

Appendix B-1

**MVHCB Second Annual
Plenary Conference
December 10-12, 2001**

Part One of Two

*The Research Working Group:
Military and Veterans Health Coordinating Board*



*Conference on Illnesses
among Gulf War Veterans:
A Decade of Scientific Research*

Hilton Alexandria
Mark Center
Alexandria, Virginia
January 24-26, 2001

Proceedings

PREFACE

It is my pleasure to provide you with this report on the Conference on Illnesses among Gulf War Veterans: A Decade of Scientific Research, which was held January 24-26, 2001 in Alexandria, Virginia. This was the fifth conference on Gulf War veterans' illnesses, the first one being held at the Armed Forces Institute of Pathology in 1995. From 1995 to the present, the Conference has grown from about 50 participants to now nearly 400, including scientists from Great Britain, Canada, Australia, France, the Netherlands, Denmark, and Israel. This growth reflects the vigor of the research activities on behalf of veterans of the Gulf War. This year's conference emphasized the current state of the science and lessons learned. Speakers were encouraged to place their new findings within the context of the implications of the research that has already been completed.

In 1990 and 1991, the United States of America deployed nearly 700,000 troops to Saudi Arabia and surrounding areas in response to the invasion of Kuwait by Iraqi forces. Although the Gulf War has been noted for its swift completion with minimal casualties to U.S. forces in the theater of operations, the U.S. Government did not anticipate the emergence of medically unexplained illnesses among the veterans of the Gulf War upon their return home.

By 1994, the Government had embarked on a mission to conduct extensive research on the nature and potential causes of these illnesses. From 1994 to the present, the Federal Government has conducted or sponsored over 192 research projects with a financial commitment of over \$155 million.

The purpose of the Conference was to bring federally sponsored researchers on Gulf War veterans' illnesses together in a common forum to:

- Provide an opportunity for researchers to present and exchange study results
- Learn from recognized experts about overarching research areas as they relate to the etiology, diagnosis, and treatment of Gulf War veterans' illnesses
- Inform clinicians of current practices for the treatment of Gulf War veterans' illnesses, and the latest research findings and their potential impact on clinical care
- Provide an opportunity for veterans and veterans' groups to learn about ongoing research and to interact directly with researchers, clinicians, and government officials
- Provide an opportunity to inform executive and legislative branches of the government about research and clinical initiatives related to the Gulf War that should be considered for future deployments
- Encourage communication, cooperation, and collaboration among researchers, clinicians, and veterans
- Evaluate the implications of research on Gulf War veterans' illnesses: current state of the science and lessons learned

Over the course of 3 days, the meeting was organized around three morning plenary sessions, two afternoon breakout sessions on specific research topics, one evening poster session, and a Public Availability Session. In addition, the Conference provided two early morning sessions and one afternoon clinical symposia addressing treatment and clinical management of Gulf War veterans' illnesses.

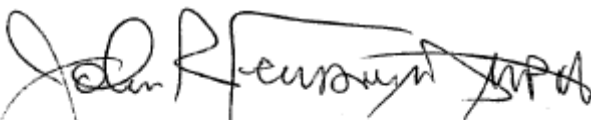
The Plenary Sessions were intended to be of broad appeal to the wider audience of participants. Nationally and internationally recognized experts focused on four major themes: longitudinal follow-up studies of Gulf War veterans; alternate approaches to case definitions; results of neuropsychological testing; and research on potential exposures during the Gulf War. During the Breakout Sessions and the Poster Session, researchers presented their research findings in a wide array of scientific areas including epidemiology, toxicology, psychology, neurology and neuropsychology, treatment, and force health

protection and prevention. The Public Availability Session provided an opportunity for veterans and other members of the public to discuss their concerns and questions directly with researchers.

These Proceedings of the Conference contain the texts of the material provided by each plenary speaker and summaries of each Breakout Session. In the appendix, there is a complete set of submitted abstracts from speakers in the Breakout Sessions and Poster Session.

It is through continuous rigorous scientific research that we will better understand the nature and causes of Gulf War veterans' illnesses. However, it is even more important that we use this research to improve the health of Gulf War veterans. This Conference is just one aspect of the research process that will lead us to these goals.

Sincerely,

A handwritten signature in black ink, appearing to read "John R. Feussner M.D.", written in a cursive style.

