. Clauw stated that he wasn't trying to criticize the Committee, but that the effect on patients who develop this belief was very real.

Mr. Robinson agreed that Dr. Clauw's point was good. He noted, however, that Gulf War veterans were just getting to the point where they could stop thinking of themselves as victims, given recent scientific advancements. He stated that it was important for the veterans to be "victims" in the beginning, because the Government refused to acknowledge that their Gulf War service had any bearing on their illnesses. He stated that this acknowledgement now allowed the focus to move to positive, proactive treatments and therapies.

Chairman Binns asked Dr. Clauw to explain the relationship between autonomic nervous system dysregulation and the pathway addressed by the drugs he had discussed. Dr. Clauw stated that most of the drugs worked on serotonin and norepinephrine, which are neurotransmitters at the epicenter of the autonomic nervous system. Chairman Binns asked whether this meant that the autonomic dysfunction was the core problem, but that therapy tended to ameliorate it. Dr. Clauw agreed it was a problem and, if addressed, it made at least a subset of individuals better.

Mr. Graves asked if FM patients experienced a higher incidence of low-impact injuries. Dr. Clauw stated that they did. He stated that earlier in their lives, the patients might have thought they were injured more than others, when it also might be that their lower pain thresholds lead to more symptoms.

With respect to the "victim" mentality, Dr. Meggs stated that it must be acknowledged that individuals do develop chronic disabilities from toxin exposure. However, he noted that the most destructive thing to the patient's health was having pending litigation that encouraged continued disability in order to achieve settlement. Dr. Clauw agreed that it was a terrible thing to have a link between proving one's disability and receiving clinical care. Mr. Steve Smithson pointed out that the VA system was based on this causal connection, i.e., the veteran must show that their illness was service connected before they could qualify for treatment. He stated that the veteran wanted to get better, but unless he or she can show what caused the condition, they aren't eligible for treatment. He said it is easy to say: "Don't worry about what causes it. Move on." But the system puts the veteran in a catch-22, which must be considered when discussing these veterans' treatments or benefits. Dr. Golomb agreed that, based on her clinical practice, patients with pending litigation did less well.

Ms. Denise Nichols, a Gulf War veteran and audience member, agreed that the adversarial process did interfere with patient care. She stated that there had to be a trust mechanism between the patient and health care provider. She noted that there was a loss of trust when the government denied a connection between the veterans' service and illnesses. She stated that the goal wasn't to find a "golden egg", but to find out the truth.

Dr. Steele asked Dr. Clauw about his thoughts about Ampligen. Dr. Clauw declined to discuss this.

Ms. Julia Dyckman asked Dr. Clauw for his thoughts about chronic pain clinics and their coordination. Dr. Clauw stated that there was no standardization for chronic pain clinics. He stated that VA wasn't any worse at providing this type of care than private pain clinics. He stated that many pain clinics have become "opiate clinics," despite findings that opiates provide little or no benefit for central nervous system dysregulation. He stated that many of the good academic pain clinics had to close because they were losing money.

Chairman Binns asked if Dr. Clauw's patients represented a broad range of severity, e.g., from very incapacitated to those who function in a moderate way, and how this related to their improvement. Dr. Clauw stated that he could help the majority of FM patients that wanted to get better. He noted that he couldn't make them "well" or symptom-free. However, with a combination of drug and non-drug therapies, he stated that these patients could get better. Dr. Clauw indicated that changes in treatment

programs at VA could make it possible to improve veterans' health care and reduce the need for disability compensation. He noted problems faced by researchers in establishing CBT programs for the clinical trials, and the reasons behind the disparity in their operation/results. Dr. Haley asked how much these types of programs (CBT) would cost. Dr. Clauw indicated that they wouldn't be very expensive.

Dr. Steele noted that, at a previous Committee meeting, Dr. Charles Engel had presented data that patients in CBT programs didn't do much better, on average, than those who didn't receive therapy. Dr. Clauw stated that he believed CBT wasn't sufficient by itself, and that it must be combined with a symptom-based pharmacological approach to help people get over the initial hurdles. Dr. Golomb asked if there were combination CBT and drug trials that reflected this finding. Dr. Clauw stated that it was well-documented in depression studies, but not for pain. He noted that there wasn't a specialized funding authority for pain research, and that pharmaceutical companies weren't interested in funding combination trials.

Ms. Venus Val-Hammack, a Gulf War veteran and audience member, stated that there were no VA medical center clinics, at least in the Northeast United States, that would evaluate a veteran for these chronic multisymptom illnesses. Dr. Clauw stated that the veteran patient needed to find an empathetic physician who was willing to work and learn with him or her. He stated that every subspecialty was trying to avoid this group of patients due to the time expenditure required. His group had set up a program at the University of Michigan to educate physicians in this type of care.

Mr. Robinson asked if Dr. Clauw had submitted information on FM for inclusion in the Veteran's Health Initiative (VHI) series on Gulf War veterans. Dr. Clauw stated that he was a member of the panel that established the VA/Department of Defense (DoD) practice guidelines for medically unexplained symptoms. He stated that, unfortunately, most physicians weren't using them, partially due to lack of knowledge of their existence. He stated that the guidelines were good, but could be improved with background information about FM, explaining underlying processes and why a patient is treated in a particular manner. He stated that in his clinic they have a "Top 10" list of advice for FM patients. The list is brutally honest, and helps because it can be difficult at times for the physician to explain these issues to a patient directly.

Dr. Bell commented that there were emerging themes relating to treatments from the field of alternative medicine. She stated that randomized controlled trials were difficult because many of the patients were trying various, and sometimes bizarre, treatment combinations.

Dr. Steele commented that the large-scale exercise and behavioral therapy (EBT) clinical trial was conducted on Gulf War veterans without preliminary work to determine the best study design and application of treatment. Dr. Clauw stated that much was learned from this study, i.e., what to do and also what not to do. Dr. Steele noted that the same approach was applied with the large-scale VA antibiotic clinical trial study. Dr. Clauw indicated that there was a push by Congress to get this study done. He stated that the VA was in a position to take the next good step in combination treatment trial studies.

Dr. Steele asked if the researchers in this group, including Dr. Clauw, had learned how to improve upon the study's design, and how EBT might best be used to treat Gulf War veterans. Dr. Clauw stated that there were several problems with the EBT study, e.g., new CBT programs and practitioners and lack of a specialized GWI patient education program that explained the illnesses and how or why the treatment would work. Dr. Steele asked whether Dr. Clauw believed that even if CBT was performed well, pharmaceutical treatment was still needed. Dr. Clauw said that he believed that to be true.

Public Comment – Day 1

Chairman Binns opened the floor to public comment.

Ms. Alison Johnson spoke to the Committee. She commented that few within VA understood MCS. She stated that there was a need for environmentally controlled research units. However, she didn't think VA was in a position to do this type of study. She stated that the success of this type of study most likely depended on nongovernmental funding. She stated that before this funding could be secured, scientific support was needed. She suggested that the Committee make a recommendation with regards to the construction of such a unit for GWI study.

Ms. Denise Nichols spoke to the Committee. She stressed the need for research coordination and improved communication with veterans about ongoing VA clinical trials in which they might be eligible to participate. She commented that the veterans needed to see results from this effort, and the establishment of a Gulf War veteran brain bank would be helpful. She suggested that information concerning research funding and proposal submission deadlines be placed on the Committee's website. Dr. Steele indicated that this was already being planned, starting with the recently announced VA request for proposals (RFP) for Gulf War illness research.

Mr. Robinson asked Dr. O'Donnell, an audience member who works for DoD's Deployment Health Support Directorate, whether the Deploymentlink website (<http://www.deploymentlink.osd.mil/>) had a medsearch capability to list current DoD clinical trials. Dr. O'Donnell stated that it did not. He stated that it only provided information about past clinical trials.

Ms. Val-Hammack spoke to the Committee and Dr. O'Donnell about the need to update the VA/DoD clinical practice guidelines on VA and DoD's websites.

Chairman Binns thanked the meeting's participants for attending. He stated that this was an example of what these meetings could be at their best. He noted that much was learned and misunderstandings addressed quickly when individuals were brought together into one room.

The meeting adjourned for the day at 5:30 p.m.

The meeting reconvened Thursday, April 7, 2005, at 8:12 a.m. Ms. Marguerite Knox was not able to be present for this day's proceedings.

Depleted Uranium CAPSTONE Aerosols Study and Human Health Risk Assessment

LTC Mark A Melanson, PhD, CHP
Program Manager, Health Physics
U.S. Army Center for Health Promotion and Preventive Medicine

LTC Melanson gave introductory remarks and provided context for DoD's Depleted Uranium Capstone Aerosols Study and Human Health Risk Assessment project. ([See Appendix – Presentation 7.](#))

Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Aerosol Study and the Capstone Human Health Risk Assessment

Mary Ann Parkhurst, MS
Principal Investigator, Capstone Depleted Uranium Aerosol Study
Battelle/Pacific Northwest National Laboratory, Richland, Washington

Ms. Parkhurst presented an overview of the findings of the Depleted Uranium Capstone Aerosols Study and Human Health Risk Assessment project. ([See Appedix – Presentation 8.](#))

Dr. Haley asked why depleted uranium (DU) had fewer or less severe health side effects than generic alpha emitters. Ms. Parkhurst stated there were many human studies relating to uranium exposure, which found no increase in cancer rates. She stated that the report's Human Health Risk Assessment examined this evidence. She stated that they were unable to say there was no risk, but that no adverse outcomes had been observed yet.

Dr. Haley asked about the meaning of the term "Capstone." LTC Melanson stated that a capstone was a crowning closure on a building. He stated, from the DoD's perspective, this report was the deciding or crowning study for modeling DU aerosol concentration inside a vehicle hit by DU munitions.

Mr. Robinson asked whether any DU armored vehicle had been penetrated. LTC Melanson indicated that DU armor was located only in a couple classified locations on the vehicle, and these sections had not been breached. Dr. Steele asked whether any DU munitions had penetrated DU armor. LTC Melanson indicated that none had.

Mr. Robinson asked whether any of the 1700 DoD personnel tested for depleted uranium were Gulf War veterans. ([See Slide 11 of Presentation 7.](#)) LTC Melanson stated that these were individuals who served in Operation Iraqi Freedom (OIF). Mr. Robinson asked whether there was urine testing data for veterans who served in the first Gulf War. LTC Melanson stated that he did not have good data for these veterans. Mr. Robinson stated that the U.S. Government Accountability Office (GAO) investigated whether returning OIF veterans were being screened for depleted uranium upon request, and found poor compliance. He asked if compliance had been improved. He also asked whether the test being utilized was sensitive enough. LTC Melanson stated that, per DoD policy, personnel with Level 1 and 2 exposures were to be tested for depleted uranium. He acknowledged that there had been concerns about whether the 442nd Military Police (MP) Unit had received this testing. He stated that, per DoD policy, personnel with Level 3 exposures who requested testing were also to be tested.

Mr. Robinson stated that there had been problems with screening 442nd Unit personnel, and once tested, issues arose as to whether the test was sensitive enough. LTC Melanson stated that one of the methodological challenges of depleted uranium testing was background uranium levels. He stated that this then raised concerns about the level at which health effects occurred. He stated that the test used by DoD (inductively coupled plasma mass spectrometry) was sensitive enough to detect DU levels 100 times below those levels that cause concern. He reviewed the situation involving the 442nd MP Unit. He stated that those who had requested testing had been screened, but that there had been a delay with their test results. He stated that the soldiers then had contacted the NY Daily News, who provided alternative testing by the Uranium Medical Research Center (UMRC). He stated that the UMRC test results reported only that depleted uranium was present but did not report the actual quantity, which was fundamental in clinical laboratory analysis. He also expressed concern that the laboratory that performed the analyses was a geochemistry laboratory, and not an accredited clinical laboratory for testing of human specimens. He noted that the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) laboratory is accredited, as are the U.S. Armed Forces Institute of Pathology (AFIP) and CDC laboratories, which are also used for depleted uranium testing of returning OIF personnel. He stated that he also had no knowledge of the quality control data for the UMRC laboratory, and therefore it was difficult to comment on the accuracy of their results. He stated that duplicate testing was conducted in another accredited laboratory, which verified the USACHPPM results for the 442nd MP Unit personnel. He stated that the levels of depleted uranium found in the 442nd MP Unit personnel were comparable to the background levels of uranium found in the general population, and therefore didn't show an overexposure to depleted uranium.

Mr. Smithson asked what percentage of the 1700 DoD personnel screened had received Level 1 or Level 2 exposures. LTC Melanson replied that it was hard to stratify the results in this manner. He stated that the exposure information came from self-reported questionnaires, which the testing laboratories did not always have, and when they did, the soldier did not always identify their exposure level, e.g., being involved in a friendly fire incident. Mr. Smithson asked how many friendly fire incidents had occurred in the current conflict, and whether this was documented separately from the self-reported questionnaire data. LTC Melanson stated that there had been fewer friendly fire incidents in OIF during the initial major combat operations with Iraqi forces, but he did not know the exact number.

Mr. Robinson asked whether there was an automatic process for battlefield exposure (Level I, II, or III) to be reported upon evacuation from the region, and whether this generated an automatic screening for depleted uranium. LTC Melanson stated that when a soldier was wounded, this individual was flagged as having potential Level 1 exposure. He stated that they couldn't guarantee 100% that every individual was being tested, but that the current policy was helping to test the majority of those exposed. He noted that most of the 1700 individuals tested had Level 3 exposures.

Mr. Robinson asked: (1) why protective measures regarding depleted uranium weren't being taught to soldiers in basic training; and (2) what protective measures were taken by Capstone personnel during the model testing. LTC Melanson stated that, based upon the conclusions of the Capstone report, he did not believe additional precautions were necessary as the radiologic and chemical risks were not significant, especially in comparison with other combat risks. He stated that the U.S. Army Medical Department still needed to make this determination. He did note that training should include advice about making sure the tank ventilation system was operating. In terms of additional protective recommendations, he indicated that there was the need to balance the risk of protection versus the risk of operational degradation. He stated, based upon the findings of the Capstone report, the risks were low.

With respect to the protective measures taken by Capstone personnel, he stated that these experiments were in a controlled peacetime environment versus the uncertain, active battlefield, and that OSHA

regulations were applicable in this situation. Mr. Robinson asked if there was a middle ground approach to training. LTC Melanson noted that there was basic instruction, e.g., don't pick up penetrators. Mr. Robinson asked if the technical manual, which covered safety standards for extraction of individuals from vehicles struck by DU, was no longer applicable based upon the Capstone findings. LTC Melanson stated that the technical manual was written without this information and should be reviewed.

Dr. Meggs asked the Committee and LTC Melanson if they thought DU played a role in the chronic multisymptomatic diseases evidenced in 150,000 Gulf War veterans, and whether the Committee should continue pursuing this as a causal factor for these illnesses. Dr. Steele stated that the rest of the morning's speakers would address possible biological mechanisms relating to DU exposure to GWI.

Dr. Haley asked what was known from the Capstone report about DU resuspension and the long-term civilian exposure to DU. LTC Melanson stated that this report did not address this question, but there was a simple qualitative experiment that would demonstrate the relative risk of the initial aerosol produced versus resuspension. He stated that the highest concentration of localized DU fall-out occurred at the time of penetration and that the DU settles close to the vehicle. He went on to discuss his work in the Balkans with the UN to study the environmental effects of DU. He stated that the conclusion of all three Balkan missions was that the primary pathway of concern for the local population was via groundwater. He noted that many rounds fired in the Balkans were lodged beneath the ground. He stated further research was needed in this area to consider possible effects 10, 100, etc., years from now, taking into consideration the prewar levels of uranium found within the soil.

Dr. Haley asked if the DU amounts deposited in the Balkans would significantly increase the exposures. LTC Melanson stated that modeling was being conducted at three test ranges in Maryland, Arizona, and Indiana. Results at these sites had found little widespread migration and uptake of uranium into the soil. The challenge was comparing the geology of these test ranges with Bosnia, Kosovo and Iraq. He stated that the National Atomic Energy Agency was conducting sampling in areas of Kuwait where DU was fired, and water sampling was being conducted near attack locations in the Balkans. Tests had found only one case of detectable levels of DU in the groundwater, and it was below the World Health Organization's limits for uranium in drinking water. He stated that, quantitatively, he didn't think DU was a big problem, but that there were questions remaining as to how best to conduct environmental monitoring.

Chairman Binns thanked LTC Melanson and Ms. Parkhurst.

The meeting adjourned for a break at 9:53 a.m.

The meeting reconvened at 10:10 a.m.

Research on Health Effects of DU in Relation to Gulf War Veterans' Illnesses

Lea Steele, PhD

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

Dr. Steele presented an overview of research findings and remaining unanswered questions pertaining to DU's relationship to Gulf War veterans' multisymptom illnesses. ([See Appendix – Presentation 9.](#))

Dr. Steele noted that the Capstone Report provided exposure measures, which had been lacking, for individuals inside tanks hit by DU munitions.

Behavioral Changes and Brain Lipid Oxidation Following Uranium Exposure

Wayne Briner, PhD

Professor, University of Nebraska at Kearney

Dr. Briner presented his research findings pertaining to DU's behavioral effects on adult and developing mice, along with his findings pertaining to brain lipid oxidation levels in adult rats following exposure to uranium. ([See Appendix – Presentation 10.](#))

Dr. Meggs asked why Dr. Briner had used uranium acetate, and how it compared to the DU used in the battlefield. Dr. Briner stated that DU oxide was used primarily for tank shells. He stated that they used uranium acetate because it is easily available and soluble in water.

Dr. Golomb asked if other studies had shown that DU could cross the blood-brain barrier. Dr. Briner indicated that there were other studies supporting this.

Chairman Binns asked whether the amount of uranium to which the mice were exposed was relatively large or small. Dr. Briner stated that, in order to do comparisons, aerosol modeling was needed to determine human exposure over a period of time.

Dr. Haley asked if these findings resembled those for lead and other heavy metals. Dr. Briner stated other heavy metals were oxidizers, e.g., aluminum, iron, copper, zinc, etc. He stated that he was the first to look at lipid oxidation in this manner.

Chairman Binns thanked Dr. Briner.

Neurological Effects of Acute Uranium Exposure

David Barber, PhD

Assistant Professor, University of Florida

Dr. Steele introduced Dr. Barber.

Dr. Barber presented his group's findings regarding the neurological effects of acute uranium exposure. ([See Appendix – Presentation 11.](#)) He stated that they believed that uranyl acetate was representative of the same transport mechanisms as other uranium exposures, because once dissolved in the blood, it was in the form of a uranyl ion, usually uranyl carbonate.

Mr. Graves asked what was known about the long-term effects of uranium in the human body. He noted that Dr. Briner had indicated the pulmonary half-life of uranium was four years. He asked what was known about neurological damage, and whether this damage was permanent or if there was a natural recovery as time passed. Dr. Barber stated that it depended on the plasma concentration and the amount that had gotten into the brain. He stated that large quantities of uranium wouldn't cross over into the brain unless there was a spike in plasma levels. He stated that at some point, a steady state would be achieved, i.e., the amount of uranium going in and out of the brain was balanced. He stated that this steady state level of uranium depended on the level of exposure and where it binds. He wasn't sure if their current studies would directly address this question, because questions about long-term effects couldn't be answered in thirty days after a single exposure. He stated that they were doing a six-month study, but it involved continuous exposure. He stated, though, that studies could be done to address Mr. Graves' question.

Mr. Graves asked if Dr. Barber planned on looking at the myelin sheath and whether uranium was present in this region. Dr. Barber stated that they could look at the ultrastructure of the myelin sheath to see if there was disruption. He noted that, as uranium is very dense, it might be possible to see if uranium was deposited in the sheath. Mr. Graves asked whether the damage would be permanent if the uranium made its way into the myelin sheath. Dr. Barber stated that it was clear that their administration of uranium caused an adverse neurological effect, but it wasn't clear how long this effect would last or why it happens. He stated that it didn't appear to be structural, at least at the gross level. He stated that closer study was needed and possible, but would be difficult with low-level functional insults.

Dr. Steele asked Dr. Barber to draw parallels between his findings and what was known about other metals. Dr. Barber stated that uranium was very similar in its distribution to other divalent metals, e.g., lead, manganese, calcium, etc. He stated divalent metals tend to go to the same locations in the body, through similar carrier mechanisms. He stated that there were probably specific uptake mechanisms that are similar, e.g., uranium binds to transferrin to cross the blood-brain barrier.

Dr. Golomb stated that there was one study which found that aluminum lead to leakiness of the blood-brain barrier. She stated that, even though they hadn't seen stress-enhanced entry of DU, it would be interesting to know if DU enhanced the potential entry of other substances. She noted that this possibility had been studied for other substances using virulent/non-virulent viruses. Dr. Barber stated this was an interesting idea and the study was possible, but noted that, with uranium, it would be hard to tease out the confounding effects of uremia.

Mr. Robinson asked if Dr. Barber found the different exposure classifications (Level I-III) helpful in doing his research. Dr. Barber stated that the single-exposure, 30-day, experiment could be considered a lower limit, while the six-month continual exposure experiment would be an upper limit. He stated that, at the end of their current study, they hoped to have data on plasma and kidney concentrations, and how these concentrations relate to brain concentrations and effects. He hoped that these data could then be used to develop a model that helps assess risk for various levels of exposure.

Chairman Binns thanked Dr. Barber, and opened the floor to discussion about the previous two presentations.

Mr. Graves commented that there was a population of soldiers who were exposed to a cocktail of toxins while driving through areas littered with burning vehicles, which had been shot with DU munitions, in Iraq. Dr. Barber stated that combinations/mixtures were a challenge for toxicologists and that it was difficult to test beyond a binary mixture. He stated it was virtually impossible to test this specific combination, but tests could be done to determine if it was a possibility that the combination could cause problems.

Mr. Robinson noted that blood was drawn before soldiers deployed in the first Gulf War, which hadn't been screened yet. He also noted the Committee's discussion about establishing a Gulf War veteran brain tissue bank. He asked if these brain tissues and blood samples would help in Dr. Barber's study, despite being fourteen years after the exposure. Dr. Barber stated that the analyses could be done to determine if uranium levels were still elevated. If they were, they could try to correlate the results to the type of brain levels seen in his group's research studies. However, without knowledge of the soldier's specific exposures, he stated it would be difficult to interpret negative results.

Dr. Steele asked if there were scenarios with other metals, in which the substance had been present but dissipated, leaving permanent damage. Dr. Barber cited methyl mercury, in which neuronal loss and

gliosis led to permanent damage/deficit. He stated that they hadn't seen this yet with a single dose of uranium, but acknowledged the possibility of this paradigm.

Dr. Golomb noted that, in light of the information about lipid oxidation and possible oxidative injury, there could be a neurodegenerative process occurring. Dr. Barber agreed, and hoped that in their six-month study, they could address this issue directly. He stated that they had looked at glutathione levels, and didn't see any differences in totals or in ratios of oxidized to reduced, an indirect marker of lipid peroxidation. Dr. Barber stated that the uranium might be in a depot that is exchanged very slowly, but it is unclear what it is bound to. He stated that they planned to do uranium affinity studies to determine this.

Dr. Steele noted that solubility played a major role in DU's effect on renal toxicity and how uranium is transported to target organs. She asked if one of the speakers could elaborate on how the different uranium forms become soluble in the blood. Mr. David Alberth, a senior health physicist with USACHPPM, stated that modeling of uranium solubility in the lung was done in the Capstone study, and that Lovelace Respiratory Institute had conducted simulated lung fluid studies for DoD. Going back to basic toxicology, the amount that enters the blood stream is most important. If the substance is highly insoluble, it would take longer to get into the blood stream than less soluble substances. Highly insoluble substances that were ingested were pretty much gone from the system within 24-72 hours. He indicated that the National Council on Radiation Protection Measurements was working on a wound/injection model for the introduction of uranium into the body, and a report on this was undergoing peer review.

Dr. Steele asked if the uranium inhaled in the tank scenarios was moderately soluble. Ms. Parkhurst provided a brief overview of dose calculations and solubility. She stated that, under the ICRP-66 model, the uranium was considered a Type M, i.e., very soluble at first with a slow decline. However, using the ICRP-30 model, the uranium was considered a Class Y, i.e., taking years to dissolve.

Mr. Robinson asked about the maximum/minimum particulate size that is respirable and could be retained in the lung. Ms. Parkhurst said that particles less than 5 microns were able to reach the alveoli. She stated that 10 microns had been the conventionally accepted number, but that this was larger than most particles that would get into the lung. Mr. Alberth stated that the Capstone researchers had looked at particles that were less than 1 micron, 1-5 microns, 5-10 microns, and 10-100 microns. He said that they were concerned about the respiratory aspects, and how this affected the physiological model of where different particle sizes reached. Ms. Parkhurst stated they had found that the smallest particles were the least soluble, where typically they were expected to be the most soluble, and that it seemed to depend on what oxide formulation it was.

Ms. Denise Nichols asked if the Capstone researchers had examined eye and oral cavity exposure to depleted uranium and resulting effects. Mr. Alberth stated that there were tear duct models. Dr. Haley noted that there were two different issues: (1) the amount of uptake into the blood system through the eye; and (2) the effects of uptake on the eye and oral cavity. Mr. Alberth stated that the ICRP model had distinguished target organs, predominantly the kidney and bone. He said that there was a lesser dose contribution in other areas. Dr. Steele asked if there were any direct effects or long-term effects on the eyes and oral cavity. Mr. Alberth stated that he would have to defer to a radiobiologist to look at the sensitivity of the cells. LTC Melanson stated that, from a radiation perspective, there were a lot of good data on radiation-induced cataracts. He stated that he wasn't aware of any research looking at the ophthalmologic effects of DU.

Dr. Haley asked if there was any research on the ophthalmologic effects of other heavy metals, e.g., lead. Dr. Briner noted that one had to reach the level for lead encephalopathy before seeing changes in the auditory pathway of the central nervous system. He questioned whether DU would remain in contact

with the eye long enough to have a direct effect, because, for example, it could be washed away by tears. He stated that he would be more concerned about systemic effects.

Chairman Binns thanked the morning speakers.

The meeting adjourned for lunch at 12:05 p.m.

The meeting reconvened at 1:10 p.m.

Gulf War Illnesses and Vaccines: Overview of Epidemiological Findings and Remaining Issues

Lea Steele, PhD

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

Dr. Steele presented an overview of the epidemiological findings and previous Committee discussions pertaining to GWI and vaccines, along with remaining issues for the Committee to review in this area. ([See Appendix – Presentation 12.](#)) While discussing the remaining issues pertaining to squalene antibodies and ill Gulf War veterans, Dr. Steele noted that Drs. Asa and Garry had been invited to present their findings at this meeting. She stated that, unfortunately, they were not able to attend.

Dr. Melling commented that one of the epidemiological difficulties was that the incidence of GWI was pretty much the same among U.S. and U.K. troops, while there were differences among the vaccines these troops received. He noted that some U.S. troops received the anthrax vaccine, while virtually all U.K. troops received the anthrax vaccine. He noted, however, that the British vaccine was different than the vaccine administered to the U.S. troops. He stated that the only commonality, that he could see, was that both vaccines contained protective antigen (PA). He stated that studies were about to begin with purified PA vaccines that would help to address this concern. He noted discussion had occurred about studies that will compare Anthrax Vaccine Adsorbed (AVA) and PA vaccines, and this should be kept in mind. With respect to squalene, he stated that he knew and would swear, as he was responsible for making the U.K. anthrax vaccine, that no squalene was deliberately put into the U.K. vaccine. He acknowledged that this did not rule out the possibility of some squalene contaminant.

Ms. Dykeman stated that it should be considered that, once they were deployed to theater, supplies of vaccine were being received from different, sometimes foreign, suppliers.

20 Studies to Evaluate Adverse Events After Anthrax Immunization

COL John D. Grabenstein, RPh, PhD

Deputy Director, Military Vaccine Agency, U.S. Army Surgeon General's Office

Scientific Director, Biodefense Vaccination Program, Department of Defense

COL Grabenstein gave an overview of research on adverse reactions to anthrax immunization. ([See Appendix – Presentation 13.](#))

Dr. Melling referenced the PA content in the AVA vaccine debate. He stated that he had not seen published data on it, and asked COL Grabenstein if he might have any information to shed light on this issue. COL Grabenstein stated that in January, 2002, the U.S. Food and Drug Administration (FDA) approved renovations to the vaccine production facility at Lansing, MI. During the process validation, tighter limits on variability between each lot were set, resulting in tighter control. Dr. Steele stated that the GAO report indicated that the change in filters occurred in 1990. COL Grabenstein stated that this

was a separate issue. Dr. Steele asked if there were data as to whether the filter change had caused a change in the mean PA levels. COL Grabenstein stated that he didn't know if these data were kept with the early lots. He stated that the potency test/biological survival index for the vaccine had stayed consistent from 1991-1998.

Dr. Golomb stated that a higher dose of PA wouldn't necessarily be expected to inhibit the potency. She indicated that the GAO report had suggested that there was a 5-100x increase in PA in the vaccine following the 1990 filter change. While lethal factor and edema factor weren't tested for in the U.S. vaccine, these factors were believed to be present in the vaccine in unknown amounts. She stated that there was no way to know whether these were comparably affected, and that there was a presumption that the previous ceramic-based filters caught a lot of anthrax toxin proteins. COL Grabenstein stated that his group was not convinced that the PA assay, which showed an astronomical elevation, was a valid assay. Dr. Melling clarified that GAO had not conducted analytical studies on this matter. He stated that this report quoted unpublished studies conducted by the Army at Fort Detrick.

Dr. Haley stated that the adverse events studied with respect to the anthrax program were not necessarily the outcomes of concern before the Committee. He stated that the Committee was concerned with subtle changes in cognitive function, sensory problems, and other symptoms compatible with GWI. He stated that the outcomes reported were generally self-reported neurological disease, self-reported cardiac disease, hospitalization, etc., which don't correlate with GWI. He stated that he wasn't aware of the CDC clinical trial, and was interested in what outcomes would be measured. COL Grabenstein stated that the SF-36 was one of the instruments being used in the CDC trial. Dr. Haley stated that this was good, and may help resolve unanswered questions. COL Grabenstein also said that there would be comparative immunogenicity studies/antibody studies of the AVA and PA anthrax vaccines.

Dr. Golomb stated that 1/5 of all drugs released to the open market by the FDA are ultimately withdrawn or have major blackbox warnings. Half of reported adverse incidents occur more than 7 years after release to the open market, and adverse effects that lead to these withdrawals normally weren't identified in randomized clinical trials. She said that healthier subjects were typically enrolled in the anthrax vaccine studies, but that one published report had suggested that individuals on medications or having comorbidities have greatly elevated rates of acute adverse effects. She stated that the researchers should actively recruit a population that might be adversely affected to show a complete picture of the vaccine's effect. COL Grabenstein agreed.

Dr. Steele noted that the Sulsky study had found that between individuals who received anthrax vaccine and those who had not, fewer people were seen for disability evaluations among those who received the vaccine. But, when results were stratified by the number of vaccines received, the people who received 1 or 2 doses of vaccine had a significantly higher rate of disability evaluations than those who did not receive AVA. She asked COL Grabenstein for his thoughts on this finding. COL Grabenstein stated that vaccination follows along with selection for overseas travel. He suggested that there was a greater scrutiny of health in individuals deployed overseas. He also noted that there were incubating diseases that weren't clinically apparent at the start of the vaccination series. He stated that the dropout rate between doses of the randomized clinical trial was 1%, and none were attributed to the vaccine, rather, they were attributed to social factors. Dr. Steele asked about the idea that individuals with 1 or 2 anthrax shots may have sought disability evaluations at a higher rate because they had adverse reactions to the vaccine, and so had stopped receiving the doses early in the vaccination program. COL Grabenstein stated that these must not be hospitalization diagnoses, and that he wasn't persuaded.

Mr. Smithson referred to COL Grabenstein's comment that the systemic effects of the anthrax vaccine were similar to other vaccines with adverse reactions affecting 5-35 percent of recipients. ([See Slide 8.](#))

He asked if COL Grabenstein had data to indicate whether these symptoms were considered chronic or not. COL Grabenstein stated that, in this particular case, he was referring to acute effects. From other studies, e.g. Hoptof, these were mostly (99%) short-lived events for the affected individuals. Mr. Smithson asked what education or encouragement to report adverse reactions was being provided to troops at the time of vaccination, in order to avoid the under-reporting errors associated with a passive reporting system. COL Grabenstein replied that there were special tri-fold brochures for anthrax and smallpox vaccines with phone number and website information. He stated that they were trying to get the CDC to do a survey of civilian versus military physicians to determine the level of awareness in these sectors. He was confident that the military physicians would fare well in this survey.

Mr. Robinson asked if any of the studies separated out severe neurological problems. COL Grabenstein stated that the data weren't collected in a format that would support such analysis. He stated that the unusual cases were compiled through the Vaccine Adverse Event Reporting System (VAERS). Mr. Robinson asked if the 1% with serious problems fell under the category of "acute" or whether they were disbursed amongst "fever", "sore arm", and "rash." COL Grabenstein stated that any vaccine could cause side effects. He stated that these reactions could be submitted to VAERS, but that they didn't track down "sore arm" and "redness" reports. He stated that this table was a summary of survey data, and didn't tell the whole story.

Mr. Robinson noted that the Committee was interested in the vaccine used on the first Gulf War veterans. He noted that the Institute of Medicine (IOM) was referring to the post-Gulf War (1998-present) vaccine when it held the vaccine to be safe and effective. COL Grabenstein agreed, and acknowledged the lack of records for the first Gulf War. He stated this makes it difficult to determine correlations between outcomes and exposures. He stated that an interesting issue would be determining the difference(s) between 1991 and 2001-2005 scenarios.

Mr. Robinson asked whether VAERS was still active following the IOM and FDA findings that the anthrax vaccine was safe and effective. COL Grabenstein stated that the VAERS remained in full operation.

Dr. Golomb and COL Grabenstein discussed the statistical findings regarding disability and the anthrax vaccine.

The meeting adjourned for a break at 2:41 p.m.

The meeting reconvened at 2:58 p.m.

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

COL Phillip R. Pittman, MD, MPH
Chief, Division of Medicine, USAMRIID

COL Pittman gave an overview of research conducted regarding the health effects of multiple vaccines. ([See Appendix – Presentation 14.](#))

Dr. Melling noted that the Fort Detrick alumni group in the squalene study (Part III) had received their shots over a long period of time. ([See Slide 31.](#)) This was different from the high concentration of immunizations given before the first Gulf War. He stated that this study addressed multiple vaccinations, but not multiple vaccinations within a very short period of time. This study was not conducted with GWI in mind, but cast a broad net to analyze a wide range of people. He stated that they could sort the data based upon immunization time intervals.

Dr. Golomb asked if the older alumni in this study, who received the anthrax vaccine before the production changes in 1990, might be distinguished more from those who received the more recent vaccine. She noted that there might have been differences in amount of antigen present in the vaccine, and manufacturing problems might have been more prevalent after the 1990 time period. COL Pittman noted that these differences had been reported. Dr. Golomb commented that the alumni, being a social group, might reflect a healthier subset of individuals who were able to travel and participate in these events. She stated that those with more significant problems might not have been part of this screening pool. She also noted that these were individuals who received an extremely large number of vaccines. She stated that the individuals who might have been vulnerable to problems received fewer immunizations. COL Pittman agreed that many individuals who had reactions found other jobs that didn't require further immunizations.

Dr. Golomb noted that the study had started with 100 more controls than cases, and was curious if this increased the statistical power of the findings and the reason behind doing this, e.g., to match age closer. Mr. Paul Gibbs, statistician on this project, stated that the analysis was stratified to balance these concerns and make the groups more comparable.

Dr. Nass noted that a large proportion of individuals who weren't treated for tularemia would develop chronic symptoms. She asked if antibiotic treatment timing had been considered for the findings relating to these individuals. COL Pittman stated that every individual who contracted tularemia was treated. Dr. Nass stated that she had a Fort Detrick publication that reported that these individuals had the disease for at least a month before receiving treatment. COL Pittman stated that she must have misread the report. Dr. Nass asked whether treatment timelines for those with Q fever had been considered. Dr. Haley stated that he was aware of the studies to which Dr. Nass' was referring, as his group had submitted a proposal a few years ago to replicate them using more modern immunological techniques. He stated that the individuals were treated once symptoms presented.

Dr. Nass noted that COL Pittman had stated that the Fort Detrick alumni squalene study hadn't been conducted with GWI in mind. She noted that the Whitecoat study volunteers, however, had been given a questionnaire that asked about several symptoms relating to GWI. COL Pittman stated the Whitecoat study had been conducted twenty years before the Gulf War, and there was no relationship between the studies. He stated that that there were several symptoms investigated, but they were not limited to GWI type symptoms.

Dr. Haley noted that earlier studies, e.g., Peeler, were flawed with the potential for the healthy worker effect. He stated that these studies were so flawed and uninterpretable that they detract from the

argument, unless heavy caveats are provided. He noted that more definitive evidence and better analyses, hopefully, would be coming from future studies, e.g. the CDC clinical trial. Dr. Golomb noted that, despite the caveats, the last study by COL Pittman's group was well done.

Mr. Robinson asked if the DoD vaccination records for the current conflict were better than for the first Gulf War, providing information about the exact date and schedule at which immunizations were given. He asked if COL Pittman would be examining multiple vaccinations given in a short period of time. He stated that some military personnel refer to these as "gang vaccinations." COL Pittman stated that the data hadn't been previously analyzed this way, but they would consider doing it.

Vaccinations and Illness in Persian Gulf War Veterans

Beatrice A. Golomb, MD, PhD

Assistant Professor, University of California at San Diego

Dr. Golomb discussed various issues involving vaccines, with an emphasis on the anthrax vaccine, including their efficacy, safety, manufacturing, chronic effects, administration of multiple vaccines, adjuvants and cytokines in relation to immune modulation, and the controversies surrounding all of these issues.

Upon conclusion of her talk, Dr. Melling commented that, in his opinion, the issue wasn't that the vaccine was ineffective. Because Phase 3 studies cannot be done, he stated that a number couldn't be placed on its efficacy. He stated this was a problem. Dr. Golomb agreed that this was a fair statement.

Dr. Meggs asked about the symptoms evidenced in the various animal models and whether they were representative of human symptoms. Dr. Golomb stated that while there may be similarities between the disease manifestations of various species, the real issue was whether there were similar reactions to vaccine. She indicated that there was evidence that suggested that human responses do differ from those of test animals. She noted that a single inoculation was enough for most animals, but that was not the case for humans. Dr. Nass stated that rhesus monkeys, which weigh 10 pounds, were given a human dose of anthrax vaccine. Dr. Golomb noted that many of the studies with rhesus monkeys had no control animals, so it is unknown whether the rate of survival is higher in vaccinated animals. She did reference one published controlled vaccine study. She stated that they found nine out of ten anthrax-vaccinated monkeys survived, but that nine out of ten control monkeys survived, too. COL Grabenstein noted that this involved post-exposure prophylaxis versus pre-exposure protection, and that the controls were not part of the 65 vaccinated monkeys. Dr. Golomb stated that her point was related to study design, and that unless there was a control group for the study, it was not clear what inferences to draw. She stated that she wasn't saying that the anthrax vaccine didn't confer protection, but that the quality of the published evidence was weak. Dr. Nass stated that there was an unpublished study in which vaccinated monkeys became sick after exposure to anthrax, but eventually survived.

Mr. Robinson asked when the RAND report on vaccines, which Dr. Golomb had authored, would be released. Dr. Golomb stated that she didn't have an exact date, but believed it would be soon. She stated that there had been scheduling issues for both RAND and her. She stated, however, that she didn't believe there was malintent by either party in the delay of the report's release.

Dr. Haley asked what Dr. Golomb would recommend be done next with respect to anthrax research. He stated that the troops needed to be protected from an anthrax attack, and hoped that the right studies had been performed to do this. Dr. Golomb stated that a large-scale, randomized trial, which used health outcomes relevant to Gulf War veterans, was needed. She noted that care was needed to not exclude the

subgroups that potentially would be the most susceptible to the vaccine's effects. She also noted that even if the current anthrax vaccine was found to be safe, this wouldn't necessarily have implications for the relationship of anthrax vaccine and health problems in Gulf War veterans. However, if there are problems, such as with production methods, she stated it would be reasonable to infer a relationship between anthrax vaccine and illness in Gulf War veterans.

General discussion occurred about the recent litigation involving DoD's anthrax vaccination program.

Chairman Binns asked Dr. Golomb if there was anything more or different that should be done, in light of the CDC's clinical anthrax trial. COL Grabenstein stated that the CDC's study was a placebo control, randomized, multi-center, double-blind trial. He said that they were looking at a stable population, with no healthy warrior effect, over a long period of time (25 years/person). He stated that there were approximately 1600 participants, with 1/6 receiving a placebo and the other 5/6 receiving various dosing regimens. Mr. Robinson asked if there were any concurrent studies at Walter Reed in which military subjects were vaccinated and then had blood drawn immediately afterward. COL Grabenstein replied that Walter Reed was one of the five sites that enrolled civilians, but not military personnel. He stated that Walter Reed hospital may draw blood for clinical use in military patients who received the anthrax vaccine, but there were no studies to draw blood for banking.

Chairman Binns thanked Dr. Golomb, and opened the floor to discussion.

Dr. Steele asked COL Grabenstein if there had been any discussion about or actual studies of squalene antibodies in ill Gulf War veterans. COL Grabenstein stated that he thought Dr. Alving was planning on analyzing blood samples of Gulf War veterans, but he didn't know any specifics about the study.

Mr. Robinson asked COL Grabenstein if he had oversight of or worked for the vaccine injury clinic. COL Grabenstein stated that there was a Vaccine Health Care Center with four sites. He stated that he did not have oversight of the Vaccine Health Care Center. He stated that he was at the Army Surgeon General's office. Mr. Robinson asked if the Committee could get information from the Vaccine Health Care Center with respect to: (1) the numbers of personnel seen, (2) what illnesses were being claimed, (3) disability outcomes, and (4) the number of those compensated for vaccine-related injury. COL Grabenstein stated there were patient records, and if provided with a list of questions, he believed the Vaccine Health Care Center would try to provide answers.

Dr. Steele noted that epidemiological studies of Gulf War veterans consistently showed some relationship between increased illnesses and vaccines. She also noted that the long term follow-up studies of anthrax and multiple vaccines presented today hadn't evidenced a similar problem. She asked the group for their thoughts on how to reconcile these findings. Dr. Melling stated that, at the time of the first Gulf War, the troops were subject to many "insults." He asked how epidemiologists had been able to tease out what vaccine was the problem. Dr. Steele stated that she did not know of any epidemiological studies that had looked at interactions between other types of exposures and vaccines. However, researchers had controlled for multiple exposures and found risk factors that weren't related to vaccines and risk factors related to vaccines.

Dr. Haley stated that his review of the epidemiological studies had revealed two types of studies, i.e., those that looked at organophosphates and those that didn't. He stated that those that focused on organophosphates didn't show any immunization effects, while those that didn't showed immunization effects. The ultimate study would measure all of the risk factors, and then control for the strongest risk factors. He stated that, in his view, immunization as a risk factor would not stand up. He believed there were confounding effects with other risks, e.g., going into combat, likelihood of taking pyridostigmine

bromide, being exposed to pesticides, etc. Dr. Steele stated that there had been subgroup analyses in some of these studies. In groups stationed in areas with multiple exposures, the odds ratios of people getting vaccines wouldn't show up as important because the people getting sick have other exposures that may look more important. Dr. Haley stated that this might be an issue that needed to be teased out through the Committee's literature review. Dr. Steele stated that the Committee staff would be presenting this type of summary review at a future meeting, but that there weren't published studies that examined the issue in this way.

Dr. Golomb stated that there would be measurement error in each variable, and that measurement error would be associated with outcomes. Dr. Melling stated that the overlap between those who received vaccines and those who took pyridostigmine bromide must be huge. Dr. Golomb stated that she didn't believe that anthrax vaccine was the "smoking gun" with respect to Gulf War illness, but this did not mean that it couldn't be contributing to the risk and effects in ill veterans. She noted that the Unwin study did include organophosphate and vaccine variables, and found effects for both. However, the strongest risk ratios were with the organophosphate exposures. There were more people exposed to pyridostigmine bromide, which had a stronger risk ratio. Thus, the attributed risk was likely to be greater for the organophosphate exposure, meaning more individuals' illness is likely to be attributable to this exposure. Dr. Haley stated that this is where the Committee needed to go in the next report, looking at these issues very carefully.

Dr. Meggs asked, given the number of Gulf War veterans who have become ill, if the anthrax vaccine or multiple vaccines were the sole cause, wouldn't more veterans have problems. Dr. Nass stated it might depend on doses.

Ms. Dyckman stated that the problem is that DoD was the one doing the studies, and nobody trusted its findings. She noted that when a soldier enters the military, he or she is forced to be vaccinated. She stated that, if an individual has a problem at the Naval Academy with a vaccine, they weren't commissioned and so are not seen in the data pool. She said there needed to be another study from a credible source. She wasn't opposed to vaccines, but wanted information about potential adverse effects. She stated that these studies were very political, and was hesitant about trusting CDC involvement in this research too.

Chairman Binns asked whether there was any reason to think there were causal factor differences, with respect to GWI, between U.S. troops and U.K. troops. Dr. Haley stated that some brainstorming was needed with regard to Dr. Hoptof's data on pre- and post-deployment vaccination. He stated that it should be examined in more detail. Discussion occurred about the findings of both Dr. Cherry's and Dr. Hoptof's studies.

Dr. Melling noted that it was important to look at the differences in the vaccinations received by the U.S. and U.K. troops. He stated that virtually all U.K. forces received one or two anthrax vaccines, while no more than 1/3 of the U.S. troops did. He stated many U.K. forces received plague vaccine, but didn't believe that U.S. troops had received this vaccine. He noted that the situation was reverse for the botulinum vaccine. He stated that, considering this, the vaccine link looked weak. He noted that both U.S. and U.K. troops were taking pyridostigmine bromide, spraying tents with organophosphate pesticides, and present when chemical alarms were sounding. Dr. Steele noted that there were ill individuals who hadn't been exposed to these other factors. Ms. Dyckman stated that the U.S. and U.K. medical forces worked together and exchanged patients. She stated that some vaccines were "brought in", while others were bought on the open market.

Dr. Golomb commented that she thought the strongest causal evidence for the most ill veterans related to chemical exposures and cholinesterase inhibitors. She stated that this was not necessarily exclusive though, and individuals may be ill for different reasons. She stated that it was important, with the current anthrax vaccine, to determine the long-term safety profile of the vaccine.

Chairman Binns asked for the veterans' thoughts on the issue of vaccines. Mr. Robinson said that the issue wouldn't be on the table if there hadn't been stonewalling in admitting that there was a problem. He stated that it was also an issue for those individuals who were injured and had been left without recognition or compensation. If veterans had been advised of the adverse effects, and were taken care of when these effects occurred, there wouldn't be a need for this discussion. He stated that veterans recognize that there are many emerging threats, and that there is a need for the best protection available. He said that he didn't work with individuals who were anti-vaccine, but that they were anti-bad-vaccine. It hurts the discussion when even the most small and minute effects won't be acknowledged. Even after the IOM report, new generation vaccine research would proceed. He stated that this might solve the problem, but it didn't answer the questions about 1990-1991 Gulf War veterans. It was important that the problems from the first Gulf War not be repeated with a new generation of soldiers.

Mr. Robinson stated that the U.S. Department of Health and Human Services (HHS) had asked for authorization to start using the vaccine due to an unknown, unspecified threat. It was not just a protection issue, but was also a political issue, and that there was a move to subvert the federal court action. He asked for open honesty from the government. He asked COL Grabenstein if he knew what the potential threat was that prompted the HHS actions. He asked what had changed, in terms of threat, from the time DoD was able to give the anthrax vaccine mandatorily and now. COL Grabenstein stated that the threat relates to the fact that anthrax is deadly and it doesn't require an elaborate delivery system. He stated that it was an emergency because there were adversaries out there who could use weapons against us. He indicated that there was no need for an FDA emergency use authorization to enable this vaccination program until the federal court's ruling. Therefore, there were troops vulnerable to enemy weapons now. Mr. Robinson asked if the emergency use authorization was going to be localized to a region and threat-specific area, or offered to the entire armed forces. COL Grabenstein stated that it would focus principally on Central Command and Korea.

Mr. Smithson stated that there was a major distrust factor when it came to the anthrax vaccine. He stated that this was a reality that must be addressed. He stated that there were, among the Gulf War community, different camps that were convinced that one particular exposure caused their problems. He stated that the research needed to explore all areas, but needed to focus on multiple exposures. He stated that he didn't believe one particular thing caused the reported problems. He stated that good research was needed, but always keeping in mind people's perception of this research.

Public Comment – Day 2

Chairman Binns opened the floor to public comment.

Ms. Val-Hammack spoke to the Committee. She stated that communication and information were stumbling blocks. She said that the Persian Gulf War Registry, the Gulf War Health Review, and physician continuing education about Gulf War concerns had disappeared. She had visited VA medical centers that have no information for Gulf War veterans in their lobby, and has approached patient advocates in VA facilities who didn't know about Persian Gulf surveys. She stated that the veterans were not being advised of the changes and whom to contact for help. She expressed her shock at the low numbers of veterans being seen at the War-Related Illness and Injury Study Centers (WRIISCs). She

stated that the veterans were not sure that the Committee had access to reasonable evidence, specifically the survey data and clinical practice guidelines follow-up. She said that the Gulf War Veterans Information System (GWVIS) report provided only an executive summary, not a breakdown of the data. She suggested that the Committee's charter should be modified so that it could review treatment protocols. Veterans see VA's Office of Research and Development (ORD) as a stumbling block for the Committee, and it didn't appear that ORD had responded to the Committee's 2004 report findings and recommendations. She stated that the announced additional research funds appeared to be an illusion. Chairman Binns stated that this issue would be addressed the following morning.

Ms. Dykman spoke to the Committee. She stated that health data were collected at the fleet hospital to which she was assigned. She stated professionals staffed this pre-positioned hospital, some of whom planned to conduct studies from this data. She stated that inquiries needed to be made to find out what happened to these records.

Dr. Nass thanked Drs. Golomb and Steele for their superb compilation of information regarding the issues pertaining to vaccines. She stated that she had six points that she wanted to make:

- (1) The Cochrane Review had changed. Tom Jefferson, who was the main author on the first study, had stated there was no evidence for the anthrax vaccine's efficacy.
- (2) There were studies in 1967 and 1968 conducted at Fort Detrick, regarding protective antigen's intrinsic toxicity that had not been followed-up in the public literature. She stated that she believed that protective antigen had intrinsic toxicity, but that the information currently available was only suggestive and more meaningful toxicity research was needed. Dr. Melling asked if Dr. Nass could provide him with these references, and she indicated she would.
- (3) The IOM report used a different method for drawing their conclusions, but didn't identify what method they did use, specifically, what weight was given to what studies.
- (4) CDC had received millions of dollars from DoD to conduct their anthrax studies. She noted that an initial *Morbidity and Mortality Weekly Report* (MMWR) article had cited two earlier (mid-1990s) CDC studies showing that anthrax vaccine was unrelated to Gulf War illnesses, but that neither of the studies cited had the ability to make that determination. She stated her belief that CDC was somewhat suspect. She was looking forward to reading the CDC's clinical anthrax vaccine trial findings, but was cautious about them.
- (5) There had been a couple hundred submissions to the FDA anthrax vaccine docket. She recommended that the Committee request access to these submissions to get a feel for what other people were saying about the anthrax vaccine.
- (6) There was a need for independent researchers to conduct the studies in this area. She stated her belief that it was impossible to get an independent, prospective study through DoD. She stated that the next best thing would be a retrospective study of veterans who have/have not received the anthrax vaccine.