John R. Feussner, M.D., M.P.H.
Chair
Research Working Group
Military and Veterans Health Coordinating Board

Table of Contents

Preface.....	iii
Technical Planning Committee	1
Plenary Presenters and Panel Members.....	2
Meeting Agenda	3
Plenary Session Abstracts.....	9
Keynote Address: Gulf War Research: Science, Policy, and Politics	11
Longitudinal Follow-up of Gulf War Veterans: The Devens Cohort Study.....	15
Longitudinal Examination of Symptom Patterns among Gulf War Registry Veterans	17
Solving Challenges in Longitudinal Research on Gulf War Illnesses	18
View from the United Kingdom	21
CDC Air Force Study: Development of a Working Case Definition	22
Criteria for a Valid Case Definition.....	25
Is There a Gulf War Syndrome? Round 3	28
Approaches to Case Definition in the Iowa Study Syndrome Analysis	29
Factor Analysis of Self-Reported Symptoms: Does It Identify a Gulf War Syndrome?.....	32
Single and Multiple Symptom-Based Case Definitions Describe Persistent Unexplained Illness in Gulf War Veterans	34
Summary of Five Years of Neuropsychological Research of Gulf War Veterans at the Portland Environmental Hazards Research Center	37
Neuropsychological Functioning in PGW Veterans: Studies from BEHC.....	40
Assessment of Cognitive Dysfunction in Gulf War Veterans: The Iowa Gulf War Case-Validation Study	42
A Controlled Study of Neuropsychological Functioning and Mood Disorder in U.K. Veterans of the Gulf War	45
US Demolition Operations at Khamisiyah	47
Report of the Institute of Medicine Committee on Health Effects Associated with Exposures Experienced during the Persian Gulf War.....	50
Force Health Protection: New Strategy to Protect Deployed Forces	51
Protecting Those Who Serve: Strategies to Protect Deployed U.S. Forces.....	53
Combat and Operational Stress Control: Preventive Interventions and Treatment of Deployment-Related Stress	55
The Recruit Assessment Program: A Program To Collect Comprehensive Baseline Health Data from U.S. Military Personnel.....	57
The Millennium Cohort Study and Other New Research Initiatives at the DoD Center for Deployment Health Research	58
Toward Population-Based Post-Deployment Care: DoD's Deployment Health Clinical Center.....	59
The Department of Defense Birth Defects Registry	61
Defense Medical Surveillance System (DMSS) and the Army Medical Surveillance Activity	63

Clinical Sunrise Symposium I	65
Post-Deployment Health Evaluation and Management.....	67
Diagnosis and Treatment Strategies for Patients with Chronic Multi-Symptom Illnesses.....	68
Clinical Sunrise Symposium II	70
Medical Surveillance Results in DU-Exposed GW Veterans.....	70
VA Gulf War Veterans Health Examination Registry.....	72
Clinical Management of Gulf War Veterans with Chronic Multi-Symptom Illnesses.....	74
Clinical Session	79
Gulf War Veterans' Illnesses Demonstration Projects	81
Demonstration Project of Alternative Health Care Delivery Models for Gulf War Veterans	82
Summary – Sleep Disorders in Gulf War Veterans VA Boston Healthcare Systems	85
Successful Outcomes of Birmingham's Gulf War Veterans' Illness Demonstration Clinic	87
Brief Targeted Treatment Can Improve Health-Related Care Quality of Life in Symptomatic Gulf War Veterans	90
Case Management and Residential Rehabilitation for Gulf War Veterans	91
Platform Session Reports, Platform Abstracts and Poster Abstracts	93
Session A: Epidemiology I	95
Session E: Epidemiology II	104
Session B: Toxicology I.....	136
Session F: Toxicology II.....	144
Session C: Treatment.....	166
Session D: Neurological, Neuropsychological, Neurobiology of Stress	179
Session G: Psychological/Psychosocial.....	200
Session H: Force Health Protection/Prevention/Surveillance.....	213
Other (Poster Abstracts Only).....	228
Author Index	233
Attendees List.....	241

DISCLOSURE STATEMENT

The views expressed in this Proceedings Book are those of the authors and do not necessarily reflect official policy or the position of the Department of Defense, Department of Veterans Affairs, Department of Health and Human Services, or the Veterans Administration Employee Education System.

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The abstracts were reproduced as submitted.

ABOUT THE MEETING

The objectives of the Conference on Illnesses among Gulf War Veterans: A Decade of Scientific Research are to bring together, in a common forum, researchers, clinicians, veterans, veterans groups, and government officials to:

- > Provide an opportunity for researchers to present and exchange study results;
- > Provide an opportunity for veterans and veterans groups to learn about ongoing research and to interact directly with researchers, clinicians, and government officials;
- > Provide an opportunity to inform executive and legislative branches of the government about research and clinical initiatives related to the Gulf War that should be considered for future deployments;
- > Inform clinicians of current practices for the treatment of Gulf War veterans' illnesses and the latest research findings and their potential impact on clinical care;
- > Learn from recognized experts about overarching research areas as they relate to the etiology, diagnosis, and treatment of Gulf War veterans' illnesses;
- > Encourage communication, cooperation, and collaboration among researchers, clinicians, and veterans; and
- > Evaluate the implications of research on Gulf War veterans' illnesses: current state of the science and lessons learned.

This conference is sponsored by the Department of Defense (DoD) with planning and execution done under the auspices of the Research Working Group of the Military and Veterans Health Coordinating Board. The continuing medical educational activity is a collaborative effort with the Office of Employee Education of the U.S. Department of Veterans Affairs, Washington, DC.

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MEETING AGENDA

Tuesday, January 23, 2001

3:00 - 6:00 PM	REGISTRATION	<i>East Lower Foyer</i>
4:00 - 6:00 PM	POSTER BOARD SET-UP	<i>Terrace Ballroom</i>

Wednesday, January 24, 2001

8:00 AM	REGISTRATION Continental Breakfast Available	<i>East Lower Foyer</i>
8:00 AM - 4:00 PM	POSTER BOARD SET-UP	<i>Terrace Ballroom</i>

Plaza Ballroom

9:00 AM - 1:30 PM	PLENARY SESSION	Chair, Kelley A. Brix
9:00 AM	Welcome	Kelley A. Brix
9:10 AM	Keynote Address: Gulf War Research: Science, Policy, and Politics	John R. Feussner
9:40 - 11:25 AM	<i>Ongoing Longitudinal Follow-up Studies of Gulf War Veterans ♦ Moderator, Gregory C. Gray</i>	
9:45 AM	Longitudinal Follow-up of Gulf War Veterans: The Devens Cohort Study	Susan P. Proctor
10:05 AM	Longitudinal Examination of Symptom Patterns among Gulf War Registry Veterans	William K. Hallman
10:25 AM	Solving Challenges in Longitudinal Research on Gulf War Illnesses	Bradley N. Doebbeling
10:45 AM	View from the United Kingdom	Simon Wessely
11:05 AM	Questions and Answers	
11:25 AM	BREAK	
11:45 AM - 1:30 PM	<i>Alternate Approaches to Case Definitions: Is There a Gulf War Syndrome? ♦ Moderators, K. Craig Hyams and Timothy R. Gerrity</i>	
11:55 AM	CDC Air Force Study: Development of a Working Case Definition	Drue H. Barrett
12:05 PM	Criteria for a Valid Case Definition	Robert W. Haley
12:15 PM	Is There a Gulf War Syndrome? Round 3	Simon Wessely
12:25 PM	Approaches to Case Definition in The Iowa Study Syndrome Analysis	Bradley N. Doebbeling
12:35 PM	Factor Analysis of Self-Reported Symptoms: Does It Identify a Gulf War Syndrome?	James D. Knoke
12:45 PM	Single and Multiple Symptom-Based Case Definitions Describe Persistent Unexplained Illness in Gulf War Veterans	Peter Spencer
12:55 PM	Questions and Answers	
1:30 - 3:00 PM	LUNCH BREAK	

MEETING AGENDA (CONT.)