Ms. Nichols spoke to the Committee. She said that there were veterans who were afraid to come before the Committee, and that they needed to have more than five minutes to address the Committee. She stated that there was a need to facilitate information exchange between the Committee and the veterans. She stated that the VA and DoD needed to help find the doctors who had information. She asked for an executive summary of the Committee's meetings. She had spoken with several Congressmen who weren't aware of the Committee and its report. She asked that the GWVIS report show what ratings were being assigned to Gulf War veterans with undiagnosed illnesses. Mr. Smithson stated that the report delineates those as "10% or more" and "0%." Ms. Nichols stated that was a wide range, and should be broken down further. She stated that the studies needed to be open recruitment, and more effort was needed to bring in Gulf War veterans for these studies. She expressed her appreciation for what the

Committee was doing, and thanked the Committee for allowing some participation from the audience in this meeting. She addressed the DoD officials in the room, and stated that veterans were not the enemy. She stated that it was time for atonement and to move things along, considering the new conflict.

Chairman Binns thanked the meeting's participants for being there. He thanked COL Grabenstein and COL Pittman for presenting, and noted that they were there on "active duty." He thanked the veterans and members of the public who had traveled to contribute to the day's conversation.

The meeting adjourned for the day at 5:35 p.m.

The meeting reconvened Friday, April 8, 2005, at 8:35 a.m.

Report to Research Advisory Committee on Gulf War Veterans Illnesses – April 2005

Brian G. Schuster, MD, FACP
Director, Clinical Science Research and Development Service
U.S. Department of Veterans Affairs

Chairman Binns introduced Dr. Schuster.

Dr. Schuster gave an overview of activities and progress in VA's Gulf War Illnesses research program since the last Committee meeting. ([See Appendix – Presentation 15.](#))

Dr. Meggs asked whether a Committee representative could be present at the April 20, 2005, treatment center meeting. Dr. Schuster stated that Dr. Steele would be attending the meeting. He said that it would also be a good idea to get together more frequently to discuss and identify other high priority issues, and develop more specific research funding announcements (RFA).

Mr. Graves inquired about Dr. Schuster's comment concerning lung cancer and oil well fires. Dr. Schuster stated that there might be an association between exposure to the smoke of the fires and lung cancer. As such, he stated that lung cancer research could become part of research efforts related to toxic exposures, and then would fall under deployment health research.

Dr. Steele asked Dr. Schuster about VA's ability to create focused RFAs. She stated that this seemed to be a common sense approach, but had understood this was difficult to do at VA. Dr. Schuster stated that deployment health research had tried to take this approach, i.e., identify key questions for Gulf War I illnesses, and then try to focus on these issues. He stated that the approach that had been taken was more like a "shotgun" approach, which diluted the program. Dr. Steele stated that the Committee had understood that the funding announcements had to be kept broad, and was pleased to hear that more specific and focused RFAs were possible. Chairman Binns stated that he was delighted to hear this too. He noted that the Committee's 2004 report contained over 50 recommendations, and it wasn't feasible to fund all of them. He stated it was good to know that the focus could be placed on a few high priority areas, and making them part of a plan. Dr. Haley stated that he was delighted to hear this news too. He thought it would be useful to explore extra mural funding coordination with the National Institutes of Health (NIH), FDA or DoD. In 1998, Congress gave the Secretary of the Department of Veterans Affairs oversight of the whole investigation into Gulf War-related illnesses. He stated that back in the early 1990s, at the start of the Clinton administration, there was a decision made that NIH and CDC were to stay out of this area of research. The decision was made that DoD and VA would be the primary agencies conducting this research. He stated that this hampered involvement by the private and university research communities. Dr. Schuster noted that research dollars had been in decline for all agencies, including VA.

He stated that, in the last six to eight months, there was a real willingness for the agencies to work together to leverage the research monies that were available. Dr. Haley stated that his group had been working with DoD over the past couple of years, and noted they were increasingly willing to solve these problems. He stated that VA was working with DoD on current deployment issues, and there was a precedent for more collaborative work between the two agencies. He thought that, in the past year, there did appear to be a positive change taking place within DoD and VA, but that NIH needed to be sent the message that it was okay for them to fund research for Gulf War veterans. Dr. Schuster stated it all depended on how the research solicitation was developed, and how both agencies' interests were addressed. Dr. Meggs commented that there was an NIH policy that if a proposal mentioned "Gulf War", it was not considered for NIH funding and applicants were directed to VA. He stated that one of the Committee's first recommendations was to open up this issue to a broader range of researchers, and that this required different agencies' help. A general discussion occurred about the source of VA research dollars and how these monies are awarded to researchers, inside and outside the VA.

Discussion turned to the proposed VA treatment center. Dr. Schuster stated that discussions were underway as to the center's organization. He stated that he was leaning towards creating a virtual center of expertise, while others might believe it should be a grounded, physical location. Based upon his experience, the affected patients were likely to be all over the country, and that creating a geographically-centered location might be more limiting compared to a virtual center. Dr. Meggs stated that, in conversations with the Durham VA, he found other researchers who were not sure how to identify these veterans.

Dr. Schuster discussed the VA's Vietnam twin registry. Dr. Meggs asked if a non-VA researcher could apply for NIH money to study twins through this registry. Dr. Schuster stated that it was done. Dr. Meggs said that, in the case of Gulf War illness, the proposal wouldn't be considered. Dr. Schuster stated that most of the non-VA investigators were not using the Vietnam twin registry to study distinctions between deployed and non-deployed twins. They were studying non-veteran health issues for which a twin pair would help answer the question.

Dr. Golomb asked for clarification of the proposed mechanism for joint VA/NIH proposals for Gulf War illnesses. Dr. Schuster stated that there had been several proposals like this, which had been organized in different ways, e.g., NIH paid for the non-VA patients and non-VA sites and VA paid for the VA patients and sites in a multi-center trial. He stated that VA money must be spent on VA investigators and VA sites. Chairman Binns noted that VA did not have a mechanism to routinely fund non-VA investigators, and that he was pleased to hear about other options to generate outside research in this area.

Chairman Binns asked that the Committee return to its discussion about the proposed treatment center. He stated that Dr. Steele would be representing the Committee, but asked the individual Committee members to provide their ideas of what should be brought to the table. Dr. Steele stated that it should be clarified that this center was not being designed as a clinical treatment center for veterans, but rather a research center for treatments. She stated that a multi-site center wouldn't necessarily mean more veterans would be treated in more locations. Dr. Schuster clarified that his earlier comments had been directed at the need of having a veteran population available for study.

Chairman Binns asked for the Committee's thoughts about having a single physical site, with several researchers located together, versus a multi-site virtual treatment research center, where collaborating researchers are all over the country.

Dr. Golomb stated her preference for the multi-site, virtual center, because it avoids dominant, restrictive approaches that might drive the entire group's work at a single site.

Dr. Haley stated that there were several tough problems to getting productive outcomes from a treatment center like this. He stated that the first one was classifying Gulf War veterans, and there was a need to designate these veterans into homogenous “bins.” He stated that it would be exciting if this was accomplished. Dr. Schuster stated that the working group needed to look at the state-of-the-art on that particular issue, identify the questions that should be addressed, and find the means to implement these ideas into studies. He stated that, in the VA’s cooperative studies program, they implement very large trials in 20-40 centers that may last several years. He stated that VA had mechanisms and expertise to plan these studies very carefully. He stated, though, that many of the Gulf War illnesses patients are probably not in the VA system.

Dr. Meggs provided a counter-argument based upon his experience with MCS. He stated that a localized facility would help facilitate people through the study process. Dr. Meggs stated that a multi-center trial was ideal for many situations, e.g., drug studies. Dr. Schuster stated that the job of the center’s working group would be to decide if an issue was important to study and develop the study plan. He stated that it was important to have a knowledgeable group that comes together to identify and test hypotheses.

Ms. Knox stated that it was very important to have the center spread across the country so more veterans would have access. Even though she was a Gulf War veteran, she didn’t utilize the VA medical system because of the long waits. It was important to capture other veterans who do utilize the VA system for healthcare. She also stated that it was important to look at where the Gulf War population was located. A majority of these veterans are in the southern United States, but most of the VA medical centers were in the northeast United States. She stated that this raised the issue of using non-VA facilities in this type of research.

Dr. Steele asked Dr. Schuster whether non-VA clinicians could be involved in developing the virtual center. Dr. Schuster stated that they would be able to be involved so long as no VA appropriated dollars were paying for their participation.

Mr. Robinson stated that Gulf War veterans are consistently being approached by “snake oil salesmen” with potential cures. Occasionally, there is someone, not within the VA or DoD, who is treating the veterans with beneficial results. Dr. Schuster stated that this would be the role of the working group, investigating the state-of-the-art ideas available and develop them further. Chairman Binns concurred that the purpose of the center was to institutionalize this approach.

Mr. Graves asked whether it was possible to have Gulf War coordinators at VA medical centers. Mr. Smithson stated that these coordinators do exist. He noted Ms. Val-Hammack’s comments from the previous day about the inability of veterans to locate them. He stated that he had faced similar problems in VAs around the country. He stated that the Committee needed to reenergize the emphasis on these coordinators, as well as updating the VHI series on Gulf War illnesses.

Chairman Binns noted that the discussion was leaving the research track, but acknowledged that it was an important issue relating to the practical aspects of VA health care for Gulf War veterans. He stated that he would allow discussion with Dr. Schuster on this topic, but asked that it be kept brief.

Ms. Nichols stated that signs needed to be placed in VA medical centers, directing veterans to the Gulf War coordinators. She asked Dr. Schuster if the VA’s Vietnam twin registry could also be utilized for Gulf War veterans. Dr. Schuster stated it could be done, but it would be complicated and would have to be funded. Ms. Nichols stated that, if a biomarker study was being considered for Gulf War illnesses, a twin registry might be beneficial in this research. Dr. Schuster stated that the working group would have

to look at the best way to study biomarkers, noting that there were other methods that might be more cost effective.

Ms. Val-Hammack asked for clarification about the separation of ORD and the Deployment Health Working Group. Dr. Schuster stated that ORD was tasked with writing up the results of the working group, and that VA had a seat on this committee. He noted that a temporary VA appointment was in place, but said that once a new ORD Gulf War coordinator was hired, he or she would be assigned to this position.

Chairman Binns stated it was good that Dr. Schuster, while focused on research concerns, could hear the veterans frustrations related to the local medical centers. Dr. Schuster stated that this actually was one of ORD's four research areas, i.e., Health Services Research and Development (HSRD). Mr. Robinson asked who the contact person for HSRD was. Dr. Schuster stated that this was Dr. Shirley Meehan.

Chairman Binns thanked the Committee for its input on the upcoming treatment center meeting. He stated that individuals scheduled to participate included: Dr Steele, Dr. John Concato, Dr. Roberta White and Dr. Wayne Jonas. Dr. Steele provided the Committee with background information about Dr. Jonas.

Chairman Binns asked Dr. Schuster about the expected funding of the FY05 RFA. He stated that the Committee had understood that former Secretary Principi had committed up to \$15 million for new research. He noted that previously-funded studies, some of which were classified as brain and nervous system research, were really post traumatic stress disorder (PTSD) research. Dr. Schuster noted that not all of the studies listed in his presentation were focused on PTSD. Chairman Binns acknowledged this, but stated his wish to see a higher number of non-PTSD studies funded with the new RFA. Dr. Schuster stated that the \$3 million figure was simply a projected amount, based upon past RFA performances. He said that more funds might be allocated if more study proposals were received. Chairman Binns thanked Dr. Schuster for the clarification.

Ms. Knox noted an earlier meeting presentation by Dr. Clauw, in which he discussed his group's development of an internet-based CBT training program. She stated that this approach might be a way to reach more veterans. Dr. Schuster stated that there was a VA web-based PTSD treatment, developed in Canada, which might be applicable to other areas. He stated this form of treatment was evolving, and agreed it might be beneficial for Gulf War veterans.

Mr. Robinson asked whether the Committee/Committee staff was aware of the specifics of the currently committed funds (\$9 million) for Gulf War studies. Dr. Schuster stated that he had shortened his presentation due to Secretary Nicholson's scheduled visit, but would be more than happy to provide more detailed information about these studies. Dr. Steele asked for clarification of the FY05 and FY06 allocations. Dr. Schuster noted that FY05 funding was for two years. He stated that ORD's current commitment was for \$9 million. He stated, with the additional studies and the carryover from FY05, approximately \$15.3 million would be spent in FY06. He stated that more discussion was needed to keep the focus on the high priority issues, which included Gulf War I concerns.

Dr. Steele asked Dr. Schuster to comment on the research enhancement award program (REAP) funding. She stated that there was a 2004 REAP announcement, inviting proposals relating to deployment health and Gulf War veterans' illnesses. Dr. Schuster stated that, due to decreases in FY05 funding, only five to six new programs were started this year. He stated that there were REAPs that dealt with environmental and toxicology issues.

Chairman Binns inquired as to how quickly high-priority RFAs could be developed and announced. Dr. Schuster stated a working group needed to be established, which could even write the RFAs themselves with ORD headquarters approval/oversight. Chairman Binns stated that he was glad to hear this.

Dr. Golomb asked if there might be a mechanism where outside researchers could apply for VA funding with the condition that, if the funding is granted, they will commit 5/8th of their time to VA. Dr. Schuster said that this was possible, and had been done.

Chairman Binns opened the floor to audience questions, and asked them to limit their comments to questions as the Committee was experimenting with audience participation in the discussions.

Mr. Albert Donnay, an audience member, noted that many veterans with undiagnosed illness had left the VA system because the VA had nothing to offer them in terms of treatment or benefits. He stated that these veterans needed to be encouraged back into the system. Dr. Schuster stated this is an approach that the VA would initiate as its research program found more answers. Mr. Donnay stated that guidance or training for physicians inside and outside the VA on Gulf War research was needed. Dr. Schuster stated this was part of the purpose of this project, e.g., take things that look like they need to be validated, and do the research.

Ms. Nichols stated that it had been a while since there had been a VA sponsored Gulf War symposium. Chairman Binns stated that he believed more was being done now in small meetings. Ms. Nichols stated it should be considered for the future to invigorate the process at a local level. Chairman Binns stated that there was a need to have workable options to present at such a meeting. It would be a disservice to “sound the alarm”, invite the veterans to come into the medical centers, and not have armed the physicians with diagnostic tools or treatments.

Mr. Robinson agreed that many Gulf War veterans weren't in the VA system because the physicians didn't know how to treat their symptoms. He stated that the veteran service organizations were working to bring veterans back to the system, providing them with information and support.

Chairman Binns noted that the development of a Gulf War veteran brain bank was a much-discussed project. He stated that he had come to appreciate the project's importance through Dr. Paul Greengard's comment that “a lot could be done with one good brain.” He asked Dr. Schuster for his thoughts about the possibility of getting this done. Dr. Haley stated that he believed a Temple University/VA researcher had proposed a cooperative brain bank for Vietnam/Gulf War veterans. Dr. Schuster stated that, as the director of the Cooperative Studies program, he had not seen such a proposal. He stated that, if it had a strong rationale or priority, it would be considered.

Ms. Knox stated that Dr. Schuster's comments were “a breath of fresh air.”

Chairman Binns thanked Dr. Schuster. Dr. Schuster announced that there would be a presentation later that morning by a stress researcher looking at the current deployment. Chairman Binns acknowledged that the Committee was aware of the importance of stress studies to the current war.

The meeting adjourned for a break at 9:55 a.m.

The meeting convened at 10:15 a.m.

Update on Research in Persian Gulf Veterans – April 2005

Beatrice A. Golomb, MD, PhD
Assistant Professor, University of California at San Diego

Dr. Golomb provided an overview of recent research findings relating to Gulf War veterans' illnesses.
([See Appendix – Presentation 16](#))

Discussion followed regarding the cited studies' controls for measured illnesses and deployment/non-deployment. Dr. Haley stated that a weakness in this literature is the use of exploratory factor analysis in the deployed and non-deployed groups, concluding that if they produce similar-looking factor analyses, this means they have the same structure. He stated that what needed to be done was the development of a factor model in one group, followed by structural equation modeling to describe that model in a series of equations, to then determine if the model fits rigorous testing criteria. Dr. Golomb and Dr. Steele stated that this approach shouldn't be used for a case definition. Dr. Haley stated that if there was a unique syndrome, it should come out of the different factors. He stated that developing two exploratory factor analyses that can be made to look the same wasn't necessarily relevant to whether the symptom structure is present in the groups.

Ms. Knox asked if there was a way to document weaknesses of the scientific approaches in this type of study, so that non-experts are aware of these problems. Dr. Steele stated that letters to the editor were one option. Dr. Golomb mentioned that a colleague had proposed a comment section on Medline. Dr. Haley stated review articles are also a way to point out these problems.

Ms. Nichols asked if there was possibility of creating a forum on the Committee's website. Dr. Haley stated that commentary on articles was a subjective matter, and the debate can become contentious and self-serving. He stated that the most productive approach was to focus on a carefully prepared report that focused on the big issues and potential advances in this field. Dr. Steele noted that, when speaking from the Committee's website, the message should be a consensus, not individual opinion.

Chairman Binns thanked Dr. Golomb.

Chairman Binns stated that Dr. Schuster had provided a good overview of ORD's activities. He said that the Gulf War illness study RFA had just been announced, and copies were provided in the Committee's notebook. He pointed out that there was a direct relationship between the amount of good research that would come from the RFA and the number of valid submitted proposals. He encouraged the scientists present to encourage their colleagues to work with VA in submitting proposals under this RFA. He noted that treatment development was receiving the highest priority.

Chairman Binns stated that ORD had announced the formation of a merit review board dedicated to Gulf War research. He stated that the Committee had submitted the names of 53 potential and qualified candidates for this board. He stated that hiring announcements had been sent out for a Gulf War research portfolio manager. He stated that the Committee was not involved in this process, but may ask ORD for a chance to provide input on the candidates. He noted that Dr. Steele had spent a considerable amount of time assisting ORD in developing the RFA. He stated that he would love to see the Committee be able to step back and become advisors once again. He noted again that it was positive and refreshing to hear Dr. Schuster's views on this issue.

Chairman Binns noted that a new Chief Research and Development Officer (CRADO) would be appointed soon. He stated that this person's outlook on Gulf War illnesses would be important. He also indicated that Dr. Jonathan Perlin had been confirmed as VA's Undersecretary of Health. He stated that it

was a positive step to see an individual with some background in Gulf War illnesses, i.e., a former acting CRADO, in this position.

Chairman Binns stated that he had spoken with Secretary Nicholson, and Secretary Nicholson had recognized the importance of Gulf War illnesses. Secretary Nicholson had expected to meet with the Committee for a full briefing and discussion. He stated that the Committee understood that Secretary Nicholson's schedule had been changed to allow him to join the U.S. delegation attending Pope John Paul II's funeral.

Chairman Binns stated that the outcome of the treatment development center meeting would be a key thing to observe in the coming months. He noted the importance of involving other agencies in Gulf War illnesses research. He pointed out that Congress had appropriated an additional \$5 million for Gulf War illnesses research by the DoD. These monies had not been committed, but the portfolio managers had done an excellent job of soliciting input from the Committee and the Congressional members/staff who were involved in securing the appropriation. He believed this DoD investment would be well spent. He noted the Committee's recommendation that Congress spend \$30 million for the next several years on Gulf War illnesses research.

Chairman Binns thanked the Committee's staff for their hard work. He noted that all of the Committee's documents, including all of the meeting minutes, were available on the Committee's website. He thanked Dr. Meggs and Dr. Golomb for presenting at this meeting. He thanked Dr. Steele for sharing her expertise and putting together the entire meeting.

Chairman Binns stated that former Secretary Principi had deferred Committee appointments and reappointments to incoming Secretary Nicholson. He didn't interpret the lack of action as a signal either way as to the Secretary's position, as the Secretary's slate was full, and this was just one of many items that needed to be addressed.

RAC Committee Business

Lea Steele, PhD

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

Dr. Steele provided the Committee with an overview of Committee activities, including plans for upcoming meetings and reports. ([See Appendix – Presentation 17.](#))

Dr. Steele asked Committee members if there were additional exposures that the Committee should investigate. Dr. Golomb stated that she saw fuel, paint, and solvents combined into one category, and an important area to consider. Dr. Melling noted the previous day's discussion of risk factors in relation to vaccines and organophosphates. He stated that there would be merit in doing further epidemiological evaluation. Dr. Steele agreed, and stated that this would fall into the presentation's second and third bullets, i.e. pull together and analyze the information about risk factors and not just list them. Mr. Graves stated that the Committee shouldn't look at any of the listed exposures, because they were all toxic. He stated that, in the wider scope of the Committee's mission, he didn't think these additional exposures played a major role for the majority of ill veterans. He stated his belief that the Committee should try to nail down the major potential causes, e.g. depleted uranium, organophosphates, etc., first. Dr. Steele stated that it might be a combination of different things that made an individual Gulf War veteran ill. Dr. Meggs stated that the Committee should be comprehensive, while mindful of the weight of the evidence for each exposure. Mr. Robinson stated his belief that the Committee would be widely criticized if it

didn't examine all known exposures. He stated if a particular exposure showed a higher likelihood of being a problem, it should receive greater attention.

Dr. Golomb stated that, if larger categories, e.g., solvents/heater exhaust, were examined, it might involve more veterans. Dr. Steele stated that there could be an "other" category which addressed the less prominent exposures. She asked for ideas about what should be included in this "other" category. Dr. Golomb stated that this would be defined by the literature. Mr. Robinson stated that the Committee might look at the environmental factors present as a result of the industrial complexes or bombing in the area. He stated he wasn't sure if relevant data existed, but noted that soldiers were being housed near these complexes. He noted that environmental monitoring was now being done, and could be reviewed. He gave an example of soldiers being stationed near a lead smelting factory in Bosnia, resulting in them having high blood lead levels. He suggested that USACHPPM might be able to provide information on this matter.

Dr. Golomb stated, with respect to the Committee's review of methodological issues, that the Committee might comment on researchers being clear on what methods were used, but should not set forth research guidelines. Dr. Steele noted that more progress had been made in CFS and FM research because standards had been established. Dr. Haley stated that he agreed with Dr. Golomb. He stated that the Committee shouldn't be too prescriptive, but should try to bring some order out of chaos. Mr. Robinson suggested a "best practices" approach. Dr. Steele noted that, while the case definitions for CFS and FM were developed for research purposes, it had resulted in patients being able to be diagnosed clinically.

Mr. Robinson stated that the Committee's 2006 report should be presented before Congress in a formal hearing.

Ms. Nichols suggested that the Committee review electromagnetic fields as a possible exposure of concern. Ms. Knox asked for clarification about the electromagnetic fields. Mr. Robinson stated that, when he worked at DoD's Office of the Special Assistant on Gulf War Illnesses (OSAGWI), he had compiled information on electromagnetic fields/pulses and radar used in the first Gulf War. He stated that there was a small group of civilian researchers who developed cancers from the early devices. He stated, however, there was not much research and data in this area. Dr. Steele stated that she had heard from soldiers in Air Force units that believe that radar/microwave exposures on their bases had adversely affected them. Mr. Robinson stated that if an individual gets in front of one of these devices, it would burn their skin.

Ms. Val-Hammack suggested that the Committee look at non-lethal weaponry, and look at the issue from an industrial hygiene point of view. She also asked the Committee to look at Gulf War illness in relation to dental disease, including talking with civilian dentists about their observations of veterans' dental hygiene. Dr. Golomb noted that veterans are only eligible for VA dental care if they have a 100% service connection. She stated that rates of periodontal diseases should be acquired in some manner. Dr. Steele stated that this information would only be available from symptom-reporting in the registry and epidemiologic studies. Mr. Robinson stated this was a situation similar to VA's collection of birth defect information.

Dr. Haley asked if the Committee felt it had sufficiently addressed the issue of birth defects. Dr. Steele noted the birth defect chapter in the Committee's 2004 report, and asked for input as to whether additional information was now known.

Mr. Albert Donnay suggested that the Committee review carbon monoxide emissions from weapons as a possible exposure of concern. Dr. Steele asked the Committee for input on this potential exposure. She

noted that, in the Gulf War literature, handling munitions or being in combat have not appeared to be risk factors. Mr. Donnay noted that Navy personnel had symptoms, and had been firing large weapons from their ships. Chairman Binns noted that the Committee needed to fulfill its obligation to look at all exposures, but needed to work within limitations and focus/prioritize sources of concern when it comes to the large multisymptom chronic illnesses affecting many Gulf War veterans. Dr. Golomb agreed that carbon monoxide emissions need further research, but noted that this exposure was not unique to the Gulf War.

Dr. Steele reminded the Committee that the articles listed in their monthly updates were available for their review, and encouraged them to do so. Chairman Binns encouraged the Committee members to remain up-to-date on the published literature in this area.

Public Comment – Day 3

Chairman Binns opened the floor to public comment.

Mr. Donnay spoke to the Committee. He distributed three handouts to the Committee pertaining to CFS and MCS. He asked that the Committee recommend more research into genetic polymorphisms for these conditions and an increase in clinical screening for these conditions by VA physicians. He stated that he was pleased to hear Dr. Haley would be starting a study characterizing Gulf War veterans, with controls, by all available case definitions and reporting his results in those terms.

Ms. Nichols spoke to the Committee. She noted that veteran service organizations would be convening in the coming months for their annual meetings, and resolutions should be put forth concerning the Committee's work. She informed the Committee that Janyce Brown, the wife of a Gulf War veteran who had worked tirelessly to bring the issue of leishmaniasis to the forefront, had passed away recently.

Ms. Val-Hammack spoke to the Committee. She stated that Mrs. Brown had worked hard to document that visceral leishmaniasis was an issue for Gulf War veterans and their families. She noted that the Gulf War veterans' multiple sclerosis support group had been growing in numbers. She suggested that the Committee look at obtaining the data on the numbers of Gulf War veterans with multiple sclerosis.

Chairman Binns thanked everyone for their participation in the meeting.

The meeting adjourned at 12:30 p.m.

Appendix

Presentation 1 – Lea Steele

CFS, Fibromyalgia, and MCS:

**Defined "Chronic Multisymptom Illnesses"
in Relation to Gulf War Veterans' Illnesses**

Lea Steele, Ph.D.

Meeting of the Research Advisory Committee
on Gulf War Veterans' Illnesses
April 6, 2005

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"Chronic Multisymptom Illnesses" in the General Population

- Unexplained symptom complexes: Historical context
- Overlap: Are they all the same?
- Multisymptom illnesses found in civilians in relation to Gulf War veterans' illnesses

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"Chronic Multisymptom Illnesses": Historical Context

- 1750: *Febricula* (Manningham) great lassitude and weariness, "flying pains", memory problems, most common in women
- 1869: *Neurasthenia* (Beard) persistent fatigue, headaches, difficulty concentrating, memory loss, diffuse pain, sleep disturbances
- 1871: *Irritable heart* or soldiers' disease (Da Costa) in Civil War veterans: fatigue, dizziness, headache, breathlessness, sleep disturbances

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"Chronic Multisymptom Illnesses": Historical Context

**Epidemic Fatigue Syndromes (Over 60 in the medical literature):
extreme fatigue, headache, weakness, somatic pain, cognitive
difficulties, neuro symptoms**

- > 1934: Los Angeles, CA
- > 1948: Akureyri, Iceland *"Icelandic Disease"*
- > 1949: Adelaide, Australia
- > 1954: Tallahassee, FL, Seward, AK *"Epidemic Neuromyasthenia"*
- > 1956: Punta Gorda, Florida
- > 1984: Incline Village, NV *"Chronic Fatigue Syndrome"*
- > 1985: Lyndonville, NY

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Contemporary "Chronic Multisymptom Illnesses (CMI)"

- **Chronic Fatigue Syndrome (CFS, CFIDS)**
 - > Myalgic encephalomyelitis (ME)
 - > Post-viral fatigue syndrome
- **Fibromyalgia (fibromyalgia syndrome, FMS, fibrositis)**
- **Multiple Chemical Sensitivity (MCS)**
 - > Environmental illness
 - > Sick building syndrome
- **Others: "Chronic Lyme Disease", IBS, MPS, TMD etc**

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"Chronic Multisymptom Illnesses"

Multiple symptoms affecting multiple organ systems:

- Symptoms not adequately explained by other diagnoses
- Etiology, underlying pathophysiology not clear
- Rarely associated with objective diagnostic indicators

Substantial overlap between symptoms of these conditions

- Fatigue, sleep difficulties
- Cognitive problems, mood disturbances
- Somatic pain
- Other (persistent headaches, GI problems, etc)

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Contemporary "Chronic Multisymptom Illnesses (CMI)":
Are They All the Same Thing?

A Venn diagram with three overlapping circles. The top circle is labeled "Chronic Fatigue Syndrome". The bottom-left circle is labeled "Fibromyalgia". The bottom-right circle is labeled "Multiple Chemical Sensitivity". The circles overlap in the center and at the intersections between adjacent circles.

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Multisymptom Syndromes Defined Differently

- CFS "gateway" defining symptom is significant, persistent fatigue
- FMS "gateway" defining symptom is pain
- MCS syndrome defined by patient's adverse response to chemicals

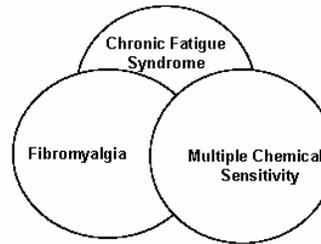
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Overlap Between CFS, FMS, and MCS

Symptoms of fatigue, somatic pain, and sensitivity to chemicals are common in patients with all 3 syndromes, but degree of overlap of defined syndromes varies in different studies and populations.

- *Buchwald (1994)*: 70% of FMS patients and 30% of MCS patients meet criteria for CFS
- *White (2000)*: 58% of FMS patients meet criteria for CFS
- *Jason (2000)*: 40% of CFS patients meet criteria for MCS, 16% meet criteria for FMS
- *Aaron (2000)*: CFS patients: 80% dx with FMS, 4% dx with MCS
FMS patients: 18% dx with CFS, 18% dx with MCS

"Chronic Multisymptom Illnesses" Overlap: Specific Diagnosis Depends on A Variety of Factors



Why Study "Civilian" Chronic Multisymptom Illnesses (CMI) in Relation to Gulf War Veterans' Illnesses?

- **Clinical similarities**
 - Many of the same symptoms in GWI, CMI patients
 - Objective diagnostic tests not generally useful
- **Possible biological similarities**
 - Similar etiologic factors? (exposures? genetic factors? infection? psych factors?)
 - Similar underlying pathophysiological processes?

Why Study "Civilian" Chronic Multisymptom Illnesses (CMI) in Relation to Gulf War Veterans' Illnesses?

- **Social and historical context similar**
 - CMIs often unrecognized/dismissed by clinicians, considered primarily psychiatric; challenging for both patients and healthcare providers
 - Controversial/political aspects: patient advocacy groups historically at odds with federal agencies charged with research
- **Progress in study of CMI may be applicable to GWI**
 - Similar methods required for study of symptom complexes without clinical markers
 - Clues from what is known re: neurological, immune, endocrine abnormalities in civilian CMI
 - CMI treatments may benefit veterans with GWI

Why Study "Civilian" Chronic Multisymptom Illnesses (CMI) in Relation to Gulf War Veterans' Illnesses?

- ★ Studies consistently find prevalence of CFS and other CMIs to be higher in Gulf War veterans than in nondeployed, era veterans

Prevalence of CFS in Gulf War Veterans

Study	Population	CFS cases	Prevalence of CFS
Bourdette, 2001	357 Gulf War vets in WAOR	Clinically diagnosed CFS	2.2 % PGW (min)
Fukuda, 1998	158 Air Guard Gulf War vets	Clinically diagnosed CFS	5.1 % PGW
Canadian MOD, 1998	6,552 Gulf and era vets	Symptom-based CFS estimate	8.5 % PGW, 1.9 % era; OR = 5.3*
Gray, 2002	6,935 Navy Seabees	Self-report of physician dx	5.2 % PGW, 0.7% era; OR = 7.6*
Kang, 2003	20,917 Gulf and era veterans	Symptom-based CFS estimate	5.6 % PGW, 1.2 % era; OR = 4.8*
Steele, 2000	2,030 Kansas Gulf, era vets	Symptom-based estimate	7.1 % PGW, 0.7 % era; OR = 8.2*
Unwin, 1999	5,157 U.K. Gulf, era veterans	Self-report of physician dx	3.3% PGW, 0.3 % era; OR = 4.4*
Australian study, 2003	3,044 Australian Gulf, era vets	Self-report of phys dx/strtd	1 % PGW, 1 % era; OR = 0.8

*statistically significant, p<.05

Prevalence of Fibromyalgia in Gulf War Veterans

Study	Population	FMS cases	Prevalence of Fibromyalgia
Bourdette, 2001	357 Gulf War vets in WAOR	Clinically diagnosed FMS	2.5 % PGW (min)
Canadian MOD, 1998	6,552 Gulf and era vets	Symptom-based FMS estimate	16.2 % PGW, 9.6 % era; OR = 1.8*
Iowa study	3,655 Iowa Gulf and era veterans	Symptom-based FMS estimate	18.2% PGW, 9.2% era; prev dif: 7.7*
Steele, 2000	2,030 Kansas Gulf, era vets	Self-report of physician dx	2.0% PGW, <0.5 % era; OR = 3.7
Smith, 2000	Gulf, era vets in military hosp	Hospitalized for FMS	0.04 % PGW, 0.04 % era; OR = 1.2*

*statistically significant, p<.05

Prevalence of MCS in Gulf War Veterans

Study	Population	MCS cases	Prevalence of MCS
Black, 2000	3,695 Iowa Gulf and era vets	Study-defined	5.4 % PGW, 2.6 % era; OR = 1.92*
Canadian MOD, 1998	6,552 Gulf and era vets	Resp to chems w/ 2+ symp types	2.7 % PGW, 0.9 % era; OR = 4.01*
Gray, 2002	6,935 Navy Seabees	Self-report of physician dx	1.6 % PGW, 0.4% era; OR = 4.5*
Proctor, 2001	226 Mass. Gulf and era vets	Cullen def, based on symps	2.9% PGW, 0% era
Reid, 2001	5,965 UK Gulf and era vets	Simon def, based on symps	1.3 % PGW, 0.2 % era; OR = 6.9*
Unwin, 1999	5,157 U.K. Gulf and era vets	Self-report of physician dx	0.8 % PGW, 0.3 % era; OR = 2.2
Australian study, 2003	3,044 Australian Gulf, era vets	Self-report of phys dx/strtd	<1 % PGW, <1 % era; OR = 1.3

*statistically significant, p<.05

Summary:
Prevalence of CMI in Gulf Veterans Compared to Era Veterans

- CFS:** 2.2 - 8.5 % of US, UK, Canadian Gulf veterans
ORs significantly elevated: ORs = 4.4 - 8.2
- FMS:** Few prevalence estimates, highly variable
2% dx FMS, ~16% based on symptom estimates; ORs = 1.2 - 3.7
- MCS:** Variable estimates based on MCS definition
Physician-diagnosed MCS low (< 2 %),
Defined MCS higher (1.3 - 5.4%); ORs = 1.1 - 6.9

***Symptoms of chronic fatigue, widespread pain, and chemical sensitivity reported by higher proportion of Gulf War veterans*

**Symptom of Chemical Sensitivity vs. MCS
in Gulf Veterans**

<i>Study</i>	<i>% of Gulf vets reporting symptom</i>	<i>"MCS" in Gulf Vets</i>
Black (2000)	13%	5%
Canadian (1998)		3%
Gray (2002)		2%
Fukuda (1998)	5%	
Kang (2000)	15%	
Proctor (2001)		3%
Reid (2002)	28%	1%
Steele (2000)	17%	

Distinctions between "Civilian" CMIs and Gulf War Illnesses

- **Occurrence of CMI and GWI**
 - > CFS appears to be 10-20 times more common in Gulf vets than the general population
 - > FMS and MCS rates in comparison to general population not clear
 - > Association of CMI with age, female sex less prominent in Gulf vets than in civilian populations
 - > CFS, FMS, MCS case criteria do not adequately describe the majority of veterans affected by excess chronic symptom complexes

Use of CFS Case Definition in Describing GWI "Cases"

- In 1994, the Defense Science Board recommended that research on illnesses affecting Gulf War veterans be coordinated with federal CFS research efforts
- A GWI case definition modeled after the CFS case definition was proposed by the federal Persian Gulf Veterans Coordinating Board
- Lacking an accepted GWI case definition, some investigators have used the CFS case definition to distinguish ill "cases" from "controls" among symptomatic Gulf War veterans
 - > Does CFS case def describe a meaningful subgroup of ill Gulf veterans?
 - > Are Gulf War veteran CFS cases similar to CFS cases in the general population?

Comparing Symptoms of Gulf Veterans with CFS to People in the General Population

Comparisons between CFS-related symptoms reported by Gulf veterans and a population-based sample in San Francisco (Steele) indicate:

- The CFS case definition identifies a highly symptomatic subgroup of Gulf War veterans, but accounts for only a fraction of the excess symptomatology observed in Gulf War veterans.
- Gulf War veterans who meet the CFS case definition also appear to differ symptomatically and demographically from CFS patients in the general population

☆☆ RAC-GWVI

Persistent Symptoms of Gulf Veterans Who Meet CFS Criteria vs. Symptoms Associated with CFS in a Population Sample

More Prevalent (by >15%) in Gulf War Veterans
Joint pain
Headache
Numbness, tingling in extremities
Night sweats
Diarrhea
Skin rashes

Less Prevalent (by >15%) in Gulf War Veterans
Sleep disturbances
Depression
Unwell after exertion
Sorethroat

☆☆ RAC-GWVI

Distinctions between "Civilian" CMI and Gulf War Illnesses: Research Considerations

- "Civilian" CMI Research
 - > Research is challenging: no clear "case" group or "at risk" group to study
 - > Research guidelines and widely used case definitions have helped to standardize research in CFS, FMS
 - > Scientific progress: Thousands of studies done, providing detailed information re: epidemiological, neurological, endocrine, immunological, and psychiatric aspects of CMI conditions
- GWV Research
 - > Research, in theory, should be less challenging: defined cohort was healthy at one point in time, shared common experiences before becoming ill; nondeployed era veterans provide suitable "unexposed" comparison group
 - > Less progress in describing key physiological and epidemiological parameters of the conditions
 - > Research methods, case definitions not yet standardized

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Gulf War Illnesses in Relation to "Civilian" CMI: The Bottom Line

- Many similarities between GWI and multisymptom conditions found in the general population
- CFS, possibly other defined CMI syndromes, are more common in U.S. Gulf veterans than the general population
- Much to be learned from research on CMIs that may contribute to understanding and treating GWI
- Not clear whether CFS, FMS, or other defined CMIs represent distinct clinical entities or symptom complexes resulting from multiple overlapping causes and pathophysiological processes.

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"Is it a Unique Disease Entity?"
Question Asked re: All Multisymptom Illnesses

A Venn diagram consisting of three overlapping circles. The top-left circle is labeled "Chronic Fatigue Syndrome". The top-right circle is also labeled "Chronic Fatigue Syndrome". The bottom circle is also labeled "Chronic Fatigue Syndrome".

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"Is it a Unique Disease Entity?"
Question Asked re: All Multisymptom Illnesses

A Venn diagram consisting of three overlapping circles. The top circle is labeled "Chronic Fatigue Syndrome". The bottom-left circle is labeled "Fibromyalgia". The bottom-right circle is labeled "Multiple Chemical Sensitivity".

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GWI likely fits into the CMI "Overlapping Syndrome" Diagram but precisely how and where it fits is unclear

A Venn diagram with four overlapping circles. The top-left circle is "Chronic Fatigue Syndrome", the bottom-left is "Fibromyalgia", and the bottom-right is "Multiple Chemical Sensitivity". A fourth circle, "Gulf War Illnesses", is positioned to the right. An arrow points from this circle to the intersection of "Chronic Fatigue Syndrome" and "Multiple Chemical Sensitivity", with a question mark above the arrow.

☆☆ RAC-GWVI

Speakers

Multiple Chemical Sensitivity	Dr. Bill Meggs Dr. Iris Bell
Chronic Fatigue Syndrome	Dr. Bill Reeves
Fibromyalgia, treating CMI	Dr. Dan Clauw

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Presentation 2 – William Meggs

Chemical Sensitivity

William Joel Meggs, MD, PhD, FACEP, FACMT
Brody School of Medicine @ East Carolina Univ.
Greenville, NC

Objectives

- Brief history of environmental medicine in the United States
- First descriptions of chemical sensitivity
- Epidemiology of chemical sensitivity
- Mechanisms of chemical sensitivity
- Research needs

What initiated my interest in Environmental Medicine?

- Personal witnessed 'miraculous cures'
- Polymyositis
 - Case of Wheat intolerance
- Rheumatoid arthritis
 - Case of milk intolerance
 - Challacombe & Brostoff, eds, Food Allergy & Intolerance, 2ed
- Crohn's disease
 - Cigarette intolerance

Basic Approach of Environmental Medicine

- Some diseases are induced &/or exacerbated by environmental factors.
- Some diseases are optimally managed by environment eliminations.
- Individual susceptibility
- Environmental factors in diseases
 - Chemicals naturally occurring in foods
 - food additives
 - chemicals and biologicals in air & water
 - body flora & fauna.

Contrast

- **Mainstream Medicine**
 - If a person is sick, they need to have chemicals added to their bodies.
- **Environmental Medicine**
 - If a person is sick, they need to have chemicals removed from their bodies.

Complementarity: if a person is sick, there are specific indications for having chemicals added to their bodies, & specific indications for having chemicals removed from their bodies. The challenge is to find these indications.

Early Beginnings

- **Food intolerance**
- **Group of allergists in the Midwest, 1930's**
- **"Masked food allergy"**
 - Tolerance of food if ingested daily
 - Period of abstinence followed by re-exposure results in acute reaction
- **Cyclical vs. Fixed food allergy**
 - REF: *Food Allergy* by Rinkel HJ, Randolph TG, Zeller M. CC Thomas, Springfield IL, 1951. [out of print]

Diagnostic Approach

- Period of avoidance
- Re-exposure
- Monitor for symptoms
- Non-reaginic allergy [not IgE mediated]

Case Report: Dr. HJ Rinkel

- Son of egg farmer
- Impecunious medical student with family
- Father sent gross of eggs each week
- Profuse rhinorrhea
 - Multiple physician visits without help
- Egg was suspected
- Egg avoidance for five days– rhinorrhea improved
- Ate birthday cake containing egg and had severe reaction

Descriptions of Systemic Manifestations of 'Food Allergy'

- Fatigue
- Headache
- Brain-fag, depression, psychosis
- Myalgias
- Arthralgias, arthritis
- Cardiovascular manifestations
 - Fluid retention
 - Tachycardia

Methodology

- Setting: private practice
- Detailed history
- Trial & error
- Abstinence followed by re-exposure
- Carefully record signs & symptoms of illness -- emphasis on subjective symptoms
- Generalizations from individual cases
- No longitudinal data other than anecdotes

Fasting

- Introduced by Dr. Donald Mitchell, Montreal dermatologist & environmental physician
- Hospital practice
- Fast on spring water with sodium and potassium bicarbonate [2:1] until symptoms clear
- Re-expose to foods one by one

Rotation Diet

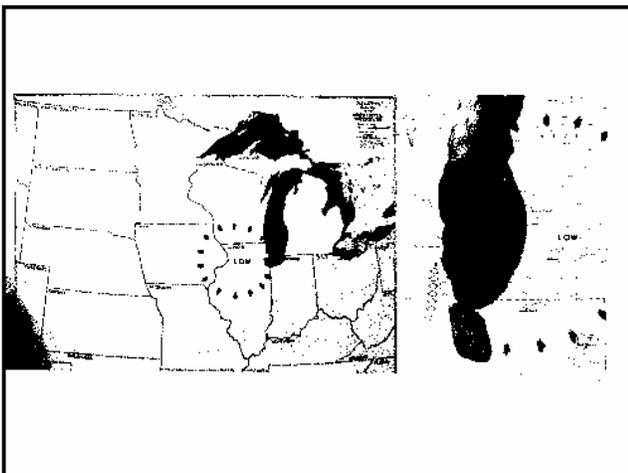
- One food per meal
- Repeat each food every 5 to 7 days
- Monitor for reactions
- Use organically grown, untreated, pure foods
- Eliminate any foods with untoward reactions

Pesticide Sensitivity

- Patient tested and found allergy to peaches
- Patient reported peaches from abandoned orchard gave no reaction
- Patient found to be intolerant of grocery store peaches but tolerant of peaches from abandoned orchard
- Sulfites, fungicides, insecticides

Sensitivity to 'Air Pollution'

- South Wind
- Industrial area
- Symptoms flare in some individuals when the winds are from the south



Gas Appliances

- Burn unvented natural gas in cook stoves, water heaters
- Patients turn off their gas for 5 to 7 days, use a hot plate, toaster oven, electric frying pan, etc., then turn it back on.
- "Shock Reactions" are diagnostic
- Homes with gas cook stoves have levels of sulfur dioxide and oxides of nitrogen above levels allowed in factories
– Hollowell et al, LBL, early 1980's

Chemical Sensitivity

- Individual susceptibility
- Products of combustion
 - Tobacco smoke, vehicle exhaust, furnace fumes, gas appliances
- Perfumes and fragrances
- Products for Cleaning
- Pesticides
- Chemicals in foods and food additives
- Paints and other solvents
 - Outgassing of VOCs

• Randolph TG. Human ecology and susceptibility to the chemical environment.
CC Thomas, Springfield, 1962.

Micro-organism Intolerance

- Life on humans
- Susceptibility to toxins from micro-organisms colonizing our bodies
- Chronic candida vaginitis
 - IgE to candida
 - TH2 vs. TH1 helper lymphocytes
 - Host defense to candida is ablated
 - Small number of organisms produce huge symptoms
 - Treatment is desensitization to candida

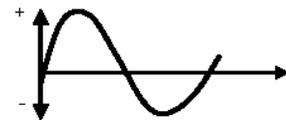


'Spreading' Phenomenon

- With continued exposures, the numbers of substances a person is sensitive to increases.

Stimulatory & Withdrawal Symptoms

- Paired sets of symptoms
 - 0, 1+ & 1-, 2+ & 2-, 3+ & 3-, 4+ & 4-
- Exposure to the agent causes stimulatory symptoms
- Elimination of the agent causes an associated withdrawal symptom
- Examples:
 - Seizure/coma
 - Mania/depression



Environmental Control Unit

- Developed in 1950's, USA
- A hospital unit to isolate patients, de-adapt them from their environment, and reintroduce agents one-by-one
- Attention to air, water, food
- All Environmental Control Units in this country have been shut down, though there are operating units in Canada, England, Germany, and Japan

Examples of Diseases Evaluated in Environmental Control Units

Respiratory	Asthma, Rhinitis, Sinusitis, Pneumonitis
Musculoskeletal	Myositis, Arthritis, Collagen Vascular diseases
Gastrointestinal	Irritable Bowel Syndrome, Inflammatory Bowel Disease
Dermatological	Dermatitis, Rosacea, Cutaneous Vasculitis

Examples of Diseases Evaluated in Environmental Control Units

Cardiovascular	Unstable angina, hypertension, Arrhythmias, Vasculitis, Recurrent Anaphylaxis
Autoimmune Diseases	Multiple sclerosis, SLE, vasculitis, myositis
Neurological	Migraine, Seizures
Psychiatric	Bipolar disorder, Depression, Psychosis

Environmental Control Unit Protocol

- Highly Individualized
- Day One
 - Admitted to unit
 - History and physical examination with extensive environmental, dietary, and occupational history.
 - Routine laboratory testing was performed.
 - No inhalants on the unit

Environmental Control Unit Protocol

- **Stage 1: Approximately 5 to 7 days**
- **Fasting stage**
 - Patients fasted on distilled spring water
 - Monitored for withdrawal symptoms: headache, nausea, vomiting, myalgias, arthralgias, etc.
 - Alkaline salts: 2:1 NaHCO₂:KHCO₂
 - Monitored for electrolyte abnormalities, dehydration: Rehydrate with IV, glass bottles
 - Fast terminated when withdrawal symptoms end

Environmental Control Unit Protocol

- **Stage 2: Approximately 10 to 20 days**
- **Food testing to establish a safe diet**
- **'Suspected Safe' Foods eaten on rotation**
- **Each meal consisted of single organically grown pure food**
- **Monitor for adverse reactions**

Environmental Control Unit Protocol

- **Stage 3: Approximately 7 days**
- **Food testing to test highly suspect foods, pesticides, additives**
- **Patients continue their safe diet on 5 to 7 day rotation**
- **Highly suspect foods and contaminated foods introduced as single feedings, one by one**

Environmental Control Unit Protocol

- **Stage 4: Approximately 7 days**
- **Chemical testing**
- **Highly individualized**
- **Challenge testing to natural gas, vehicle exhaust, items from home**

Environmental Control Unit Protocol

- Stage 5: Discharge
- Patients have been taught to evaluate reactions and avoid those things that make them sick
- Patients instructed to continue rotation diet of safe foods
- Patients instructed to modify home and work environment, automobile, etc.

Interpretation of Results

Adaptation Syndrome(s)

Generalized Adaptation Syndrome

REF: Selye, H.

Stage I. Preadaptation (Nonadapted)	Shock Reaction (Acute reactivity to chemicals)
Stage II. Addicted (Adapted)	
Ila. Adapted	Tolerance
Iib Maladapted	Chronic Illness
Stage III. Postadapted (Nonadapted)	Exhaustion

Specific Adaptation Syndrome

- Mal-adaptation to a single substance
- Substance is tolerated without acute reactions but there is chronic disease
- Elimination of one substance leads to withdrawal symptoms then resolution of chronic disease
- Re-exposure to that substance leads to acute reactions

Chemical Stress Syndrome.

Stage 0. Normalcy	Tolerance of chemical exposures, wellness without symptoms
Stage 1. –algia	Sensory Hyper-reactivity. Subjective symptoms associate with chemical exposures. (arthralgias, myalgias, irritable bowel syndrome, etc.)
Stage 2. –itis	Inflammatory reactions to chemicals (arthritis, myositis, inflammatory bowel disease, etc.)
Stage 3. –osis	Fibrosis. Necrosis. Tissue destruction (arthritic deformities, muscle atrophy and necrosis, etc.)

Chemical Stress Syndrome

- **Dynamic**
- **Patients move back and forth through the stages**
- **Exposures drive patients between the stages**
 - Eliminating inflammatory chemicals moves patients to lower stages
 - Exposure to inflammatory chemicals move patients to higher stages
- **Stage 3 – Fibrosis and scarring – is permanent**

Emphasis

- Exposures to the Chemical Environment induces and exacerbates known diagnosable valid medical conditions with findings on physical exam and laboratory testing.
- These diseases can go into remission with environmental control

Suppression of Environmental Medicine in the USA

- Small group of physicians
- Close ties to commercial interests
- “There is no scientific evidence that environmental medicine is efficacious.”
- **Argumentum *ad hominem* – attack the person, not the argument.**
 - Led to name change from *Clinical Ecology* to *Environmental Medicine*
 - Distinct from the specialty of *Occupational & Environmental Medicine*

Suppression of Environmental Medicine in the USA

- **Position statements: pts are crazy & doctors are quacks**
 - AMA, AAAAI, California Medical Society
- **Industry funded conferences**
 - After National Research Council Conference recommended federal funding of research ECU
- **Insurance companies to deny payment**
- **Physicians lost their licenses**
- **Network TV shows roasting physicians & pts**

Treatments

- Avoidance
- Provocative/neutralization
 - Dermal injections
- Vitamins
- Sauna detoxification
- Anti-fungals

Controlled Studies of Treatment Efficacy

- Literature is sparse.
- Controlled studies of provocative/neutralization were negative.

Survey of Treatment Efficacy

- Self-reported
- 917 self-reported MCS patients
- 101 treatments
 - Environmental medicine
 - Holistic therapies
 - Nutritional supplements
 - Detoxification techniques
 - Prescription drugs, ...

Gibson PR, Elms AN, Ruding LA. Perceived Treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity. Environ Health Perspective 2003;111:1498-1504.

Survey of Treatment Efficacy

- Treatments were expensive
 - Averaged spending 1/3 of income on Rx
- Three most highly rated therapies
 - Chemical avoidance rated beneficial by 95% of respondents
 - Creating a chemical-free living space rated beneficial by 95% of respondents
 - prayer
- Other therapies had mixed ratings

Gibson PR, Elms AN, Ruding LA. Perceived Treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity. Environ Health Perspective 2003;111:1498-1504.

Recommendation of patient advocacy group

- Avoidance
 - Avoid physicians. They are expensive and will not make you better.
 - Avoid chemicals. Put all of your funds into creating a chemically free living space.

Contemporary Era

Chemical Sensitivity in General Populations

State	Prevalence	Seriously affected
NC*	30%	4%
CA**	15.9%	7%
NM**	15%	
GA**	12.6%	4%
Sweden	30%	

* Chemical sensitivity, ** multiple chemical sensitivity syndrome

References

- NC: Meggs WJ, Dunn KA, Bloch RM, Goodman PE, and Davidoff AL. Arch Environ Health 1996;51:275-282.
- CA: Kreuzer R, Neutra RR, Lashuay N. Amer J Epid 150:1-12 (1999).
- NM: Voorhees RM. Memorandum from New Mexico Deputy State Epidemiologist to Joe Thompson, Special Council, Office of the Governor. 13 March 1998.
- GA: Caress SM, Steinemann AC, Waddick C. Arch Environ Health (in press).
- Sweden: Millqvist E. Presentation, 19th International Symposium on Man and His Environment in Health and Disease. Dallas, TX. June, 2001.

Chemical sensitivity

- **Acquired Intolerance of airborne chemicals**
- **Products of combustion**
 - Tobacco smoke, vehicle exhaust, furance fumes, gas appliances
- **Perfumes and fragrances**
- **Products for Cleaning**
- **Pesticides**
- **Paints and other solvents**
 - Outgassing of VOCs

Accepted & Associated syndromes

- **Accepted**
 - Irritant contact dermatitis
 - Airborne contact dermatitis
 - Irritant induced asthma & rhinitis
 - Solvent neurotoxicity
- **Associated**
 - MCS
 - RADS
 - RUDS
 - SBS

MCS

- Multiple chemical sensitivity syndrome
- Defined by occupational physician
 - Mark Cullen, MD, Yale University
- Onset with a chemical exposure
 - No longer considered necessary
- Sensitive to multiple chemicals of diverse classes
- More than one organ system involved
 - Respiratory system
 - Nervous system
 - Cullen M. Occup Med: State of Art Reviews. 1987;2:655-662

RADS

- Reactive airways dysfunction syndrome
- Defined by pulmonologist
- Asthma-like illness
 - Bronchial hyper-reactivity
- MCS with one organ system involvement
- Onset with a single acute chemical exposure
 - Brooks S et al. *Chest* 1985;88:376-384.

RUDS

- Reactive upper-airways dysfunction syndrome
- Upper airway analogue of RADS
- Rhinitis and sinusitis developing in association with an acute chemical exposure
- Subjects meet Cullen definition for MCS
 - Meggs WJ and Cleveland CH Jr. Rhinolaryngoscopy findings in patients with the multiple chemical sensitivity syndrome. *Arch of Environ Health* 1993;48:14-18.

SBS

- Sick building syndrome
- First described by WHO committee
- Widespread reports of illness among workers in tightly sealed buildings containing a host of indoor air pollutants
- Respiratory & neurological symptoms dominant
- Prevalence is 30% of inhabitants of sick buildings

Studies of MCS Patients

Highly Biased List

Olfaction in 'MCS'

- **Controlled study**
- **Odor thresholds**
- **Nasal resistance**
- **Beck depression inventory**
 - Doty RL et al. Olfactory sensitivity, nasal resistance, and autonomic function in patients with multiple chemical sensitivities. Arch Otolaryngol Head Neck Surg. 1988 Dec;114(12):1422-7.

Olfaction in MCS

- results do not support the hypothesis that MCS is associated with greater olfactory threshold sensitivity
- MCS is associated with:
 - **decreased nasal airway patency exacerbated by challenge**
 - **depression**
 - **increased respiration rate**

Challenge Tests

- **Controlled study**
 - Subjective sensitivity versus tolerant
- **Exposure to side-stream tobacco smoke**
- **Significant increase in symptoms**
 - nasal congestion, headache, chest discomfort or tightness, and cough
- **Significant increase in nasal resistance**
 - Bascom et al.

Physical Findings in MCS

- **Edema and hypertrophy of the airways**
- **Abnormal mucous**
 - Thick, white to yellow, crusty exudates
- **Nodular hyperplasia**
- **Hemorrhage**
- **Injection**
 - Posterior pharynx, uvula, soft pallet
- **Discoloration**
 - Pale yellow to white patches of mucosa with prominent blood vessels

Meggs WJ, Cleveland C. Rhinolaryngoscopic examination of patients with the multiple chemical sensitivity syndrome. Arch Environ Health. 1993 Jan-Feb;48(1):14-8.



Nasal bx study of MCS pts

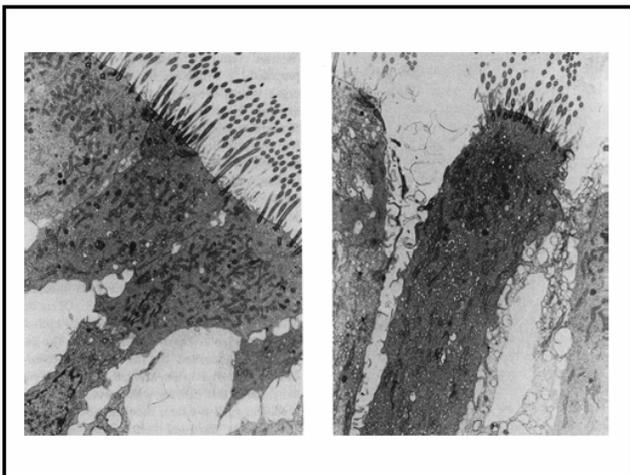
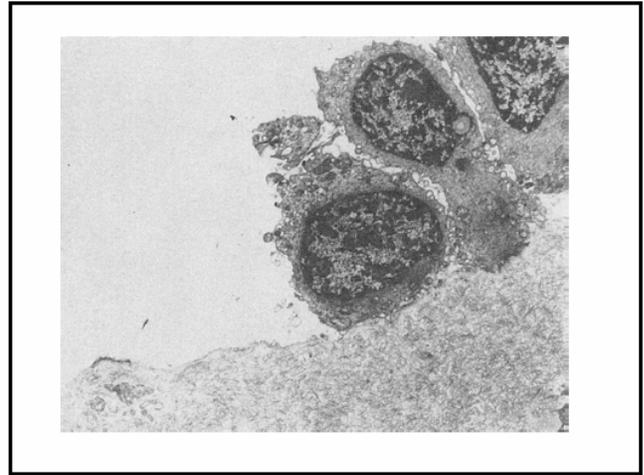
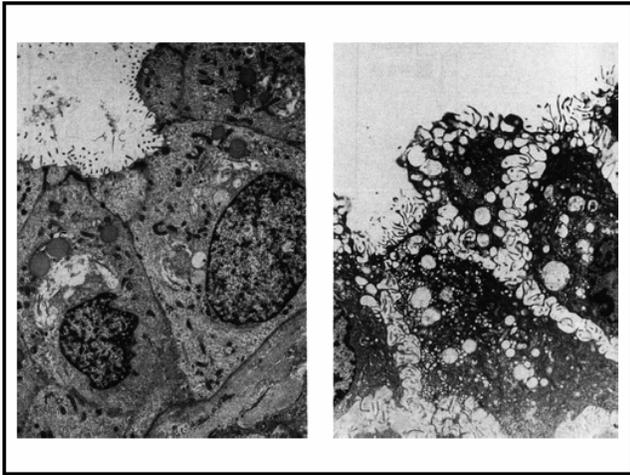
- Controlled study
- Patient group developed chemical sensitivity after chlorine dioxide exposure
- Meet case definitions for MCS
- Nasal biopsies
 - H&E
 - Light microscopy

Stains for nerve fibers & SP
RE: [http://www.ncbi.nlm.nih.gov/pubmed/9963441](#); 383-96.

Pathological Features

- Chronic inflammation with lymphocytic infiltrates
- Glandular hyperplasia
- Basement membrane thickening
- Nerve fiber proliferation
- Desquamation of the respiratory epithelium
- Defects in tight junctions





End Organ Sensitization

A

- Respiratory epithelium
- Basement membrane
- Glands
- Sensory nerve fibers

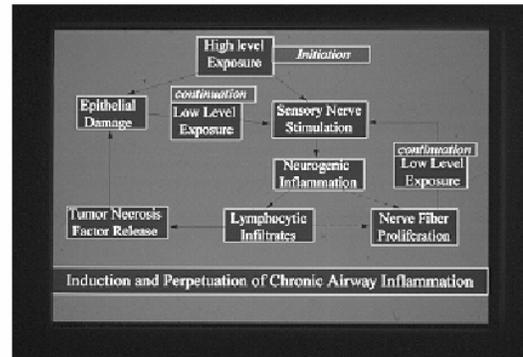
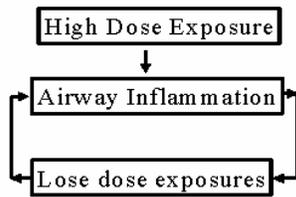
B

- Respiratory epithelium: tight junction defects and desquamation
- Basement membrane: thickening
- Glands: hyperplasia lymphocytic infiltrates
- Sensory nerve fibers: proliferation

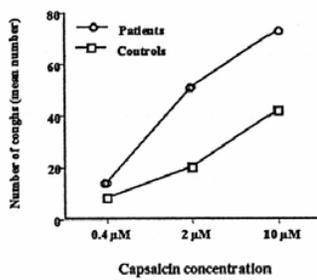
The diagram on the left shows two panels, A and B, illustrating the progression of end organ sensitization. Panel A shows a normal state with a layer of respiratory epithelium, a basement membrane, glands, and sensory nerve fibers. Panel B shows a sensitized state with tight junction defects and desquamation of the epithelium, thickening of the basement membrane, hyperplasia and lymphocytic infiltrates in the glands, and proliferation of sensory nerve fibers. To the right of the diagram is an electron micrograph showing glandular structures, likely corresponding to the 'Glands' mentioned in the diagram.

Induction Mechanism

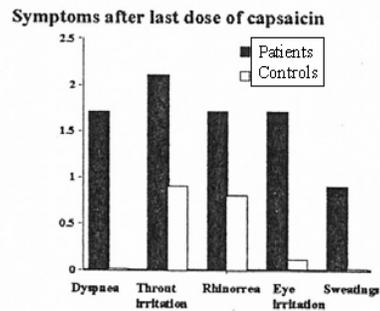
- Positive feed back loop
- Induction exposure produces neurogenic inflammation



Millqvist Capsaicin inhalation cough test in patients with "Sensory Hyperreactivity"

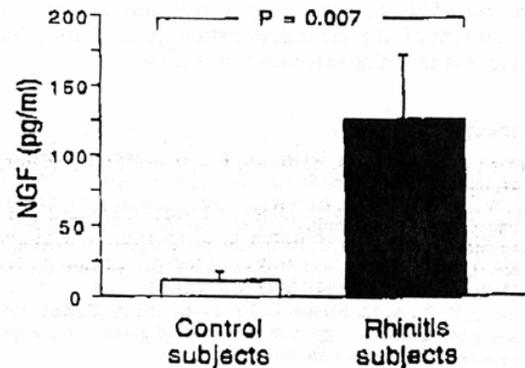


Millqvist Capsaicin inhalation cough test in patients with "Sensory Hyperreactivity"



Millqvist E, et al. Provocations with perfume in the eyes induce airway symptoms in patients with sensory hyperreactivity. *Allergy*. 54(5):495-9, 1999 May.

- single-blindly in a placebo-controlled, randomized study
- 30-min exposure to perfume,
- increase in eye irritation, cough, and dyspnea, after both the airway and eye exposures



Sanico et al. *Am J Respir Crit Care Med*. 2000 May;161(5):1631-5.

Plasma Levels of substance P, VIP, NGF

- Controlled study
- Three groups
 - MCS
 - Atopic eczema/dermatitis
 - Normal control group
- Measurements at baseline and after chemical challenge
 - Oil based paint

REF: Kimata H. Effect of exposure to VOCs on plasma levels of neuropeptides, NGF & histamine in patients with self-reported chemical sensitivity. *Int J Hyg Environ Health* 2004;207:159-163.

Results

- Baseline plasma levels of SP, VIP, NGF, but not histamine were elevated in MCS group but not other groups.
- VOC exposure increased plasma SP, VIP, NGF in MCS pts but not other two groups.
- Exposure to VOCs increased skin wheal response to histamine in MCS but not other two groups.

REF: Kimata H. Effect of exposure to VOCs on plasma levels of neuropeptides, NGF & histamine in patients with self-reported chemical sensitivity. *Int J Hyg Environ Health* 2004;207:159-163.

Controlled Study of Male Painters with MCS

- Controlled challenge booth study, community recruitment
- no difference in sensations of smell
- No difference in CNS symptoms
- Difference in subjective rating of symptoms related to irritation (i.e., eyes, nose, throat, skin, and breathing difficulties)
- No differences in nasal cavity, eye redness and serum cortisol levels.
- Trend ($P = 0.056$) in decline of serum prolactin levels
 - Georgellis et al. Multiple chemical sensitivity in male painters; a controlled provocation study. *International Journal of Hygiene & Environmental Health*. 206(6):531-8, 2003 Oct.

Mechanisms

Older Concept

- Extrinsic Airway Inflammation
 - Allergic in origin
- Intrinsic Airway Inflammation
 - Allergy testing is negative
 - No extrinsic cause, intrinsic to the system
 - Non-allergic or Intrinsic asthma
 - Non-allergic rhinitis

Contemporary Concept

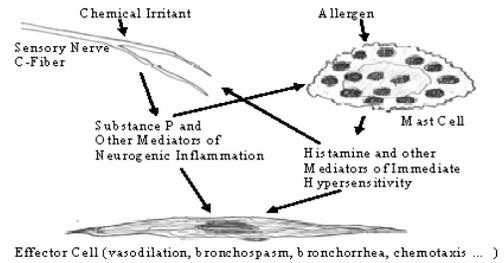
- Allergic Airway Inflammation
 - Inflammation initiated by airborne proteins on pollen grains, mold spores, dust mite feces, cockroach debris, airborne mammalian proteins
- Irritant Airway Inflammation
 - Inflammation initiated by non-protein, lower molecular weight chemicals such as solvents, fumes, products of combustion, VOCs

Mechanisms

- Allergic Inflammation
 - **Proteins** cross link IgE molecules on Mast Cell surfaces, leading to the release of histamine and other allergic mediators
- Neurogenic Inflammation
 - **Chemicals** bind to chemoreceptors on sensory nerve C-fibers, leading to the release of Substance P, Calcitonin Gene Related Peptide, and other neurogenic mediators

Crossover Network

- Nerve fibers have histamine receptors
- (some) Mast cells have substance P receptors



What about extra-airway manifestations of chemical sensitivity?

Organ system involvement in chemical sensitivity

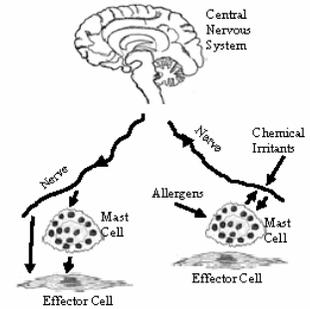
Respiratory	Asthma, Rhinitis, Sinusitis, Pneumonitis
Musculoskeletal	Myositis, Arthritis, Collagen Vascular diseases
Gastrointestinal	Irritable Bowel Syndrome, Inflammatory Bowel Disease
Dermatological	Dermatitis, Rosacea, Cutaneous Vasculitis

Organ system involvement in chemical sensitivity

Cardiovascular	hypertension, Arrhythmias, Vasculitis, Recurrent Anaphylaxis
Neurological	Migraine, Fatigue, Cognitive dysfunction, Seizures, Coma
Psychiatric	Bipolar disorder, Depression, Psychosis

Neurogenic Switching

- The site of inflammation can be switched from the site of stimulation
- Occurs in both allergic and irritant airway inflammation
- May play a role in many disease processes



Examples of Neurogenic Switching

- Gustatory rhinitis
- Food allergy leading to asthma & rhinitis
- Millqvist perfume challenges
- Airbourne contact dermatitis
- Systemic anaphylaxis
 - Animal models with ablation of neural pathways

MCS & Gulf War Illnesses

Bell IR, Warg-Damiani L, Baldwin CM, Walsh ME, Schwartz GE. Self-reported chemical sensitivity and wartime chemical exposures in Gulf War veterans with and without decreased global health ratings. *Mil Med.* 1998 Nov;163(11):725-32.

- “Among PGW veterans, the subset with worse health associated with marked increases in chemical odor intolerance since their military service had a significantly higher odds ratio for exposure to multiple chemicals, notably wartime pesticides and insect repellent, than did comparison groups.”

MCS & Gulf War Related Illnesses

- **British cohort study**
- **“Operational Criteria”**
- **Gulf cohort: MCS & pesticide exposure, {adjusted OR = 12.3, 95% CI [5.1, 30.0]}:**
 - Reid S et al. Multiple chemical sensitivity and chronic fatigue syndrome in British Gulf War veterans. *American Journal of Epidemiology.* 153(6):604-9, 2001 Mar 15

	MCS	CFS
Gulf	1.3%	2.1%
Bosnia	0.3%	0.7%
Era	0.2%	1.8%

Proctor SP. Chemical sensitivity and gulf war veterans' illnesses. [Review]. *Occup Med.* 15(3):587-99, 2000 Jul-Sep.

- “In several studies of GW veterans, using differing criteria and varying assessment measures for CS and MCS, the prevalence rates for CS are reported to be 36-86% in Department of Veterans' Affairs patient populations and 0.8-20% in general cohorts of GW veterans. The rates of MCS are 2-6%.”

Kipen et al. Prevalence of chronic fatigue and chemical sensitivities in Gulf Registry Veterans. *Archives of Environmental Health.* 54(5):313-8, 1999 Sep-Oct.

- **VA's Gulf War Registry**
- **Questionnaire responses**
- **“CFS & MCS may constitute an appreciable portion ...”**

CFS	15.7%
MCS	13.1%
Both	3.3%

Animal Model of MCS

- Flinders Sensitive Line (FSL) rats
- selective breeding for increased responses anticholinesterase agent
- increased sensitive both to a variety of drugs
- Increased broncheal hyper-responsiveness
 - Overstreet DH, Djuric V. A genetic rat model of cholinergic hypersensitivity: implications for chemical intolerance, chronic fatigue, and asthma. [Review] [56 refs] *Annals of the New York Academy of Sciences*. 933:92-102, 2001 Mar.

Research Needs: Study of Specific Diseases in Environmental Control Units

- Controlled studies
 - Blinded whenever possible
 - Consider sleep challenges to odorous chemicals
- Diseases with definite parameters that can be followed
 - Subjective symptoms, physical findings, laboratory parameters
- Longitudinal studies
- Long term follow-up

Summary

- Environmental medicine grew out of and extended the scope of allergy
 - Extended diseases with environmental factor
 - Extended substances that induce disease in humans
- Research needs to be done to define the extent of and indications for specific diseases being induced and/or exacerbated by environmental exposures

References to Early Works

- Randolph TG, Moss R. *An Alternative Approach to Allergies*. Perennial, 1990.
- Dickey LD. *Clinical Ecology*. Thomas 1976.
- Rea WR. *Chemical Sensitivity*. Vol 1-4. CRC. 1992-1996.
- Randolph TG. *Human ecology and susceptibility to the chemical environment*. Thomas, 1962.
- Ashford NA, Miller CS. *Chemical exposures, Low levels and high stakes*. Van Nostrand Rheinhold. 1991. 2nd edition 1998.

Presentation 3 – Iris Bell

**TIME-DEPENDENT
SENSITIZATION
IN CHEMICAL INTOLERANCE
AND GULF WAR ILLNESSES**

Iris R. Bell, MD PhD
The University of Arizona
College of Medicine

Chemical Odor Intolerance

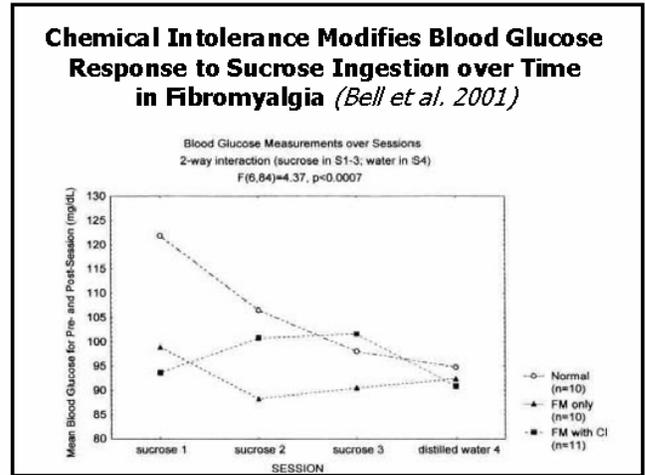
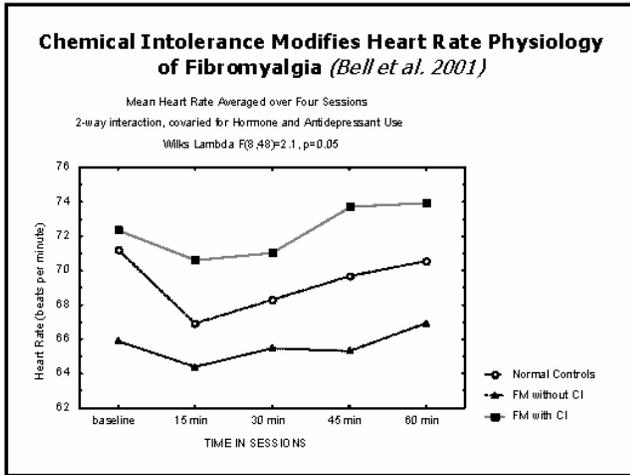
- negative hedonic response in the host
- illness symptoms from low levels of chemicals tolerated by most people
 - headache
 - nausea
 - difficulty concentrating
 - dizziness

Prevalence of Chemical Intolerance

- ◆ 15-30% of general population, mild, usually without disability
- ◆ 4-6% of general population, MCS, severe, usually with disability

Rates of Worsened Symptoms from Environmental Chemicals
(Buchwald & Garrity 1994)

	CFS	FM	MCS
pollution/ exhaust	53%	60%	97%
cigarette smoke	57%	64%	87%
gas/paint/ solvent fumes	67%	67%	97%
perfumes	57%	46%	90%



- Medical Comorbidities in Chemical Odor Intolerance**
- ovarian cysts/breast cysts
 - menstrual disorders
 - migraine headache
 - irritable bowel syndrome
 - food intolerances
 - sinusitis
 - rhinitis

- Family Histories in Chemical Odor Intolerant Individuals**
- hypertension and heart disease
 - diabetes mellitus
 - rhinitis/"allergies"
 - substance abuse, esp. paternal alcoholism

Phenomenology of Low Level Chemical Intolerance

- ◆ multiple symptoms in multiple systems
- ◆ different agents trigger similar symptoms in an individual patient (non-specificity)
- ◆ non-specific symptoms, with no clear relationship to toxicological properties of a specific chemical
- ◆ single symptom in all cases is "cacostmia," i.e., illness from low level chemicals with negative hedonic rxn

Representative Initiating & Eliciting Agents in Chemical Intolerance

- | <u>Initiating</u> | <u>Eliciting</u> |
|-------------------|----------------------|
| ■ solvents/VOCs | ■ solvents/VOCs |
| | ■ cleaning products |
| ■ pesticides | ■ pesticides |
| | ■ tobacco smoke |
| | ■ perfumes |
| | ■ automotive exhaust |
| | ■ natural gas |
| | ■ new carpet |

Working Hypotheses

- Chemical odor intolerance is a manifestation of neural sensitization.
- Individuals high in chemical odor intolerance are especially sensitizable.
- The capacity to demonstrate sensitization in chemically intolerant persons requires proper experimental design (2 or more sessions).

Two Step Dynamical Process

Initiation

Elicitation

Neural Sensitization Definition

- ◆ neural sensitization is the progressive increase in the size of the host's response to repeated, intermittent exposures to an initially novel stimulus.
- ◆ animal model for multiple chemical sensitivity, chronic fibromyalgia pain, temporal lobe epilepsy, craving in drug addiction, PTSD, recurrent depression

Neurochemistry of Sensitization: Neural Plasticity

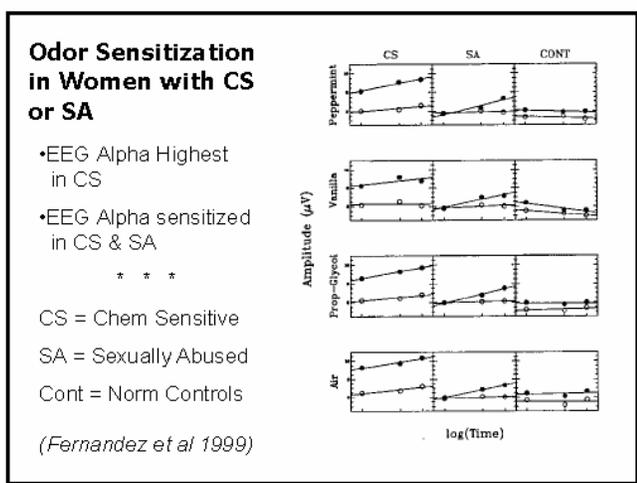
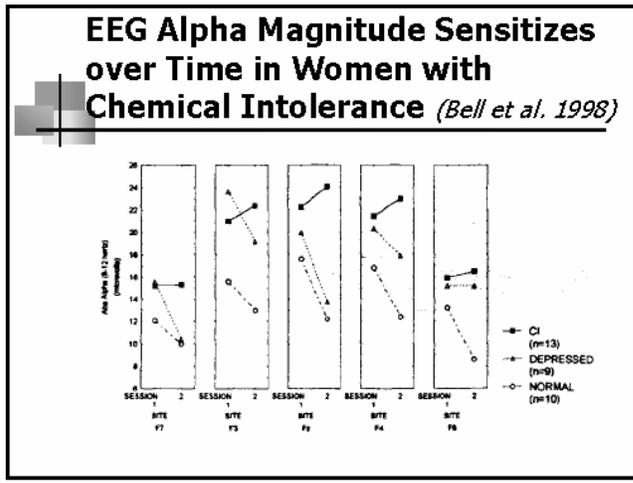
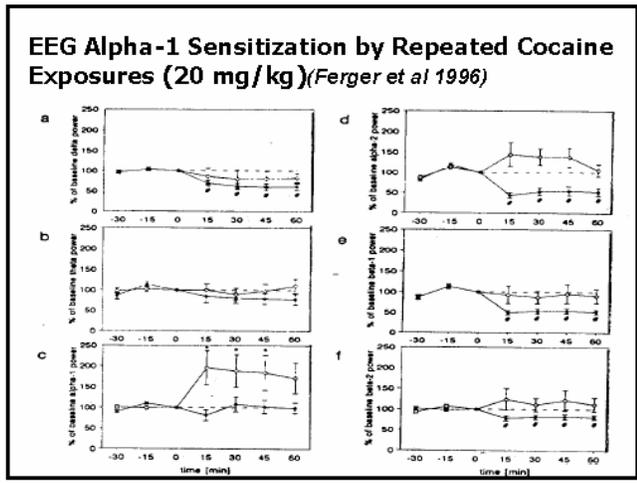
- Mesolimbic dopaminergic pathway - from ventral tegmental area to nucleus accumbens (reward pathway)
- Prefrontal dopaminergic pathways and limbic excitatory amino acid pathways modulate process

Animal Studies Showing Sensitization to Chemicals over Time

- formaldehyde (Sorg et al. 1996, 1998)
 - psychomotor activity to cocaine
- toluene, peppermint (Kay 1996)
 - limbic field potential 15-30 hertz activity
- toluene (vonEuler et al. 1994; Beyer et al 2001)
 - psychomotor activity to apomorphine, cocaine
- ethanol (Antelman et al. 1991; Grahame et al. 2000)
 - haloperidol-induced catalepsy
- lindane (Gilbert 1995)
 - electrical kindling of amygdala

Agents that Favor Mesolimbic Sensitization

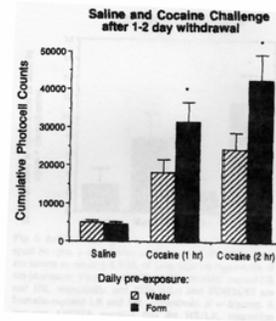
- ◆ cocaine, amphetamine
- ◆ physical or psychological stress
- ◆ lindane (*pesticides*)
- ◆ ethanol
- ◆ toluene (*solvents*)
- ◆ formaldehyde (*other VOCs*)
- ◆ interleukin-2; substance P agonists (*endogenous mediators*)



Cross-Sensitization: Agent "Nonspecificity"

- **Definition.** One agent initiates the sensitized state of heightened reactivity over repeated intermittent exposures, then a different, structurally-unrelated agent elicits the same level of reactivity upon its first exposure
- Stress with amphetamine or cocaine
- Cocaine with amphetamine
- Cocaine with morphine
- Formaldehyde with cocaine
- Toluene with apomorphine or cocaine
- Sucrose with amphetamine or cocaine

Formaldehyde Cross-Sensitizes with Cocaine (Sorg et al. 1996)



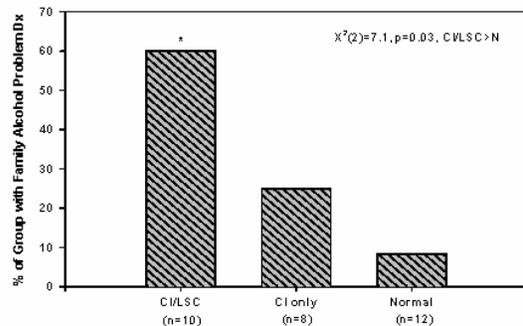
Host Factors in Animals that Increase Sensitizability

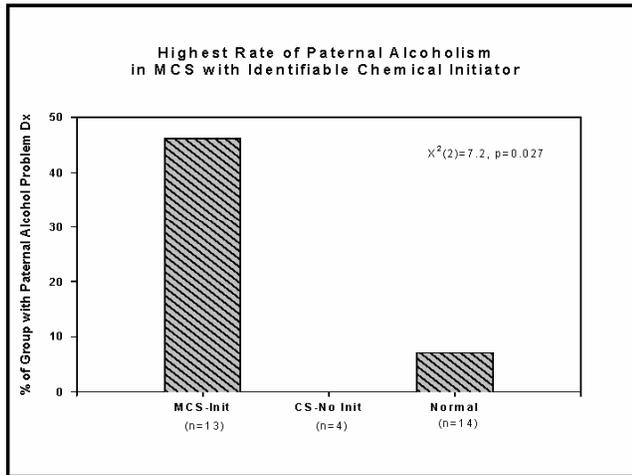
- genetic vulnerability
- sucrose/sweet preference
- hyperreactivity to novelty
- female gender
- lateral asymmetry (leftward turning)

Human Evidence for Mesolimbic Neural Sensitization Model in CI

- ◆ increased family histories of drug or alcohol problems in CI
(genetic vulnerability)
- ◆ increased scores on Carbohydrate Addicts Test in CI
(increased sucrose intake predicts sensitizability)
- ◆ Altered resting EEG alpha & beta activity in CI
(cf., alcoholics' offspring & in stimulant drug-sensitized animals)
- ◆ more women than men report CI
(female animals are more sensitizable than males)

Highest Prevalence of Family Alcoholism Diagnoses in Chemically Intolerant with Lifestyle Changes





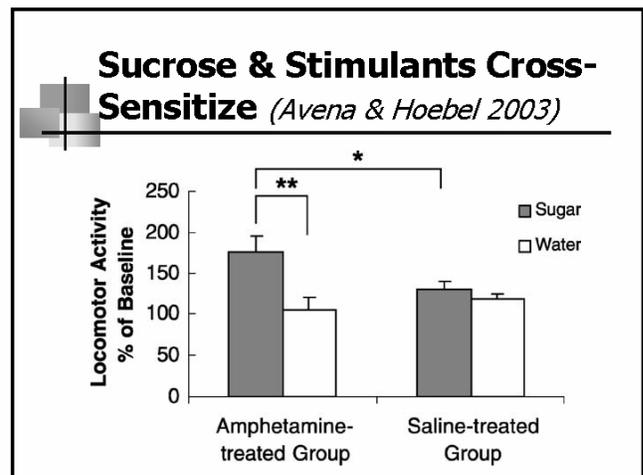
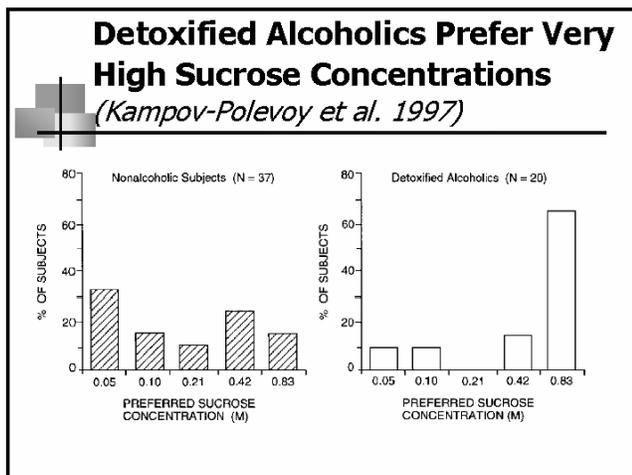
Different Rates of Psychiatric Comorbidity by Group
(Fiedler et al. 1996)

Current Psychiatric Disorders (p=.002)

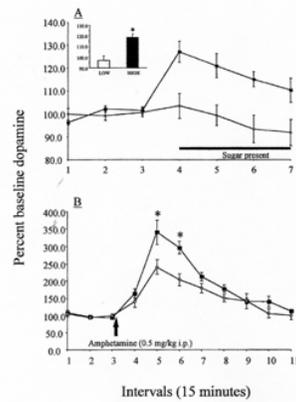
- MCS (identifiable chem initiator) 26%
- CS (no identifiable initiator) 62%
- CFS 39%

Lifetime Psychiatric Disorders (p=.004)

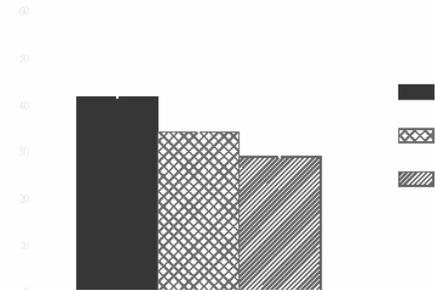
- MCS (identifiable chem initiator) 43%
- CS (no identifiable initiator) 69%
- CFS 72%



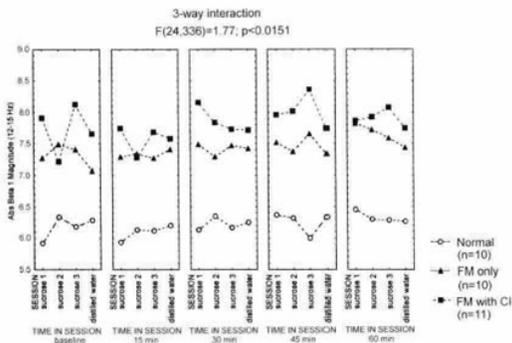
Sucrose Enhances Dopamine in Nucleus Accumbens of High vs Low Sugar Feeders
(Sills et al. 1998)



Highest Carbohydrate Addicts Scale Scores in Fibromyalgia Patients with Chemical Intolerance (CI)



EEG Beta 1 Sensitization/Oscillation in Fibromyalgia after Lab Sucrose Ingestion
(Bell et al. 2001)



PGW Study Subjects

- 4 groups:
 - Unhealthy (ill) Gulf vets *with* chemical intolerance (CI) (n=22)
 - Unhealthy (ill) Gulf vets *without* chemical intolerance (n=24)
 - Healthy Gulf veterans (n=23)
 - Healthy veterans in military at same time but not deployed to Persian Gulf (Era vets) (n=20)

PGW Study Design I

- 4 sessions, once/week, same procedures for all subjects
- 1st 3 sessions – jet fuel (JP-8) or clean air sham; 4th session - perfume
- 15 randomized trials of acoustic startle stimuli during sessions for all subjects in all sessions

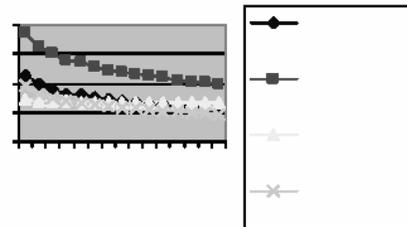
PGW Study Design II

- Parallel groups, randomized, double-blind assignment:
 - ½ of each group received 3 sessions of sub-olfactory threshold JP-8 jet fuel exposures;
 - ½ of each group received 3 sessions of clean air
- All groups received perfume exposure in Session 4 (cross-sensitization test)

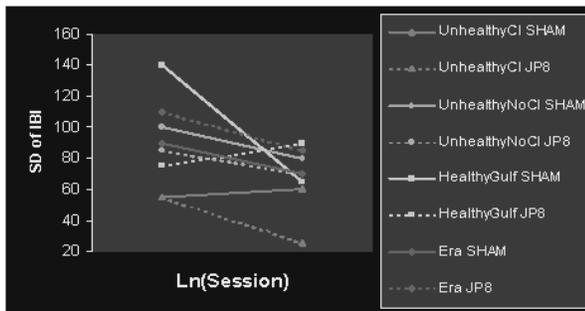
Descriptive Characteristics of Veteran Sample

- Mean age 40 SD 8 years, 85% male
 - Era veteran controls were older than the other 3 groups ($p < 0.01$)
- More Hispanic veterans in ill Gulf veteran groups (both with and without chemical intolerance)
- No group differences for education, gender distribution, marital status, employment status/income

Novelty Hyperreactivity in Unhealthy Gulf Vets with Chemical Intolerance: *Initial Blink Hyperreactivity to Noise AND Chemical Exposure (JP-8 jet fuel)*



Unhealthy Gulf Vets with CI Start Low and Decrease HR Variability over Three JP-8 Jet Fuel Exposure Sessions (Bell et al. 2003)



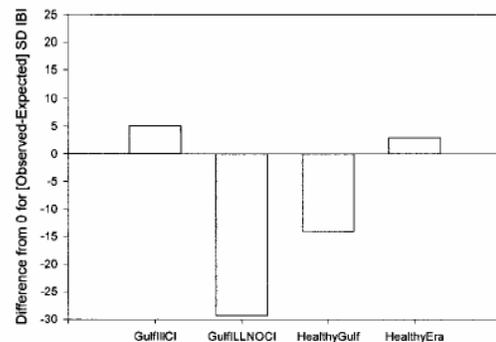
Gulf War Study: Heart Rate Variability Conclusions

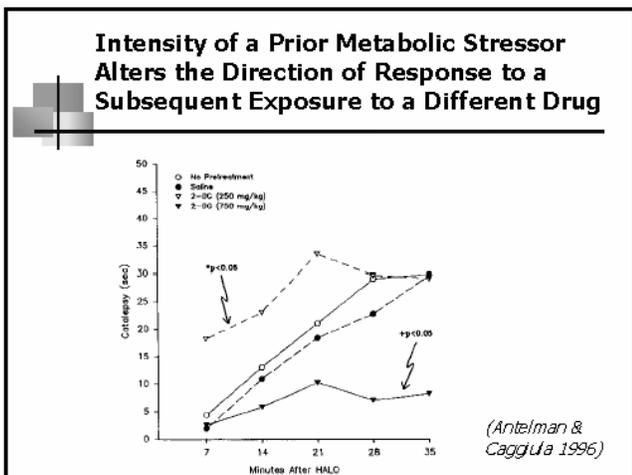
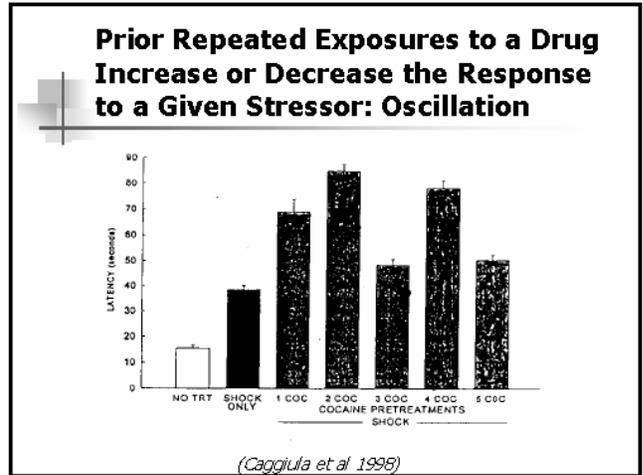
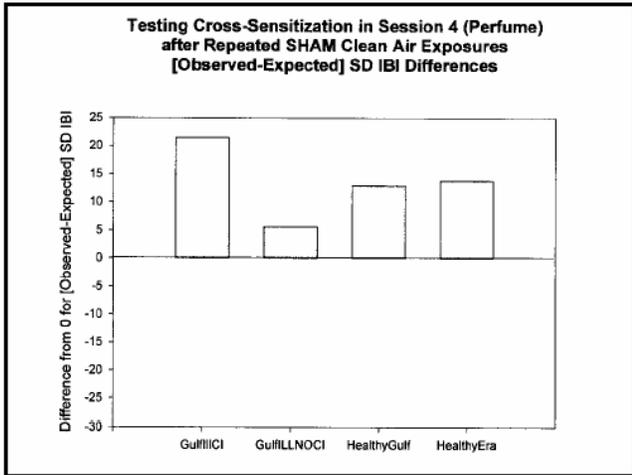
- ◆ As a function of JP-8 jet fuel exposure vs SHAM clean air over Sessions 1-3, all 3 contrasts for HR variability (SD IBI) differed significantly, after controlling for covariates:
 - Unhealthy Gulf Veterans with CI differ from Unhealthy Gulf Veterans without CI
 - Healthy Gulf Veterans differ from Healthy Era Veterans
 - Combined Unhealthy Gulf groups differ from Combined Healthy groups

Cross-Sensitization

- Replicated animal studies demonstrate that stress and drugs (stimulants) cross-sensitize
- Replicated animal studies demonstrate that drugs (cocaine) and environmental chemicals (formaldehyde, toluene) cross-sensitize

Testing Cross-Sensitization in Session 4 (Perfume) after Repeated JP-8 Fuel Exposures
[Observed-Expected] SD IBI Differences



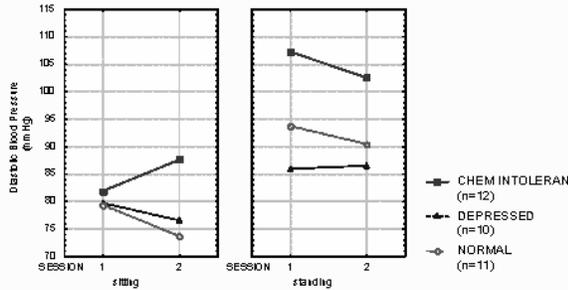


Cardiovascular Sensitization

- drug activation of mesolimbic dopaminergic system (D1, D2 receptors) induces increases in blood pressure & heart rate via vasopressin release (Cornish & vandenBuuse 1995)
- repeated stimulant drug administration induces sensitized increases over time in blood pressure, heart rate, body temperature, & locomotor activity (Yoshida et al. 1993)

Sitting Diastolic Blood Pressure Sensitization in CI (Bell et al. 1998)

Sensitization of Sitting Diastolic BP over Sessions in Chem Intolerant
3-way interaction (covaried for age)
 $F(2,29)=3.73; p<.0361$



Conclusions - MCS/CI

- Chemical intolerance may be a nonspecific marker of heightened sensitizability
- Chemical intolerance is physiologically different from depression or prior abuse
- Chemical intolerance may reflect in part dysfunction of limbic & mesolimbic pathways
- Past exposure history matters: chemicals, drugs, or life stressors may all initiate subsequent chemical intolerance
- Dietary factors, e.g., sucrose, facilitate time-dependent sensitization in susceptible persons

Gulf War Study Collaborators

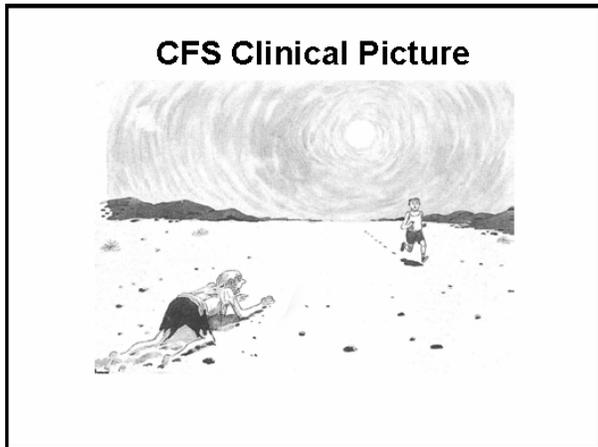
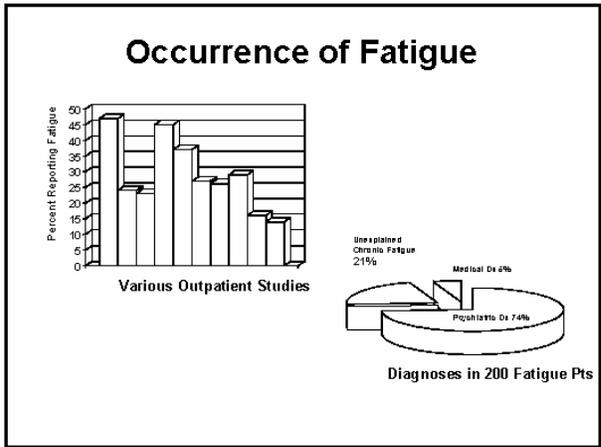
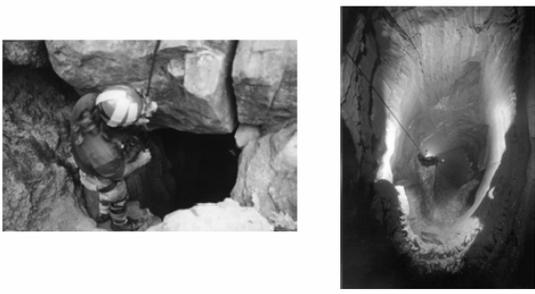
- Carol M. Baldwin, RN PhD
- Mercedes Fernandez, PhD
- Susanne Haugebak, BA
- Audrey Brooks, PhD
- Aurelio J. Figueredo, PhD
- Gary E. Schwartz, PhD

Funded in part by a VA Merit Review Grant and NIH K24 AT 00057.