3:00 - 5:10 PM	CONCURRENT PLATFORM SESSIONS	
3:00 - 3:10 PM	SESSION A: EPIDEMIOLOGY I Co-Chairs: Bradley N. Doebbeling and Han K. Kang	<i>Beech A & B</i>
3:10 - 3:35 PM	Health Services Utilization Five Years Post Gulf War ◆ Bradley N. Doebbeling	
3:35 - 4:00 PM	Health Care Utilization and Disability of Gulf War Era Women ◆ Tomoko R. Sampson	
4:00 - 4:20 PM	BREAK	
4:20 - 4:45 PM	Prospective Follow-up of Health Status in Gulf War Veterans and Era Controls ◆ Margaret D. Voelker	
4:45 - 5:10 PM	Spatial Analysis (Using GIS Techniques) of Gulf War Troop Location Data in Relationship with Symptom Reports ◆ Susan P. Proctor	
3:00 - 3:10 PM	SESSION B: TOXICOLOGY I Co-Chairs: Mark Brown and James Romano	<i>Plaza I</i>
3:10 - 3:35 PM	Sarin-Induced Increase in Blood-Brain Barrier (BBB) Permeability Is Augmented by Co-Exposure with Stress, Pyridostigmine Bromide (PB), DEET, and Permethrin in Rats ◆ Mohamed B. Abou-Donia	
3:35 - 4:00 PM	Effects of Inhalation Exposure to Low Levels of Sarin in Fischer 344 Rats ◆ Rogene F. Henderson	
4:00 - 4:20 PM	BREAK	
4:20 - 4:45 PM	Neuroimmune Effects of Subclinical Doses of Sarin: Sarin Suppresses T Cell Responsiveness through the CNS ◆ Mohan L. Sopori	
4:45 - 5:10 PM	Depleted Uranium Fragments Cause Soft Tissue Sarcomas in the Muscles of Rats ◆ Fletcher F. Hahn	
3:00 - 3:10 PM	SESSION C: TREATMENT Co-Chairs: Daniel J. Clauw and Simon Wessely	<i>Plaza II</i>
3:10 - 3:35 PM	Measurement of Tenderness in Gulf War Veterans: What Does It Tell Us?: Results from the VA Cooperative Study #470 ◆ Daniel J. Clauw	
3:35 - 4:00 PM	Physical Functional Status and Its Relationship to Common Symptoms of Chronic Multisymptom Illnesses in Gulf War Veterans: Results from the VA Cooperative Study #470 ◆ David A. Williams	
4:00 - 4:20 PM	BREAK	
4:20 - 4:45 PM	Predicting Costs of VA Health Care for Gulf War Veterans ◆ M. Jan Tackett	
4:45 - 5:10 PM	Doxycycline Therapy of Mycoplasma Positive Veterans with Gulf War Illness ◆ Sam T. Donta	
3:00 - 3:10 PM	SESSION D: NEUROLOGICAL, NEUROPSYCHOLOGICAL, NEUROBIOLOGY OF STRESS Co-Chairs: Timothy R. Gerrity and Karl Friedl	<i>Plaza III</i>
3:10 - 3:35 PM	Effects of Pyridostigmine Bromide on Physiology and Performance in Humans ◆ Mary R. Cook	

MEETING AGENDA (CONT.)

3:35 - 4:00 PM	Side Effects of Low-Dose Pyridostigmine Bromide Are Not Related to BCHE Genotype or Enzyme Inhibition ♦ Mary R. Cook	
4:00 - 4:20 PM	BREAK	
4:20 - 4:45 PM	Heart Rate Variability in Ill Gulf War Veterans, Fibromyalgia Patients, and Healthy Controls ♦ Timothy R. Gerrity	
4:45 - 5:10 PM	Abnormal Circadian Variation in Autonomic Nervous System Activity in Ill Gulf War Veterans ♦ Robert W. Haley	
5:30 - 7:30 PM	POSTER SESSION AND RECEPTION	<i>Terrace Ballroom</i>

Thursday, January 25, 2001

8:00 - 9:00 AM	Continental Breakfast	<i>East Lower Foyer</i>
7:30 - 8:45 AM	CLINICAL SUNRISE SYMPOSIUM I: Clinical Practice Guidelines ♦ Moderator, Charles C. Engel	<i>Beech A&B</i>
	Post Deployment Health Evaluation and Management	Oded Susskind
	Diagnosis and Treatment Strategies for Patients with Chronic Multi-Symptom Illnesses	Daniel J. Clauw

Plaza Ballroom

9:00 AM - 12:30 PM	PLENARY SESSION	
	<i>Results of Neuropsychological Research of Gulf War Veterans</i> ♦ Moderator, Drue H. Barrett	
9:05 AM	Summary of Five Years of Neuropsychological Research of Gulf War Veterans at the Portland Environmental Hazards Research Center	Daniel Storzbach
9:25 AM	Neuropsychological Functioning in Persian Gulf War Veterans: Studies from Boston Environmental Hazard Center	Roberta F. White
9:45 AM	Assessment of Cognitive Dysfunction in Gulf War Veterans: The Iowa Gulf War Case-Validation Study	Joseph Barrash
10:05 AM	A Controlled Study of Neuropsychological Functioning and Mood Disorder in U.K. Veterans of the Gulf War	Anthony S. David
10:25 AM	Questions and Answers	
10:40 - 10:55 AM	BREAK	
10:55 AM	<i>State of the Science: Potential Exposure to Sarin, Pyridostigmine Bromide, Depleted Uranium, and Vaccines</i> ♦ Moderator, Barry W. Wilson	
11:00 AM	US Demolition Operations at Khamisiyah	Michael Abreu
11:40 AM	Report of the Institute of Medicine Committee on Health Effects Associated with Exposures Experienced during the Persian Gulf War	Harold C. Sox
12:20 PM	Questions and Answers	
12:30 - 2:00 PM	LUNCH BREAK	

MEETING AGENDA (CONT.)