Presentation 4- William Reeves

Chronic Fatigue Syndrome

Occurrence, Case Definition, Pathophysiology



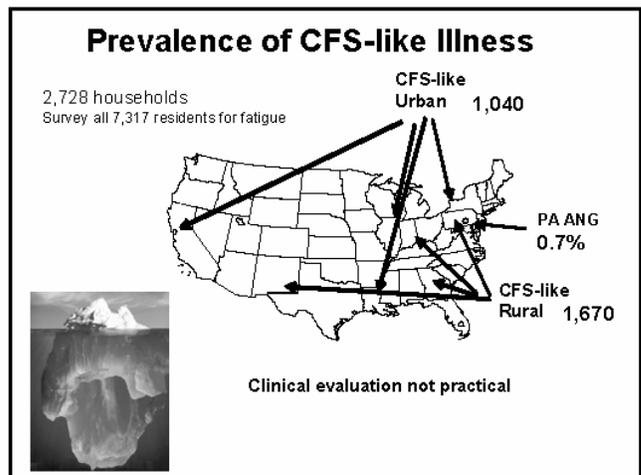
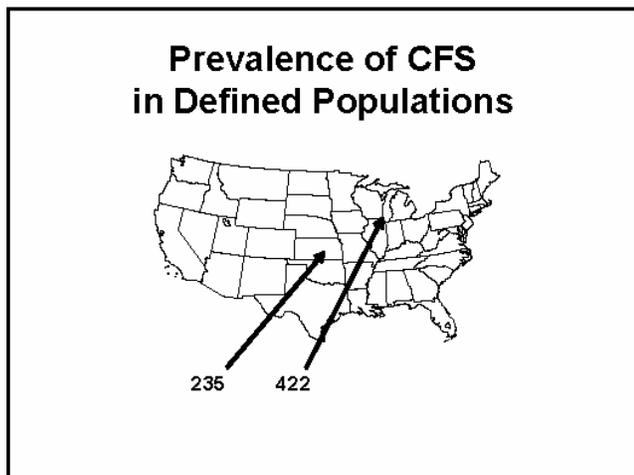
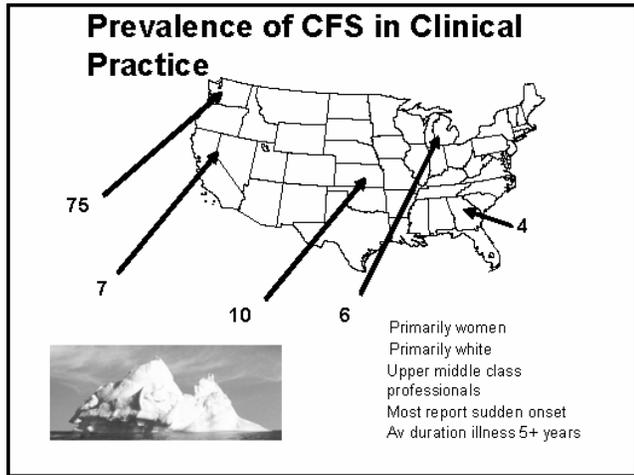
1994 CFS Case Definition

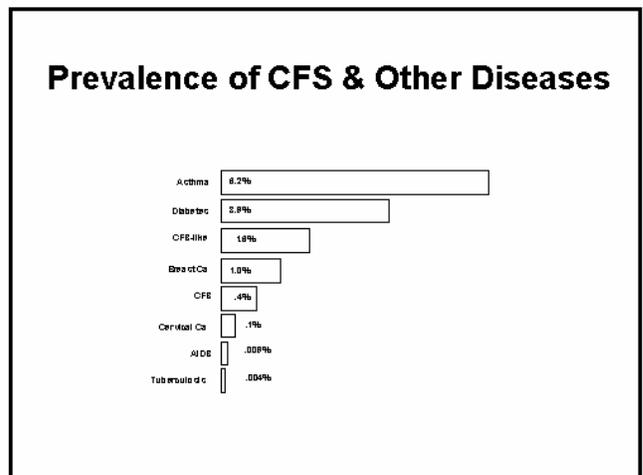
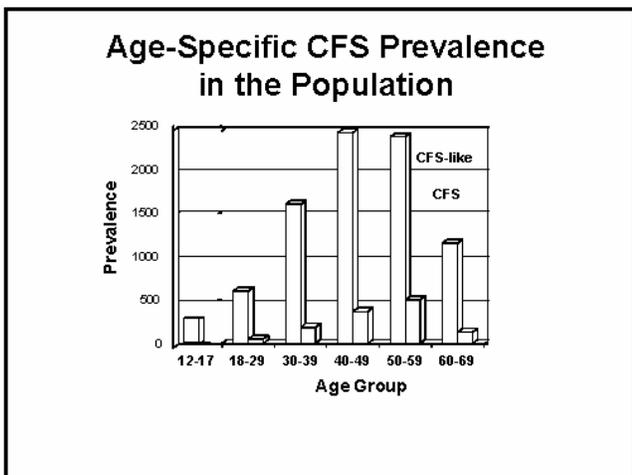
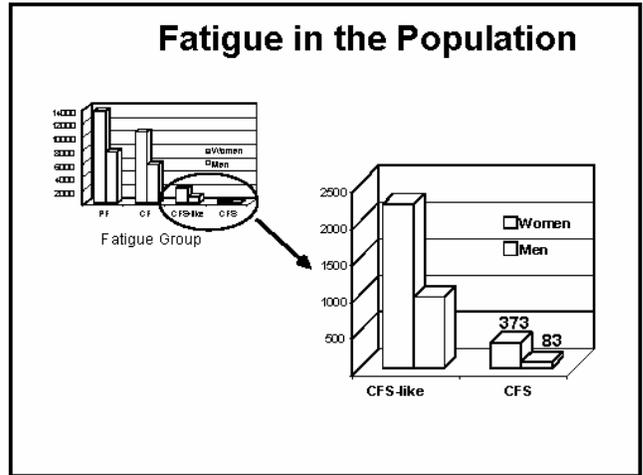
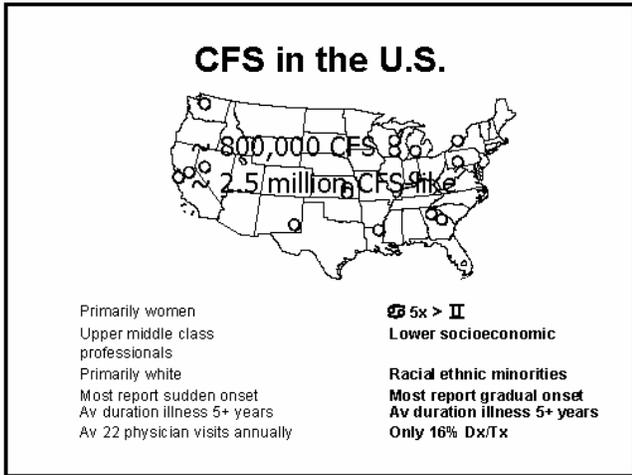
FATIGUE
Persistent/relapsing > 6 Mo.
Not alleviated by rest
Substantial reduction in activities

No explanatory medical or psychiatric causes

Accompanying Symptoms

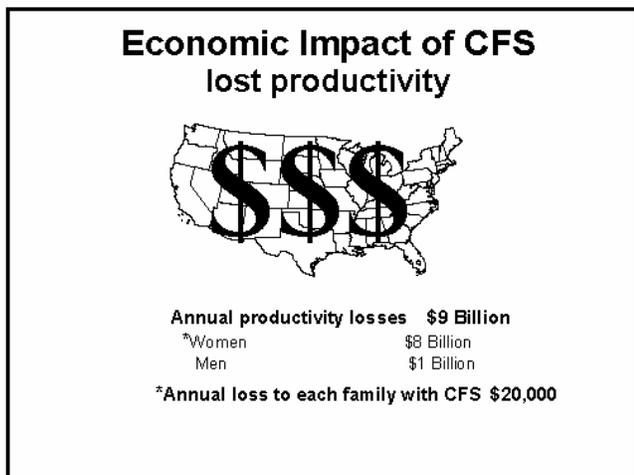
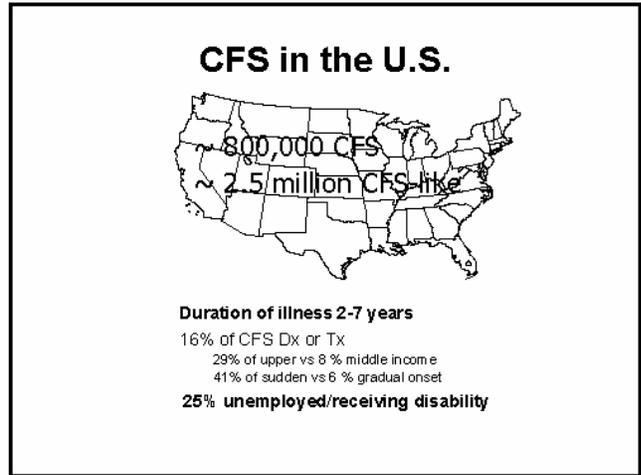
impaired memory/concentration	muscle pain
post exertional fatigue	multi-joint pain
unrefreshing sleep	sore throat
headaches	tender lymph nodes





Impairment and Disability (SF-36)

			NP	CFS	CBD	CCPD	Others	Depressed
Physical activity	Limited a lot performing all physical activities including bathing or dressing due to health	Performs all types of physical activities including the most vigorous without limitations due to health	90	59	46	57	57	72
Social activity	Extreme & frequent interference with normal social activities due to physical or emotional problems	Performs normal social activities without interference due to physical or emotional problems	95	59	71	72	79	57
Role physical	Problems with work or other daily activities due to physical health	No problems with work or other daily activities due to physical health	89	30	34	34	38	44
Role Emotional	Problems with work or other daily activities due to emotional problems	No problems with work or other daily activities due to emotional problems	96	69	64	60	75	40
Bodily pain	Very severe & extremely limiting pain	No pain or limitations due to pain	78	45	63	55	55	59
Mental health	Nervous & depressed all the time	Peaceful, happy, calm all the time	68	74	75	68	78	46
Vitality	Tired or worn out all the time	Peppy and energetic all the time	72	23	44	45	50	40
General health	Personal health poor & likely to get worse	Personal health excellent	85	59	47	45	60	53



CFS - Unanswered Questions



Race/ethnicity
Socioeconomic
Health care utilization
Rural vs. Urban
Economic impact

Risk Factors
Biomarkers

CFS has been studied for more than a decade and there are 3,000 articles in MEDLINE investigating the etiology or markers of CFS.

- Infectious
 - EBV, enteroviruses, HTLV, other viruses
 - Bacteria, rickettsia, novel agents
- Immune function
 - Immune system characterization
 - cell types, cytokines
 - Functional analysis
 - transformation, NK activity
- Neuroendocrine
 - HPA axis
 - Neuroendocrine/immune interaction
- Environmental

CFS has been studied for more than a decade and there are 3,000 articles in MEDLINE investigating the etiology or markers of CFS.

Why haven't we identified a consistent association?



- Problems with case definition
- Studies have been clinic-based
- Only prevalent cases studied
- CFS not amenable to classic case control design

CFS has been studied for more than a decade and there are 3,000 articles in MEDLINE investigating the etiology or markers of CFS.

Why haven't we identified a consistent association?



- Problems with case definition

Problems with Case Definition

FATIGUE

Persistent/relapsing > 6 Mo.

Not alleviated by rest

Substantial reduction in activities

No explanatory medical or psychiatric causes

Accompanying Symptoms

impaired memory/concentration

muscle pain

post exertional fatigue

multi-joint pain

unrefreshing sleep

sore throat

headaches

tender lymph nodes

Limitations of the CFS Case Definition

Developed by consensus not empirically

Based on clinical experience not population-based

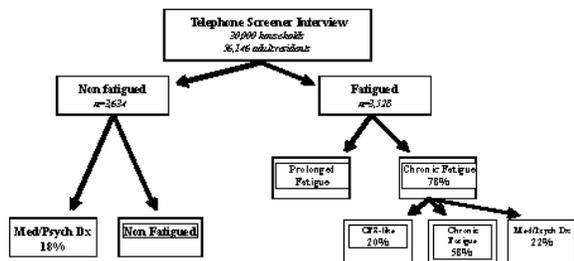
Defined by symptoms and disability

Focuses on Fatigue

Sensitivity/specificity not defined

Specific pathophysiologic process associated with CFS not identified

Empiric Case Definition Population Data Is the Consensus Construct Correct?



Wichita - Symptoms Lasting > 6 Months

• Unrefreshing sleep	62%	• Severe headaches	34%
• Go sleep or wake up	61%	• Numbness/tingling	32%
• Muscle aches/pain	50%	• Shortness of breath	32%
• Joint Pain	49%	• Stomach/abdominal pain	24%
• Sinus/nasal problems	47%	• Diarrhea	16%
• Depression	44%	• Nausea	14%
• Forgetfulness	44%	• Tender lymph nodes	11%
• General weakness	43%	• Chills	11%
• Difficulty thinking	43%	• Sore throat	7%
• Fatigue post exertion	43%	• Fever	6%
• Photophobia	36%		

• 4 CFS Symptoms 13%

Wichita - Factor Analysis

- Dichotomous factor analysis
 - Symptoms coded as 0 or 1
- Exploratory phase (n=718)
 - To estimate number of factors and factor structure
- Confirmatory phase (n=673)
 - To test exploratory model

Wichita - Three-factor Model

	Musculoskeletal	
Muscle aches or pain	89	◆
Joint pain	88	◆
Unusual fatigue post-exertion	48	◆
General weakness	40	
Shortness of breath	31	◆
Sore throat	72	◆
Tender lymph nodes	70	◆
Nausea	61	
Fever	57	
Diarrhea	55	
Stomach or abdominal pain	55	
Chills	41	
Sinus or nasal problems	34	◆
Difficulty thinking or concentrating	80	◆
Forgetfulness or memory problems	75	◆
Unrefreshing sleep	45	◆
Depression	50	
Problems go to sleep or wake up	47	
<i>Factor correlations</i>	<i>0.55, 0.27, 0.33</i>	

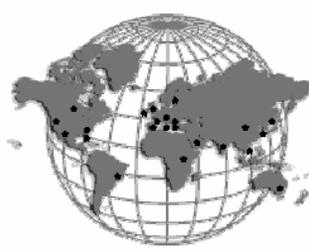
Empiric Case Definition Population Data Is the Consensus Construct Correct?



22 Countries
50 Sites
37,724 chronic fatigue patients

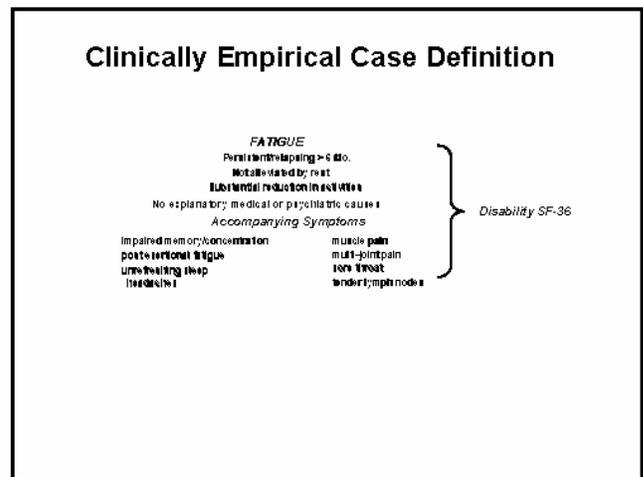
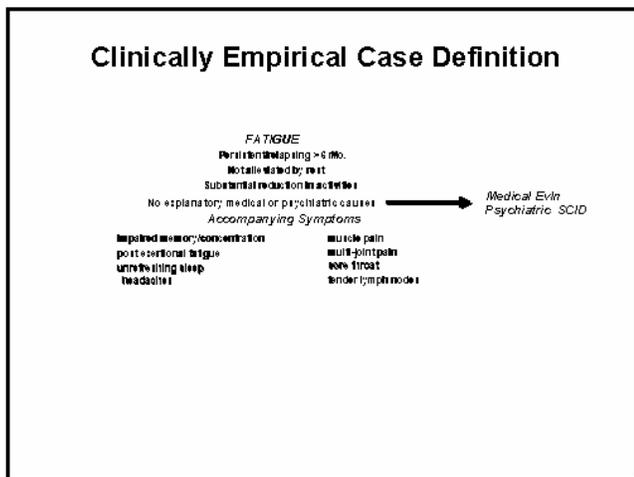
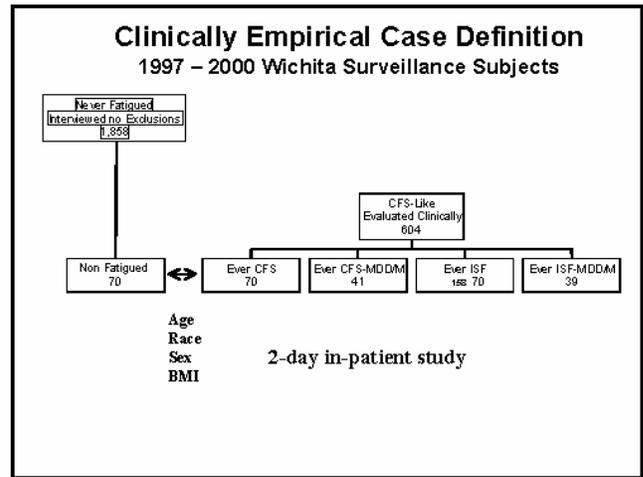
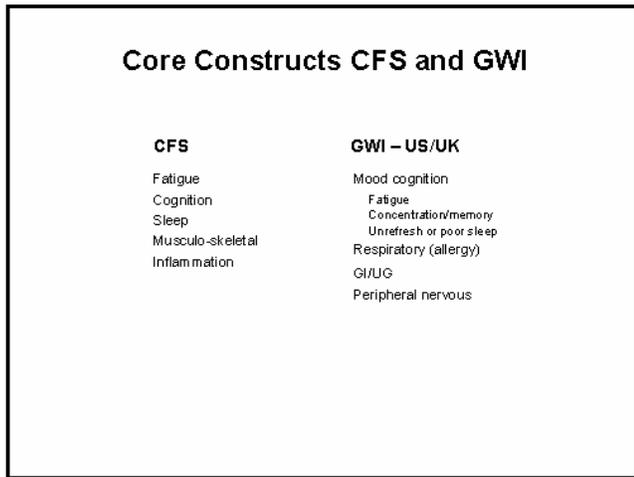
15,749 Community
 19,472 Primary
 2,503 Referral

International Study - Factor Analysis The Construct



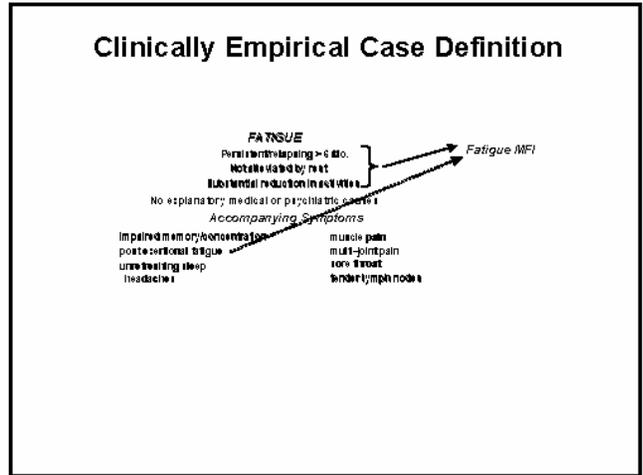
Key Elements
 Mood
 Musculoskeletal
 Inflammation-Infection
 Cognition
 Sleep

Consistent across cultures
Tertiary care unstable



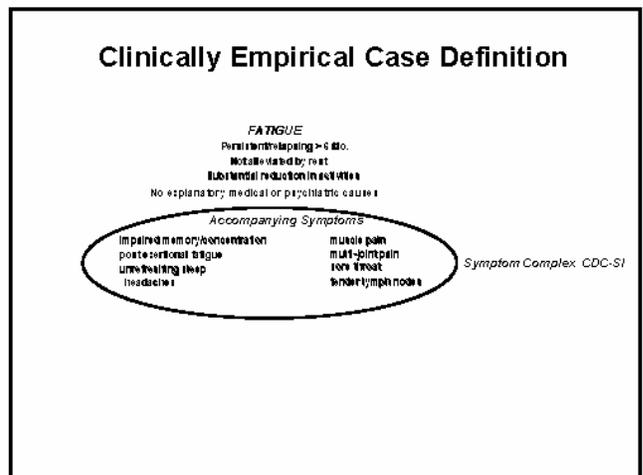
Function/Well Being SF-36

Physical function	Limited a lot performing all physical activities including bathing or dressing due to health	Performs all types of physical activities including the most vigorous without limitations due to health
Social function	Extreme & frequent interference with normal social activities due to physical or emotional problems	Performs normal social activities without interference due to physical or emotional problems
Role physical	Problems with work or other daily activities due to physical health	No problems with work or other daily activities due to physical health
Role Emotional	Problems with work or other daily activities due to emotional problems	No problems with work or other daily activities due to emotional problems
Bodily pain	Very severe extremely limiting pain	No pain or limitations due to pain
Mental health	Nervous & depressed all the time	Peaceful, happy, calm all the time
Vitality	Tired or worn out all the time	Pep and energy all the time
General health	Personal health poor & likely to get worse	Personal health excellent



Fatigue Characteristics MFI

General fatigue	I feel fresh	I feel tired
Physical fatigue	Physically I feel able to do a lot	Physically I feel only able to do a little
Mental fatigue	It takes little effort to concentrate	It takes a lot of effort to concentrate
Reduced motivation	I feel I can do anything	I don't feel like doing anything
Reduced activity	I think I do a lot in a day	I think I do very little in a day



Symptom Characteristics CDC Symptom Inventory

- Case Definition
 - Post-exertional malaise
 - Unrefreshing sleep
 - Impaired memory/concentration
 - Muscle pain
 - Multi-joint pain
 - Headaches
 - Sore throat
 - Tender cervical/axillary nodes
- Other symptoms
 - Feverishness
 - Diarrhea
 - Chills
 - Nausea
 - Stomach/abdominal pain
 - Sinus/nasal problems
 - Shortness of breath
 - Sensitivity to light
 - Depression

CDC Symptom Inventory

- Frequency
 - 1 = rarely
 - 2 = Some of the time
 - 3 = Most of the time
 - 4 = All of the time

*

- Intensity
 - 1 = Mild
 - 2.5 = Moderate
 - 4 = Severe

Clinically Empirical Case Definition

SF-36	Physical Function ≤ 70 or Social Function ≤ 75 or Role physical ≤ 50 or Role Emotional ≤ 67 and	
MFI	General fatigue ≥ 13 or Reduced activity ≥ 10 and	
CDC SI	Post-exertional malaise Unrefreshing sleep Impaired memory/concentration Muscle pain Multi-joint pain Headaches Sore throat Tender cervical/axillary nodes	} > 3 Symptoms and Score > 24

Comparison of Standard 1994 and Clinically Empirical Definitions

Standard 1994 Definition	Empiric Definition			
	CFS	ISF	NF	
CFS	10 (63%)	6 (38%)	0	16
ISF	32 (42%)	38 (50%)	6 (8%)	76
Not Fatigued	0	13 (18%)	58 (82%)	71
	42	57	64	

Correlations of disability, fatigue, and symptoms with classification

	CFS	ISF	NF
<i>Physical function</i>	53	77	90
<i>Social function</i>	50	74	95
<i>Role physical</i>	18	61	89
<i>Role Emotional</i>	56	76	96
Bodily pain	42	60	78
Mental health	66	75	87
General health	51	70	85
Vitality	19	37	72
<i>General fatigue</i>	18	15	8
<i>Reduced activity</i>	15	11	6
Physical fatigue	14	11	7
Mental fatigue	14	10	7
Reduced motivation	12	10	6
Symptom Inventory	47	18	6

Other Parameters to Evaluate in Context of Clinically Empirical Case Definition

- Polysomnography
- Cognitive Function
- Autonomic Nervous System
- Neuroendocrine
- Immune system
- Psychometrics
- Gene Activity
- Proteomics

CFS has been studied for more than a decade and there are 3,000 articles in MEDLINE investigating the etiology or markers of CFS.

Why haven't we identified a consistent association?

- Studies have been clinic-based
- Only prevalent cases studied



CFS Not Amenable to Classic Case-Control Design

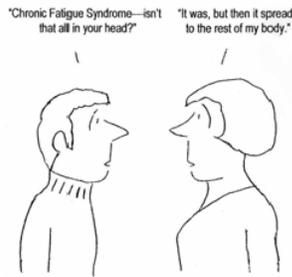
CFS is a Complex Illness

- Illness represents alterations in complex systems of homeostasis
- Not a result of a single mutation or single environmental factor
- Arise from a combined action of many genes, environmental factors and risk-conferring behavior
- Understanding complex illness may elucidate the common pathways of other complex diseases



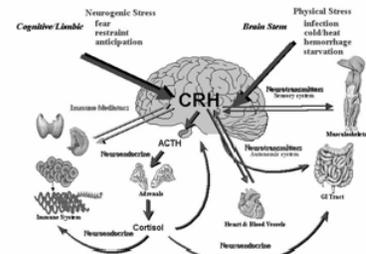
CFS is a Complex Illness

The pathophysiology of CFS appears to involve afferent and efferent pathways of brain-body communication



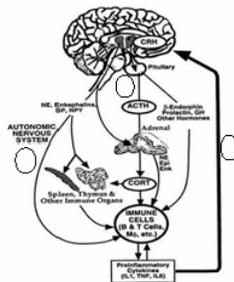
CFS is a Complex Illness

The pathophysiology of CFS appears to involve afferent and efferent pathways of brain-body communication

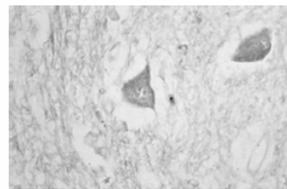


CFS, what to sample?

- No identified lesion
- What sample representative of CFS disease?

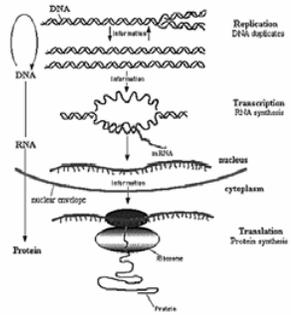


Is Peripheral Blood a Reasonable Sample?

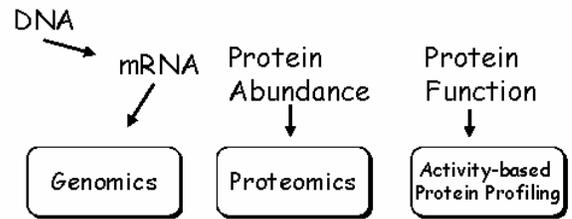


- PBMC reflect immune system
- PBMC reflect endocrine system
- Leukocytes in CNS in normal and disease states
 - Activated T cells - enter/leave
 - NK cells - enter/leave
 - B cells - random traffic
 - Monocytes - assist in maintenance and function of BBB enter/leave CNS

Central Dogma of Molecular Biology



Biomarker Discovery Strategy



Gene Expression Profiling

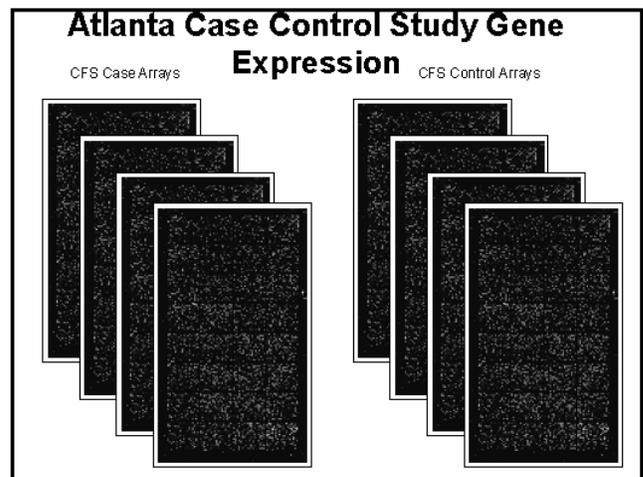
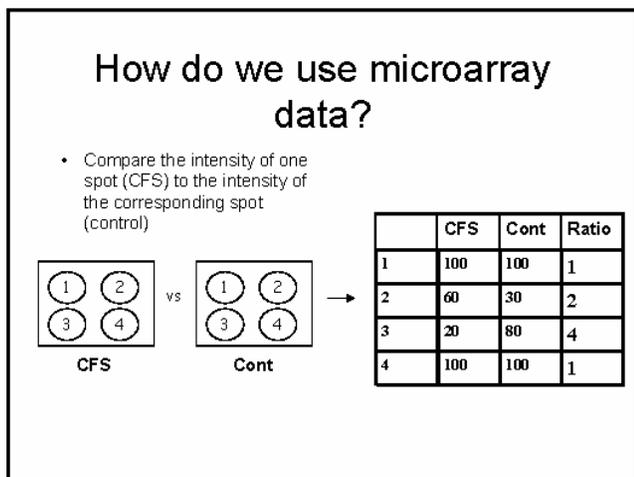
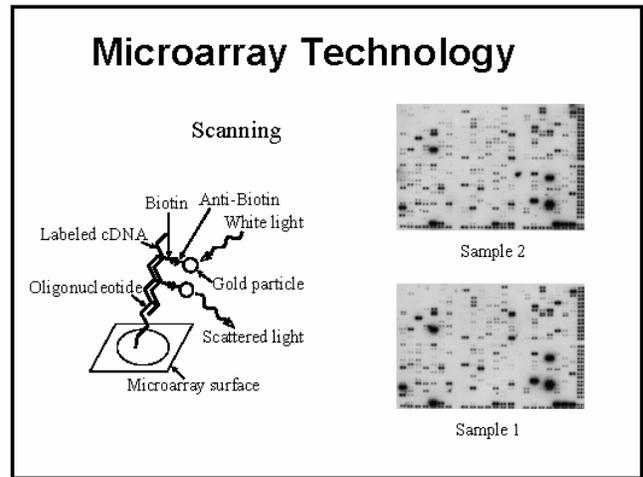
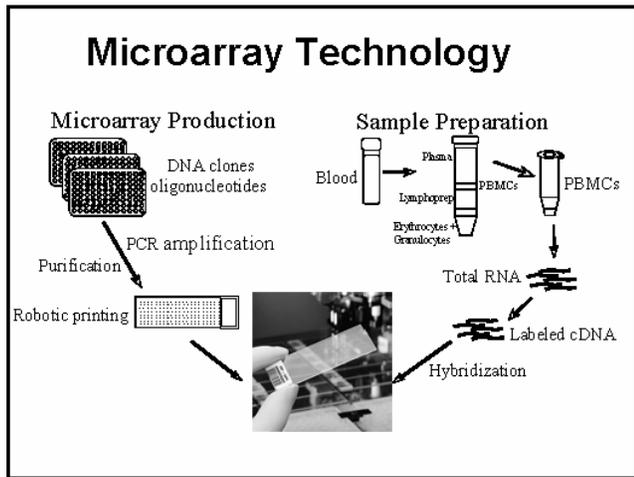
- An attempt to measure expression levels of all genes in a cell and to correlate the pattern with disease phenotype

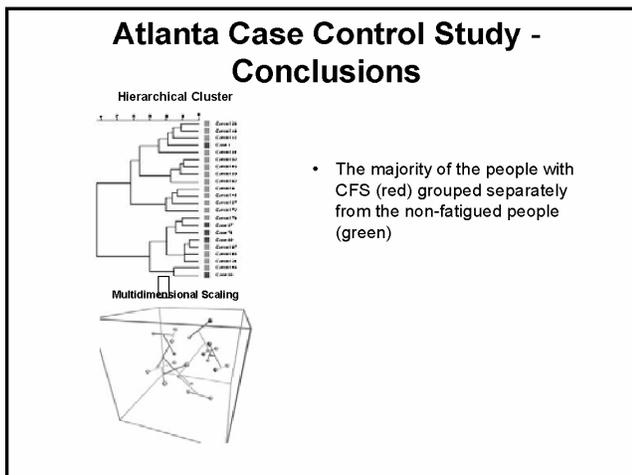
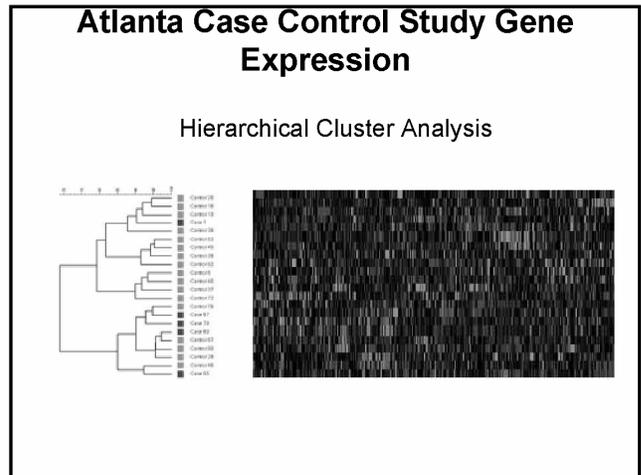
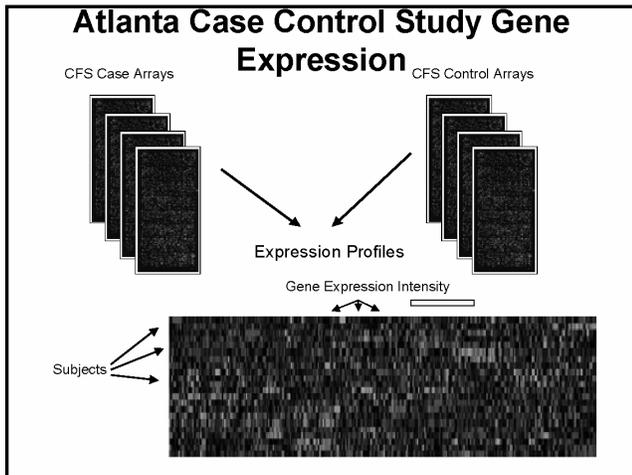


Gene Expression Profiling

- An attempt to measure expression levels of all genes in a cell and to correlate the pattern with disease phenotype







To Empirically Subtype CFS

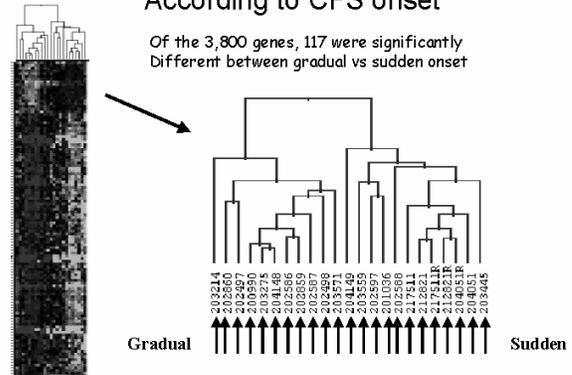
- 23 women with CFS from Wichita
- Measure expression of 3,800 genes
- Question:
 - Could gene expression profiles and differentially expressed genes distinguish subtypes of CFS?

Gene Expression to Define CFS ...

- Gene expression profiles compared by clinical characteristics
 - Gradual onset versus sudden onset
 - ≤50 years of age versus >50 years of age
 - ≤10 years of illness vs. >10 years of illness
 - 4 or 5 symptoms vs. ≥6 symptoms
 - Body mass index (normal, overweight, obese)
 - Symptom severity group

Hierarchical cluster analysis on genes According to CFS onset

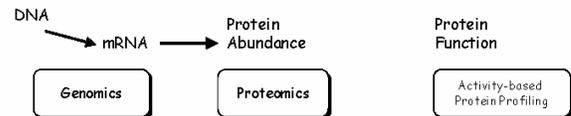
Of the 3,800 genes, 117 were significantly Different between gradual vs sudden onset



CFS Subtyping - Conclusions

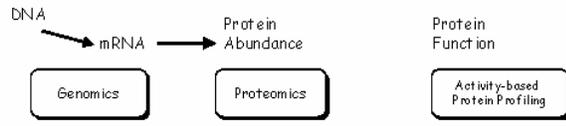
- First "molecular" evidence of a difference between people whose CFS occurred suddenly & those with gradual illness onset
- Different profiles imply different pathophysiology
- Several immune, endocrine and metabolic genes and pathways involved
- Differentially expressed genes in RNA processing and metabolic pathways account for most of the (significant) differences between CFS and controls

Biomarker Discovery Strategy



- Gene expression of PBMC tells us how the body is responding to the illness from the perspective of the PBMC

Biomarker Discovery Strategy

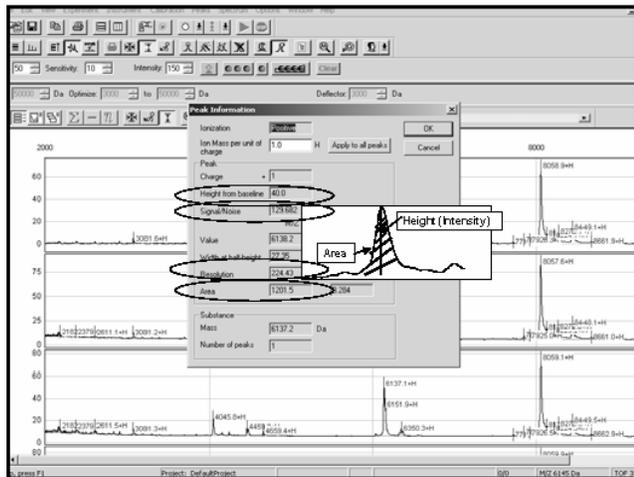
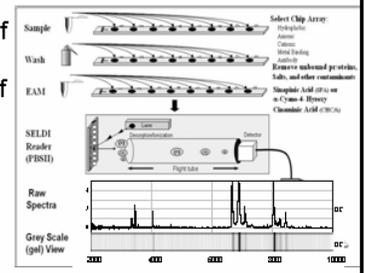


- Gene expression of PBMC tells us how the body is responding to the illness from the perspective of the PBMC
- Protein profiling (proteomics) of the serum will tell us about any process going on in the body
 - Serum is ideal for biomarker discovery as it samples that entire body and contains protein spillover from most bodily processes

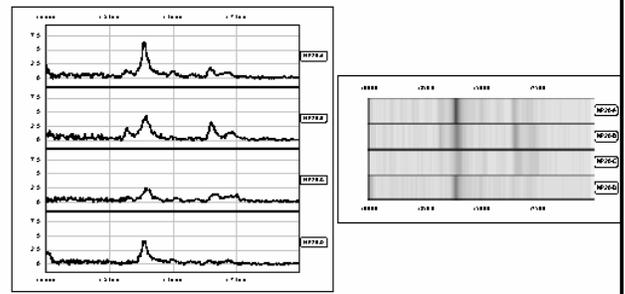
Proteomics

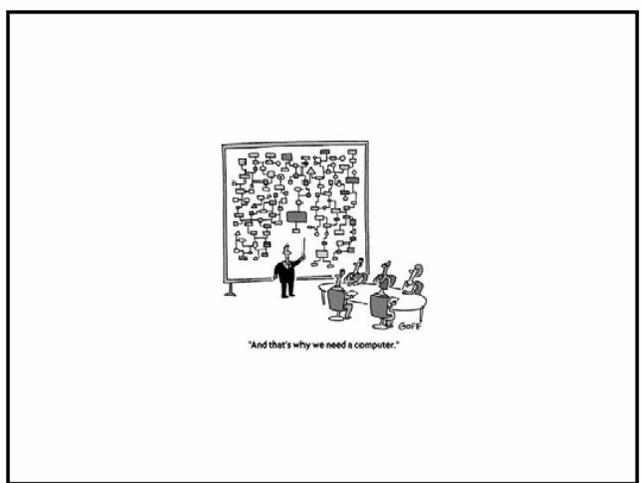
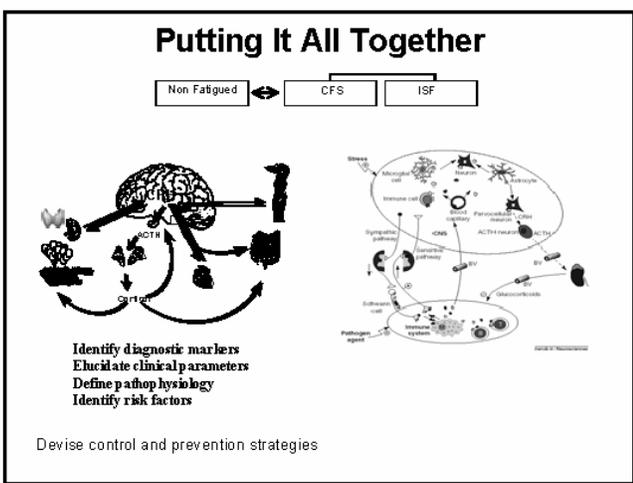
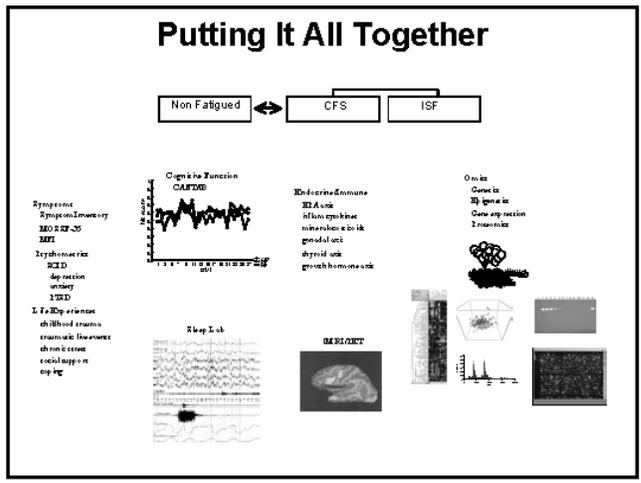
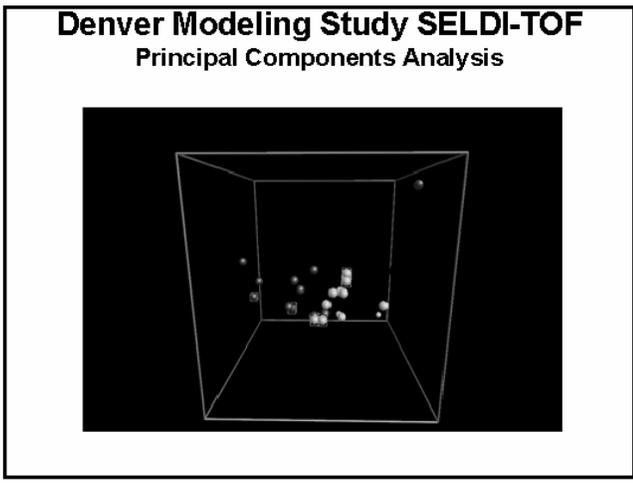
- Mass spectrometry of serum proteins to identify biomarkers of disease and to characterize the pathophysiology of disease

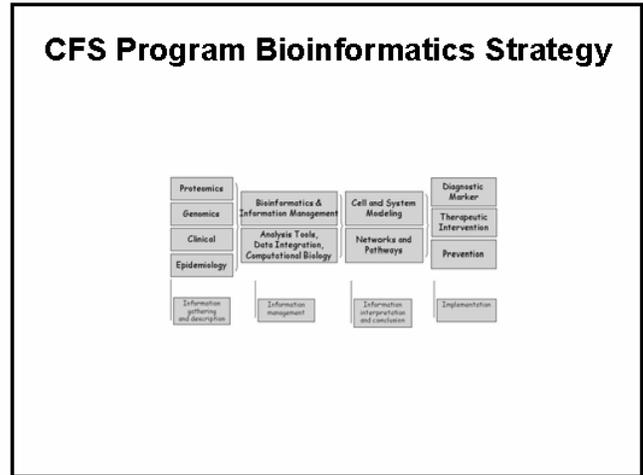
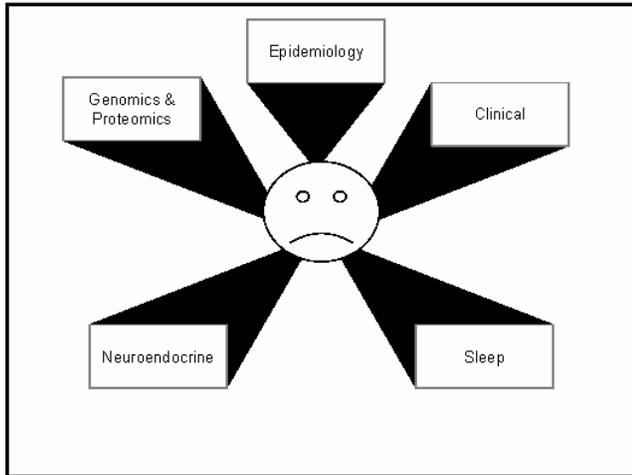
SELDI-TOF



SELDI-TOF Output







Presentation 5 – Daniel Clauw

The Pathophysiological Basis of Fibromyalgia

Daniel J. Clauw, MD

Professor of Medicine, Division of Rheumatology
 Assistant Dean for Clinical and Translational Research
 Director, Chronic Pain and Fatigue Research Center
 University of Michigan Medical Center

Paradigm Shift in Fibromyalgia

- Discrete illness
- Pain, focal areas of tenderness
- Psychological and behavioral factors nearly always present

American College of Rheumatology Criteria

- Chronic widespread pain
- Tenderness in $\geq 11/18$ tender points

- Part of a larger continuum
- Many somatic symptoms, diffuse tenderness
- Psychological and behavioral factors play roles in some individuals

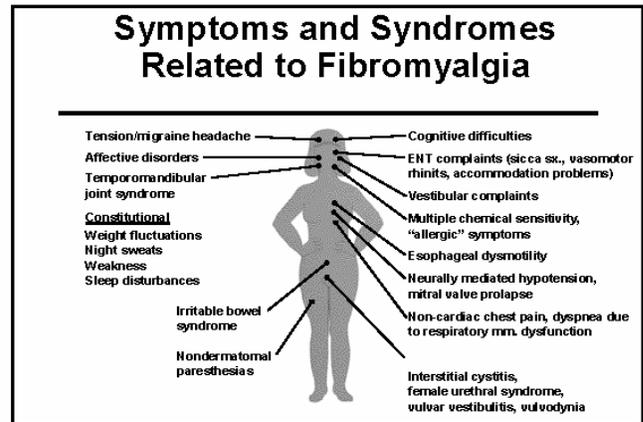
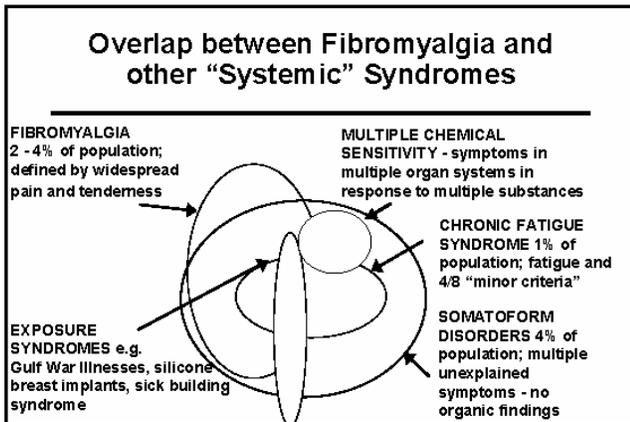
Tenderness in the General Population

- Pain and other somatic symptoms occur as a continuum rather than as "yes" or "no"
- In fact, all of the defining features of somatic syndromes such as FM, IBS, etc. occur as a continuum
- In the absence of a peripheral injury tenderness throughout the body is highly correlated

Prevalence of Chronic Somatic Symptoms/Syndromes in U.S.

Symptom	Males (%)	Females (%)
Widespread Pain	~10	~15
Regional Pain	~15	~20
Fatigue	~10	~15
Irritable Bowel	~10	~15
Migraine	~10	~15
Tension HA	~50	~70

Wolfe et. al. 1994; Chey 2002; Saito 2002; Jason 1999



Summary : What is Fibromyalgia?

- A discrete disorder
- The prototypical chronic central pain state, that can help us understand central mechanisms that may play a role in pain and other symptoms seen in chronic multisymptom illnesses

Summary

- **Peripheral (nociceptive)**
 - Primarily due to *inflammation* or mechanical damage in periphery
 - NSAID, opioid responsive
 - Responds to procedures
 - Behavioral factors minor
 - Examples
 - OA
 - Acute pain models (e.g. third molar, post-surgery)
 - RA
 - Cancer pain
- **Central (non-nociceptive)**
 - Primarily due to a central disturbance in pain processing
 - Tricyclic, neuroactive compounds most effective
 - Behavioral factors more prominent
 - Examples
 - Fibromyalgia
 - Irritable bowel syndrome
 - Tension headache
 - Idiopathic low back pain
 - Interstitial cystitis / vulvodynia, non-cardiac chest pain / etc.

What causes fibromyalgia?

- **Genetics**
- **“Triggers”**
- **Mechanisms**
 - Relationship between physiologic and psychologic factors
 - Disordered sensory processing
 - Autonomic/neuroendocrine dysfunction

Genetics of Fibromyalgia

- Clearly is a strong *familial* predisposition
 - Most recent work by Arnold, Hudson, et. al. suggest > 8 OR for first degree relatives, and much less familial aggregation (OR 2) with affective disorders
- Genes that may be involved
 - 5 HT 2A receptor polymorphism T/T phenotype (Bondy 1999)
 - Serotonin transporter (Offenbaecher 1999)
 - COMT (Catecholamine O-Methyl Transferase)
 - Shown to be involved in pain transmission (Zubieta 2002)
 - Slightly different in FM (Gursoy 2003)

What causes fibromyalgia?

- **Genetics**
- **“Triggers”**
- **Mechanisms**
 - Relationship between physiologic and psychologic factors
 - Disordered sensory processing
 - Autonomic/neuroendocrine dysfunction

“Stressors” capable of triggering these illnesses – supported by case-control studies

- Infections (e.g., parvovirus, EBV, Lyme, Q fever; not common URI)
- Physical trauma (automobile accidents)
- Psychological stress / distress
- Hormonal alterations (e.g., hypothyroidism)
- Drugs
- Vaccines
- Certain catastrophic events (war, but not natural disasters)

Clauw, Chrousos; Neuroimmunomodulation, 1997

What causes fibromyalgia?

- **Genetics**
- **“Triggers”**
- **Mechanisms**
 - Relationship between physiologic and psychologic factors
 - Disordered sensory processing
 - Autonomic/neuroendocrine dysfunction

The Physiological / Psychobehavioral Continuum



Population	Primary Care	Tertiary Care
<i>Neurobiological</i>		<i>Psychosocial factors</i>
<ul style="list-style-type: none">● Abnormal sensory processing● Autonomic dysfunction● HPA dysfunction● Smooth muscle dysmotility		<ul style="list-style-type: none">● General “distress”● Psychiatric co-morbidities● Cognitive factors● Maladaptive illness behavior● Secondary gain issues

What causes fibromyalgia?

- **Genetics**
- **“Triggers”**
- **Mechanisms**
 - Relationship between physiologic and psychologic factors
 - Disordered sensory processing
 - Autonomic/neuroendocrine dysfunction

Sensory Processing in Fibromyalgia

A problem with pain “volume control”

- Patients display a normal “detection threshold” to sensory stimuli, but an decreased “noxious threshold”
- This is not just to pressure, but also other stimuli, e.g. heat, noise, electrical stimulation.
- The general increase in sensory sensitivity could theoretically be due to:
 - psychological (e.g. “expectancy” or hypervigilance) or
 - neurobiological changes in nociceptive processing (e.g., sensitization or reduced descending pain inhibition).

Neurobiological Pain Amplification Mechanisms

- Peripheral
 - Sensitization
 - Recruitment of silent nociceptors (e.g. A-beta fibers in inflammation)
 - Alteration in phenotype
 - Hyper-innervation (Ruda, 2001)
- Central
 - Central sensitization (Woolf, 1983)
 - De-afferentation
 - Disinhibition
 - Structural reorganization

Using Experimental Pain Testing to Examine Pain Processing

- Hyperalgesia / allodynia distant from site of pain
 - FM (Petzke/Clauw/Gracely; Geisser/Casey/Crofford)
 - IBS (Mayer, Haliboff, Chung; Whitehead)
 - TMD (Maixner; Kashima)
 - Tension HA (Langemark)
 - Low back pain (Clauw)
 - Vulvodinia/vulvar vestibulitis (Giesecke/Reed)
- Potential Mechanisms in FM
 - Wind-up in FM (Price, Staud)
 - Absence of DNIC (Kosek; Marchand)

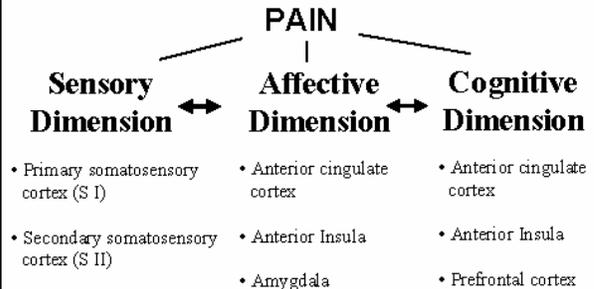
Functional MRI in Chronic Pain

It is "all in your head"

- fMRI takes advantage of magnetic moment of deoxygenated blood, and thus can detect neuronal activations associated with stimuli
- Most imaging sequences take advantage of "on-off" paradigms, where the difference between the blood flow in a "neutral" condition (e.g. touch) and pain is imaged
- PET and fMRI have identified a number of brain regions involved in pain processing

Pain Processing

(Melzack & Wall; Melzack & Casey)



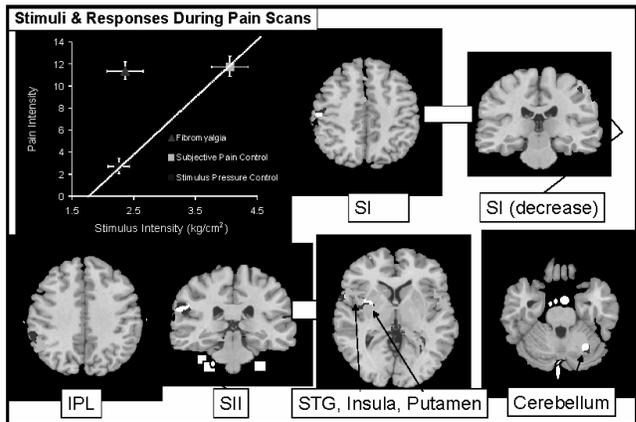
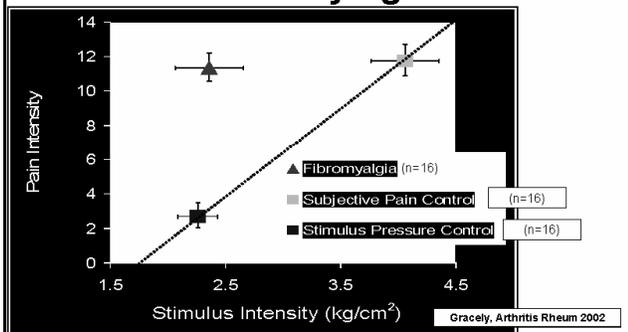
fMRI in Fibromyalgia and Related Conditions

- Is there objective evidence of augmented pain processing in fibromyalgia? (Gracely et. al. Arthritis Rheum 2002)
- Role of depression in pain processing in FM (Giesecke et. al. Arthritis Rheum, in press)
- Role of cognitive factors in pain processing in FM
 - Locus of control
 - Catastrophizing (Gracely et. al. Brain, 2004)
- Is there objective evidence of augmented pain processing in idiopathic chronic low back pain? (Giesecke et. al. Arthritis Rheum, 2004)
- Is FM a more global problem with interoception?

fMRI in Fibromyalgia and Related Conditions

- Is there objective evidence of augmented pain processing in fibromyalgia?
- Role of depression in pain processing in FM
- Role of cognitive factors in pain processing in FM
 - Locus of control
 - Catastrophizing
- Is there objective evidence of augmented pain processing in idiopathic chronic low back pain?

Functional MRI in Fibromyalgia



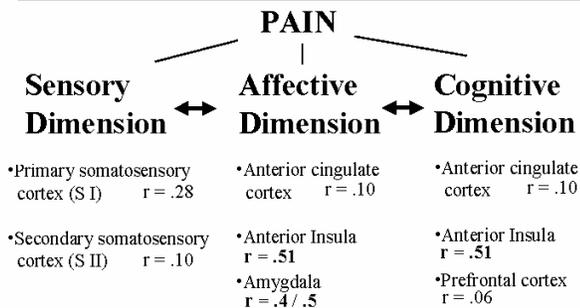
fMRI in Fibromyalgia and Related Conditions

- Is there objective evidence of augmented pain processing in fibromyalgia?
- **Role of depression in pain processing in FM**
- Role of cognitive factors in pain processing in FM
 - Locus of control
 - Catastrophizing
- Is there objective evidence of augmented pain processing in idiopathic chronic low back pain?
- Is FM a more global problem with interoception?

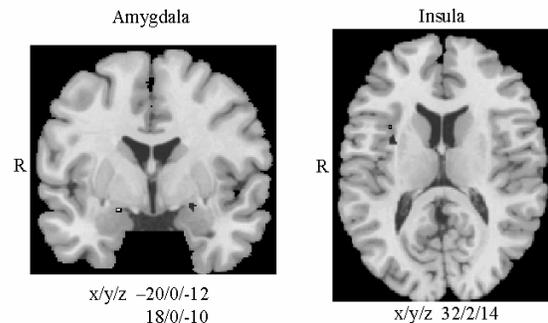
Influence of Depression on Pain Processing

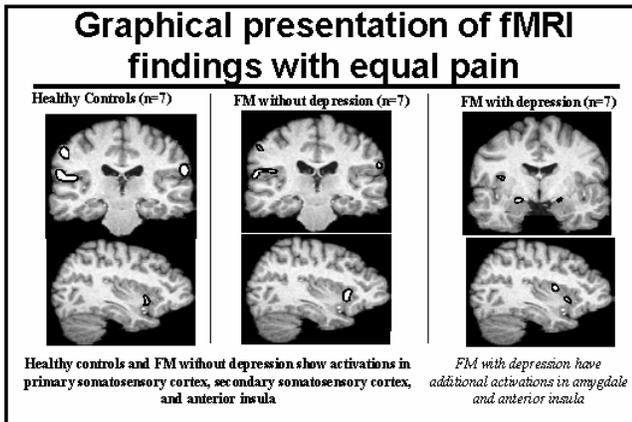
- **30 subjects with FM and various levels of depressive symptomatology**
- **Received painful stimuli to left thumb**
- **Neuronal activations in pain processing areas**
 - **Correlated with depressive symptoms as measured by CES-D**
 - **Group comparisons performed comparing FM with major depression, FM without major depression, and controls**

Correlational Results

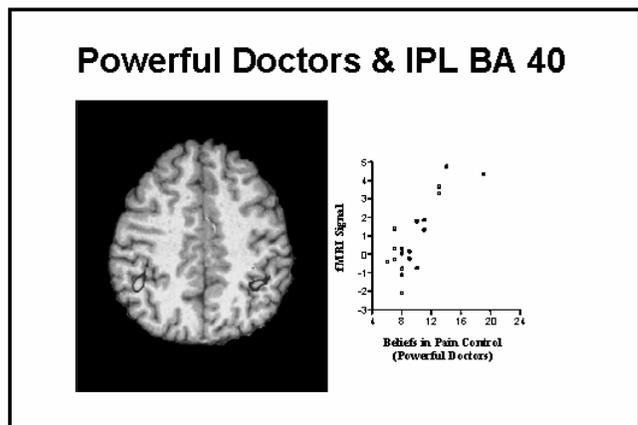
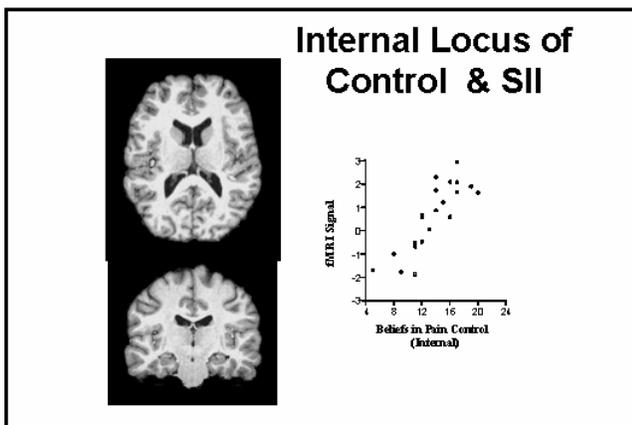


fMRI correlations with CES-D





- ### fMRI in Fibromyalgia and Related Conditions
- Is there objective evidence of augmented pain processing in fibromyalgia?
 - Role of depression in pain processing in FM
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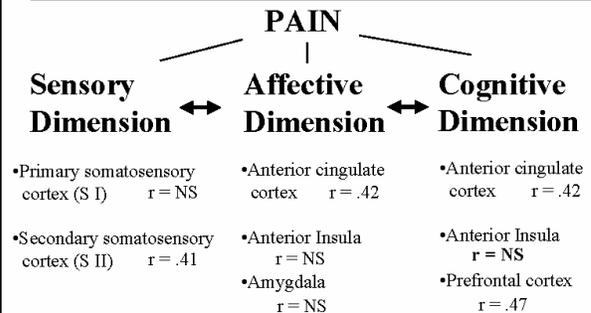


Influence of Catastrophizing on Pain Processing

- Refers to the fact that individual characterizes pain as awful, horrible, unbearable
- Predicts poor response to therapy
- **29 fibromyalgia subjects had fMRI performed with pressure on left thumbnail and correlations between neuronal activations and residual catastrophizing were calculated, after controlling for depression**

Gracely et. al., Brain, 2003

Correlational Results



fMRI in Fibromyalgia and Related Conditions

- Is there objective evidence of augmented pain processing in fibromyalgia?
- Role of depression in pain processing in FM
- Role of cognitive factors in pain processing in FM
 - Locus of control
 - Catastrophizing
- Is there objective evidence of augmented pain processing in idiopathic chronic low back pain?
- Is FM a more global problem with interoception?



Patient A - Low pain threshold
 Normal MRI of spine
 Severe back pain

Patient B - High pain threshold
 Prominent bulging disc
 No pain or symptoms

Clauw et. al. Spine 1999

fMRI in Fibromyalgia and Related Conditions

- Is there objective evidence of augmented pain processing in fibromyalgia?
- Role of depression in pain processing in FM
- Role of cognitive factors in pain processing in FM
 - Catastrophizing
 - Locus of control
- Is there objective evidence of augmented pain processing in idiopathic chronic low back pain?
- Is FM a more global problem with interoception?

Functional Imaging in Other “Central” Pain Syndromes

- Innumerable studies showing abnormalities in PET, SPECT in a number of chronic pain states
- Proton spectroscopy (Apkarian)
 - Proton spectroscopy abnormal in chronic low back pain (Grachev, Pain, 2000)
 - The degree of abnormality is influenced by co-morbid anxiety (J Neural Transm 2002)
 - May be atrophy of brain regions in low back pain (J Neuroscience 2004)

What causes fibromyalgia?

- Genetics
- “Triggers”
- Mechanisms
 - Relationship between physiologic and psychologic factors
 - Disordered sensory processing
 - Autonomic/neuroendocrine dysfunction

HPA axis and autonomic nervous system in chronic pain syndromes

- HPA abnormalities have been consistently identified in fibromyalgia, TMD syndrome, LBP
- Autonomic abnormalities have been consistently identified in FM, IBS, tension and migraine H/A
- The precise nature, and even direction, of these abnormalities is dependent on
 - the methodologies used,
 - the population studied, and
 - whether these axes are studied at baseline (where there is sometimes increased activity) or in response to stressors (where there is usually an attenuated response)

Why Should the RAC on Gulf War Veteran's Illnesses Care?

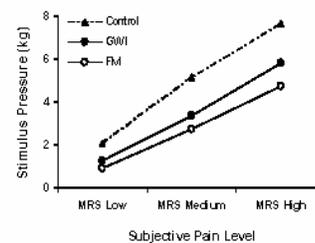
Studies of Physiology of Gulf War Veterans vs. Healthy Controls, with FM as "Positive Control" Group

- Sensory processing
- Autonomic function

Sensory Processing in Gulf War Veterans

- **Quantitative sensory testing for pressure pain threshold**
 - 20 GWI participants with chronic multisymptom illnesses
 - 36 age- and gender-matched controls
 - 27 individuals with fibromyalgia
- fMRI in a representative cohort from above

Pressure Pain Threshold



Presentation 6 – Daniel Clauw

Treatment of Fibromyalgia and Other Chronic Multisymptom Illnesses

Daniel J. Clauw, MD

Professor of Medicine, Division of Rheumatology
Director, Chronic Pain and Fatigue Research Center
Assistant Dean for Clinical and Translational Research
The University of Michigan Medical Center

Summary

- ◆ **Peripheral (nociceptive)**
 - Primarily due to *inflammation* or mechanical damage in periphery
 - NSAID, opioid responsive
 - Responds to procedures
 - Behavioral factors minor
 - Examples
 - ◆ OA
 - ◆ Acute pain models (e.g. third molar, post-surgery)
 - ◆ RA
 - ◆ Cancer pain
- ◆ **Central (non-nociceptive)**
 - Primarily due to a central disturbance in pain processing
 - Tricyclic, neuroactive compounds most effective
 - Behavioral factors more prominent
 - Examples
 - ◆ Fibromyalgia
 - ◆ Irritable bowel syndrome
 - ◆ Tension headache
 - ◆ Idiopathic low back pain
 - ◆ Interstitial cystitis / vulvodynia, non-cardiac chest pain / etc.

The Physiological / Psychobehavioral Continuum

Population	Primary Care	Tertiary Care
Definition factors (e.g., tender points, behavioral components)		

Physiologic factors

- ◆ Abnormal sensory processing
- ◆ Autonomic and HPA axis dysfunction
- ◆ Peripheral factors

Psychobehavioral factors

- ◆ General “distress”
- ◆ Psychiatric comorbidities
- ◆ Maladaptive illness behavior
- ◆ Secondary gain issues

HPA = hypothalamic-pituitary-adrenal.

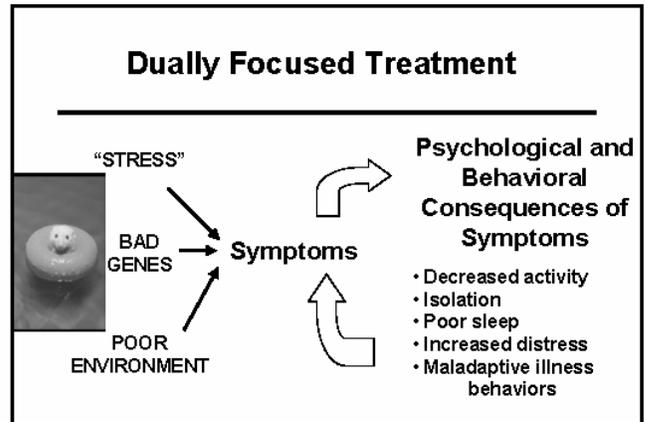
Sub-grouping FM patients

- ◆ 97 FM patients (85 female) were administered a battery of self-report questionnaires and subjected to evoked pain testing.
- ◆ The study variables were chosen a priori to reflect
 - a) measures of hyperalgesia that were less influenced by distress than tenderpoints (e.g. dolorimeter and supra-threshold random pressure testing);
 - b) affect (i.e. CES-D (depression), STPI (trait anxiety))
 - c) cognitive/evaluative factors (i.e. catastrophizing and control subscales of the Coping Strategies Questionnaire).
- ◆ Clustering of patients into subgroups

Geescke et. al.
Arthritis Rheum 2003

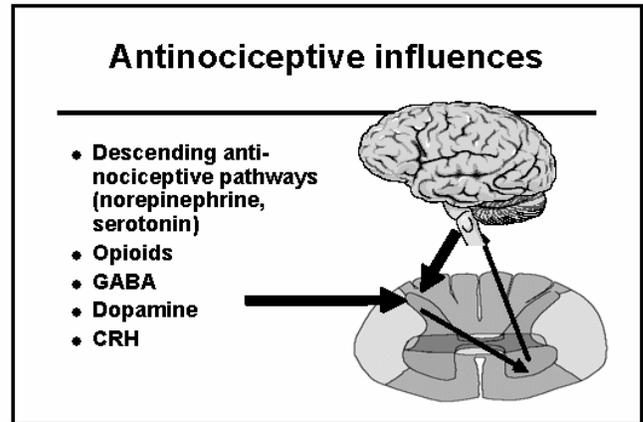
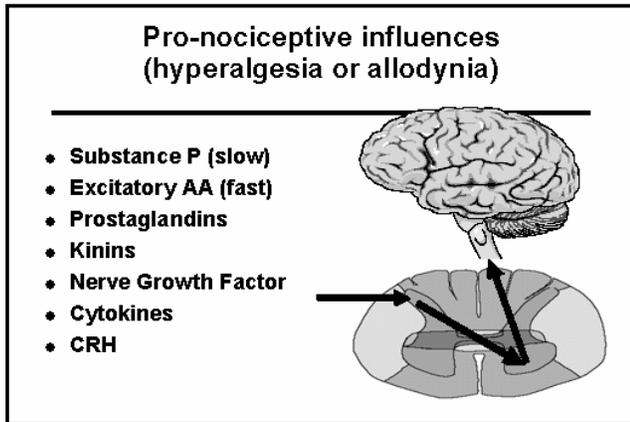
Subgroups of FM patients

<p><i>Group 1 (n=50)</i></p> <ul style="list-style-type: none"> •Low depression/anxiety •Not very tender •Low catastrophizing •Moderate control over pain 	<p>Psychological factors <i>neutral</i></p>
<p><i>Group 2 (n=31)</i></p> <ul style="list-style-type: none"> •Tender •High depression/anxiety •Very high catastrophizing •No control over pain 	<p>Psychological factors <i>worsening symptoms</i></p>
<p><i>Group 3 (n=16)</i></p> <ul style="list-style-type: none"> •Extremely tender •Low depression/anxiety •Very low catastrophizing •High control over pain 	<p>Psychological factors <i>improving symptoms</i></p>



- ### Treatment of Fibromyalgia and Other Central Pain Syndromes
- Education
 - Pharmacologic
 - Aerobic exercise
 - Alternative therapies
 - Cognitive behavioral therapy

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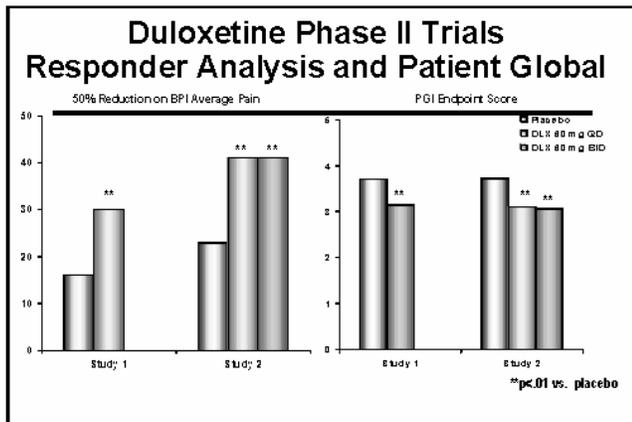
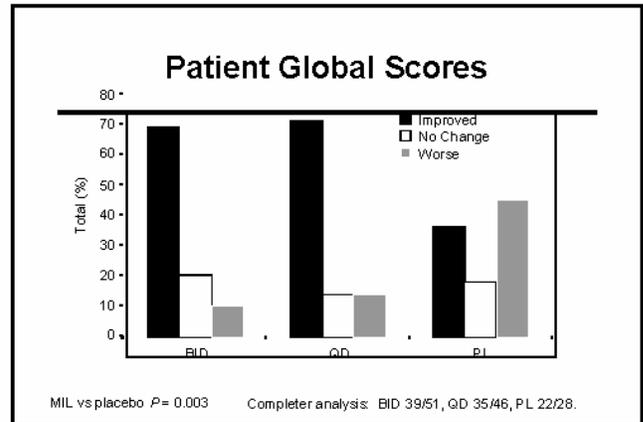
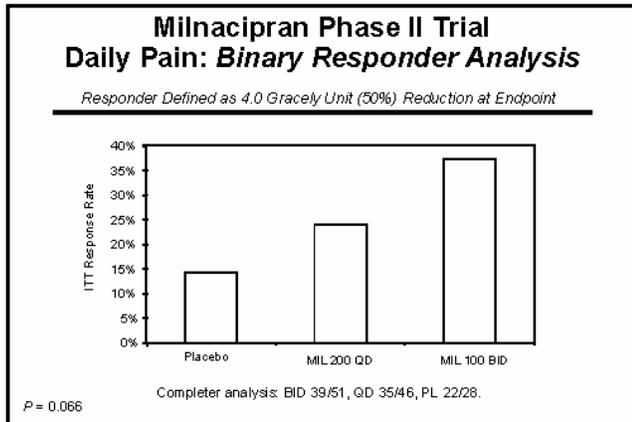
Pharmacologic Therapy Supported by RCT in FM

- Low doses of tricyclic drugs (e.g. amitriptyline, cyclobenzaprine) best studied
 - tolerance increased by starting at low dose (≤ 10 /mg), giving several hours before bedtime, increasing slowly
- SSRIs, NSAIDs ineffective or less effective
- Mixed noradrenergic / serotonergic agents
 - Atkinson et. al. Pain 1999: Maprotiline > Paroxetine > Placebo for non-depressed LBP
- Symptom-based therapy
 - Tramadol
 - Gabapentin

NSAIDs = nonsteroidal antiinflammatory drugs; RCT = randomized controlled trials; SSRI – selective serotonin reuptake inhibitors.

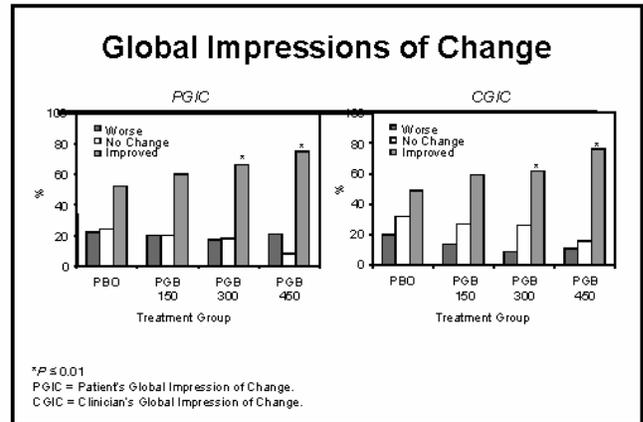
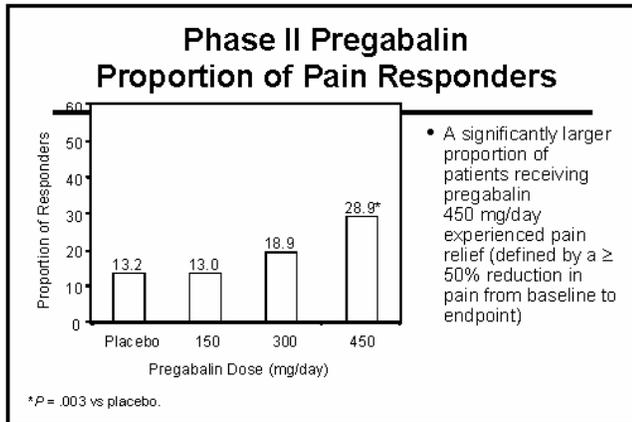
Relative Serotonin and Norepinephrine Re-uptake Amongst Antidepressants

Serotonin	Mixed	Norepinephrine
Citalopram	Amitriptyline	Maprotiline
Fluvoxamine	Duloxetine Milnacipran	Desipramine
Sertraline	Imipramine	Nortriptyline
Paroxetine		Reboxetine
Fluoxetine		



Pregabalin

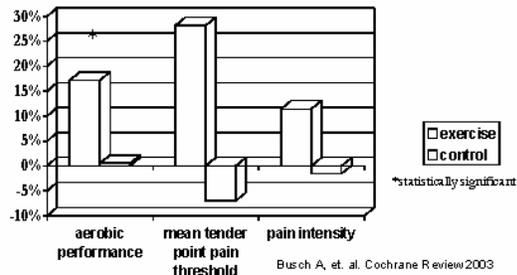
- Binds to $\alpha_2\delta$ subunit of voltage-gated calcium channels of neurons
- Reduces calcium influx at nerve terminals and therefore inhibits release of neurotransmitters
 - Glutamate, noradrenaline, substance P



- ### Treatment of Fibromyalgia and Other Central Pain Syndromes
- Education
 - Pharmacologic
 - Aerobic exercise
 - Alternative therapies
 - Cognitive behavioral therapy

- ### Exercise
- Aerobic nearly universally beneficial; tolerance, compliance, adherence are biggest issues
 - To maximize benefits:
 - Begin several months after pharmacologic therapy
 - Begin with low-impact exercises; avoid strength training until late
 - Both physician and patient should consider this as a "drug"
 - Less evidence supporting strengthening, stretching

Improvements in aerobic exercise vs non-exercise controls (combined data 4 studies)



Exercise Tolerability

- High intensity (heart rate > 150) aerobic exercise is poorly tolerated with high drop-out rates over time
- Moderate intensity programs (50 to 70% of age-adjusted maximal heart rate) can be well tolerated
- Exercise should start at just below the capacity of the participant and gradually increase in duration to goal of 30 min of moderate intensity aerobic exercise

Gowans SE et. al Curr Opin Rheumatol. 2004

Treatment of Fibromyalgia and Other Central Pain Syndromes

- Education
- Pharmacologic
- Aerobic exercise
- Alternative therapies
- Cognitive behavioral therapy

Complementary and Alternative Therapies

- Some evidence supporting
 - Acupuncture
 - Physical modalities
 - Myofascial release therapy
 - Trigger point injections (dry needling may be as effective)
 - Chiropractic manipulation
 - Biofeedback

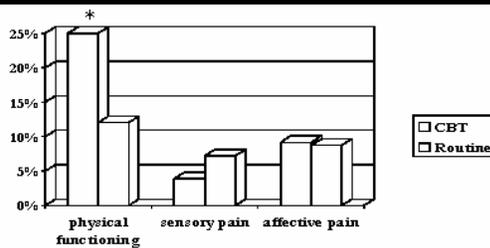
Treatment of Fibromyalgia and Other Central Pain Syndromes

- Education
- Pharmacologic
- Aerobic exercise
- Alternative therapies
- Cognitive behavioral therapy

Cognitive behavioral therapy

- A program designed to teach patients techniques to reduce their symptoms, to increase coping strategies, and to identify and eliminate maladaptive illness behaviors
- Shown to be effective for nearly any chronic medical illness
- Not all CBT is created equally; very dependant on therapist and program

Improvements noted, CBT vs standard care over 12 months (n=122)



OR 2.9, p<0.05

Williams DA, et al. J Rheum 2002

Veterans Affairs Cooperative Study (CSP #470) CSP #470

- Multi-center trial carried out at 18 VAMC and Department of Defense military hospitals
- Hypothesis – The proportion of patients who had a clinically important difference in self-report physical function would be better with either exercise or CBT than those receiving usual care, and the combination of the therapies would be more effective than either single therapy

Inclusion criteria

- To be eligible veterans had have been deployed to the Gulf War between August 1990 and August 1991, and to endorse ≥ 2 of the following symptoms:
 - fatigue limiting usual activity
 - pain in ≥ 2 body regions
 - neurocognitive symptoms
- These symptoms had to begin after August 1990, last for more than six months, and be present at the time of screening.

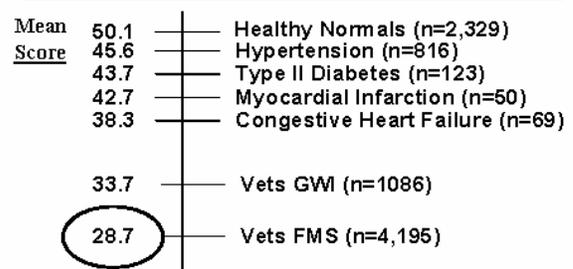
Subjects / Methods

- 1092 veterans who satisfied the eligibility criteria and gave written informed consent were randomized to one of four treatment arms: 1) CBT alone, 2) exercise alone, 3) CBT + exercise, or 4) usual care.
- Both CBT and exercise were delivered in groups of three to eight participants.
- CBT Treatment sessions were 60-90 minutes long and met weekly for 12 weeks.
- Exercise prescriptions focusing on low impact exercise were individualized for each participant after they performed a submaximal cycle ergometer exercise test at baseline. Veterans in the exercise group were asked to exercise once/wk in the presence of the exercise therapist, and 2 - 3X / wk independently during the 12-week treatment phase.

Results – Demographics of Participants

- 85% male
- Mean age 40.7
- 81% presented with all three cardinal symptoms of GWVI at the time of screening
- The mean duration of symptoms was 6.7 years
- Based on the Prime MD:
 - 45% percent of veterans had either a major depressive disorder or dysthymia,
 - 35% had an anxiety disorder
 - 43% had posttraumatic stress disorder
- 24% percent of veterans had a pending disability claim and 42% were receiving disability payments.

PCS (SF-36)



Kazis, (1999; P.C.); Ware, Kosinski, Keller, 1995

Response to Treatment

- There was a modest difference in the proportion of veterans who reported an improvement in physical function at one year among the treatment groups:
 - 11.5% for usual care
 - 11.7% for exercise
 - 18.4% for CBT
 - 18.5% for CBT + exercise
- More significant improvements in fatigue, cognitive symptoms, distress, and mental health functioning were observed with exercise alone, and with exercise plus CBT compared to usual care.
- CBT alone had a statistically significant effect on cognitive symptoms and in mental health functioning.

Recommended Approach

- For patients that need or want medications start with low doses of tricyclics; start low, go slow
- If patient tolerates and but symptoms persist:
 - Add mixed reuptake inhibitor (e.g. venlafaxine, duloxetine) or SSRI
 - For additional analgesic effect add gabapentin, tramadol, tizanidine
- If patient doesn't tolerate TCA use zolpidem, zaleplon, trazadone
- Aggressively introduce non-pharmacological therapies, consider tapering pharmacologic therapies

Presentation 7 – Mark Melanson

Depleted Uranium CAPSTONE Aerosols
Study and Human Health Risk Assessment



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



Introduction

- Depleted uranium (DU) is the by-product of enriching uranium for use as a fuel or weapon
- DU is 40 % less radioactive than the natural uranium that we all eat, drink, and breathe daily
- The health effects of uranium (including DU) are very well understood and are based on over a half-century of scientific research that continues to this day
- As with all potentially hazardous materials, the amount of intake determines the risk



Military Applications of Depleted Uranium

- DU is used in armor-penetrating munitions and tank armor packages
- Its ability to "self-sharpen" makes DU the most effective anti-armor munition on the battlefield
- DU munitions allow U.S. Forces to kill enemy tanks at greater distances
- When used in armor, DU resists penetration – it has never been perforated in combat



Military Unique Exposures

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



DU Exposure Categories

Category	Description
I	Service members in, on, or near (within 50 meters) of armored vehicle struck with DU at the time of penetration by the DU munition
II	Service members whose military occupational specialty (MOS) require entering vehicles damaged by DU
III	Service members who have incidental exposure to DU



DU CAPSTONE Aerosol Study and Human Health Risk Assessment

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







Operated by Battelle for the U.S. Department of Energy
Pacific Northwest National Laboratory


Lovelace Respiratory Research Institute


Los Alamos National Laboratory

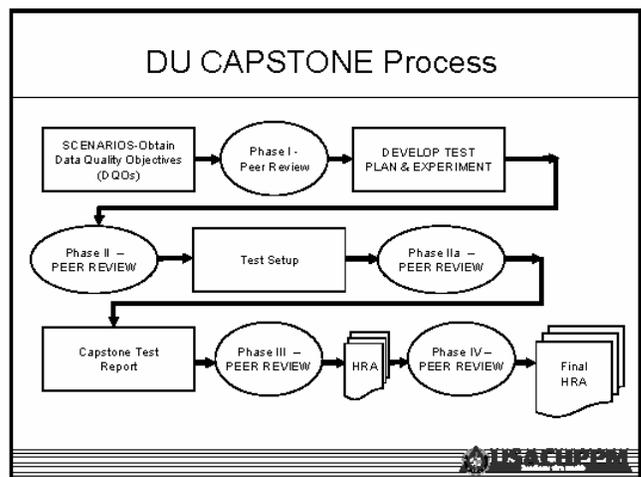

U.S. Army Medical Command


U.S. Army Heavy Medical Office


U.S. Army Test & Evaluation Command




U.S. Army Medical Command
U.S. Army Center for Health Promotion & Preventive Medicine

Other Depleted Uranium Initiatives



Environmental Base Camp Assessments

- Environmental sampling at bivouac sites to ensure areas are safe
- Sampling includes direct measurements, air, soil, and water sampling
- Analysis includes radioactivity and DU



Post Deployment Screening for Depleted Uranium

- 24-hour urine specimen analyzed by Inductively Coupled Plasma Mass Spectroscopy (ICP-MS)
- DoD policy requires testing for Level I and II personnel. Level III may be tested if desired.
- Lab analysis by accredited lab with over 30 years experience
- Over 1,700 personnel tested with 5 DoD Service Members identified as having elevated DU in their urine and referred to the Baltimore VA DU Medical Follow Up Program



Reevaluation of Areas of Potential DU Contamination

- As Samawah, Iraq, location of the 442nd Military Police Company, New York Army National Guard
- Allegations of DU contamination
- Laboratory analysis of samples is ongoing



International Cooperation

- Participation in three United Nations Environment Programme (UNEP) missions to the Balkans (Kosovo, Serbia and Montenegro, and Bosnia)
- Consultative support to the World Health Organization (WHO)
- Consultative support to the International Atomic Energy Agency (IAEA)



 USACHPPM



 USACHPPM

Presentation 8 – Mary Ann Parkhurst

**Estimating Depleted Uranium Aerosol Doses
and Risks:**

**An Overview of the Capstone Depleted
Uranium Aerosol Study
and the Capstone Human Health Risk
Assessment**

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

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

Study Objectives

- **Generate data to fill knowledge gaps about aerosols created by perforation of armored vehicles with DU munitions**
- **Apply data in dose and risk assessment of DU aerosol exposures**
 - Retrospective assessments
 - Prospective assessments

Data to Be Generated

**Underlying question: Are health risks high
enough to warrant changes in**

- Medical policy for treatment?
- Monitoring?
- Protective Measures?

Peer Review Committee

Dr. Roy Reuter, Team Coordinator
Dr. Arthur Upton—Radiobiology
Dr. John Doull—Toxicology
Dr. Rogene Henderson—Inhalation Toxicology
Dr. David Hoel, Health Physics, Industrial Hygiene
Dr. Morton Lippmann—Air Sampling
Dr. Paul Strickland—Toxicology
Dr. Wes Van Pelt—Health Physics
Dr. Paul Baron—Aerosol Physics
Dr. Tony James—Health Physics, Computer Modeling
Dr. Wesley Bolch—Health Physics, Computer Modeling

Capstone DU Aerosol Study

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

Field Tests

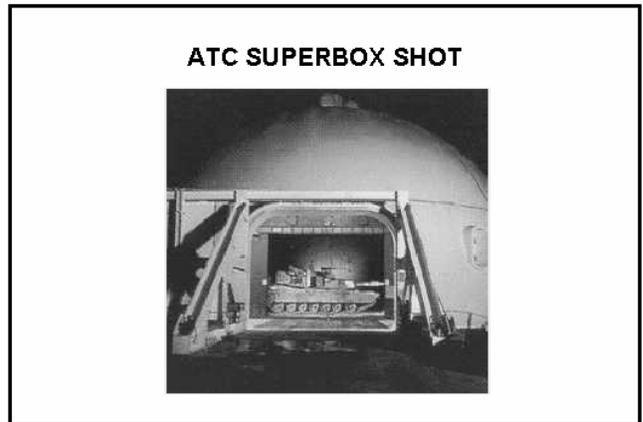
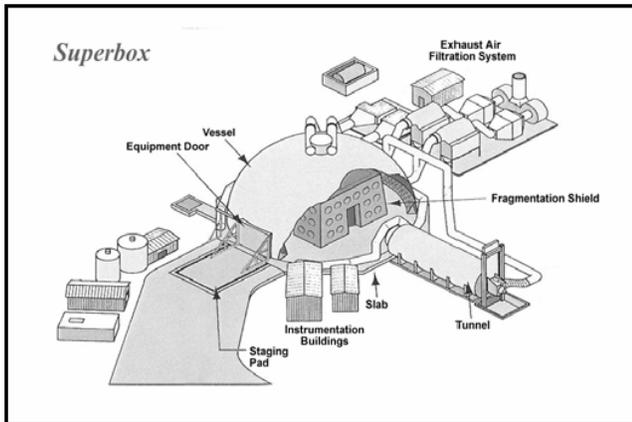
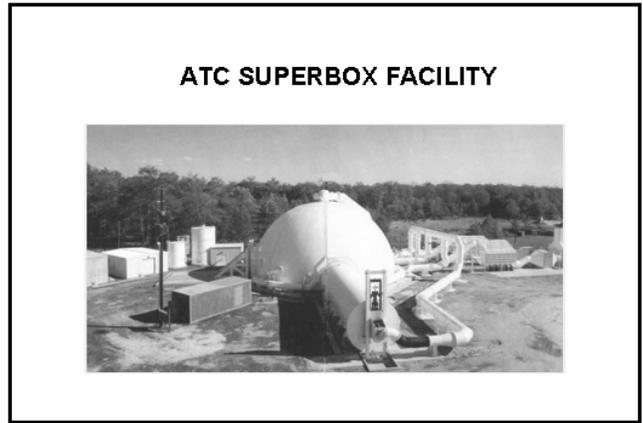
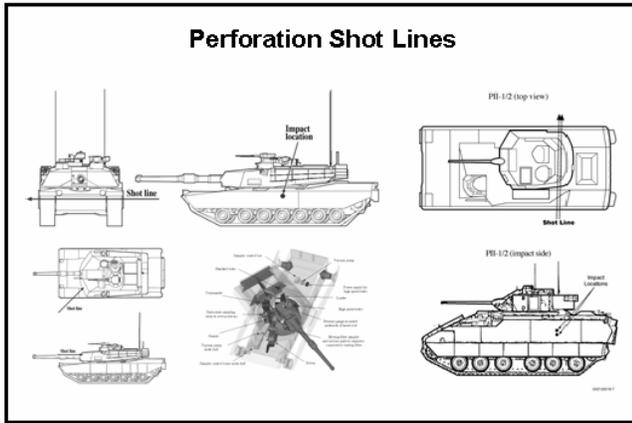
- **Phase I – Abrams tank with conventional armor**
 - Crossing shots (4)
 - Breech shots (2)
 - Hull shot (1)
- **Phase II – Bradley Fighting Vehicle**
 - Crossing shots (2)
 - Turret/breech shot (1)
- **Phase III – Abrams tank with DU armor**
 - Armor packaged shots (2)
- **Phase IV – Abrams operational tank**

Abrams Tank— with Conventional or DU Armor



Bradley Fighting Vehicle—Conventional Armor





Sampling Environments

- **Interior (primary sampling)**
 - Turret air (and passenger compartment in Bradley) immediately after shot
 - Periodically up to 2-hr post shot
 - During recovery operations
 - Turret interior surfaces
- **Exterior (secondary sampling)**

Sampler Requirements

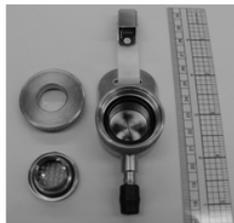
- **Survive a high energy environment**
 - Robust aerosol samplers
 - Physical shielding against immediate pressure and temperature pulses and fragments
 - Sampler Redundancy
- **Accommodate computerized time sequencing control**
- **Overall sampling rate <200 Lpm**

Interior Sampling Equipment Selected

Filter Cassettes

(IOMs): used for time-sequenced sampling

- stainless steel
- Gelman Supor membrane discs
- Replaced with Zefluor filters



Interior Sampling Equipment Selected (Cont.)

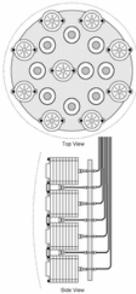
Cascade Impactors:
used for time-sequenced sampling

34- μ m, 8 stage, inlet modified, with backup filter

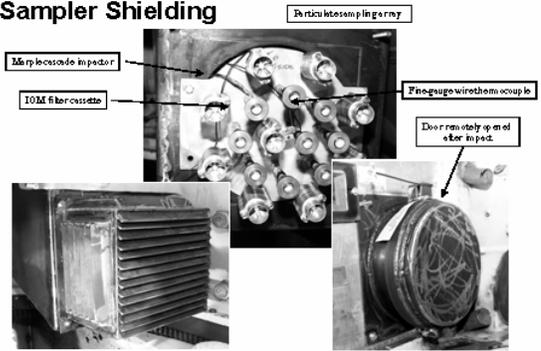
- Effective cutoff diameter at 2 Lpm: 21, 15, 10, 6, 3.5, 1.5, 0.9, 0.5 μ m, respectively
- Mixed cellulose ester substrate
- Medium of 0.8 μ m pore size



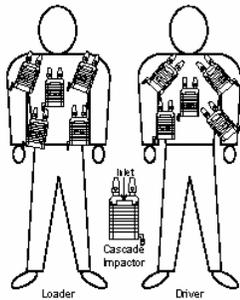
Sampling Arrays—Placed at Commander, Driver, Gunner, and Loader Positions (Right and Left Scout in BFV)



Sampler Shielding



Phase IV Samplers



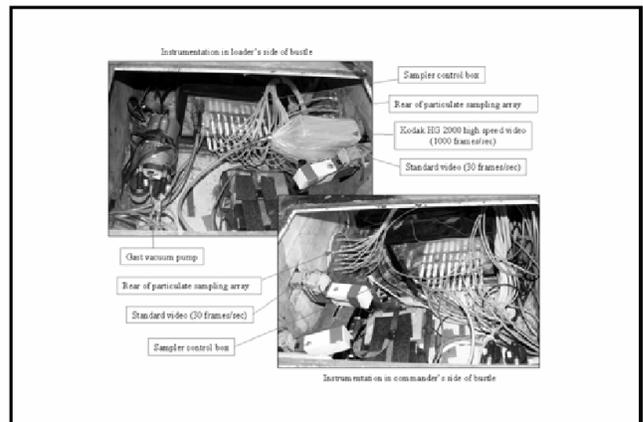
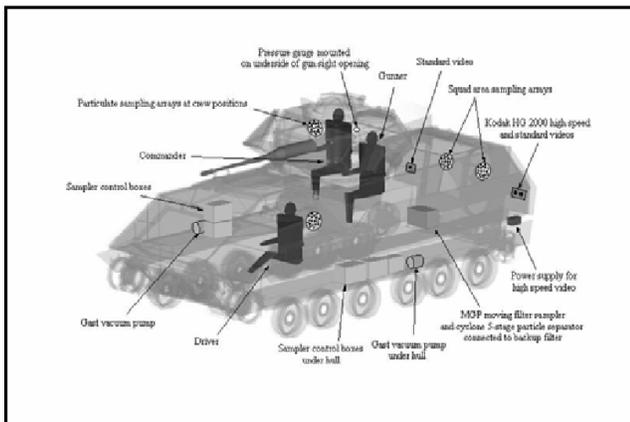
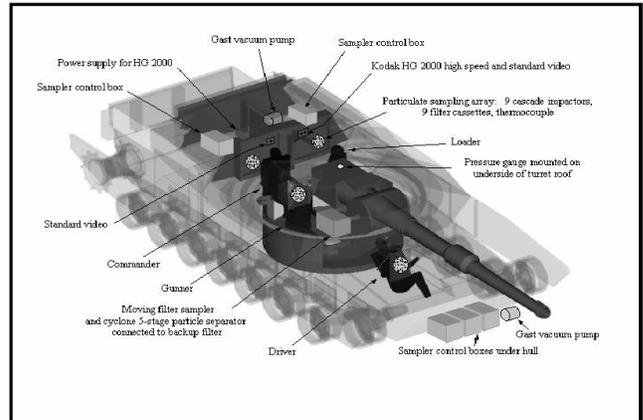
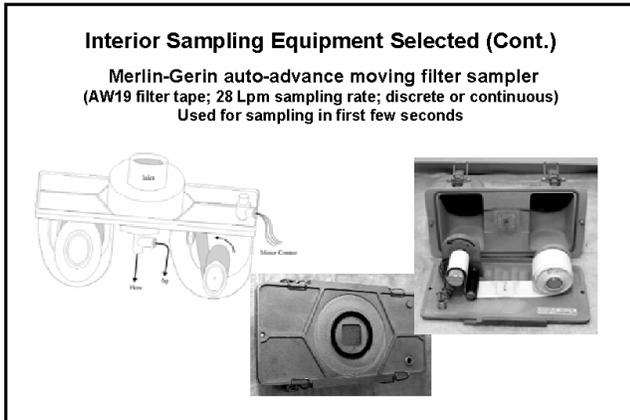
Interior Sampling Equipment Selected (Cont.)

5-stage SRI cyclone train

- Stage cutoff diameters of aerodynamic diameters (μm) at 10 Lpm flow rate: 10, 4.3, 2.9, 2, 1.2 (<1.2 backup filter)

Used for bulk aerosol sampling





DU Aerosol Analysis

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

Laboratory Analysis

- **Radioactivity on filters, gloves, wipes, cyclone**
 - Alpha/beta counts
 - Gamma counts – cyclones, gloves
- **Chemistry**
 - Uranium analysis
 - DU/U analysis (U235/U238 ratios)
 - Oxide analysis
- **Morphology by scanning electron microscopy**
- ***In vitro* solubility**

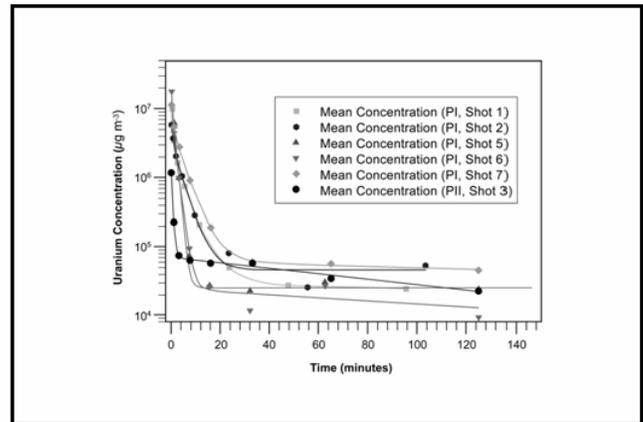
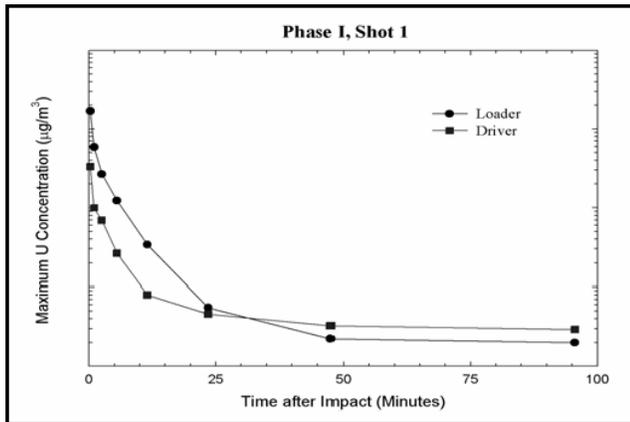
Example of Filter Cassette Samples Collected



Mass Concentration

**Uranium Mass Concentration ($\mu\text{g}/\text{m}^3$)
(adjusted for ingrowth) =**

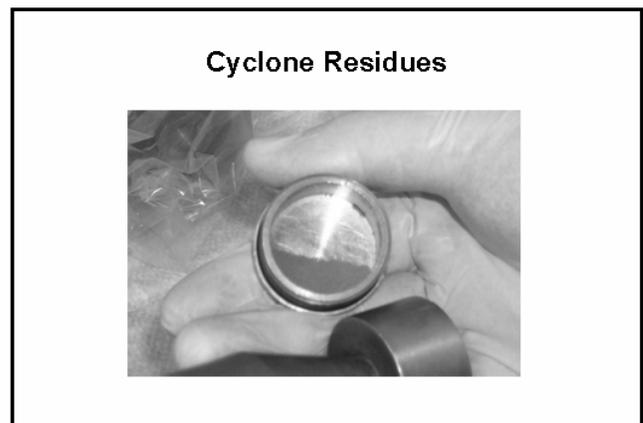
$$\frac{[\text{Sample Mass (Max U } \mu\text{g)} - \text{Field Blank (Max U } \mu\text{g)}]}{[\text{Sample Volume (L)} \times 1.0 \text{ E-3 m}^3/\text{L}]}$$



DU Aerosol Summary Table

Shot Description	Mean DU Concentration (g/m ³)					
	10 sec	30 sec	1 min	30 min	1 h	2 h
Retrospective						
Abrams—crossing hull	11	9.0	6.0	0.11	0.057	0.047
Bradley—turret and passenger comp't	3.0	2.7	2.2	0.13	0.049	0.024
Prospective						
Abrams—crossing turret	8.8	7.9	5.7	0.15	0.064	.. ^(a)
Abrams—crossing turret into breach	16	12	6.4	0.020 ^(b)	0.029	0.019
Abrams—into DU armor	10	7.9	4.2	0.049	0.017	0.013
Abrams—into DU armor (F1V-4, with ventilation)	0.092	0.14	0.22	0.011	.. ^(a)	.. ^(a)

(a) Averages not extrapolated past last sample.
 (b) Samplers for both shots showed similar pattern in large reduction from 1 min; most 30 min DU concentrations were lower than at 1 h.