2:00 - 4:35 PM	CONCURRENT PLATFORM SESSIONS	
2:00 - 2:10 PM	SESSION E: EPIDEMIOLOGY II Co-Chairs: Michael E. Kilpatrick and John T. Graham	<i>Beech A&B</i>
2:10 - 2:35 PM	Anthrax Vaccination and Self-Reported Symptoms, Functional Status and Medical Conditions in the National Health Survey of Gulf War Era Veterans and Their Families ❖ Clare M. Mahan	
2:35 - 3:00 PM	Histopathologic Study of Skin Biopsies in Gulf War Veterans. The Kuwait Registry, AFIP ❖ Charles S. Specht	
3:00 - 3:20 PM	BREAK	
3:20 - 3:45 PM	How Many Veterans are Affected by Gulf War-Related Health Problems? A Review of Population-Based Estimates ❖ Lea Steele	
3:45 - 4:10 PM	The Gulf Veterans' Medical Assessment Programme (GVMAP) London (UK) - A Case Series of 3,000 Cases ❖ Harry A. Lee	
4:10 - 4:35 PM	The Impact of Military Deployments on Health: A Comparison of the Post Deployment Hospitalization Risk between U.S. Veterans of the Gulf War and Veterans of Subsequent Peacekeeping Missions to Bosnia and Southwest Asia ❖ Besa Smith (Did not present)	
2:00 - 2:10 PM	SESSION F: TOXICOLOGY II Co-Chairs: Barry W. Wilson and Mark Brown	<i>Plaza I</i>
2:10 - 2:35 PM	Interaction of DEET, Permethrin, and Pyridostigmine with Cholinergic Receptors and Cholinesterases ❖ Richard K. Gordon	
2:35 - 3:00 PM	Systemic Pyridostigmine Suppresses Inflammatory Cytokines Released after Topical Permethrin and DEET Exposure ❖ Nancy A. Monteiro-Riviere	
3:00 - 3:20 PM	BREAK	
3:20 - 3:45 PM	Running and Restraint Stress Fail to Influence Pyridostigmine-Induced Acetylcholinesterase Inhibition in Rat Brain ❖ Carey N. Pope	
3:45 - 4:10 PM	Low Level Effects of Pyridostigmine Bromide and Delayed Neuropathy Organophosphates in Experimental Animals ❖ Barry W. Wilson	
2:00 - 2:10 PM	SESSION G: PSYCHOLOGICAL/PSYCHOSOCIAL Co-Chairs: Roberta F. White and Charles C. Engel	<i>Plaza II</i>
2:10 - 2:35 PM	Who Believes They Have Gulf War Syndrome? ❖ Simon Wessely	
2:35 - 3:00 PM	Neuropsychological Functioning in Danish Gulf War Veterans ❖ Susan P. Proctor	
3:00 - 3:20 PM	BREAK	
3:20 - 3:45 PM	The Impact of Sexual Assault and Harassment on Posttraumatic Stress Disorder among Deployed Persian Gulf Veterans ❖ Erick K. Ishii	

MEETING AGENDA (CONT.)