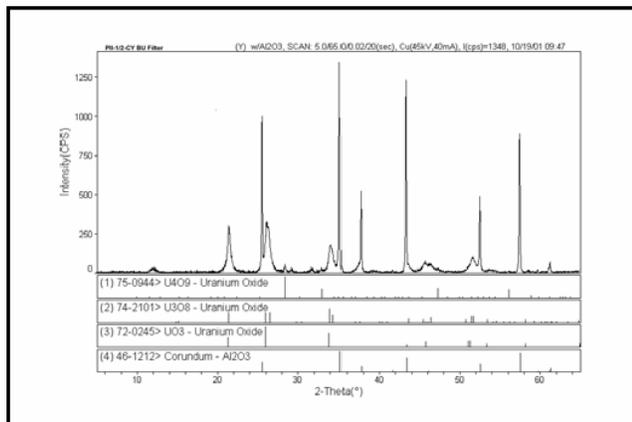


Chemical Composition of Total Aerosol Mass

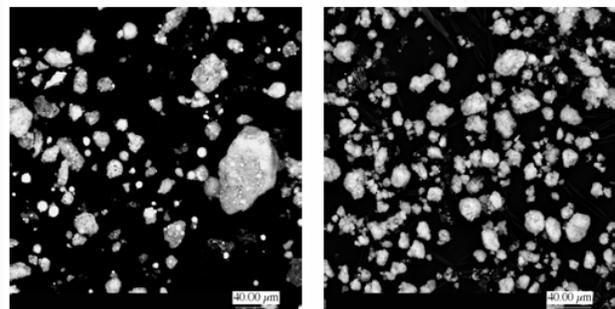
- **DU Concentration**
 - 38 to 54% in the Abrams BHT/hull, conventional armor
 - 43 to 72% in the Abrams BHT/turret shots, conventional armor
 - 60 to 72% in the Abrams BHT/turret shot, DU armor)
 - 18 to 29% in the Bradley BHT/passenger compartment shots
- **Other Metals Concentration**
 - Mostly aluminum and iron
 - Some titanium, zinc, and copper
 - Additional trace metals

DU Particle Composition and Morphology

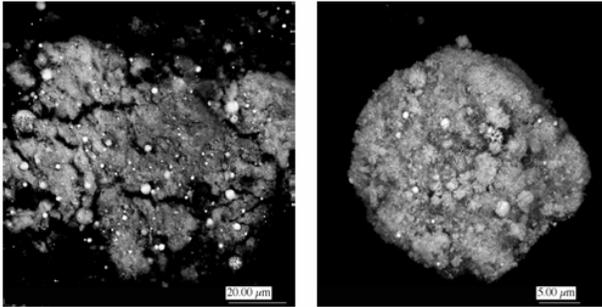
- **DU oxide using X Ray Diffraction**
 - Predominant phase was U_3O_8/UO_3 believed to be primarily hyperstoichiometric forms of U_3O_8
 - U_4O_9 also present especially in larger particles
 - A small amount of schoepite ($UO_3 \cdot 2H_2O$) found in several samples
- **Morphology examined using scanning electron microscopy**
- **Composition of individual particles analyzed using energy dispersive spectroscopy**



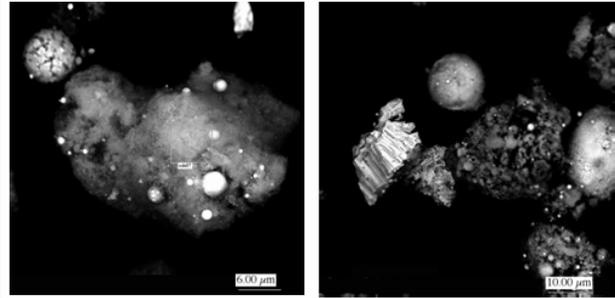
Stages 1 and 4 Distributions



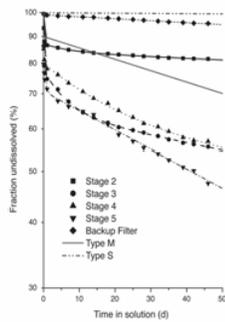
Typical U Aggregates



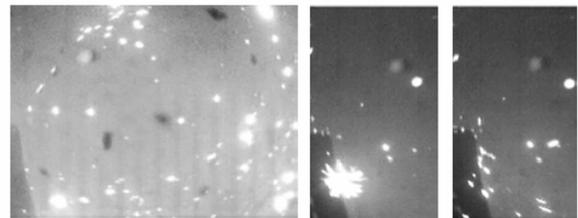
Less Dense Aggregates



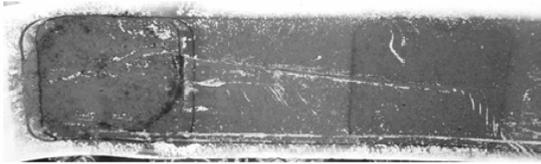
In Vitro Solubility in Simulated Lung Fluid



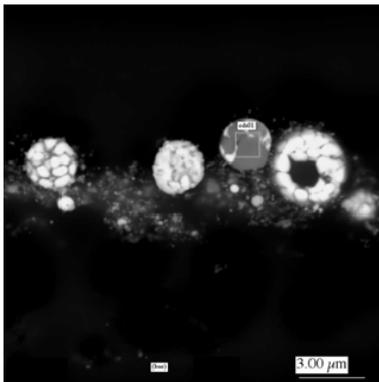
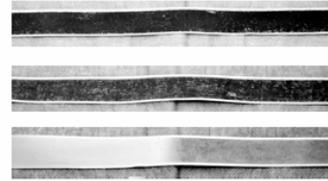
Transient Fireflies



Moving Filter Residues—Discrete Interval Sampling



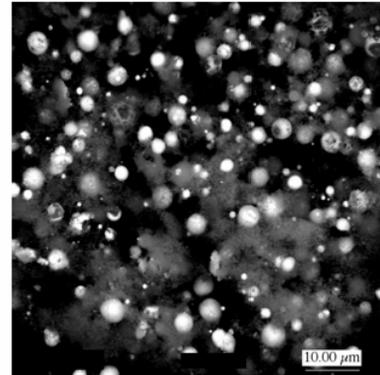
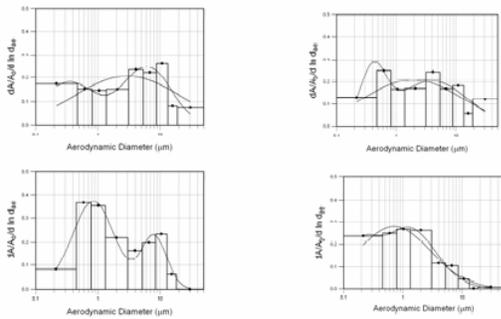
Moving Filter Residues—Continuous Time Sampling



Example of Cascade Impactor Samples Collected: Respirability of Particles



AMAD Graphs: 10 sec, 1 min, 3 min, 33 min



General Characteristics of Particle Size Distributions

- **Particle size distributions changed as a function of time with larger particles settling out more quickly**

Exposure Categories for HHRA

- **Level I (modeling limited to the following)**
 - Personnel in vehicle at time of impact
 - First responders
- **Level II**
 - Personnel whose job functions require them to work in and around vehicles containing DU fragments and particles, usually within hours to few days
- **Level III**
 - Personnel with brief or incidental exposure
 - Includes those entering equipment, downwind of DU impacts and fires

Level I Scenario Development

- **Personnel in vehicle at time of impact**
- **First responders**
 - Stay-time in vehicle
 - Breathing rates
 - Type of breathing (nose/mouth)
 - Individuals' characteristics (Reference Man)
 - Respiratory tract (ICRP-66)
 - Bone (ICRP-70)
 - Other organs (ICRP-23, ICRP-89)

Summary of Level I, In-Vehicle Personnel Exposure Scenarios

Scenario	Time of Exposure	Exposure Duration	Breathing Rate
Crew Inside Vehicle			
A	From impact to exit 1 min post shot	1 min	3 m ³ /h
B	From impact to exit 5 min post shot	5 min	3 m ³ /h
C	From impact to exit 1 h post shot	1 h	3 m ³ /h for first 15 min, 1.5 m ³ /h thereafter
D	From impact to exit 2 h post shot	2 h	3 m ³ /h for first 15 min, 1.5 m ³ /h thereafter
First Responder			
E	Entry 5 min post shot, exit 10 min later	10 min	3 m ³ /h

Primary DU Aerosol Characteristics used in Intake and Dose Modeling

- DU concentration as a function of time
- Particle size distribution as a function of time
- *In vitro* solubility as surrogate for dissolution and transfer of inhaled particles within human body

Aerosol Concentration (Source Term)

- **DU Concentration over time (IOM)**
- **Particle-size distributions over time (CI)**
 - Also DU concentration
- **CI data selected**
 - IOM conc > CI stages summed conc
 - IOM conc > early time intervals (<10 min)
 - Larger particle sizes collected by IOMs
 - Adjustments for CI wall loss
 - Field blank adjustments to all time intervals except first

Inhalation Intakes

- Time integral of aerosol concentration times the scenario breathing rate
- Statistical approaches
 - Conventional approach
 - Bayesian approach

Median DU Intakes

Scenario	Uranium Intake (ng)			
	Abrams Tanks Conventional Armor, No Ventilation	Abrams Tanks DU Armor, No Ventilation	Abrams Tanks DU Armor, E C/NBC Operating	Bradley Vehicle: Conventional Armor, No Ventilation
Most Likely				
A - Crew, exit in 1 min	280	250	10	83
B - Crew, exit in 5 min	590	710	43	220
E - First responders	160	200	27	99
Upper Bound				
C - Crew, exit in 1 h	760	970	91	330
D - Crew, exit in 2 h	780	1000	110	380

Dose Calculations

- **Dosimetry models**
 - HRTM (ICRP-66)
 - Deposition
 - Clearance (mechanical and absorption)
 - GI Tract (ICRP-30)
 - U systemic biokinetic (ICRP-78)
- **DU aerosol solubility in lung/extracellular fluids**
 - *in vitro* solubility results rather than ICRP-68 defaults (Types F, M, S)

Quantities Calculated

- **Radiological quantities**
 - Committed effective dose – E(50)
 - ICRP-68 with modifications
 - Gonadal $H_T(50)$ – testes only
 - Thymus and uterus eliminated from remainder organs
 - No splitting applied – ET assigned $w_T = 0.025$
 - Organ dose equivalents – $H_T(50)$
 - Lung, BS, ET, kidney, LN-TH, RM, Liver reported
- **Chemical concentration**
 - Peak kidney concentration

Median 50-yr Committed Effective Doses

Scenarios	E(50) rem			
	Abrams Tank: Conventional Armor, No Ventilation	Abrams Tank: DU Armor, No Ventilation	Abrams Tank: DU Armor, E C/NBC Operating	Bradley Vehicle: Conventional Armor, No Ventilation
Most Likely				
A - Crew, exit in 1 min	2.0	2.2	0.090	0.39
B - Crew, exit in 5 min	3.7	6.0	0.44	1.7
E - First responders	0.92	1.9	0.41	0.89
Upper Bound				
C - Crew, exit in 1 h	4.8	8.3	1.02	2.1
D - Crew, exit in 2 h	5.0	8.7	1.20	2.4

E(50) Relative to NRC Occupational Dose Limits

- Annual occupation TEDE limit is 5 rem (10 CFR 20).
- Although the E(50) is different from the TEDE, the concepts are similar, and for radiation protection purposes, can be compared (ICRP [60] 1991).
- The NRC's planned special exposure limit is 10 rem in a year (two times the annual limit, not to exceed five times the annual limit in a lifetime [10 CFR 20.1206]).
- Although the E(50)s exceed the occupational radiation limits for some scenarios, all E(50)s are less than the planned special exposure limit.
- For all scenarios modeled, radiation doses are at levels unlikely to cause adverse health effects.

Median 50-yr Committed Equivalent Doses to the Lung

Scenario	Lung H _T (50) rem			
	Abrams Tank: Conventional Armor, No Ventilation	Abrams Tank: DU Armor, No Ventilation	Abrams Tank: DU Armor, E C/NBC Operating	Bradley Vehicle: Conventional Armor, No Ventilation
Most Likely				
A - Crew, exit in 1 min	14	18	0.66	5.2
B - Crew, exit in 5 min	32	44	3.3	14
E - First responders	8.8	14	3.1	6.7
Upper Bound				
C - Crew, exit in 1 h	38	60	7.6	20
D - Crew, exit in 2 h	39	61	8.7	22

H_T(50) Relative to NRC Occupational Dose Limits

- Annual occupational radiation dose limits include a 50 rem committed dose equivalent (10 CFR 20).
- Although the HT(50) is different from the committed dose equivalent, the concepts are similar, and for radiation protection purposes, the two quantities can be compared (ICRP [60] 1991).
- Except for the case in which an Abrams tank was perforated through DU armor and the stay-time was 1 to 2 h, the predicted doses to the organs were less than this occupational limit.
- For all scenarios modeled, organ doses are at levels unlikely to cause adverse health effects.

Radiological Dose to Risk

- ICRP-60/NCRP-115 approach
- Cancer mortality risk coefficients
- Summed organ risk approach (non-uniform irradiation)

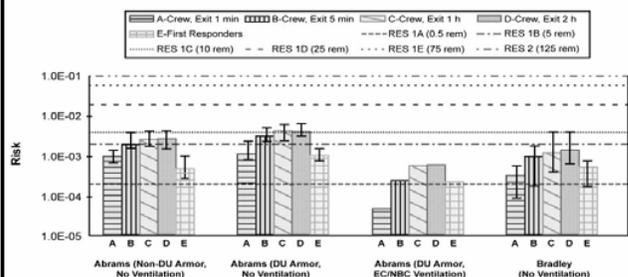
Median Lifetime Risk Increase of Fatal Cancer from DU Inhalation

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

Radiological Risk

- "Generic" lung cancer mortality risk coefficients were based on alpha emitters.
- Lifetime cancer mortality risks calculated using the Linear No-Threshold model of effect, thought to be protective of health.
- For rapid exits (1 min or less), the risks are slightly greater than the risks associated with the annual general population dose limit of 0.5 rem.
- For all vehicle types, the estimated risks at the 90th percentile are below or slightly exceed (by less than 10%) the risks associated with planned special exposures.
- Risks for first responders are below the risks associated with the occupational limit of 5 rem/yr.

Median Radiation Risks w/ 10th & 90th Percentiles for All Phases and Scenarios (Compared to Radiation Standards and Emergency Guidelines)



Development of a Risk Model

- **Goal:** Predict the severity of renal effects following an acute exposure to uranium
- **Methodology:** Develop a model that was based upon documented renal effects in humans following acute uranium exposures, and the calculated kidney burdens
 - 27 cases were selected
 - clinical symptoms or the biochemical indicators of renal dysfunction
 - peak renal concentrations of uranium in the kidneys
 - Fisher *et al* (1990) [health effects in workers following an accidental exposure to uranium hexafluoride]
 - The Royal Society (2002) [renal effects occurring within a few days after acute uranium exposures]

Acute Human Exposures to Uranium

Intake Route (n)	Chemical Form	Intake (mg U)	Peak $\mu\text{g U/g}$ kidney	Effect	Reference
Ingestion	Acetate	8500	100	+++	Pavakis <i>et al.</i> 1998
Dermal	Nitrate	130	35	+++	Zhao and Zhao 1990
Inhalation	Tetrafluoride	920	10	++	Zhao and Zhao 1990
Injection (2)	Nitrate	11 - 18	4 - 6	+	Luessenhop <i>et al.</i> 1968
Dermal	Nitrate	10	3	++	Buttenworth 1955
Inhalation	Hexafluoride	24	2.5	+	Fisher <i>et al.</i> 1990a
Injection	Nitrate	6.9	2	+	Luessenhop <i>et al.</i> 1968
		5.6	2	-	
		4.3	1.5	-	
Inhalation (3)	Hexafluoride	40-50	1.2 - 4	+	Kathren and Moors 1988
Inhalation (7)	Hexafluoride	11 - 18	1.1 - 1.9	-	Fisher <i>et al.</i> 1990a
Ingestion	Nitrate	470	1	+	Buttenworth 1955
Inhalation	Hexafluoride	20	1	-	Boback 1975
Inhalation (5)	Hexafluoride	6 - 8.7	0.62 - 0.9	-	Fisher <i>et al.</i> 1990a

Modified from the Royal Society, 2002

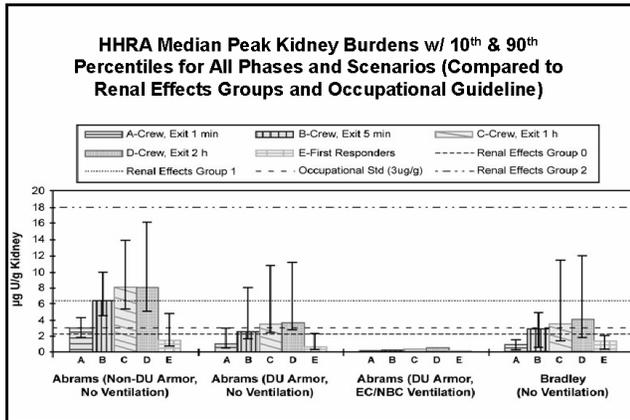
Renal Effects Groups (REGs)

REG	Effects	D (range)	$\mu\text{g U/g}$ kidney
0	No effect	≤ 0.0	≤ 2.2
1	Transient	$> 0.0 - 2.0$	$> 2.2 - 6.4$
2	Protracted	$> 2.0 - 4.0$	$> 6.4 - 18$
3	Severe	> 4.0	> 18

Median Peak Kidney Uranium Concentrations

Scenarios	Peak Kidney Uranium Concentrations ($\mu\text{g U/g}$ Kidney)			
	Abrams Tanks: Conventional Armor, No Ventilation	Abrams Tanks: DU Armor, No Ventilation	Abrams Tanks: DU Armor, E/C/NBC Operating	Bradley Vehicle: Conventional Armor, No Ventilation
Most Likely				
A - Crew, exit in 1 min	3.0	1.1	0.05	1.0
B - Crew, exit in 5 min	6.4	2.6	0.23	2.9
E - First responders	1.5	0.67	0.14	1.4
Upper Bound				
C - Crew, exit in 1 h	8.2	3.5	0.46	3.5
D - Crew, exit in 2 h	8.0 ^(a)	3.7	0.56	4.0

(a) The sampler data used to calculate Scenarios C and D differed slightly and was responsible for the lower dose for the longer exposure time.



DU Health Risks in Perspective

- ODS incidents involved crews of 6 Abrams tanks and 14 Bradley Fighting Vehicles—104 survived.
- Of those struck by DU fragments, most continue to be medically monitored. To date, no clinical symptoms of DU toxicity have been observed in this group.
- Crewmembers in these vehicles were exposed to DU oxide aerosols in addition to any DU fragments resulting from impact.
- Uranium is a much-studied material and its toxicity is relatively well known. Although some risk may exist, no compelling evidence from human epidemiologic studies associate natural or DU uranium with an increased cancer risk.

The Bottom Line—Radiological Effects

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

The Bottom Line—Toxicological Effects

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



Presentation 9 – Lea Steele

**Research on Health Effects of DU in
Relation to Gulf War Veterans' Illnesses**

Lea Steele, Ph.D.

Meeting of the Research Advisory Committee
on Gulf War Veterans' Illnesses
April 7, 2004

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DU in Relation to Gulf War Veterans Illnesses

- Summary of findings of major DU reports
- Unanswered questions re: DU and the health of Gulf War veterans
- Epidemiologic research on DU and the health of Gulf War veterans
- Brief review of relevant DU research previously presented to RAC

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Major Reports on the Health Effects of DU

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

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**Major Reports on the Health Effects of DU:
Summary of General Conclusions**

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

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**Unanswered Questions re:
 DU and the Health of Gulf War Veterans**

- DU reports have focused on modeled and observed effects of DU exposure on the kidneys, cancer risk
- Reports have not specifically addressed questions re: possible relationship between DU and multisymptom illnesses in Gulf veterans

**Unanswered Questions re:
 DU and the Health of Gulf War Veterans**

- Baltimore VA studies have followed a cohort of 40-60 Gulf veterans with embedded DU shrapnel; focus primarily on renal effects of DU
 - > Little information re: GWI-type problems in this cohort
 - > Cohort too small to determine risk from most types of cancer, other health problems
 - > Route of DU exposure in majority of Gulf War veterans was inhalation, ingestion
- Animal research presented to the RAC indicates:
 - > Embedded DU pellets can be associated with chromosomal, mutagenic, neurological, and immunological changes
 - > Embedded DU pellets result in DU accumulation in different regions of the brain
 - > Nasal penetration of inhaled DU into the brain is enhanced by nasal inflammation

**Unanswered Questions:
 Is DU Associated with Gulf War Illnesses?**

- Biological plausibility of association between GWI and DU?
- Requires information from human and animal studies

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

Study	Exposure	Outcome	OR
Spencer, 2001 (241 GWI cases, 113 controls)	sr DU exposure	GWI case CMI case	OR = 3.69 (1.54 - 8.8) OR = 4.46 (1.74 - 11.40)
Suardini, 1999 (686 Danish Gulf War vets)	sr DU exposure	3+ neuro- psych symptoms	OR = 2.3 (0.95-5.7)
Australian study (1,456 Australian vets)	sr contact with DU shell casings	functional impairment in prior 2 weeks	OR = 1.1 (0.8-1.6)

**Unanswered Questions:
 Is DU Associated with Gulf War Illnesses?**

Human Studies

- Little epidemiologic information
- Baltimore VA cohort: ongoing longitudinal study of 40-60 Gulf veterans with embedded DU shrapnel
 - > Neurocognitive and hormonal (prolactin and thyroxine) differences in Gulf veterans with elevated urine DU levels
- Additional information on multisymptom illnesses, effects of inhaled DU exposures requires larger studies that compare DU-exposed Gulf veterans to nonexposed

**Unanswered Questions:
 Is DU Associated with Gulf War Illnesses?**

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

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

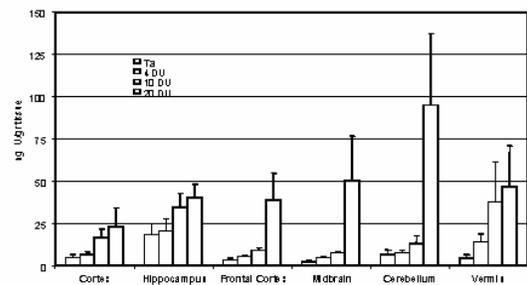
**Unanswered Questions:
 Is DU Associated with Gulf War Illnesses?**

Animal Studies

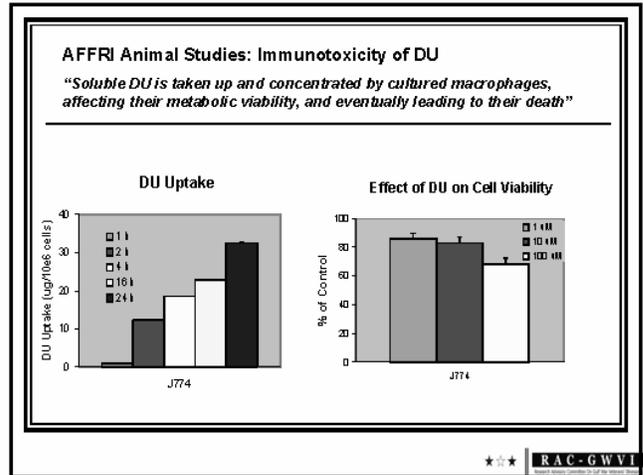
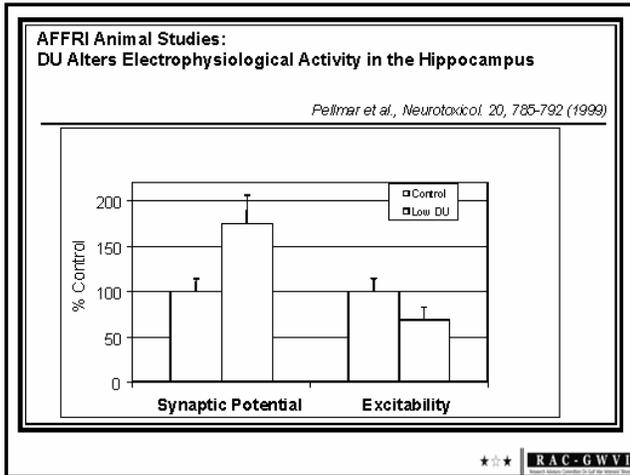
- > Animal studies of neurological, immune/inflammatory, and behavioral effects of DU exposure
- > Studies of DU in combination with other exposures of interest

**AFRRI Animal Studies
 Non-homogeneous distribution of uranium in the brain**

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



AFRRI studies presented by Dr. Terry Pellmar at Feb, 2004 RAC Meeting



- Inhalation of Uranium Oxides:
Preliminary Results Presented by Dr. Johnnye Lewis**
- **Very Short/High Dose – Tank-Impact scenario**
 - > no detectable CNS uptake regardless of solubility
 - > Solubility-related neuroinflammation
 - > Most soluble forms result in extensive renal deposition and renal toxicity
 - > Females more sensitive to CNS & renal toxicity
 - **Short-term/ Moderate Dose – March-Through Scenario**
 - > Nasal inflammation increases the probability of CNS deposition and transport with low dose inhalation for 6 hr durations
 - **Longer-duration/ Moderate Dose – Clean-Up Scenario**
 - > No uptake observable in animals without inflammation
- Results presented by Dr. Johnnye Lewis at Feb, 2004 RAC Meeting
- ☆☆ RAC-GWVI

- Ongoing Animal DU Studies Potentially Relevant to GWI**
- **AFRRI:** Continuing studies of immunotoxic effects of embedded pellets of DU, tungsten alloys
 - **Lewis (New Mexico):** Continuing studies of neurological effects of inhaled DU
 - **Lasley (Illinois):** Neurochemical effects of chronic DU exposure
 - **Aschner (Wake Forest):** Blood-brain barrier transport of uranium
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**Animal DU Studies Relevant to GWI:
Our speakers**

- Dr. Wayne Briner: Behavioral changes and Brain Lipid Oxidation Following Uranium Exposure
- Dr. David Barber: Neurological and Behavioral Effects Following Coexposure to Uranium and Stress

Presentation 10 – Wayne Briner

**Behavioral Changes and Brain
Lipid Oxidation Following
Uranium Exposure**

Wayne Briner
Jennifer Murray



Animal Findings

- DU accumulates in brain as well as skeleton, muscle, spleen, liver, heart, lung, lymph nodes, testes (Pellmar et al., 1999).
- DU accumulates in hippocampus & striatum, as well as cortex & striatum (Barber et al., 2005)
- DU pellets inhibited spike formation in the hippocampus of rats, no evidence of renal damage (Pellmar et al., 1998 & 1999).
- Rats given high doses of U exhibit tremors (Domingo et al., 1987).
- U may compete with calcium at the cellular level, in particular the neuromuscular endplate (Lin et al., 1988)

- No effect of U on DA or 5-HT or catabolite levels in a variety of brain structures (Houpert et al., 2004).
- No behavioral effects seen after 6 months DU pellet implantation (Pellmar et al., 1998)

- Developmental Effects
- U produces variety of adverse effects when administered prenatally on litter size and viability. Some teratogenic effects, esp. skeletal (native U, Domingo et al, 1989; Bosque et al, 1993; Paternian et al, 1989)
- Gestational day 10 (neural tube formation) most vulnerable time (Domingo, 1994)
- DU implanted rats demonstrated no effect on pregnancy or rat pups. DU does cross placental barrier and fetal tissue accumulates DU (Benson, 1998)

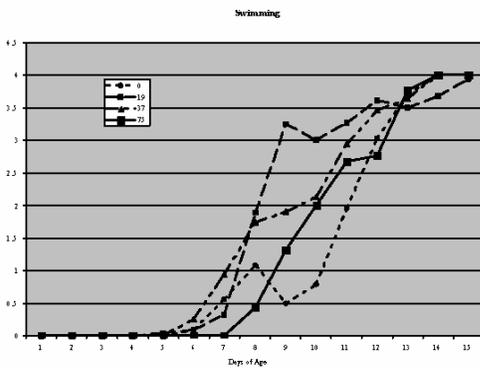
Human Findings

- DU found in urine of those exposed (Hooper et al., 1999; McDiarmid et al, 1999, 2000, 2001; Hodge et al, 2001). Issues concerning utility.
- Relationship between urinary DU and computerized neurocognitive testing (McDiarmid et al, 2000).
- Relationship between urinary DU elevated serum prolactin levels (McDiarmid et al, 2000).

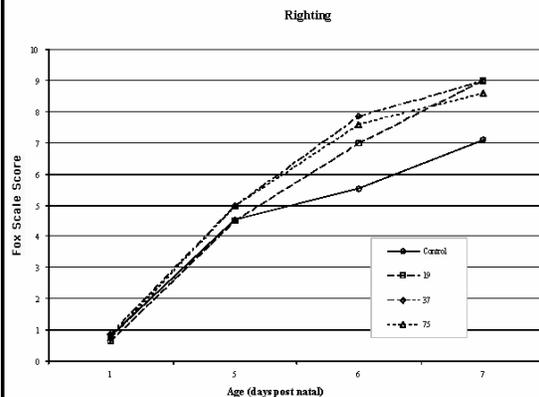
Developmental Research

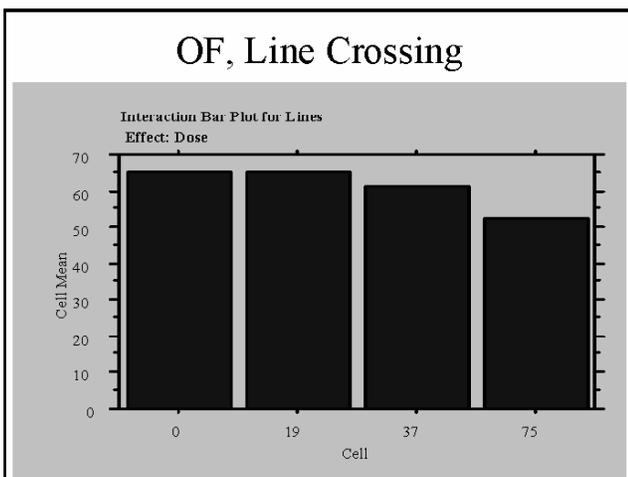
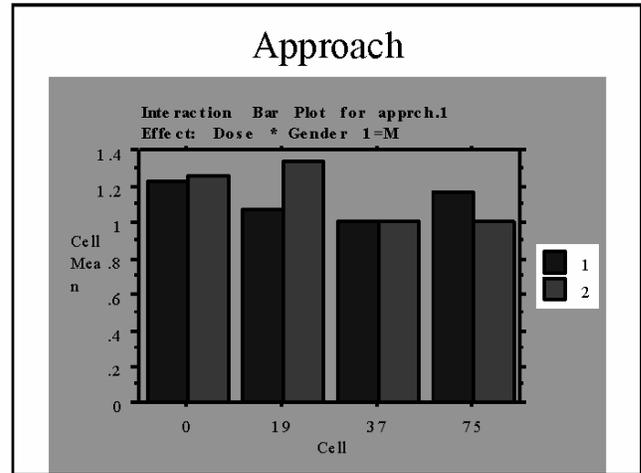
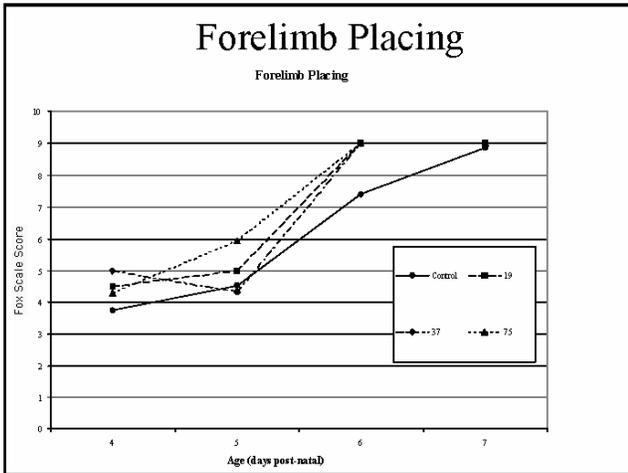
Female mice were exposed to 0, 19, 37, or 75 mg/L of uranium acetate for two weeks, then mated. Exposure of dams and pups continued until sacrifice. Mice were assessed using the Fox Developmental Scale until age 21 days. At 21 days of age the pups were assessed with a Functional Observation Battery after-which the brains were removed for study.

Swimming



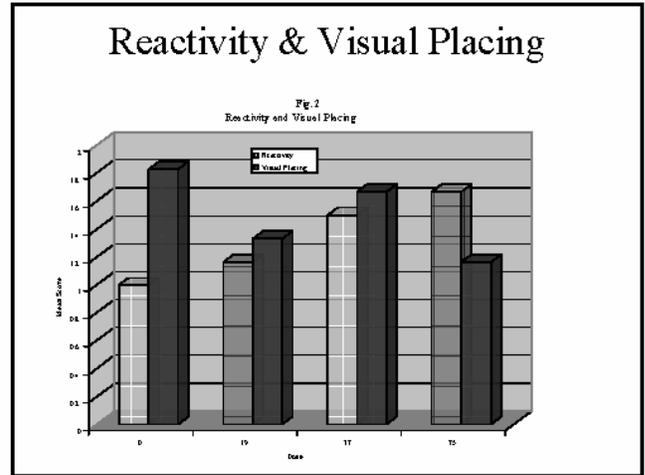
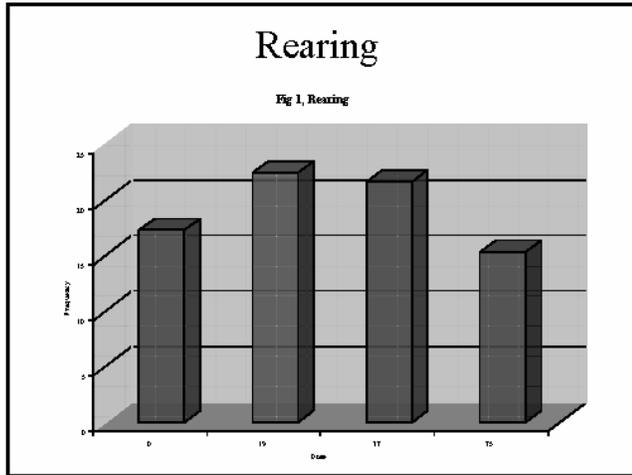
Righting





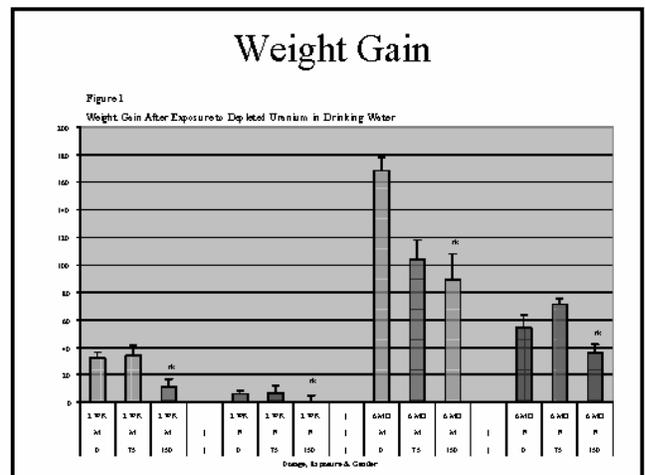
Adult Mice

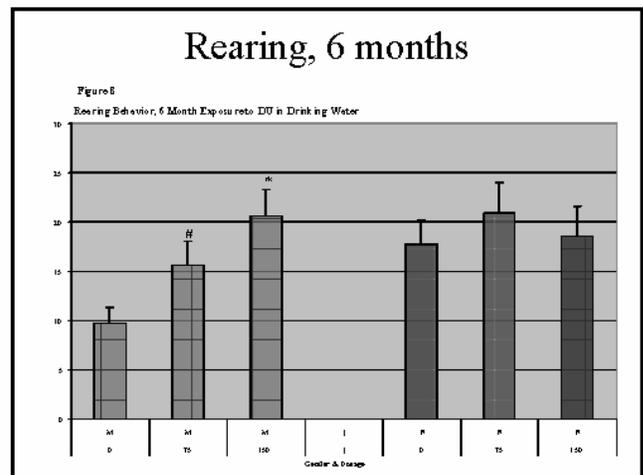
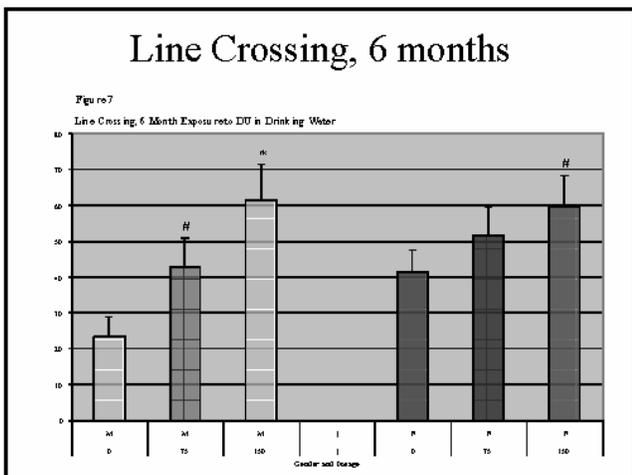
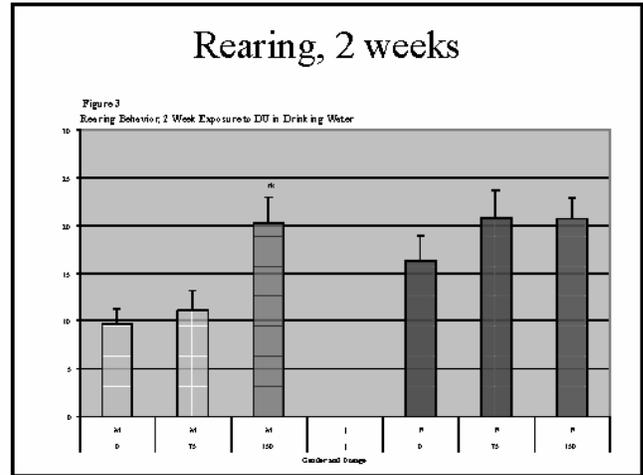
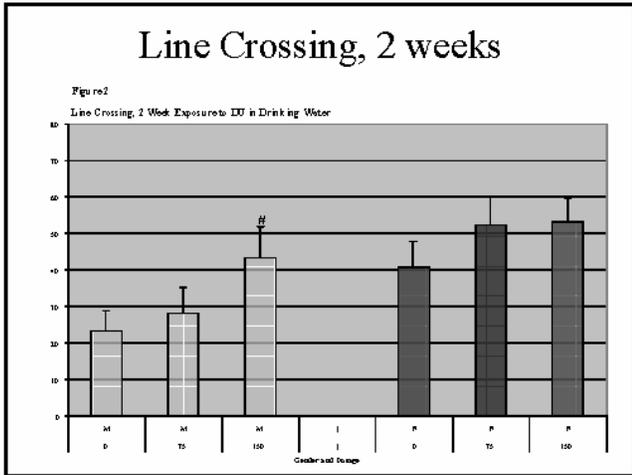
- Male adult mice were reared under standard laboratory conditions and exposed to DU acetate in drinking water at 4 dosage levels (0, 19, 37, and 75 mg/L) for 2 weeks.

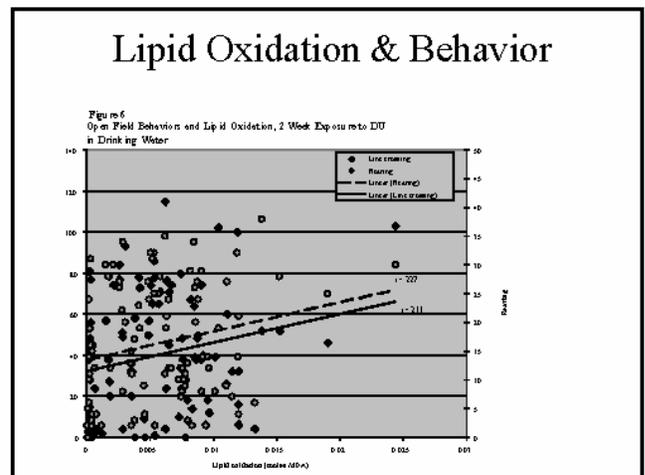
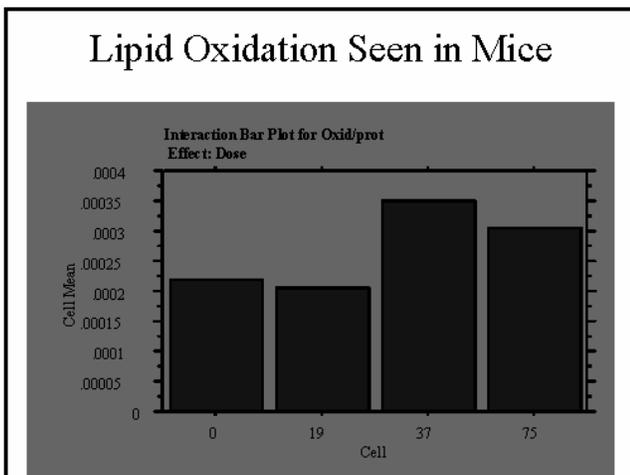
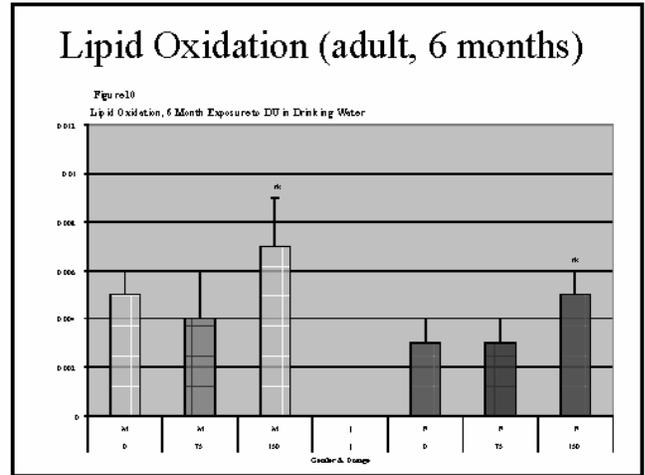
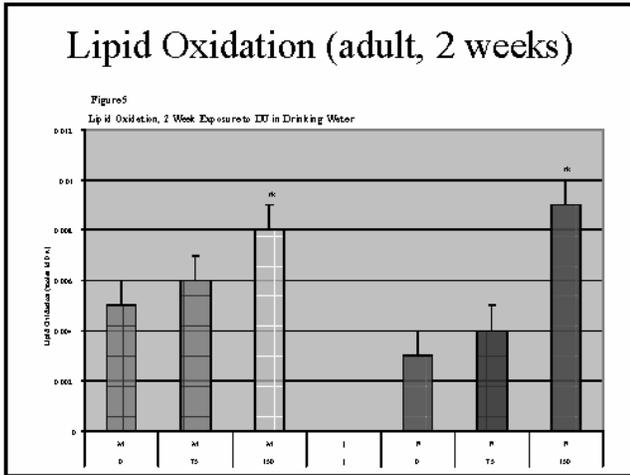


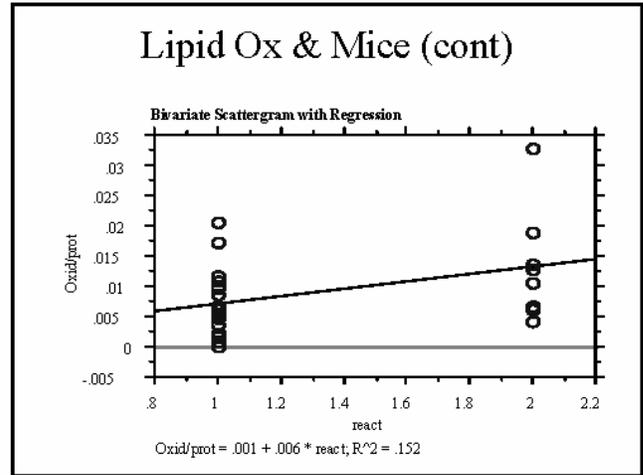
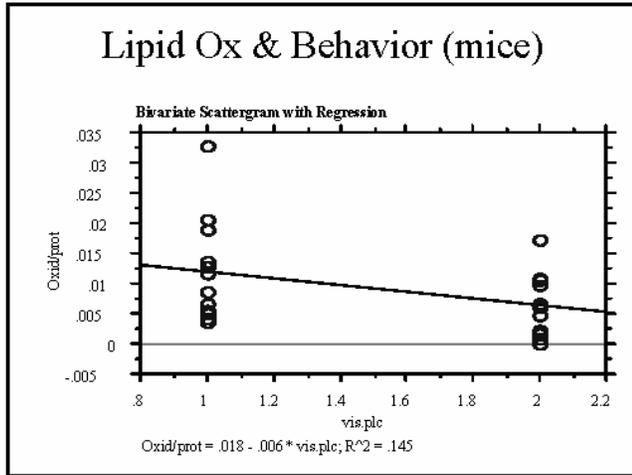
Rat Behavior (adult)

- Rats were exposed to depleted uranium acetate dihydrate in drinking water at doses of 0, 75, or 150mg/L for 2 weeks or for 6 months. At the conclusion of exposure, animals were tested in the open-field maze.
- Lipid oxidation levels determined using TBA method.



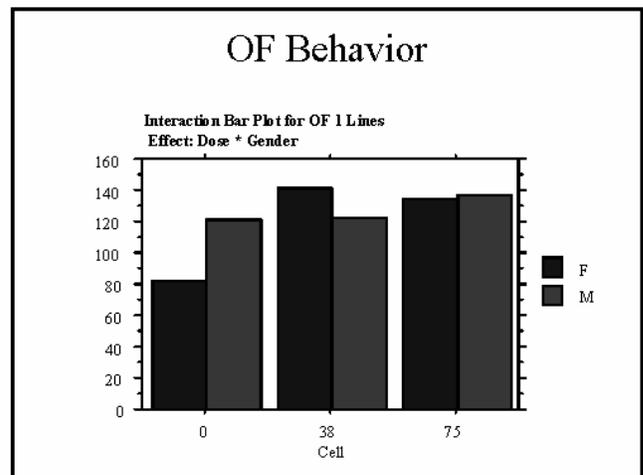


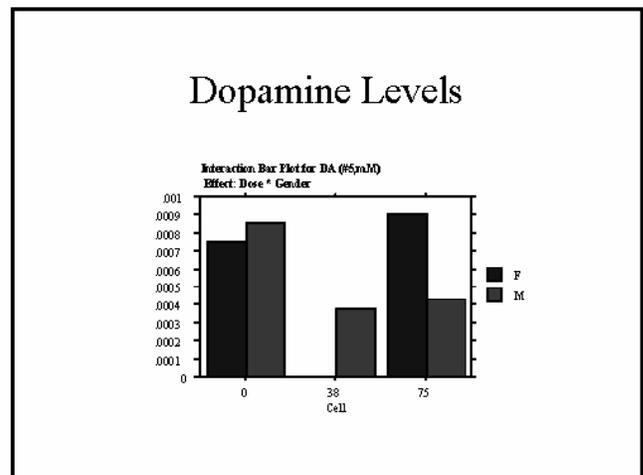
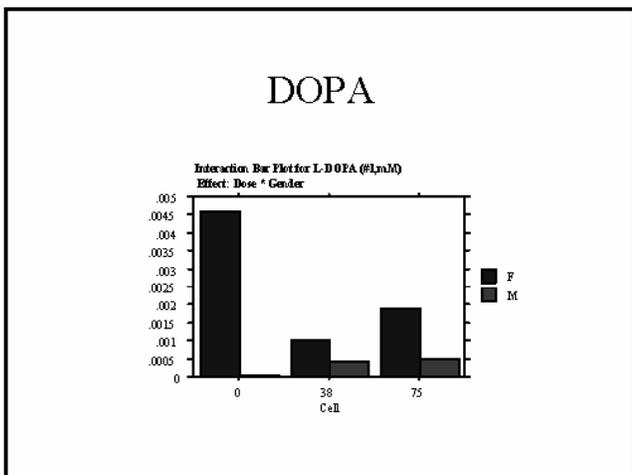
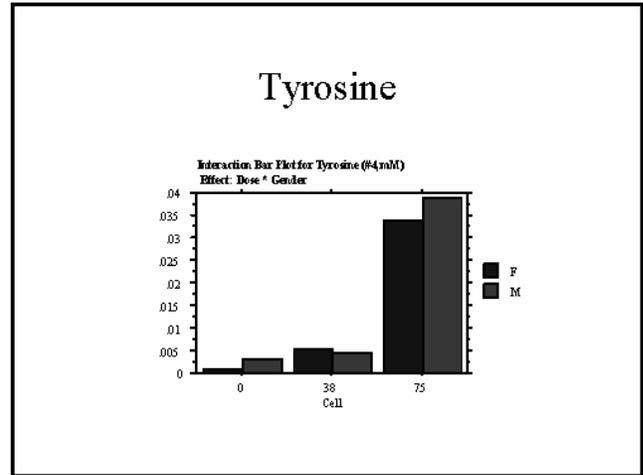
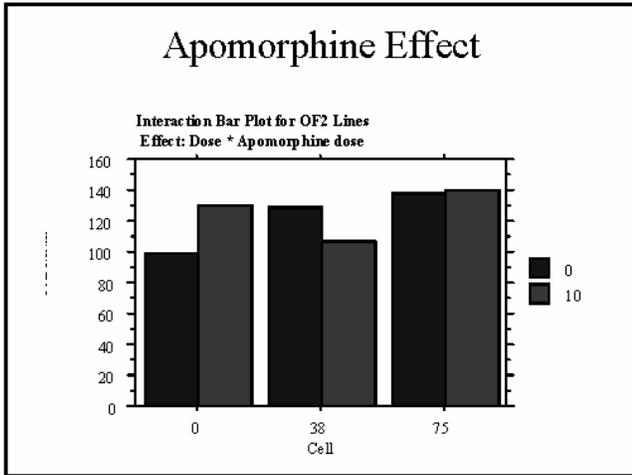




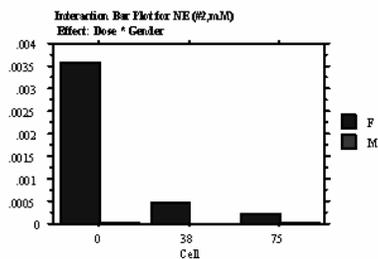
Neurotransmitter Studies

- Mice exposed to 0, 39, 75 mg/L DU acetate dihydrate for 2 weeks.
- Open field followed by repeat with apomorphine trial.
- HPLC determination of monoamines using an ion-pairing method with UV detection. Midbrain.
- PRELIMINARY FINDINGS!!

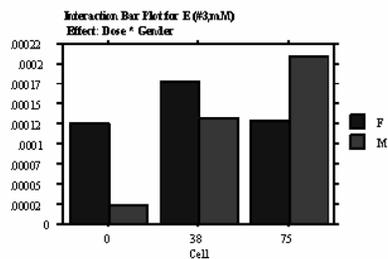




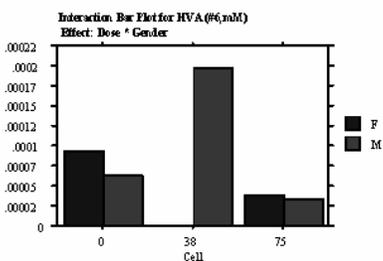
Norepinephrine



Epinephrine



HVA



Overview

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

Thanks

- Research Services Council
- Mary Burkhart
- Dawn Belle Isle
- Kevin Byrd
- Carmen Richman
- Brenda Petersen
- Bridget Abboud
- Daniel Davis

Presentation 11 – David Barber



Neurological Effects of Acute Uranium Exposure

David Barber
University of Florida



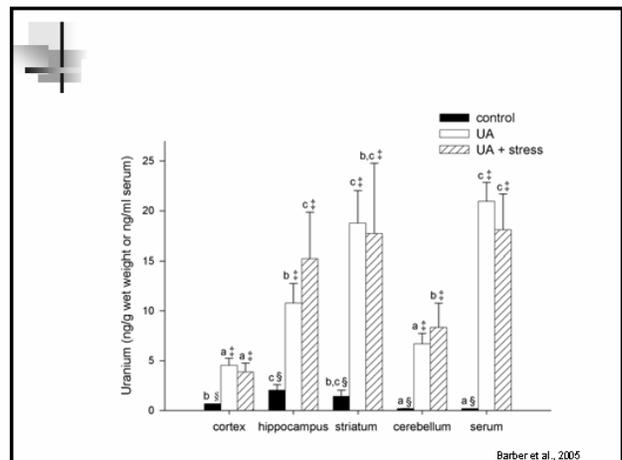
Background

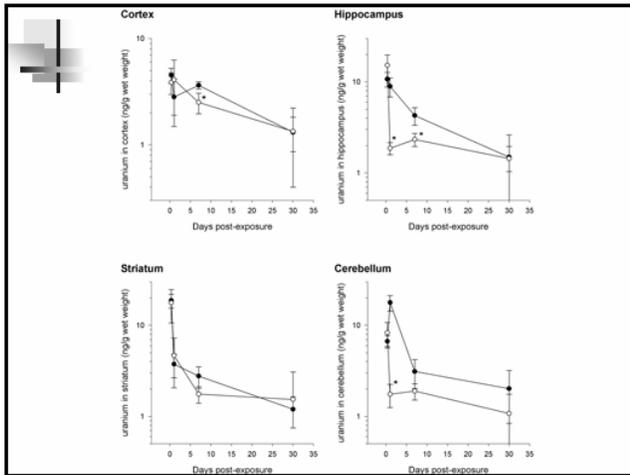
- Many symptoms of GWI are potentially neurological in origin
- Two studies indicated that depleted uranium may have neurological effects
 - Pellmar *et al.* (1999) Hippocampal dysfunction in rats implanted with DU pellets
 - McDiarmid *et al.* (2000) Neurological deficits in exposed veterans with highest uranium excretion
- Chemical similarity of uranyl ion to lead and calcium
- Stress may alter the uptake of uranium



Goals of Study

- Several studies have shown that uranium enters the brain, but little information on kinetics of deposition and elimination or effects of DU on the nervous system
 - Examine the deposition and elimination of uranium in the brain
 - Determine if acute exposure to uranium produces neurological effects
 - Determine if prolonged exposure to uranium produces neurological effects
 - Determine if stress alters uranium deposition or neurological effects

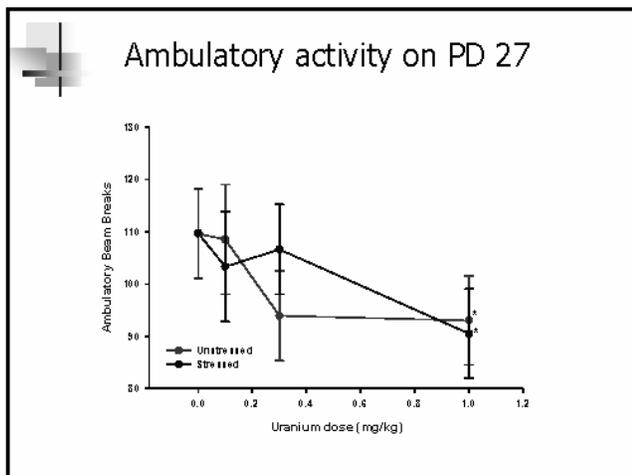
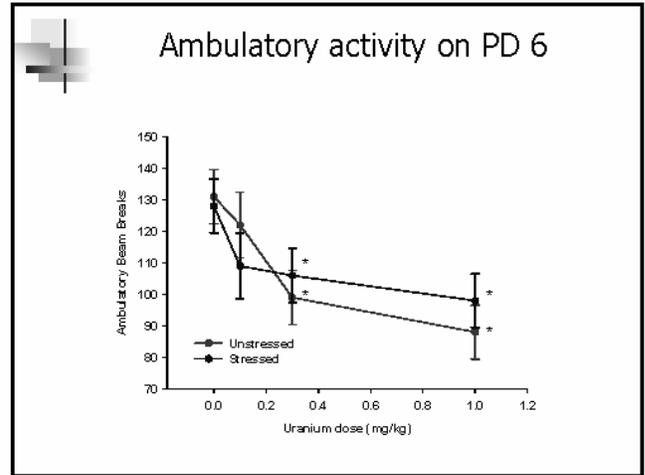
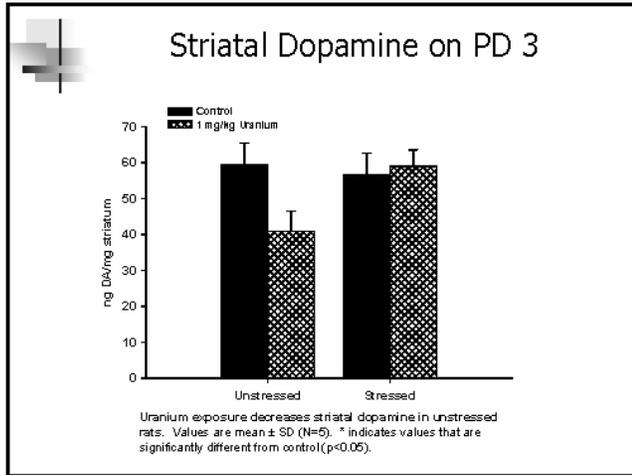




- This study demonstrated that:
 - There are regional differences in brain uranium distribution
 - There are several phases of uranium elimination from the brain with the last phase being very long
 - Prior stress did not exacerbate the entry of uranium into the brain, if anything increased its elimination

- ### Research Questions for Acute Toxicity Study
- It is clear that acute uranium exposure increases brain uranium levels, but are there observable effects on neuronal structure or function?
 - Does the application of stress at the time of uranium exposure alter the effects of uranium on the nervous system?

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

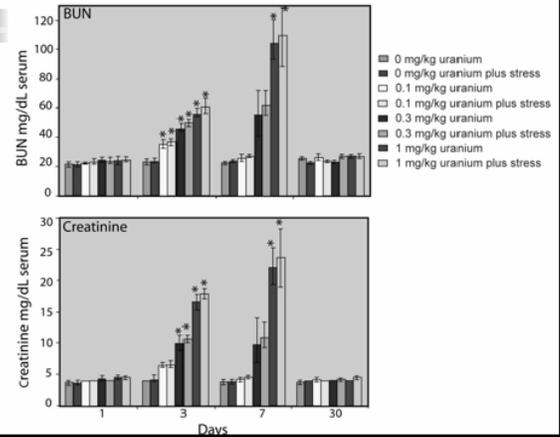


Uranium exposure decreases forelimb grip strength

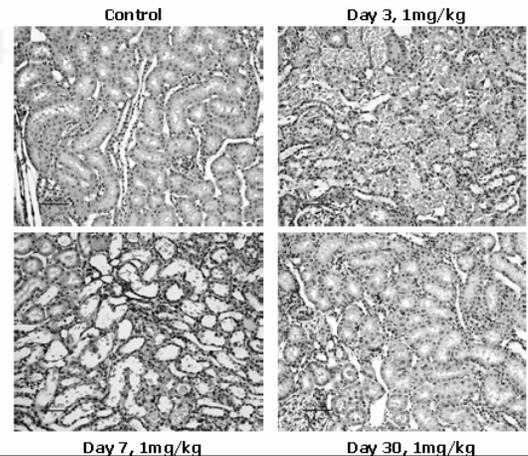
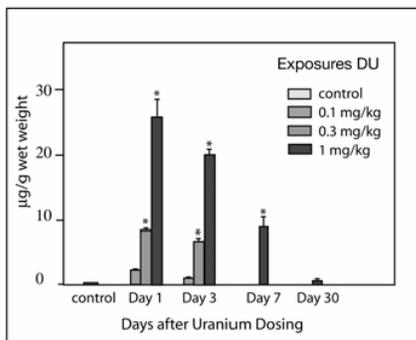
Day post-dosing	Uranium dose (mg/kg)	Forelimb Grip Strength (kg)	
		Unstressed	Stressed
6	0	1.83 \pm 0.04	1.81 \pm 0.05
	0.1	1.87 \pm 0.04	1.79 \pm 0.05
	0.3	1.79 \pm 0.03	1.76 \pm 0.03
	1.0	1.70 \pm 0.07	1.79 \pm 0.04
13	0	1.96 \pm 0.04	1.94 \pm 0.04
	0.1	2.01 \pm 0.02	2.05 \pm 0.03
	0.3	1.91 \pm 0.04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

Other Results

- DU treatment initially produced decreased weight gain, but weights were equivalent to control by PD27
- DU and/or stress did not affect GABA, serotonin, norepinephrine, or glutathione content in striatum, hippocampus, cortex, or cerebellum
- DU did not affect performance in the passive avoidance assay, or indicators of CNS excitability, autonomic activity, equilibrium, or sensory perception
- No histopathological lesions in the CNS were visible on H&E stained sections
- All doses of DU produced some degree of renal injury and uremia



Kidney uranium



Summary

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

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

Future Studies

- We are completing assays of D2 receptors in striatum, nACh receptor numbers in cortex and NMDA receptors in hippocampus.
- We are currently conducting a 6 month study utilizing implanted uranium and tantalum pellets (Pellmar et al., 1999) with stress applied throughout study.

Acknowledgements

- Collaborators
 - Dr. Bernie Jortner
 - Sandy Hancock
 - Jonathan Hinckley
 - Alex McNally
 - Tamece Knowles
 - Mike Kopplin
- Studies funded by the US Army MOMRP

Presentation 12 – Lea Steele

**Gulf War Illnesses and Vaccines:
Overview of Epi Findings, Remaining Issues**

Lea Steele, Ph.D.

Meeting of the Research Advisory Committee
on Gulf War Veterans' Illnesses
April 7, 2004

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**Possible Association of Gulf War Illnesses with
Vaccines Received during the Gulf War**

- Review of Epi Findings and RAC Discussions to Date
- Remaining Issues re: Vaccines and GWI

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**Vaccines and Gulf War Illnesses:
Issues Discussed**

- Epi studies consistently show association of GWI with vaccines
- Greatest concerns have been raised about the anthrax vaccine
 - > High rate of acute reactions, little info re: long-term effects
 - > Problems associated with manufacturing process?
 - > Problems with individual components of the vaccine?
- GWI-type problems among nondeployed veterans, recipients of the anthrax vaccine?

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**Vaccines and Gulf War Illnesses:
Remaining Issues**

- Research re: squalene antibodies in Gulf War veterans, AVA recipients
- Additional research related to long-term followup of AVA recipients
- Problems with vaccines other than anthrax given during the Gulf War?
- Additional research related to receipt of multiple vaccines
- Considerations re: combinations of specific vaccines, vaccines with other exposures?
- Evidence related to chronic immune activation associated with receipt of vaccines, TH1-TH2 shift (Rook hypothesis)
- Other aspects of vaccine safety (e.g. scheduling, individual components)

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Vaccines and Gulf War Illnesses: Remaining Issues Squalene

- Anti-squalene antibodies in Gulf War veterans?
 - > Do veterans with Gulf War illnesses have an elevated level of antibodies to squalene?
 - > Is presence of these antibodies a marker for and/or a cause of GWI?
- Was squalene in vaccines used during the Gulf War?
 - > Used as an adjuvant to enhance vaccine immunogenicity?
 - > In vaccines for some other reason?
 - > Levels capable of causing chronic illness?

Vaccines and Gulf War Illnesses: Remaining Issues
 Squalene Antibodies in Ill Gulf War Veterans?

Asa, Cao, Garry (2000)

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

Vaccines and Gulf War Illnesses: Remaining Issues
 Squalene Antibodies in Post-Gulf AVA Recipients?

Asa, Wilson, Garry (2002)

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

Squalene: Additional Information

- No other identified studies have compared levels of anti-squalene antibodies in ill vs. healthy Gulf War veterans
- Squalene and related compounds are known to cause an autoimmune condition when injected into animals
- FDA testing identified extremely low levels of squalene in several lots of AVA, as well as diphtheria and tetanus vaccines
- Government reports indicate that squalene has never been used as an adjuvant in AVA

The Squalene Issue:
Boils down to a simple question

Are anti-squalene antibodies associated with Gulf War illnesses?

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The Squalene Issue: The primary question

Are anti-squalene antibodies associated with Gulf War illnesses?

- If NO, there is no issue
- If YES, secondary questions:

Do anti-squalene antibodies result from an immune response to squalene in AVA (as an adjuvant or for some other reason), which caused chronic illness?

OR

Are anti-squalene antibodies a marker for other pathological mechanisms underlying Gulf War illnesses (e.g., poorly understood immune abnormalities resulting from multiple vaccines, specific vaccines, or other causes)?

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The Squalene Issue: The primary question

Are anti-squalene antibodies associated with Gulf War illnesses?

- Asa/ Garry paper on GWI and squalene antibodies raises a straightforward question and testable hypothesis
- GAO report concurred, and recommended that a study be done to address this question
- If Asa findings are refuted, the issue can be put to rest
- If anti-squalene antibodies are found disproportionately in ill Gulf veterans, additional questions should be addressed

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Vaccines and Gulf War Illnesses: Remaining Issues

Other Potential Problems with AVA?

- Problems with manufacturing process, quality control?
- Problems with specific components of the vaccine?
 - > Earlier review by Dr. Melling
 - > PA common to both UK and US vaccines
 - > Higher level of PA associated with change in manufacturing process?
- 1990 AVA vs. current AVA?

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Vaccines and Gulf War Illnesses: Remaining Issues

Other Vaccines Received During the Gulf War

Identified problems with vaccines other than AVA?

- > Hasn't been looked at in detail, among U.S. personnel with complete shot records
- > No long-term follow up data for most vaccines; some known to be associated with rare cases of chronic neurological complications

IMMUNIZING AGENT	ARMY	NAVY	AIR FORCE	MARINE CORPS	COAST GUARD
Adeno virus (Types 4 and 7)	B	B	B	B	H
Cholera	F	F	F	F	F
Hepatitis B	E,O,H	E,O,H	E,O,H	E,O,H	O,H
Influenza	A,B,H	A,B,R	A,B,R	A,B,R	E,O,H
Meadowc	E,O	E,O	E,O	E,O	E,O
Meningococcal (A,C,Y,W135)	E,H	B,H	E,H	E,H	E,H
Mumps	O,H	O,H	O,H	O,H	O
Plague	C,D,E,O	D,O	E	A,O	E
Polio	A,R	A,R	A,R	A,R	A
Rabies	D,O,H	D,O,H	D,O,H	D,O,H	H
Rubella	E,O	E,O	E,O	E,O	B
Smallpox	E,H	E,H	E,H	E,H	E,H
Tetanus/diphtheria	A,B,R	A,B,R	A,B,R	A,B,R	A,B
Typhoid	C,E,H	H	C,E,H	H	E
Yellow fever	C,D,E	A,R	C,E	A,R	E,E

A: All active duty personnel
 B: Routine
 C: Anti-bio
 D: Special Operating Forces component
 E: W/extended stay or housing in high risk areas
 F: Only when required by host country's endemicity
 O: High risk occupational groups
 H: As directed by applicable Surgeon General
 R: Reserve component
 X: Reserve personnel active 30 days during AU season

Association of Individual Vaccines with Health of Gulf Veterans

Study	Outcome	Vaccine	Findings
Boyd, 2003 (975 Gulf vets in Registry)	High vs. low # of symptoms	Botulinum	OR = 1.78*
		Anthrax	OR = 1.72*
		Meningococcus	OR = 1.57*
		Others	NS
Canadian MOD (3,113 Gulf vets)	Chronic fatigue Cogn dysf	"nonroutine" (anthrax, plague)	OR = 1.92* OR = 1.28*
Gray, 2002 (3,881 POW vets)	GWI case def	Meningococcus	OR = 3.64* (unadj); 1.30* (adj)
		Botulinum	OR = 4.92* (unadj); 1.29 (adj)
		Anthrax	OR = 3.72* (unadj); 1.01 (adj)
		Plague	OR = 3.23* (unadj); 0.94 (adj)
Wolfe, 2002 (1,290 Gulf vets)	CMI	Typhoid	OR = 2.34* (unadj); 0.93 (adj)
		Anthrax	OR = 1.5* (adj)
Urwin, 1999 (2,755 Gulf vets)	CMI	Anthrax	OR = 1.5*
		Plague	OR = 1.3*
		Tetanus	OR = 1.3*
		Any biological Other	OR = 1.5* NS

* Indicates statistical significance, p < 0.05

Vaccines and Gulf War Illnesses: Remaining Issues
Multiple Vaccines

- Problems with Receipt of Multiple Vaccines Simultaneously?
 - > Epi studies of Gulf-era veterans suggest association of GWI with # of vaccines received
 - > Little detail re: combinations of specific vaccines
 - > Some studies of effects of multiple vaccines in other populations

Association of Multiple Vaccines with Health of Gulf Veterans

Study	Outcome	Vaccine	Findings
Cherry, 2001 (8210 Gulf vets)	Symptom severity score	0	ALL* 2.0 -26.4
		1-3	2.8 -2.7
		4-6	3.5 9.2
		7-9	4.2 23.6
		10+	4.5* 34.4
Hotopf (823 Gulf vets w/shot records)	CMI	Postdeployment	
		0/1	OR = 1.0
		2	OR = 2.2*
		3	OR = 2.4*
		4	OR = 2.2*
5+	OR = 5.0*		
Australian study (1,428 Australian vets, used shot records)	# of symptoms	0	Ratio of means = 1.0
		1-4	RM = 0.9
		5-9	RM = 1.0
		10+	RM = 1.3*

* Indicates statistical significance, p < 0.05

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- Vaccines and Gulf War Illnesses**
-
- Epi studies suggest associations
 - > ORs not particularly large for individual vaccines, but little attempt to look at exposure subgroups
 - > Role of multiple vaccines and combinations of individual vaccines requires additional study
- ☆☆ RAC-GWVI

- Vaccines and Gulf War Illnesses:
 Recent Research Informs Remaining Questions**
-
- Additional research related to long-term followup of AVA recipients
 - Research re: squalene antibodies in vaccine recipients
 - Additional research related to receipt of multiple vaccines
- ☆☆ RAC-GWVI

- Vaccines and Gulf War Illnesses:
 Speakers**
-
- Dr. John Grabenstein
 - Dr. Phillip Pittman
- ☆☆ RAC-GWVI

Presentation 13 – John Grabenstein

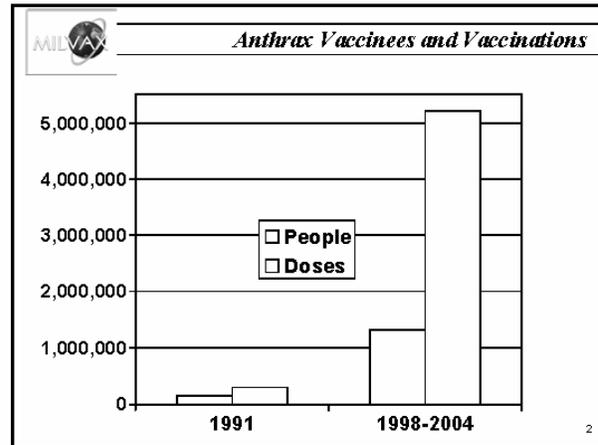
MILVAX

20 Studies to Evaluate Adverse Events After Anthrax Immunization

7 Apr 05
 COL John D. Grabenstein, RPh, PhD, U.S. Army

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

1



MILVAX *World War II Shot Records*

IMMUNIZATION REGISTER AND OTHER MEDICAL DATA
(SEE 45.6-7)

NAME (Last, First, Middle Initial) SSN
Grabenstein, Herman J Jr 0863988

DATE OF BIRTH: 22Apr21 RACE: W BLOOD GROUP: O MED. OFF.: WJH

DATE	SMALLPOX VACCINE	TYPE OF REACTION	MED. OFF.
19Nov43	1	Immune	N/A
19Oct44	1	Immune	N/A

DATE	TRIPLE TYPHOID VACCINE	TYPE OF REACTION	MED. OFF.
Comp	1		N/A
Nov42	1		N/A
19Nov43	1		N/A
19Oct44	1		N/A
88Sep45	1		N/A

IMMUNIZATION REGISTER

LAST NAME: Sandquist, Eric ARMY SERIAL NO: 31257823

GRADE: REGT. OR STAFF CORP. AGE: RACE: W

DATE	SMALLPOX VACCINE	TYPE OF REACTION	MED. OFFICER
3 Jan 43	Vaccinoid		N/A
12 Mar 43	Vaccinoid		N/A

DATE	TRIPLE TYPHOID VACCINE	TYPE OF REACTION	MED. OFFICER
1st dose	1		N/A
2d dose	1		N/A
3d dose	1		N/A

MILVAX *Science*

Anthrax: Evidence for vaccine effectiveness

- Brachman study, 1,249 people, *Am J Public Health* 1962
- Rhesus monkeys: 62 of 65 survive inhalation challenge
- Rabbits: 114 of 117 survive inhalation challenge
- FDA decisions: 1970, 1985, 2004 Jan + Dec
- National Academy of Sciences: 2002

Anthrax: Evidence for vaccine safety

- 20 human safety studies, 34 peer-reviewed publications
- FDA decisions: 1970, 1985, 2004 Jan + Dec
- National Academy of Sciences: 2002
- ACIP-2001, CDC-2005

4

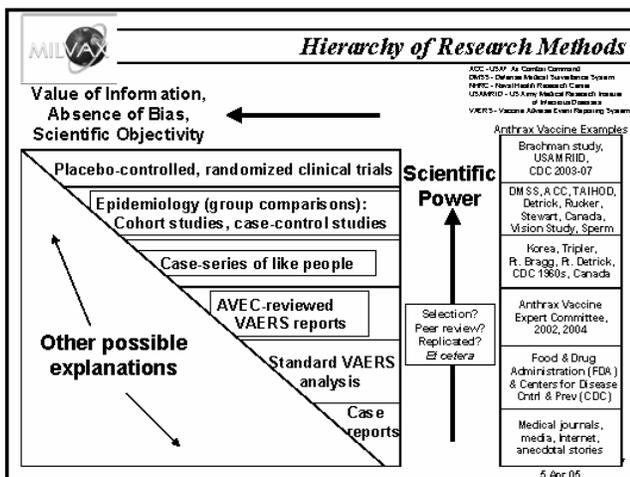
MILVAX *IOM Report, 2002, Tables 4-1, 6-1, 6-2*

	Fever	Systemic, Any	Erythema or Swelling	Pain, Any
Acellular pertussis	0 - 7%	17 - 29%	12 - 15%	51 - 77%
Hepatitis A	0 - 3%	4 - 22%	4 - 40%	40 - 52%
Hepatitis B	0 - 4%	10%	1 - 99%	11 - 43%
Influenza	1 - 13%	11 - 34%	11 - 21%	24 - 86%
Rabies	2 - 18%	3%	1 - 18%	4 - 52%
Tetanus - diphtheria (Td)	1 - 9%	17 - 26%	22 - 35%	43 - 85%
Anthrax	1 - 8%	1 - 36%	3 - 42%	Sore: 67 - 83%

www.nap.edu/catalog/10310.html 5

MILVAX *Anthrax Vaccine Safety Litany*

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



- MILVAX** *Anthrax Vaccine Safety Surveillance*
- Mar 98 to Oct 04, > 5.2 million doses of anthrax vaccine to > 1.3 million people.
 - Soreness, redness, itching, swelling at injection site:
 - Less than 2.5 cm: 30% of men, 60% of women.
 - More than 12 cm: 1% to 2%, both genders
 - Inject over deltoid (not triceps)
 - Lump at injection site common, lasts a few weeks, goes away.
 - Systemic symptoms—muscle or joint aches, headaches, rashes, chills, low-grade fever, nausea.
 - 5% to 35%, like other vaccines
- 8

Rate Ratios for Hospitalization & Anthrax Vaccination
(Hospitalization Rate Among Anthrax Vaccine Recipients
Divided by Rate Among Nonrecipients, for Active-Duty Personnel)

Recipients = 350,296 person-years of experience
Nonrecipients = 2,368 million person-years of experience

Category	Rate per 100,000 per Year		Rate Ratios		95% Confidence Interval (Adj.)	Significant Elevation?
	Vaccinated	Unvaccinated	Unadj.	Adjusted		
Mental Health	383.1	728.7	0.52	0.58	0.54 — 0.63	no
Endocrine / Immunol.	29.1	50.7	0.57	0.69	0.58 — 0.82	no
Blood / Blood Formtn.	12.8	21.8	0.59	0.73	0.55 — 0.96	no
Musculoskeletal	432.4	708.7	0.61	0.74	0.70 — 0.79	no
/ Connective Tissue						
Ill-Defined Conditions	177.3	249.7	0.71	0.81	0.73 — 0.89	no
Respiratory	156.7	238.9	0.66	0.81	0.73 — 0.90	no
Genitourinary—Male	74.8	96.8	0.77	0.82	0.72 — 0.95	no
Neoplasms	83.4	123.1	0.65	0.85	0.71 — 1.02	no
Nervous System	61.7	91.5	0.67	0.86	0.74 — 0.99	no
Circulatory	110.2	152.9	0.72	0.88	0.79 — 0.99	no
Injury or Poisoning	555.2	580.6	0.96	0.89	0.84 — 0.94	no
Digestive	405.0	478.2	0.85	0.92	0.87 — 0.98	no
Skin	82.2	100.0	0.82	0.94	0.84 — 1.04	no
Infectious	84.5	102.7	0.82	1.01	0.90 — 1.13	no
Genitourinary-Female	895.2	822.9	1.09	1.13	0.97 — 1.32	no
Complications of Pregnancy	372.7	848.0	0.44			no

Key Finding: No category of hospitalization is elevated among anthrax vaccine recipients at a statistically significant level.

Rate ratios adjusted by standard manner (regression) to control independent effects of age, gender, rank, deployment, service, ethnicity, previous hospitalization, year, and occupation. If confidence interval includes 1.00, then difference between vaccinated and unvaccinated group is not statistically significant.

Source: Defense Medical Surveillance System, 10 May 2003. Data for Jan 1986 to Dec 1999.

Lange JL, et al. *Vaccine* 2003; 21 (Apr 2): 1620-28.

Institute of Medicine (IOM) Report April 2002
National Academy of Sciences, www.nap.edu/catalog/10310.html

- **EFFECTIVE:** "The committee finds that the available evidence from studies with humans and animals, coupled with reasonable assumptions of analogy, show that AVA as licensed is an effective vaccine for the protection of humans against anthrax, including inhalational anthrax, caused by all known or plausible engineered strains of *B. anthracis*."
- **SAFE:** "The committee found no evidence that people face an increased risk of experiencing life-threatening or permanently disabling adverse events immediately after receiving AVA, when compared with the general population. Nor did it find any convincing evidence that people face elevated risk of developing adverse health effects over the longer term, although data are limited in this regard (as they are for all vaccines)."
- **SAFE: Side effects "comparable to those observed with other vaccines regularly administered to adults."**



The Everyday Environment

- At a summer picnic:
 - Bacteria in unrefrigerated food
 - Abrasions sliding into 2nd base
 - High-fives after game
 - Sneezes from summer "colds"
 - Water swallowed while swimming
 - Didn't wash hands after bathroom
 - Bee sting
 - Ragweed pollen in the air
 - Poison ivy in the outfield
 - Unprotected intercourse
- At a training camp or barracks:
 - Bacteria in unrefrigerated food
 - Abrasions on obstacle course
 - High-fives after team success
 - Sneezes from summer "colds"
 - Water shared from buddy's canteen
 - Didn't wash hands after latrine
 - Bee sting
 - Ragweed pollen in the air
 - Poison ivy at the range
 - Unprotected intercourse (?)

• The human body is built to function normally amid an environment filled with multiple antigens.

11

Simultaneous Immunization

Advisory Committee on Immunization Practices. MMWR 2002; 51(RR-2):1-35 ftp.cdc.gov/pub/Publications/mmwr/rr/rr5102.pdf

- "Experimental evidence + extensive clinical experience strengthen scientific basis for administering vaccines simultaneously. ... Simultaneous administration critical when preparing for foreign travel + if uncertainty exists that person will return for further doses of vaccine."

Armed Forces Epidemiological Board (AFEB), Symposium on Simultaneous Immunization, Feb 2004:

- www.ha.osd.mil/afeb/meeting/021704meeting/default.cfm
- www.ha.osd.mil/afeb/2004/2004-04.pdf

- 'support the practice of concurrent immunization'
- offers 'strategies to ↓ concurrent vaccinations, minimize discomfort'

Bibliography on simultaneous vaccinations: 94+ articles

12

 **Hotopf, et al. BMJ 2000**

- Hotopf M, David A, Hull L, et al. Role of vaccinations as risk factors for ill health in veterans of the Gulf war: Cross sectional study. *BMJ* 2000;320:1363-7.
- Multiple vaccinations given in a theater of war, but not multiple vaccinations given before deployment, associated with multi-symptom illness, fatigue, psychological distress, health perception, and physical functioning.
- Analysis limited to veterans who kept vaccination records.
- Exposures other than vaccination not controlled, except pesticide use. Anthrax vaccine was not analyzed independently.
- Authors recommend Armed Forces be vaccinated before deployment: "... folly to allow service personnel to be committed to a modern battlefield without all necessary means of protection against endemic infection and biological weapons."
- Shaheen, editorial, *BMJ* 2000;320:1351-2 evidence "inconclusive," design limitations, contrary findings.

13

 **Length of Anthrax Vaccine Safety Studies**

	Surveillance points <u>after each dose</u>	Total surveillance <u>after dose # 1</u>
Fort Bragg	0, 1, 2, 3, 7, 30 days	= 30 days
RIID DR-RC	0, 1, 2, 3, 7, 30 days	= 6 months
Korea	2 weeks to 5 months	= 6 months
ACC-Langley	n/a	6 months
USAF Vision	n/a	≥ 6 months
Langley AFB	n/a	≥ 6 months
VAERS / AVEC	n/a	minutes to years
Canada	n/a	8 months after return
Tripler (TAMC)	≥ 7 days	≥ 1 year
Brachman	24, 48 hours	≥ 1.5 years
Inpt / Outpt Cohort	n/a	≥ 6 to 18 months
CDC DR-RC	days 2, 14, 14-28	3.5 years
Disability Evaluation	n/a	4.25 years
Fort Detrick long-term-99	n/a	27 years
Fort Detrick long-term-142	n/a	15 to 55 years (mean 43)

14

 **Disability Discharge Evaluations**

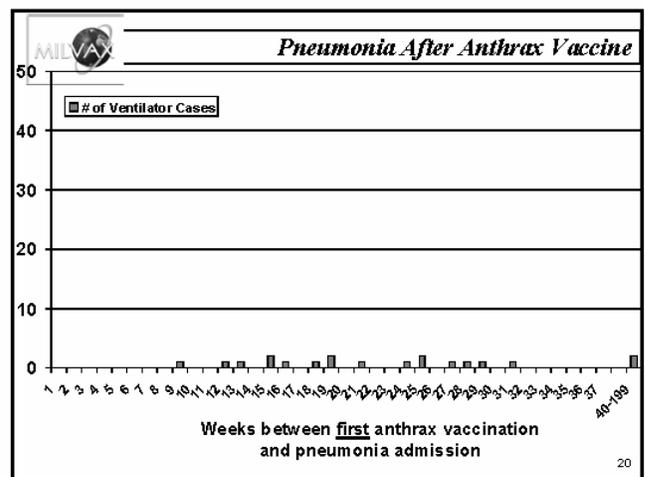
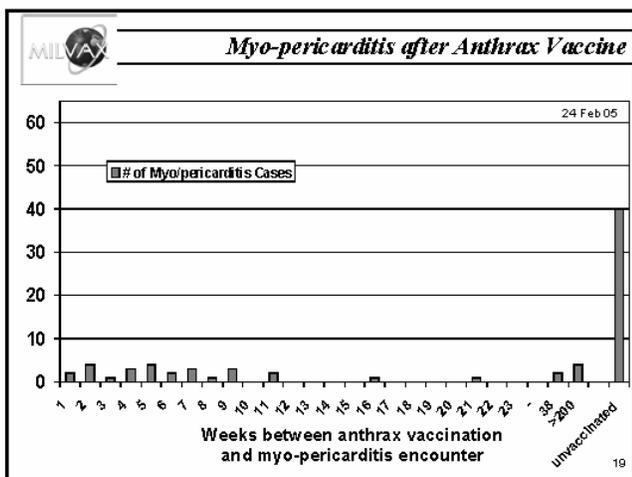
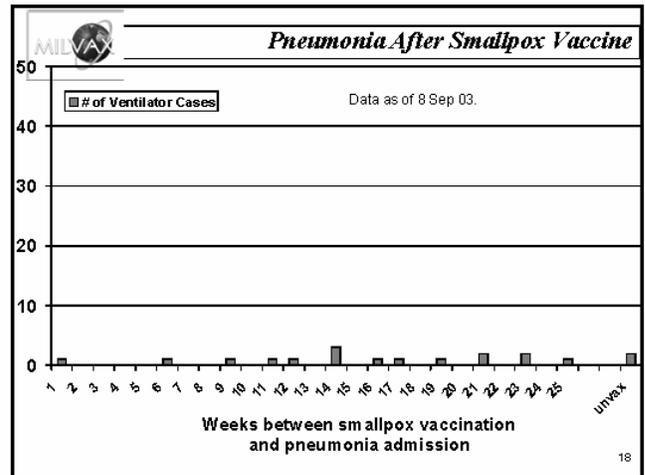
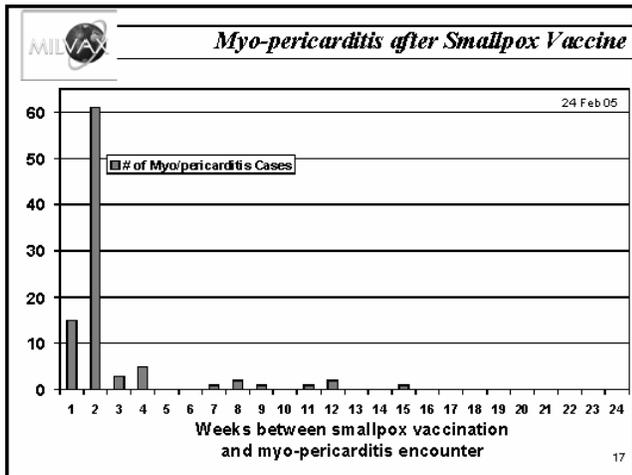
- Sulsky SI**, et al. Disability among U.S. Army personnel vaccinated against anthrax. *Journal Occupational & Environmental Med* 2004;46:1065-1075.
- Subjects:** U.S. Army personnel receiving ≥ 1 dose of anthrax vaccine adsorbed (AVA) between Mar 98 and Feb 02 vis-à-vis disability evaluation.
- Methods:**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

15

 **Long-term Safety Data: Lab Workers**

- Pittman PR**, et al. Long-term health effects of repeated exposure to multiple vaccines. *Vaccine* 2004;23:525-36.
- Workers:** 155 former biolab workers, 1943 to 1969, median 154 vaxtns or skin tests, median 17.3 y elapse. 92% received anthrax vaccine, 1943 to 1996. Interval from 1st vaccination to survey was 15 to 55 y (mean 43.1 y). Mean age: 69 years old.
- Controls:** 265 community controls from central Maryland matched on age, ethnicity and gender.
- Results:** Lab workers reported fatigue more than controls, but fatigue not associated with # of injections, # of vaccines, or time. No differences for self-reported medical conditions. Several laboratory abnormalities were more common in workers, but none clinically significant. Frequency of monoclonal spikes or paraprotein peaks (12.5% vs 4.5%), but no association with lifestyle, vaccine exposure, or medical conditions.
- Conclusion:** Intensive vaccination is not associated with an elevated risk of disease or medical condition.

16



 ***Squalene as an Adjuvant***

Squalene is an oil. Produced in human liver, required for life.
Squalene naturally present in blood at 250 parts per billion (ppb). Fingerprint oils. Food. Supplements (olive oil).
Squalene alone may induce antibodies, but it is not an adjuvant (help antigens) by itself.
Squalene needs to be in the form of an emulsion (like mayonnaise) to be an adjuvant.
To be an adjuvant, squalene needs to be present at 1% to 5%
10,000,000 parts per billion (1%) to
50,000,000 parts per billion (5%)
FluAd (Italian influenza vaccine), given to > 10 million people, contains MF59 adjuvant, which includes 1.95% squalene, 19,500,000 parts per billion

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 ***Squalene and Squalene Tests***

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

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

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

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

22

 ***Antibodies that Bind Squalene***

A1. Asa, Garry, et al. reported anti-squalene antibodies in Gulf War veterans. *Vanity Fair* 1999. *Exp Molec Path* Feb 2000.

IOM: "...does not regard study as providing evidence that investigators successfully measured antibodies to squalene..."

A2. *Exp Molec Path* Aug 2002. Test positive: 8/25 vaccinees, 3/19 unvaccinated. Antibodies associated with specific lots.

B1. Matyas, Alving, et al. *J Immunol Methods* Apr 2000. Mice given 71% squalene make squalene-binding antibodies. Antibodies don't cross react with squalene or cholesterol.

B2. *J Immunol Methods* Mar 2004. Squalene antibodies found: 0% of Fort Knox blood donors, 7.5% of Fort Detrick alumni, 15% of Frederick civilians. Conclusion: age-related effect.

23

 ***Our Responsibility***

- **"Vaccines, of one sort or another, have conferred immense benefit on mankind but, like aeroplanes and motor-cars, they have their dangers . . . it is for us, and for those who come after us, to see that the sword which vaccines and antisera have put into our hands is never allowed to tarnish through over-confidence, negligence, carelessness, or want of foresight on our part."**

- The Hazards of Immunization, Sir Graham Wilson, 1967

24



Presentation 14 – Phillip Pittman

USAMRIID 

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

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

Phillip R. Pittman, MD, MPH
COL, MC, USA
Chief, Division of Medicine
USAMRIID
Fort Detrick, MD

7 April 2005

Hyper Immunization

- **Repeated vaccination with a variety of antigens has become common practice for immunization against a variety of pathogens.**
- **Common reactions have included acute local and/or systemic reactions and rare hypersensitivity reactions**
- **Otherwise, few other adverse events have been clearly linked to vaccination.**
- **Experimental animals injected with large doses of antigens may produce delayed adverse effects, such as, amyloid deposition, arteritis, etc., but similar reactions have not been observed in humans**

Hyper Immunization

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

What are the Fort Detrick Vaccine Safety Studies

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

Study 1: The Peeler Study 1956-7: M & M

- **99 Caucasian males**
- **Ages 28-65 years**
- **Duration of immunization 8-12 years (1944--1956)**
- **Total amount of antigen 35.8 ml -- 74.4 ml**
- **All subjects received the followed antigens:**
 - botulism, tularemia, Rocky Mountain spotted fever, Q fever, typhus, plague, psittacosis, and the viral encephalitides. In addition,
 - brucellosis = 34; smallpox = 95; anthrax = 28; etc.
- **93 had complete medical history and physical examination**
- **Hospital and outpatient records were reviewed for each subject for the period.**

Peeler 1: Results

- **Clinical Evaluations**
 - Men NOT ill as a group!
 - Occupational illness
 - tularemia 1
 - brucellosis 1
 - Q fever 1
 - febrile illness of undetermined origin (URIs) 9
 - Physical findings
 - hepatomegaly 7
 - 2 tularemia & brucellosis
 - 5 ? Etiology
 - macroglossia 1

Peeler 1: Conclusion

- No clinical abnormality found
- Two clinical laboratory deviations noted
 - abnormal PEP pattern (~23%)
 - lymphocytosis (~25%)
- No demographically matched control group

Study 2 : 5-year follow-up 1962: M & M

- **76/99 Caucasian males**
- **Ages 33-70 years (mean age 46.3)**
- **Duration of immunization 12-18 years (1944--1962); mean 13.3 years**
- **Total volume of antigen 42 ml -- 101 ml (mean 21 ml)**
- **All subjects received the followed antigens:**
 - botulism, tularemia, Rocky Mountain spotted fever, Q fever, typhus, plague, psittacosis, and the viral encephalitides. In addition,
 - brucellosis = 34; smallpox = 70; RVF 66, Diphtheria 20, influenza 54, anthrax = 72; etc.
- **76 had complete medical history and physical examination**
- **Hospital and outpatient records were reviewed for each subject for the period.**

Study 2 : 5-year follow-up 1962: M & M

- **Additional clinical laboratory tests added compared to 1956: BUN, SGOT, SGPT, Urea clearance, Fasting glucose, U/A, VDRL, serum hexosamines, Zinc turbidity test for gamma globulin level, RF, etc**
- **Gingival (7) & renal punch biopsies (3) were performed; 4 died of intercurrent and unrelated illnesses.**
- **Controls for electrophoretic data and hexosamine determinations were 102 serial serum specimens from healthy blood donors at the Johns Hopkins Hospital Blood Bank. Same age group but not matched by other demographics.**

Study 2 : 5-year follow-up 1962: Results

- **Clinical Laboratory Findings**
 - Hematologic
 - HCT -- normal in all men.
 - Leukopenia 4
 - Leukocytosis 11
 - Monocytosis 0 (3 subjects had monocytosis in 1956 --not seen in 1962)
 - Lymphocytosis
 - 1956 27% had > 40%
 - 1962 31.6%
 - Eosinophilia (> 3%) 17 in 1956; 23 in 1962
 - Renal Function
 - Proteinuria
 - Liver Function
 - Alkaline Phosphatase slightly elevated in 3 men

Study 2 : 5-year follow-up 1962: Results

- **Clinical Laboratory Findings**
 - Serum Electrophoresis --
 - No quantitative abnormalities of the various protein fractions in 1958 report or in 1962.
 - Same qualitative abnormality described in 23% in 1956 now in 34%
 - Serum Hexosamines-- mean hexosamine value elevated for test group
- **Pathological Studies**
 - 4 deaths between 1956 -1962
 - MI 3
 - carcinoma of colon 1
 - sections of liver, spleen and kidneys were examined after staining and showed no evidence of amyloid deposition or other abnormality
 - Gum biopsies (7 of the most suggestive laboratory abnormalities). Percutaneous renal punch biopsy on 3 men demonstrating persistent proteinuria. All of these sections were normal for hematoxylin and eosin and thioflavin-T.

Study 2 : 5-year follow-up 1962: Conclusion

- **“Follow-up examinations of these intensively immunized men failed to demonstrate any evidence of illness attributable to the immunizations.”**
- **“There is no indication that intensive immunization interfered with the ability to produce adequate antibody titers after antigenic challenge.”**
- **Several clinical laboratory abnormalities were noted but of no clinical significance**
- **No proper control group**

Study 3 : 25-year follow-up 1971: M & M

- 77/99 Caucasian males
- Ages 43-79 years (mean age 55)
- Number of immunogens = 21
- Total volume of antigen 52 ml -- 134 ml (mean 97 ml); mean skin tests = 55
- Control group was 26 age-matched, long-term, civilian, male employees from Fort Detrick who had never received special immunizations or been exposed to laboratory infections.

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

• Laboratory Evaluations

- Serums concentrations of IgG, IgA, IgM, or C3 were similar for both groups.
- Mean lymphoproliferative response to phytohemagglutinin was not significantly different for the immunized subject group and age-matched control group
- In 1971, 15.5 years after their selection for study, 11/99 immunized persons had died, a mortality rate in agreement with the 10.76 deaths predicted by actuarial data.
 - ASCVD 4
 - Cancer 3 (oat-cell ca of lung, colon adenocarcinoma, brain tumor)
 - COPD 2
 - 2 died suddenly without postmortem examination
 - IDDM 1
 - LBBB & PVCs on old EKGs
 - Tissue sections obtained from 4 postmortem examinations and one biopsy showed no evidence of amyloidosis

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

- Evaluations in 1962 suggested that laboratory abnormalities might be transient because there was no continuing abnormality in some individuals and seven men who had not received an immunization within the preceding 2 years had no antigammaglobulin factors.
- Hexosamine elevations noted in all 3 studies—the significance of this finding is not known. The test is no longer done.
- Other unexplained differences: ESR, Serum iron and copper levels; serum albumin, alpha-2 globulin and beta globulin values and PTT. The significance of findings for the alpha and beta globulins is less impressive because most values for the immunized subjects fall within the 95% confidence limits of the control mean.

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

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



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www.elsevier.com/locate/vaccine



www.elsevier.com/locate/vaccine

Long-term health effects of repeated exposure to multiple vaccines^{2c}

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

Long-term health effects?

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

Table 1
Population characteristics

Characteristic	MIP (N = 155)	Control (N = 265)	P-value ^a
Gender	100.0%	100.0%	
Male	80.7%	81.5%	0.179
Mean age (range) (years)	50.5(37–69)	48.3(25–94)	0.006
Served in military	11.2%	46.4%	< 0.001
College degree or higher	21.4%	40.8%	0.001
Current employment status			
Retired	71.4%	63.0%	0.049
Employed full-time	3.2%	6.8%	
Employed part-time	21.2%	20.4%	
Not working/disabled	0.9%	3.8%	
Current residence level			0.820
Rural	30.0%	23.5%	
More than 3 mi/week	17.4%	17.0%	
Up to 3 mi/week	60.0%	59.0%	
Disabled	2.0%	1.9%	
Tobacco history			
Ever smoked cigarettes	64.5%	58.7%	0.251
Ex-smoker (years)	1.2	1.3	0.173
Of those smoked (years)	21.7	21.1	0.061
Quit	90.0%	89.8%	0.420
Years since quitting (mean)	19.6	22.6	0.087
Ever smoked pipe	36.4%	26.0%	0.041
Ever smoked cigar	23.7%	22.1%	0.429
Alcohol use			
Ever drink	30.3%	22.6%	0.081
Hepatitis markers			
Hepatitis A antibody	51.0%	53.0%	0.714
Anti-hepatitis B core antibody	5.0%	8.0%	0.041
Hepatitis B surface antigen	0.0%	0.0%	NT
Anti-hepatitis C antibody	0.0%	2.0%	1.000
MVA-89D	9.8%	10.4%	0.568

NT, not tested.
^a Tests are two-tailed except hepatitis markers which test only for elevations in study group percentage compared to controls.

Table 2
Vaccines and skin test exposures among MIP subjects

Vaccine	Total doses administered (n)	#Subjects receiving product (n)	#Doses/subject Mean Range	Antigenic component(s) (μg)	
Tetanus	4376	156	29.2	1–78	5.3 0.1–17.4
Diphtheria	1246	142	22.8	1–56	6.7 0.7–17.5
Poliomy	2100	138	18.2	1–43	0.4 1.0–14.8
Botulinum toxin (ABCD)	1709	136	12.6	1–34	4.5 1.0–24.8
Neisseria meningitidis polysaccharide (MNEP)	1644	145	11.3	1–28	5.3 0.5–16.8
Vaccinia	1180	136	8.1	1–17	0.2 <0.1–1.7
Tuberculin	1074	137	7.8	1–74	0.6 <0.1–5.7
Trypsin	905	141	6.4	1–28	0.7 0.1–2.9
Lysozyme	768	120	6	1–15	5.8 0.4–15.0
O-Herx	706	119	6.4	1–16	4 0.4–9.1
Poliovirus	617	100	6.8	1–26	4.9 0.5–19.1
Rocky mountain spotted fever	616	115	5.4	1–17	4.4 0.5–11.4
Coccidioidomycosis	445	112	3.3	1–22	0.5 0.1–2.2
Brill-Nellie fever	370	125	4.7	1–23	0.7 1.0–23.0
Eastern equine encephalitis (EEE)	411	90	7.2	1–20	1.3 0.4–4.3
Typhus	406	100	3.4	1–13	1.7 0.4–10.0
Yellow fever	338	114	2.7	1–6	1.4 0.4–6.1
Poliovirus	330	79	4.4	1–14	1.2 0.4–11.5
Typhus	332	90	6.7	1–28	1.6 0.4–8.5
Poliovirus	275	109	2.1	1–9	0.2 0.4–0.9
Poliovirus	260	88	2.7	1–4	2.0 0.2–8.0
EEE/NEE/VEE ^b	235	42	4.1	1–7	2 0.3–3.1
Poliovirus	230	77	2.1	1–8	1.2 0.2–2.9
Rocky mountain spotted fever ^b	199	45	3.3	1–4	1.7 0.4–3.1
Cholera	194	44	9.6	1–21	2.7 0.3–16.0
Bifunctional	128	4	4	1–10	0.4 0.1–0.5
Typhoid	77	22	3.5	1–13	1.4 0.4–5.3
Japanese encephalitis	84	14	3.1	1–4	3.0 0.4–5.1
Erythrina	82	14	3	1–5	0.7 0.1–3.7
Poliovirus	37	6	6.6	1–9	4.4 1.0–16.1
Chikungunya	25	14	1.9	1–5	1 0.5–1.1
Cholera	15	12	1.3	1–2	6.2 0.4–16.1
Hepatitis B	17	4	4.3	3–7	4.1 3.0–6.1
Typhoid	11	2	5.5	2–9	2.8 1.0–6.5
EEE/VEE	9	9	1	1–1	0.3 0.1–0.5
Mumps	7	7	1	1–1	0.1 0.1–0.1
Poliovirus	3	3	1	1–1	1 0.5–1.6
Unspec. J	1	1	1	1–1	0.8 0.5–0.7

^a Poliovirus vaccine (inactivated) may not be the same as monovalent products.

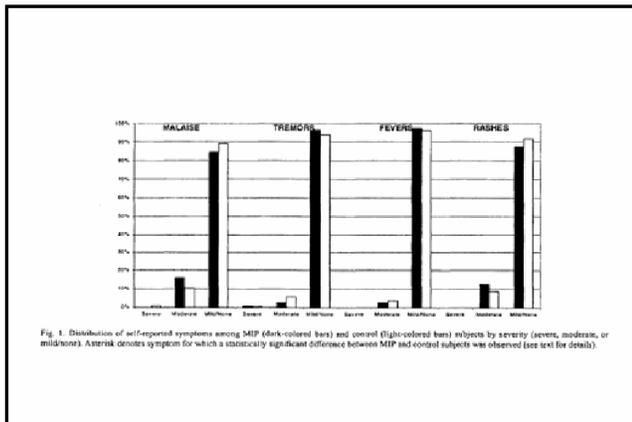
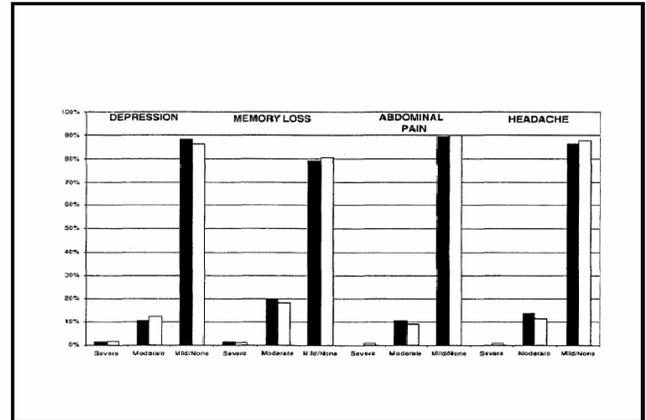
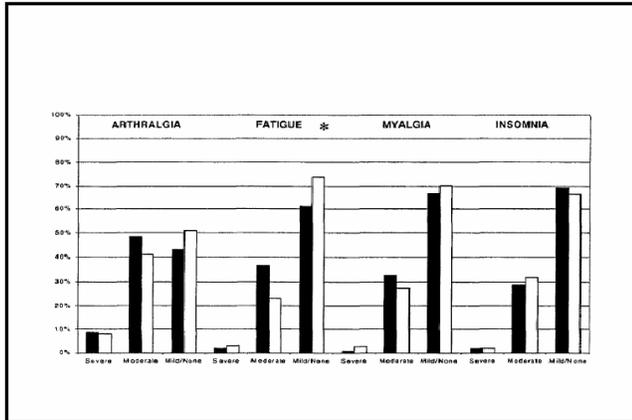


Fig. 1. Distribution of self-reported symptoms among MIP (dark-colored bars) and control (light-colored bars) subjects by severity (severe, moderate, or mild/none). Asterisk denotes symptom for which a statistically significant difference between MIP and control subjects was observed (see text for details).

Table 3
Self-reported diseases and conditions

Condition	MIP (N)	Control (N)	P-value ^a
Arthritis	18	100	0.000
Hypertension	16	161	0.000
Diabetes	16	161	0.000
Cholesterol	16	161	0.000
Stroke	16	161	0.000
Heart disease	16	161	0.000
Alzheimer's disease	16	161	0.000
Depression	16	161	0.000
Memory loss	16	161	0.000
Abdominal pain	16	161	0.000
Headache	16	161	0.000
Malaise	16	161	0.000
Tremors	16	161	0.000
Fevers	16	161	0.000
Rash(es)	16	161	0.000
Other	16	161	0.000
Total	300	461	0.000

^a Fisher exact test (one-tailed for increasing risk in the MIP group compared to control, adjusted for multiple comparisons).
^b Total reported conditions and percent of total assessed questions.

Table 4
Protein and immunoglobulin measures

Test	MIP		Control		P-value*	
	n	Out of reference range, low (%)	n	Out of reference range, low (%)	Out of range, low	Out of range, high
Albumin (%)	133	10.5	265	10.0	0.997	0.238
Albumin (g/dl)	133	3.3	265	2.6	0.993	0.831
Total protein (g/dl)	133	0.7	265	0.8	1.000	1.000
Alpha-1 globulin (%)	133	1.3	265	0.8	1.5	0.994
Alpha-1 globulin (g/dl)	133	0.0	265	0.0	1.3	1.000
Alpha-2 globulin (%)	133	6.5	265	0.0	1.9	0.681
Alpha-2 globulin (g/dl)	133	0.7	265	0.0	1.5	0.970
Beta globulin (%)	133	0.0	265	0.0	1.9	1.000
Beta globulin (g/dl)	133	0.0	265	0.0	2.6	1.000
Gamma globulin (%)	133	2.0	265	1.1	2.3	0.981
Gamma globulin (g/dl)	133	1.3	265	0.4	6.4	0.927
C ₃ (mg/dl)	133	0.0	265	0.0	22.3	1.000
C ₄ (mg/dl)	133	3.9	265	1.9	3.4	0.725
C reactive protein (mg/dl)	133	0.0	265	0.0	16.9	NT
Copper (mg/dl)	133	4.6	265	5.3	5.3	1.000
IGM (mg/dl)	133	1.3	265	1.9	12.1	1.000
IgA (mg/dl)	133	3.5	265	2.3	10.9	0.975
Total IgG (mg/dl)	130	0.7	261	0.9	10.3	0.959
IgG1 (mg/dl)	132	0.7	265	0.8	4.2	1.000
IgG2 (mg/dl)	132	0.0	254	0.0	14.8	1.000
IgG3 (mg/dl)	132	0.7	264	1.1	7.2	1.000
IgG4 (mg/dl)	132	4.6	261	0.0	0.0	0.005

* One-tailed upper t-test for MIP > control group, adjusted for multiple comparisons.
 † Not tested.

Table 5
Rheumatological assays

Test	MIP		Control		P-value*
	n	%	n	%	
Anti-thyroglobulin antibody (1:20 or greater)	3	2.00	6	2.30	1.000
Anti-thyroid microsomal antibody (1:100 or greater)	7	4.60	16	6.00	1.000
Mip-2 ANA titer (1:40 or greater)	80	52.30	147	55.50	1.000
ANA fluorescent patterns					
None detected	73	47.70	118	44.50	0.555 [†]
Classroom	0	0.00	2	0.80	
Nucleolar	1	0.60	2	0.80	
Speckled	79	51.60	139	52.40	
Speckled multinuclear	0	0.00	4	1.50	
Mouse kidney/stomach ANA titer (1:40 or greater)	19	12.40	26	9.80	0.975
Fluorescence pattern					
None detected	134	87.60	239	90.20	0.616 [†]
Nucleolar	1	0.60	1	0.40	
Speckled	18	11.80	25	9.40	
Quantitative RF (IU/ml)	17	11.10	27	10.20	1.000

* One-tailed upper t-test for MIP > control group, adjusted for multiple comparisons.
 † Fisher exact test for trend (unadjusted for multiple comparisons).

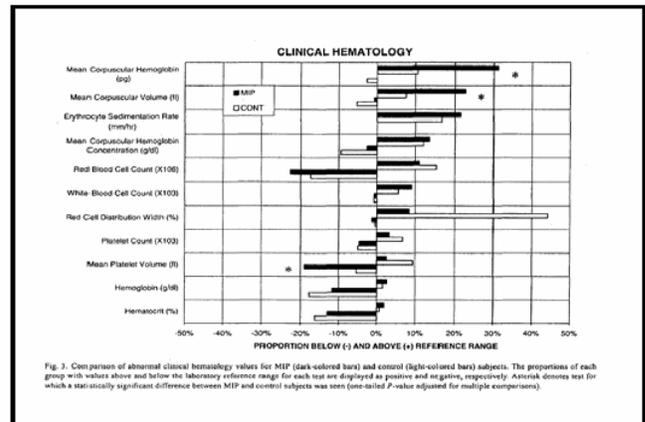
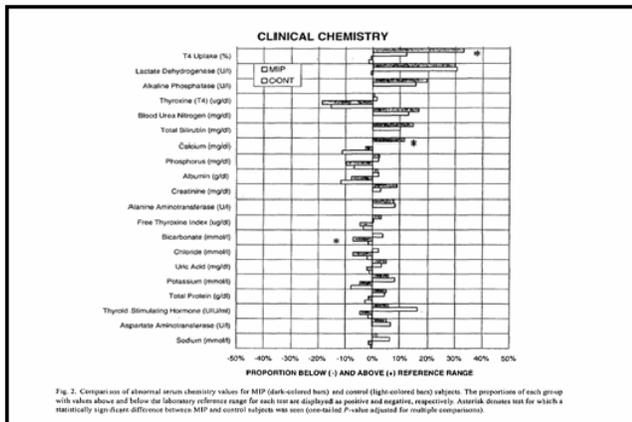


Table 6
Monoclonal paraproteins

Volunteer	Finding	Sub-class	Chain
Study-8V97	Monoclonal spike	IgM	lambda
Study-6B99	Monoclonal spike	IgG	lambda
Study-9H18	Monoclonal spike	Unk*	Unk*
Study-5N01	Monoclonal spike	IgM	kappa
Study-8P02	Monoclonal spike	IgM	kappa
Study-4S19	Paraprotein	Unk	kappa
Study-7E15	Monoclonal spike	IgG	kappa
Study-1W64	Monoclonal spike	IgG	kappa
Study-5W67	Monoclonal spike	IgA	lambda
Study-8R54	Paraprotein	IgG	kappa
Study-1U44	Paraprotein	IgA	kappa
Study-5S26	Monoclonal spike	IgG	lambda
Study-5D45	Paraprotein	IgA	kappa
Study-2Q41	Paraprotein	IgG	lambda
Study-1C28	Monoclonal spike	IgA	lambda
Study-7Y83	Paraprotein	IgG	kappa
Study-7K87	Paraprotein	Unk*	kappa
Study-8L76	Monoclonal spike	IgM	kappa
Study-0A47	Monoclonal spike	IgG	kappa
Control-3V34	Paraprotein	IgM	kappa
Control-0N06	Paraprotein	IgA	lambda
Control-1G06	Monoclonal spike	IgG	kappa
Control-3J71	Monoclonal spike	IgM	kappa
Control-4X66	Paraprotein	Unk*	lambda
Control-0Z41	Monoclonal spike	IgG	lambda
Control-0W41	Paraprotein	IgM	lambda
Control-2T41	Monoclonal spike	IgM	kappa
Control-8C44	Monoclonal spike	IgG	lambda
Control-6L20	Monoclonal spike	IgG	lambda
Control-5W15	Monoclonal spike	IgG	lambda
Control-9C83	Monoclonal spike	IgM	lambda

* Unk, unknown/indeterminate.

MONOCLONAL GAMMOPATHY

GROUP	Positive	Negative	TOTAL
	n (%)	n (%)	
Study	16 (10.3)	139 (89.7)	155
Control	12 (4.5)	253 (95.5)	265
TOTAL	28	392	420

P-value by Fisher's exact test (1-tailed) = 0.0196



Journal of Immunological Methods 286 (2004) 47–67
www.elsevier.com/locate/jim

Research Paper

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

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Received 25 August 2003; received in revised form 7 November 2003; accepted 11 November 2003

Table 2
Age, sex, ANA status, and antibodies to SQE among the USAMRIID cohort.

ID no.	Age	Sex	ANA status	SQE IgG	SQE IgM
1	59	M	3	0	0
2	66	M	13	0	0
3	65	F	0	0	0
4	82	F	11	Pos	Pos
5	68	M	Unknown	0	Pos
6	75	M	0	0	0
7	69	F	0	0	Pos
8	69	M	15	0	Pos
9	72	M	25	0	0
10	70	M	Unknown	Pos	0
11	66	M	47	Pos	Pos
12	65	M	16	0	0
13	79	M	27	0	Pos
14	76	M	0	0	0
15	Unknown	M	41	0	0
16	60	M	24	0	0
17	74	M	39	0	Pos
18	59	M	14	0	0
19	65	M	40	0	Pos
20	75	M	28	0	0
21	68	F	20	0	Pos
22	69	M	19	0	0
23	64	M	4	0	0
24	72	M	32	0	Pos
25	70	M	31	0	Pos
26	61	F	0	0	0
27	71	M	30	0	0
28	69	M	26	0	0
29	Unknown	M	35	0	0
30	75	M	33	0	0
31	76	M	36	0	0
32	78	M	33	0	0
33	67	M	23	0	0
34	71	M	29	0	0
35	59	M	26	0	0
36	64	M	14	0	0
37	71	M	45	0	Pos
38	Unknown	M	9	0	Pos
39	70	M	24	0	0
40	72	M	20	0	Pos

Table 3
Appearance of antibodies to SQE in mouse serum as function of age

Age (months)	BALB/c % positive († positive/total) [95% confidence interval]		B10.Br % positive († positive/total) [95% confidence interval]		C57BL/6 % positive († positive/total) [95% confidence interval]	
	IgG	IgM	IgG	IgM	IgG	IgM
2*	0 (0/49)	0 (0/60)	0 (0/25)	0 (0/25)	0 (0/25)	0 (0/25)
10	[0.0 - 5.9]	[0.0 - 4.9]	[0.0 - 11.3]	[0.0 - 11.3]	[0.0 - 11.3]	[0.0 - 11.3]
16	[1.4 - 34.7]	[2.6 - 56.6]	0 (0/18)	10.5 (2/19)	[1.5 - 36.4]	[11.9 - 54.3]
17	[1.3 - 23.1]	[16.3 - 61.6]	[1.2 - 31.7]	[0.0 - 13.9]	[48.8 - 90.9]	[68.3 - 98.8]
18	0 (0/19)	63 (12/19)	5 (1/20)	5 (1/20)	65 (13/20)	80 (16/20)
19	[0.0 - 14.6]	[38.4 - 83.7]	[0.1 - 24.9]	[0.1 - 24.9]	[40.8 - 85.6]	[56.3 - 94.3]
21	N.D.	39 (7/18)	85 (17/20)	5 (1/20)	100 (17/17)	89 (16/18)
24	6 (1/17)	[17.3 - 64.3]	[62.1 - 96.8]	[0.1 - 24.9]	[83.8 - 100]	[65.3 - 98.6]
At any time point	65 (11/17)	40 (12/20)	25 (5/20)	100 (18/18)	72 (13/18)	72 (13/18)
	[0.1 - 28.7]	[38.3 - 85.8]	[36.1 - 80.9]	[8.7 - 49.1]	[84.7 - 100]	[46.5 - 90.3]
	10 (1/10)	62 (8/13)	45 (9/20)	55 (11/20)	94 (16/17)	62 (10/16)
	[0.3 - 44.9]	[31.8 - 86.1]	[23.3 - 48.5]	[13.3 - 78.9]	[71.3 - 99.9]	[35.4 - 84.8]
	17 (1/6)	86 (6/7)	0 (0/17)	50 (9/18)	46 (6/13)	58 (7/12)
	[0.4 - 64.1]	[42.1 - 99.6]	[0.0 - 16.2]	[26.0 - 74.0]	[19.2 - 74.9]	[27.7 - 84.8]
	35 (7/20)	85 (17/20)	95 (19/25)	65 (13/20)	100 (20/20)	100 (20/20)

Mice were bled at the time intervals indicated and the sera were assayed for antibodies to SQE. Serum was scored as positive for IgG or IgM antibodies to SQE if the absorbance was >3 times the baseline at both the 1:50 and 1:100 dilutions. Baseline absorbances ranged from 0.1 to 0.19 in different assays.
*Sera from 2 month old mice were from different animals than the retired breeders used for the remaining time points.

Further study to determine if there are there long-term adverse effects of AVA?

Hypothesis: The frequency of death, chronic disease, laboratory abnormalities, and/or degradation of quality of life in individuals who received Anthrax Vaccine, Adsorbed (AVA, BioPort Corporation) plus other vaccines administered in the Special Immunizations Program (SIP) and/or Special Procedures Program (SPP) at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, Maryland, is not greater than that observed in individuals in SIP/SPP who received other vaccines but not AVA.

Further study to determine if there are there long-term adverse effects of AVA?

Objective: To determine whether AVA accounts for differences in the frequency of death, chronic diseases, laboratory abnormalities, and degradation in quality of life in a population that is receiving or has received multiple vaccines over time.

Further study to determine if there are there long-term adverse effects of AVA?

Objective: This retrospective, single-site study will enroll current and former SIP/SPP volunteers (those who are currently enrolled in the SIP and those who were previously enrolled). Table 6 profiles the characteristics of the SIP/SPP participants from which the study subjects will be drawn. The maximum number of eligible SIP/SPP volunteers is 3421. Of those, 2102 have been exposed to AVA and other vaccines, whereas 1319 have been exposed to other vaccines but not to AVA.

Further study to determine if there are there long-term adverse effects of AVA?

- **Primary outcome measures are:**
 - Death (from all causes)
 - Chronic diseases (latency)
 - Degradation of quality of life (as determined by SF-36 questionnaire)
 - Abnormal laboratory results of blood tests/assays and salivary cortisol test

Further study to determine if there are there long-term adverse effects of AVA?

- **The measure of AVA exposure is whether or not the subject received the AVA vaccine. The measures of concomitant SIP/SPP exposure are the following:**
 - Years in SIP/SPP
 - Number of non-AVA doses received
 - Volume of non-AVA doses received
 - Number of different non-AVA antigen exposures

Further study to determine if there are there long-term adverse effects of AVA?

- **Potential secondary analysis to be conducted, as data permit include:**
 - Adherence measure of AVA exposure
 - Number of doses (2 vs minimum)
 - Change of number of doses (4 or 7 doses)
 - Volume of AVA (2 vs minimum)
 - Length of time between 1st and 2nd dose
- **Non-AVA vaccine variable:**
 - Live-attenuated vs inactivated
 - Vaccination site
 - Monovalent vs. polyvalent
 - Volume
 - Adjuvant exposure
- **Demographic variable:**
 - Gender
 - Age at time of receipt of 1st and 2nd dose of each vaccine and at review
 - Race
 - Ethnicity
- **Other exposure variable:**
 - Length of time since leaving SPP
 - Pre-existing conditions
 - Tobacco use
 - Alcohol use
 - Occupational exposure
 - Family medical history
- **Other outcome variable:**
 - Death (specific causes)
 - Prevalence of chronic diseases
 - Measurement values for the results of blood tests and assays and salivary cortisol test

Further study to determine if there are there long-term adverse effects of AVA?

- **Study Progress**
 - **LONG-TERM SAFETY STUDY (Ongoing)**
 - Enrolled 1124
 - SF 36 1124
 - CATI 958
 - Blood draws 616
 - Enrollment closes 27 April 2005

Project Whitecoat Program

An Assessment of Health Status among Medical Research Volunteers Who Served in the Project Whitecoat Program at Fort Detrick, Maryland. Military Medicine, 170, 3:183, 2005.
COL Phillip R. Pittman, Sarah L. Norris, Kevin M. Coonan, Kelly T. McKee.

Project Whitecoat Program

Between 1954 and 1973, more than 2000 men entering military service as conscientious objectors participated in Project Whitecoat as medical research volunteers for the Army's biological warfare defense program.

Project Whitecoat was the title given to the Army research program "to use human volunteers in medical studies to evaluate the effect of certain biological pathogens upon humans in an effort to determine the vulnerability to attack with biological agents.

The objectives of the studies involved were to develop medical defenses against biological warfare and included techniques for rapid diagnosis, improved therapeutic and prophylactic agents, and development of vaccines against biological weapons and endemic disease threats.

Project Whitecoat Program

The program evolved after a series of meetings in 1954-1955 between representatives of the Army Surgeon General and the Seventh Day Adventist Church.

With the background of the Church's philosophy and practice of medical service and encouragement of noncombatancy and its longstanding cooperation with the military in health and medical practice, Project Whitecoat became an accepted and respected vehicle by which conscientious objectors could serve the nation.

From its inception in 1954 to its termination in 1973, approximately 2,300 individuals participated in this program, more than 90% of whom were Seventh Day Adventists.

Project Whitecoat Program

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

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

METHODS

- **Volunteers recruited from Whitecoat Alumni Association in 1998**
- **Questionnaire survey; returned by mail**
 - 522 respondents
- **Records of study participation abstracted from USAMRIID archives**

EXPOSURES

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

EXPOSURES (CONT)

- **Participated in 1 study: 303**
- **Participated in 2 studies: 75**
- **Participated in 3 studies: 17**
- **Participated in 4 studies: 1**

VACCINE EXPOSURES

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

DISEASE AGENT EXPOSURES

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

NON-AGENT EXPOSURES

- Tetracyclines: 25
- Amino Acids: 15
- Chloramphenicol: 4
- Tyrosine: 4

DEMOGRAPHICS

		STUDY (N=358)	CONTROL (N=166)	p-value *
Race	White	90.8%	91.5%	0.832
	Black	3.6%	4.3%	
	Other	5.3%	4.3%	
		100.0%	100.0%	NT
Mean Age (range) (yrs)	58.4 (47-6)	58.5 (46-79)	0.822	
Mean Time Spent at Ft Detrick (range) (yrs)	1.5 (1-5)	1.5 (1-3)	0.636	
Served in Military	100.0%	100.0%	NT	
College Degree or Higher	65.9%	63.4%	0.126	
Current Employment Status	Retired	11.7%	15.2%	0.145
	Employed Full-time	51.1%	40.9%	
	Employed Part-time	31.0%	36.4%	
	Not working b/c disability	5.6%	5.5%	

*Yes to are 2-tailed
 NT=Not tested

HEALTH AND BEHAVIORAL CHARACTERISTICS

		STUDY (N=358)	CONTROL (N=166)	p-value *
Current Health Status	Excellent	39.4%	47.6%	0.375
	Good	46.6%	41.5%	
	Fair	10.6%	9.1%	
	Poor	2.8%	1.8%	
Current Exercise Level	None	25.4%	20.1%	0.579
	more than 5X/wk	10.9%	10.4%	
	up to 5X/wk	60.1%	65.5%	
	Disabled	3.1%	3.0%	
Tobacco History	Ever Smoked Cigarettes	14.8%	15.2%	0.896
	#Packs/Day (mean)	1.0	1.5	0.285
	# Yrs Smoked (mean)	10.0	11.8	0.500
	Quit (among those ever smoked)	56.2%	60.0%	0.031
	Yrs Since Quitting (mean)	23.0	16.5	0.084
	Ever Smoked Pipe	7.5%	8.5%	0.726
	Ever Smoked Cigars	7.8%	7.3%	1.000
Ever Use Snuff/Use Chewing Tobacco	1.4%	0.6%	0.570	
Alcohol Use	Ever Drink	15.1%	19.5%	0.206

*Yes to are 2-tailed

REPRODUCTIVE OUTCOMES

TABLE 3
REPRODUCTIVE OUTCOMES

	STUDY (N=352)	CONTROL (N=161)	p-value*
Number of Children (mean [range])	2.0 (0-1)	2.0 (0-6)	0.502
Had any Children	212 (60.1%)	111 (68.9%)	0.511
Had Children With Birth Defects or Mental Retardation	25 (7.1%)	15 (9.3%)	0.381
Number of Children (0-1, All)			
	* Normal Birth*	306 (85.2%)	0.510
	With Birth/Congenital Defects	11 (3.1%)	
	With Mental Retardation	2 (0.6%)	

* Test on 2-tailed

MEDICAL CONDITIONS (FREQUENT)

TABLE 4
SELF-REPORTED DISEASES AND CONDITIONS

CONDITION	STUDY N	STUDY %	CONTROL N	CONTROL %	p-value*
Hypertension	78	21.8%	41	25.0%	1.000
Arthritis	55	15.4%	25	15.2%	1.000
Bay Fever	55	15.4%	26	15.9%	1.000
Pneumonia	43	12.0%	24	14.6%	1.000
Cancer	26	7.3%	17	10.4%	1.000
Asthma	25	7.0%	4	2.4%	0.165
Diabetes	25	7.0%	17	10.4%	1.000
Ulcers	23	6.4%	7	4.2%	0.538
Frequent Colds	20	5.6%	8	4.9%	0.598
Eczema	13	3.6%	5	3.0%	1.000

Whitecoat Project

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

DEATHS & DISABILITIES

- Small number and incomplete knowledge of total N makes statistical assessment infeasible at this time.
- No link found

CONCLUSIONS

- “Exposed” and “unexposed” groups similar in terms of demographics, education, current employment status, and behavioral risk factors
- No differences between “exposed” and “unexposed” with regard to self-reported general health status and self-reported exercise activity

CONCLUSIONS (CONT)

- No differences between “exposed” and “unexposed” volunteers with regard to reproductive outcomes
- No significant differences between “exposed” and “unexposed” subjects with regard to self-reported symptoms

CONCLUSIONS (CONT)

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

Does receipt of multiple vaccines increase risk for adverse health effects?

- Available evidence does not suggest there are any disease or disease complex that result from repeated injections with multiple antigens.
- We are investing whether the finding of monoclonal immune globulin represents an association or an epiphenomenum.

Are antibodies to squalene related to receipt of anthrax vaccine or related to any disease, symptom or symptom complex?

- We found no such association with anthrax vaccine or to any disease, symptom or symptom complex.
- Squalene antibodies prevalence was related to increasing age.

CONCLUSION

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

Presentation 15 – Brian Schuster

	<p>Report to Research Advisory Committee on Gulf War Veterans Illnesses April 2005</p> <p>Brian G. Schuster, MD FACP Director, Clinical Science Research & Development Department of Veterans Affairs</p>
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	<p>Agenda</p> <ul style="list-style-type: none">■ What is ORD?■ What is Deployment Health Research and where does PGWI fit?■ Report on current PGWI research.■ Plans for PGWI research.■ Future Directions.
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	<p>ORD Research Services</p> <p>Intramural Program:</p> <ul style="list-style-type: none">■ Biomedical: basic biology and physiology■ Clinical: clinical research, treatment trials including multi-site cooperative studies■ Rehabilitation: recovery of function■ Health Services: healthcare outcomes, costs
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	<p>ORD Research Services</p> <ul style="list-style-type: none">■ Further understand and treat consequences of deployment, including the illnesses affecting Gulf War veterans.■ Positively affect clinical care outcomes through rigorous scientific investigation.
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Funding Opportunities	
	<ul style="list-style-type: none">■ Merit/IIR mechanism■ Training programs■ Cooperative Multi-Site Studies■ Center Based Research Activities

Deployment Health	
	<ul style="list-style-type: none">■ The deployment health research (DHR) portfolio is a major priority for ORD in meeting our goal of supporting research relevant to veterans' healthcare needs.

Deployment Health	
	<ul style="list-style-type: none">■ Research involving subjects who were deployed to foreign military conflicts, such as Persian Gulf War I.■ Basic research designed to improve our understanding of problems related to deployment.

Deployment Health	
	<p>DHR portfolio includes the following subject categories:</p> <ul style="list-style-type: none">Pre-VietnamVietnam EraPersian Gulf War IOperation Enduring FreedomOperation Iraqi FreedomOther DeploymentsDeployment Related Research

Persian Gulf War I	
	<ul style="list-style-type: none">■ Illnesses (Dx and no Dx) affecting Gulf War veterans present a significant healthcare problem.■ ORD continues to support an active research program to better understand and treat Gulf War illnesses.

Coordination	
	<ul style="list-style-type: none">■ ORD is working with other federal funding agencies to develop a research agenda and meet reporting requirements for illnesses affecting Gulf War veterans.

Deployment Health Working Group Research Subcommittee	
	<ul style="list-style-type: none">■ DoD, HHS and VA representatives.■ Coordinate research efforts on Gulf War.■ Provide and share information regarding funding.

Gulf War Report to Congress	
	<ul style="list-style-type: none">■ Updates from HHS and DoD on Gulf War research continue to be sent to VA ORD for production of the annual report.

Collaboration	
	<ul style="list-style-type: none"> ■ With the RAC GWVI, ORD has been working to advance knowledge about GW illnesses by expanding opportunities for research funding and by active portfolio management.

Results of 2004 GW RFA	
	<ul style="list-style-type: none"> ■ 14 <u>additional</u> Merit Reviews starting in FY 2005: <ul style="list-style-type: none"> - Brain & Nervous System 7 - Pyridostigmine Bromide 1 - Symptoms & General Health 2 - Diagnosis 1 - Immune Function 2 - Treatment 1

Current PGWI Studies by Topic FY05	
	<ul style="list-style-type: none"> ■ Brain & Nervous System 15 ■ Environmental Exposures 10 ■ Epidemiology 6 ■ Immune Function 1

Current PGWI Studies by Service FY05	
	<ul style="list-style-type: none"> ■ Biomedical 15 ■ Clinical 14 ■ Health Services 2 ■ Rehabilitation 1

Current PGWI Studies by Type FY05	
■ Epidemiology	6
■ Treatment	5
■ Pathophysiology	21
■ Etiology	1

Planned Efforts: FY05
■ Ongoing funding mechanisms including Deployment Health Initiative.
■ HSRD Solicitation for Deployment Health Research.
■ RFA for Research directed to understanding illnesses affecting Gulf War veterans.

FY 2005 RFA
■ Published March '05.
■ Studies may include: <ul style="list-style-type: none">- Long-term health effects of hazardous substances to which Gulf War veterans were exposed during deployment.

FY 2005 RFA
- Improvements in understanding pathophysiological processes and identifying biomarkers associated with GWI's.
- Epidemiologic investigations of diagnosed conditions.

FY 2005 RFA	
	<ul style="list-style-type: none">- Studies of the health of GW veterans' family members.- Integration and utilization of current data resources.■ PTSD proposals are considered under other funding opportunities.

FY 2005 RFA	
	<ul style="list-style-type: none">■ Proposals that address treatment issues will be given priority.<ul style="list-style-type: none">- Identification of new treatments that provide benefit to ill veterans.- Evaluate the effectiveness of treatments currently utilized.- Investigate biological mechanisms that are amenable to treatment.

FY 2005 RFA	
	<ul style="list-style-type: none">■ Principal Investigators may request up to 3 years of funding.■ Budget of \$200,000 per year.■ Proposals are due <u>June 30, 2005</u>.

FY 06 Projected	
	<ul style="list-style-type: none">■ Current commitments ~\$9 M.■ Planned Funding:<ul style="list-style-type: none">- ~\$3M RFA.- ~\$1M Treatment Center.- ~\$1M Neuroimaging studies.- ~\$575K New HSRD Projects.- ~\$250K New RRD Projects.■ FY 06 Total: ~\$15.3 M.

Related Research Funding

- ALS Research ~\$3M.
- PTSD Research ~\$3.3M.
- Deployment Related ~\$32M.
e.g.: Hearing loss, wound healing, IBS, other toxic exposures, lung cancer, etc..

Begin Discussions about Center for Treatment

- Meeting planned for April 20.
- Brainstorm how to make best use of resources for identifying, validating and implementing the treatment of illnesses affecting Gulf War veterans.

Gulf War Portfolio Manager

- Position has been posted.
- Plan to hire is as soon as possible.

Future Directions

- Focused Research Areas:
 - Target a few specific high priority issues.
 - Issue multiple, specific RFAs rather than large broad efforts.
 - Develop and follow specific cohorts.

	<h2 style="text-align: center;">Future Directions</h2>
	<ul style="list-style-type: none">■ Improve information exchange between VHA and DoD.■ Share information with other federal funding agencies to advance the state of our knowledge.



Presentation 16 – Beatrice Golomb

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

April 2005

Beatrice Alexandra Golomb, MD, PhD

EPIDEMIOLOGY

Australian factor analysis

SS: 1322 male GWV from whole cohort of 1871 Australian GWV; VS 1459 male era Australian Defence Force controls, from 2924 stratified random sample of 26,411 era personnel

Data: 63 self-reported symptoms; sz in last 1m o omitted due to low prevalence; Queried non, mild, mod, severe.

Analysis: Factor analysis of polychoric correlations

Polychoric: resp categories "none" "mild" etc presumed to be in a continuum with threshold for transition; continuum presumed Gaussian with overlap; Polychoric correlation coefficients are the bivariate correlations btn two such underlying continua derived by an iterative procedure. Reportedly robust to skewed nonnormal distributions of the underlying continua.

Australian factor analysis

Factor 1	Factor 1, cont'd	Factor 2	Factor 3
<u>Psychophysiological</u>		<u>Cognition</u>	<u>Muscular</u>
Vomiting	Sore throat	Loss concentration	Stiffness several joints
Stomach cramp	Flatulence/burping	Feeling distant	Pain sev joints
Diarrhea	Bowel/bladd ctrl	Unrefreshing sleep	Gen muscle ache/pain
Indigestion	Burning sex organs	Forgetful	↓Sensation hands/feet
SOB		Loss interest sex	Low back pain
Dry mouth		Sleep problems	Tingling/burning hands/feet
Feel feverish		Avoid situations	
LN swelling		Easily startled/jumpy	
Persistent cough		Sex dysfcn	
Pain on urination		Distressing dreams	
Constipation		Fatigue	
Trouble speaking		Irritability/anger outburst	
Dizzy, faint, blackout		Word finding. Disoriented.	
Loss balance/coordination		Sensitive to noise; light; smells	

Forbes et al 2004 Occup Environ Med 61: 1014-1020

Australian factor analysis

Factor Rotation

- Factors: items internally intercorrelated; but anticorrelated with one another
- Varimax: goes for orthogonal solutions
- Promax: allows oblique i.e. correlated solutions
- How many Factors to retain: chosen by examination of eigen values (crudely amount of variation accounted for by each factor)
- Arbitrary "but conventional" threshold of 0.4 chosen for factor loadings (i.e. retain items with loadings >0.4 in each factor)

Forbes et al 2004 Occup Environ Med 61: 1014-1020

Australian factor analysis

Factor Analysis: Split halves sample:

Split to random halves & obtained factor structure in each 2, 3, and 4-factor solutions obtained for each; congruence of the solutions by Pearson product-moment and one-way random-effects intra-class correlation coefficients

Validation:

Construct validity by correlate PCS-12, MCS-12 of SF-12
Internal consistency of each factor by Cronbach's alpha
Intraclass correl coeff to see if factor loading sim in GW & comparison group
Invariance of obtained solution for GW & comparison gp

Forbes et al 2004 Occup Environ Med 61: 1014-1020

Australian factor analysis

Result: 3 factor solution. 41% of variance by 1st factor; then 3.3, 2.7; then 1.9, 1.7%

Scree plot of Eigen values on vertical axis and factor number on horiz; dominant 1st factor with possible contributions by 2 others, rest look like detritus (scree)

Factor 1: "Psychophysiological distress"

Factor 2: "Cognitive distress"

Factor 3: "Arthronemuscular distress"

Promax did better: more interpretable and distinct factor solutions with nonorthogonal than orthogonal Varimax:

The underlying factors were moderately correlated

Forbes et al 2004 Occup Environ Med 61: 1014-1020

Australian factor analysis

Similar factors in era controls -- not very informative.

- Conditions with ANS problems (whether DM or Shy Drager) will cause many ANS sx
- Conditions disrupting sleep -- e.g. OSA or depression -- will produce factor 2 symptoms
- Conditions producing widespread musculoskeletal pain: whether FM or statins or metabolic myopathy -- will cause the items in factor 3

Even if items within each factor are not always correlated there will be enough that are correlated from these sources to provide the factor structure...

Forbes et al 2004 Occup Environ Med 61: 1014-1020

PGW ALS Replication Study

Rationale: concern about case-ascertainment bias in prior GWV studies: GWV may have all been captured but nonGWV may have had less motivation or knowledge. Capture-recapture.

Coffman, Horner et al 2005. Estimating the occurrence of ALS among Gulf War (1990-1991) veterans using capture-recapture methods. An assessment of case ascertainment bias. *Neuroepidemiology* 2005; 24:141-150

PGW ALS Replication Study

Method:

A. Sample ALS by several approaches. □

1. VA database
2. DoD database
3. Phone-line database (toll-free number)
4. ALS assn database (survey by natl ALS assn).

B. Cross-check list 3 ways to gauge differential undercount of ALS in nondeployed (to model fraction missed in both groups): log linear model; sample coverage; ecological models

Coffman, Horner et al 2005. Estimating the occurrence of ALS among Gulf War (1990-1991) veterans using capture-recapture methods. An assessment of case ascertainment bias. *Neuroepidemiology* 2005; 24:141-150

PGW ALS Replication Study

Result: Though all showed *modest* differential undercount of ALS in nondeployed, there remained an age-adjusted increase in ALS among those deployed to SW Asia in 1991 PGW.

Comment: VA database: deployed & nondeployed listed at similar rates (72% of deployed, 71% non)

DoD database: nondeployed are listed at slightly higher rate (72%); & deployed cases at a lower rate (45%) than overall population percent (62%)

Coffman, Horner et al 2005. Estimating the occurrence of ALS among Gulf War (1990-1991) veterans using capture-recapture methods. An assessment of case ascertainment bias. *Neuroepidemiology* 2005; 24:141-150

RISK FACTORS

Anthrax: Canadian Forces

Finding: anthrax vaccine did not cause health problems in Canadian post-GW personnel

Actually: With two samples not comparable at baseline, who were deployed at different times to different places, there were not large differences in change rate for fraction-of-total dx (and sx codes) for each among a set of most common dx and sx codes -- based on chart abstraction (not active inquiry).

Symptom rates were not actively elicited.

Hunter D 2004 Military Med 169 (10) 833
Health effects of anthrax vaccination in Canadian Forces

Anthrax – Canadian Forces

SS: N = 848 total, actively deployed

Of 1143 identified for study: 571 vaccinated; 572 randomly selected from larger group of 1655 not.

- **AVA exposed:** Gulf-deployed; Feb-May 98
- **Control unexposed:** Kosovo-deployed Jun-Dec 99

Anthrax vaccine Exposure:

Lot 010-1 from BioPort; 3 inoculations on or about Mar 15, Mar 30, Apr 15 1998

Other systematic exposure differences: Time of deployment. Place of deployment.

Anthrax – Canadian Forces

Design: “quasi-experimental” retrospective chart review. (Collect data for 4.5 years; but confine analyses to 8mo since comparison group deployed later, don't have flu for whole group beyond 8mo)

Comment: A quasi-experiment involves assignment (intervention vs control) without randomization. But here: the groups systematically differ in two other ways.

Anthrax - Canadian Forces

Outcome: % change in frequency of dx & sx rates by chart abstraction between the 12-mo period before deployment and the 8mo period after deployment

BUT states: rates were calculated by “dividing the number of events (e.g. diagnoses) for specific codes by the total number of events [sic] and multiplying by 1000” – vs by person-time!! Thus Sx 1 can “↑” just b/c Sx 2 ↓d (so fraction rises)

Also: AVA acute AE may have been included in predeployment diagnosis.

Anthrax - Canadian Forces

Sx-Dx procurement:

ICD-10-CA codes from chart review abstraction blinded to vaccination status: Each charted diagnosis, symptom, or injury

Chart retrieval rate: 86% control, 82% vaccinated: some charts not provided by Canadian Forces: 12 not found; 125 not available since "in movement" or currently deployed; 27 required for current treatment.

Anthrax - Canadian Forces

Result:

•Not wholly comparable at baseline

	Anthrax	Not
Age 35-44	26%	14%
Age 45-54	1.5%	1.8%
Women	4.8%	8.5%

Anthrax - Canadian Forces

Result:

Not wholly comparable: Different top diagnoses

Top dx, PGW (Anthrax vaccinated)

- Disorders of refraction & accommodation
- Soft tissue d/o related to use overuse & pressure

Top dx, Kosovo (not vaccinated)

- Acute URI of multiple & unspecified sites
- Other disorders of muscle
- Soft tissue d/o related to over/use & pressure

Anthrax - Canadian Forces

Sx decreased in AxVax-- incl those likely related to vaccine. Deployment effect? Vaccine predepl?

Result: Anthrax vax _____ No vaccine _____ p

symptoms: later values are % of these numbers

_____ **2653pre->1712post** **2689pre->2054post**

% of symptoms caused by:

- **Localized swelling, mass & lump of skin** & subcutaneous tissue

5.7->3.3, -2.4 3.8->3.4, -0.4 .01

- Other skin changes

6->3.3, -2.7 5->5.3, +0.3 0.00

Anthrax - Canadian Forces

**Diagnoses: Pre-post change as fraction of that groups total dx.
 Not much difference by these categories. Selected findings:**

Result: Ax change

- D/o of refraction & accommodation
 -1.9% vs -0.2%, p = 0.08
- Tissue disorders related to use, overuse & pressure
 +0.3% vs -1.6%, p = .627
- Soft tissue disorders related to use, overuse, pressure
 +0.6% vs +2.3%, p = 0.115

Anthrax - Canadian Forces

Result	Anthrax vax	No vaccine	p
Disturbance of skin sensation	4.9->3.2, -1.7	3.4->3.9, +0.5	0.00
Abd/pelvic pain	3.5->3, -0.5	2.8->3.1, +0.4	.069
Other S&S involving digestive system & abd	3.7->3.2,-0.5	3.4->3.9, +0.5	.048

BUT as these go down in vaccine group as % of total sx, something else is going up -- as a %.

Anthrax - Canadian Forces

Concerns: bias & confounding

- Diff populations: not comparable @baseline in demographics; not comparable at baseline in proportion of prior diagnoses
- Systematic differences in "treatment" unrelated to anthrax vaccine:
 Why not call it a quasi-experiment of deployment place and time (secular trend)?
- Small N: But larger N would not overcome bias
- Says change rate: but as % of events!!

Anthrax - Canadian Forces

Concerns:

- Sx DUE TO vaccine may have amplified predeployment rates:
 Note high rate of "localized swelling, mass and lump of skin and subcutaneous tissue" before deployment for vaccine vs control group, "decreased" after deployment

MARKERS

Markers

HEART RATE VARIABILITY

- SS: FM N=26 ; 19 FEM
- GWI N=11; 5 FEM
- HEALTHY N=36; 18 FEM

ASSESSMENT: HRT 24°, DAY; NIGHT

RESULT:

HEALTHY CTRL: MALE=FEM

GWV & FM: HRV DECREASED IN FEM

BUT: that's not quite the whole story:

Stein, ..., Clauw 2004. Am Coll Rheumatol 51(5): 700-8

HRV = hrt rate variabil; HR = heart rate; SDNN = SD of nl to nl intervals;
 ULF = ultra low frequency; SDNNDIX = age DDSD of nl to nl interval
 over 5 minutes; pNN50=% normal to nl intervals >50ms dif from prior;
 rMSSD = root mean square dif btn successive nl-to-nl intervals; VLF =
 very low freq; LF = low freq; HF = hi freq

Markers: HRV (Stein 2004)

GW > FM > CTRL: GW ALWAYS MORE DIFFERENT- E.G. 24° HRV

Long term HRV:		GW	FM	CTRL
• Hi HR bpm	.065	76	74	70
• low SDNN	.056	117	125	140
• Low n ULF power:	NS	9.19	9.24	9.41
Intermed term HRV:				
• Low SDNNDIX:	.056	53	63	68
• Low Ln LF power	.054	7.2	7.5	7.7
• Low Ln LF ratio	.050	6.4	6.9	7.0
Short term HRV				
• Low pNN50(%)	.023	7	13	18
• Low rMSSD (msec)	.036	27	37	43
• Low Ln HF power	.044	5.2	5.9	6.1

P-values for analysis of variance

Markers: HRV

- Diffs are even more extreme for women: 24°, Day, & night
- Intermed term HRV: GWV women are signif different from FM women despite N=5 in female GWV group.
- Most GWV HRV are signif dif from normal, despite small N
- FM differs from Ctrl & GWV : Only for FM are ratio-based HRV items NOT different for men vs women
- In contrast, the remaining HRV factors show M-F differences in GWV and FM but not control
- ∴ GWV shows both different pattern; and different quantitation than either FM or control (sm all N, needs replication)

P-values for analysis of variance

Stein PK, ..., ClauwDJ 2004. Arthritis and Rheumatism 51(5):700-8

Markers: EMG with PN symptoms

Decreased prevalence of peripheral nerve pathology by electrodiagnostic testing in Gulf War veterans
Ss: 56 GWV and 120 nonGW referred to EMG lab, Walter Reed. Consecutive GW referrals 1994-5.
NonGWV med records randomly chosen from retained med records of persons referred in same time.
GWV ~ older (39 vs 36); fewer females (6 v 62%)
More radiculopathy in nonGWV ($p = 0.000$ for active duty males; and for all). No diff peripheral or compression neuropathy
Pasquina 2004. Military Medicine 169: 11

Markers: EMG with PN symptoms

Another difference from the civilian population: AMONG THOSE citing sx that lead to referral for EMG, fewer have positive electrodiagnostic testing.
They interpret this as lower threshold for referral.
These people still have sx; the question is, what is the origin? (lower pain threshold? Other abnormality?)

Pasquina 2004. Military Medicine 169: 11

Markers: EMG with PN symptoms

Not known true; can't r/o a higher threshold.
It is equally consistent with higher prevalence of a distinct cause for these sx that does not show up on electrodiagnostic testing; or that amplifies sx for the same degree of subevident pathology. EMG may be another marker that, statistically, distinguishes GWV with similar symptoms.

Pasquina 2004. Military Medicine 169: 11

Markers: flow resp to Ach iontophoresis

Finding: Exaggerated response of bloodflow to ACh iontophoresis in CFS vs controls; but NOT in GWV; and NOT in persons with fatigue associated with occupational exposure to OP pesticides.
Another factor distinguishing GWV from the mass of CFS & fibromyalgia patients – and rendering them similar to OP cases.

Pasquina 2004. Military Medicine 169: 11

Markers: Ach iontophoresis

Subjects:

- **CFS N=53** (randomly selected from prev studied group with dx of CFS). Excluded 6 with DM, angina, other.
- **GWS N=24** (from registry)
- **Post-Organophosphate:** N=25 (Hx ill health from definite OP exposure; from registry)
- **Healthy control:** N=40, matched on age, sex for each group

Pasquina 2004. Military Medicine 169: 11

Markers: Ach iontophoresis

Marker: blood flow response to iontophoresis of Ach and methacholine challenge

Iontophoresis = drug delivered on arm, dissolved in water, through administration of current. Laser doppler imaging to assess cutaneous perfusion.

Outcome: median laser doppler flux over delivery site.

Result: GWV differ from CFS; same pattern as OP.

- Signif ↑ bloodflow resp to ACh in CFS (p = .029).
- Normal (no ↑) in GWS & OP-exposed

Pasquina 2004. Military Medicine 169: 11

Markers: Pulmonary Function

Finding: No increase in pulm fcn abnormalities 10 years later in GWV

Rationale: Published reports have documented increased prevalence of self-reported respiratory sx among PGWV

Ss: 1036 deployed & 1103 nondeployed PGWV. Not selected by illness status.

Phase III cohort from Natl Health Survey of Gulf War Era Veterans & Their Families -- Kang, Murphy etc

Gave "final list matched DV's & NDVs

Diff: PGWV ↓age, ↑white, ↑enlisted, ↓education.

Markers: Pulmonary Function

Result: No difference in distribution of PFT results: 64% nl; 16-18% nonreversible awy ds; 10-12% restrictive; 6=7% small airway; 0.9-1.3% reversible airway obstruction.

No diff MD visits for pulm complaints; pulm hospitalizations; # documented episodes asthma, bronchitis, emphysema; pulm meds in last year.

GWV more likely to cite smoking and wheezing.

Interpretation: If more SOB and not worse pulm fcn, consider something else going on. (BUT: tested subgroup not shown to have more SOB)

Karlinsky... Eisen, Kang, Murphy 2004. Late prevalence of respiratory symptoms and pulmonary function abnormalities in Gulf War I veterans. Arch Intern Med 164: 2488-91.

Anthrax - Disability Study

Ss: 716,833 US Army;
includes 154,456 s/p AVA w ≥ 1 day fl.u.
Active duty 12/97-12/01. Exclude if AVA pre1997
Exposure: Rec'd ≥ 1 dose AVA btn 3/98-2/02
dose; vaccine period; specific lots
Follow-up: 4.25 years total: rates of eval for disability discharge through 2-02.
Analysis: Cox proportional hazards. Person time accruing pre-vaccine is considered "unexposed"
Adjustments: occupation, sociodemographics

Sulsky Sl, Grabenstein JD, Delbos RG 2004 JOEM 46 (10): 1065-75

Anthrax - Disability Study

Analysis:
Collinearity: check for corrol coeff > 0.5 , retain member of pair most plausibly associated.
Candidate variables for inclusion: If lead to 15% change in HR (hazard ratio) for vaccine *in any stratum*. Then check for confounding in multivar:
Confounding: 15% change in HR for vaccination felt to ID confounding -- not based on stat signif due to large sample (everything significant)
Assumption: risks constant over the timeframe.

Sulsky 2004 JOEM 46 (10): 1065-75

Anthrax - Disability Study

Additional analysis:
Men vs women
By 1st reason disability: muscskel or neurologic
By disabil eval state: permanent vs temporary
Duty location within SW Asia - to partially mitigate healthy vaccinee effect

Sulsky 2004 JOEM 46 (10): 1065-75

Anthrax - Disability Study

Results: 22% had at least 1 dose (154K/717K)
Higher fraction vaccination in certain groups: special ops; stationed abroad at any time.
99% of those in SW Asia on/after 6-98 and 95% in Korea on/after 1-98 got at least one dose
4% eval'd for disab of whom 15% had rec'd AVA
Unadjusted rate: 1/2 as high for vaccinated 68 vs 140 per 100,000 person months
Unadjusted HR: 0.77 (0.74-0.79): 23% lower likelihood of undergoing disabil eval

Sulsky 2004. JOEM 46 (10): 1065-75

Anthrax - Disability Study

Results: adj for ever stationed abroad during f/u; major command. Vaccinated vs not.

Adj HR all: 0.96 (0.97-0.99)* "benefit"

Adj HR men: 0.96 (0.92-1.00)* "benefit"

Adj HR women: 1.04 (.96-1.13)

AVIP period 1: 1.04 (1.00-1.09)* "harm"

AVIP period 2: 0.84 (0.79-0.89)

Sulsky 2004. JOEM 46 (10): 1065-75

Anthrax - Disability Study

Results: adj for ever stationed abroad during f/u; major command. Vaccinated vs not.

1 dose AVA: 1.83 (1.6-2.1)

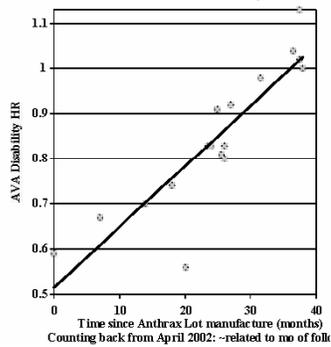
2 dose AVA: 1.64 (1.43-1.87)

3 dose AVA: 0.91 (0.87-0.94)

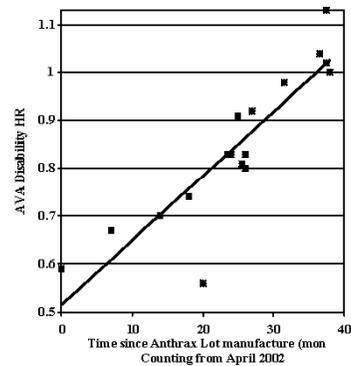
Sulsky 2004. JOEM 46 (10): 1065-75

Anthrax Vaccine: Disability

Anthrax Vacc: Disability vs Ti



Anthrax Vacc: Disability vs Ti



Presentation 17 – Lea Steele

RAC Committee Business

April 8, 2005

☆☆ RAC-GWVI

RAC Committee Business

- Appointments
- Future Meetings, Reports

☆☆ RAC-GWVI

Future RAC Meetings

- Upcoming Meeting Topics
 - > Additional research related to Gulf War exposures
 - > GWI treatments research
 - > Special topics

☆☆ RAC-GWVI

Next RAC Meeting

- Update from Dr. Concato re: AChE-R study
- Data presentation from Dr. Kang re: preliminary results of lifestyle, treatment questions from longitudinal survey

☆☆ RAC-GWVI

Future RAC Meetings: Exposure Topics

- Outstanding items re: exposure topics already addressed
- Additional exposure topics: which are of interest?
 - > Jet fuel
 - > CARC paint
 - > Solvents
 - > Sand
- Overview/analysis of research relating to combinations of exposures
- Overview/comparison of evidence re: all Gulf War-related exposures

Future RAC Meetings: GWV Treatments

- Detailed review of research studies on treatments for multisymptom illnesses
- Information from clinical practices that treat Gulf veterans' illnesses, other multisymptom illnesses

Future RAC Meetings: Possible Special Topics

- Development of Gulf War veteran brain tissue bank
- What we know about diagnosed conditions in Gulf War veterans: Info from epi research, benefits information
- Possible links and insights into GWV research from what is known about etiology and treatment of neurodegenerative conditions
- Neuro-immune interactions potentially associated with GWV (e.g. autonomic regulation of inflammation)
- Methodological issues in GWV research: Standards of study design, GWV case definition, etc.

Plans for 2005 Meetings, Next Committee Report

Sept 2005 Meeting

- Wrap-up of research on remaining exposure topics
- Review of treatment information
- Preliminary discussion of findings, recommendations on specific topics

Plans for 2005 Meetings, Next Committee Report

Dec 2005 Meeting

- Clean up loose ends re: topics covered
- Review of VA GWI research program and progress
- Discussion of content, findings, and recommendations of 2006 RAC Report

Plans for 2005 Meetings, Next Committee Report

Early 2006

- Circulate draft 2006 RAC Report for review and comments

Future RAC Meetings, Report

- Questions?
- Suggestions?

RAC website: www.va.gov/rac-gwvi

RAC email: RAC@med.va.gov