3:45 - 4:10 PM	<p>Fatigue, Pain, Cognitive Symptoms and Mental Health-Related Functioning among Gulf Vets with Chronic Multisymptom Illnesses: Results from the VA Cooperative Study #470 ♦ Charles C. Engel</p>							
4:10 - 4:35 PM	<p>Are Veterans Seeking VA Primary Care as Healthy as Those Seeking Department of Defense Primary Care? A Look at Gulf War Veterans' Symptoms and Functional Status ♦ Ralph D. Richardson</p>							
2:00 - 2:10 PM	<p>SESSION H: FORCE HEALTH PROTECTION/ PREVENTION/SURVEILLANCE Co-Chairs: Brian J. Balough and Craig Postlewaite</p>	<i>Plaza III</i>						
2:10 - 2:35 PM	<p>Induction and Detection of Antibodies to Squalene ♦ Carl R. Alving</p>							
2:35 - 3:00 PM	<p>Comparison of Psychological Health Assessments for Soldiers Deploying to Kosovo with and without Deployment Experience ♦ James W. Ness</p>							
3:00 - 3:20 PM	<p>BREAK</p>							
3:20 - 3:45 PM	<p>Characteristics of Army Personnel Remaining in the National Guard Six Years after Gulf War Deployment: A Descriptive Analysis ♦ Susan P. Proctor</p>							
3:45 - 4:10 PM	<p>DoD-Wide Surveillance for Ill-Health Requiring Hospitalization Potentially Associated with Anthrax Immunization: 1998 Data ♦ Paul A. Sato</p>							
4:10 - 4:35 PM	<p>Post-Combat Syndromes from 1900: An Intra- and Inter-War Comparison ♦ Simon Wessely</p>							
5:15 - 6:45 PM	<p>PUBLIC AVAILABILITY SESSION (This session is designed to give veterans and interested members of the public an opportunity to discuss their concerns and questions with scientists currently researching illnesses among Gulf War Veterans.)</p> <p>Participants:</p> <table border="0" style="width: 100%;"> <tr> <td>♦ Mark Brown</td> <td>♦ Simon Wessely</td> </tr> <tr> <td>♦ Charles C. Engel</td> <td>♦ Roberta F. White</td> </tr> <tr> <td>♦ Michael E. Kilpatrick</td> <td>♦ Barry W. Wilson</td> </tr> </table>	♦ Mark Brown	♦ Simon Wessely	♦ Charles C. Engel	♦ Roberta F. White	♦ Michael E. Kilpatrick	♦ Barry W. Wilson	<i>Magnolia Room</i>
♦ Mark Brown	♦ Simon Wessely							
♦ Charles C. Engel	♦ Roberta F. White							
♦ Michael E. Kilpatrick	♦ Barry W. Wilson							

Friday, January 26, 2001

8:00 - 9:00 AM	<p>Continental Breakfast</p>	<i>East Lower Foyer</i>
7:15 - 8:55 AM	<p>CLINICAL SUNRISE SYMPOSIUM II: ♦ Moderator, Stephen C. Hunt</p>	<i>Beech A&B</i>
7:20 - 8:05 AM	<p>Medical Surveillance Results in DU-Exposed Gulf War Veterans</p>	Melissa A. McDiarmid
8:05 - 8:50 AM	<p>VA Gulf War Veterans Health Examination Registry</p>	Don Salisbury
	<p>Clinical Management of Gulf War Veterans with Chronic Multisymptom Illnesses</p>	Ralph D. Richardson & Stephen C. Hunt

MEETING AGENDA (CONT.)

<i>Plaza Ballroom</i>		
9:00 AM - 12:00 Noon	PLENARY SESSION	
9:00 AM	<i>Force Health Protection: Strategies to Protect Deployed Forces</i> ♦ Moderator, James R. Riddle	
9:05 AM	Force Health Protection: New Strategy to Protect Deployed Forces	Robert G. Claypool
9:25 AM	Protecting Those Who Serve: Strategies to Protect Deployed U.S. Forces	John Moxley
9:45 - 10:00 AM	BREAK	
10:00 AM	Combat and Operational Stress Control: Preventive Interventions and Treatment of Deployment-Related Stress	Elspeth Cameron Ritchie
10:20 AM	The Recruit Assessment Program: A Program to Collect Comprehensive Baseline Health Data from U.S. Military Personnel	K. Craig Hyams
10:35 AM	The Millenium Cohort Study and Other New Research Initiatives at the DoD Center for Deployment Health Research	Gregory C. Gray
10:50 AM	Toward Population-Based Post-Deployment Care: DoD's Deployment Health Clinical Center	Charles C. Engel
11:05 AM	The Department of Defense Birth Defects Registry	Margaret A. K. Ryan
11:20 AM	Defense Medical Surveillance System (DMSS) and the Army Medical Surveillance Activity	Mark Rubertone
11:35 AM	Questions and Answers	
12:00 Noon	PLENARY SESSION ADJOURNS	
12:00 - 1:30 PM	LUNCH BREAK	
1:30 - 4:30 PM	<i>Plaza II & III</i>	
1:30 - 1:35 PM	Gulf War Veterans Illness Demonstration Projects ♦ Moderator, Artie Shelton	
1:35 - 2:05 PM	Demonstration Project of Alternative Health Care Delivery Models for Gulf War Veterans	David Hickam
2:05 - 2:35 PM	Summary – Sleep Disorders in Gulf War Veterans VA Boston Healthcare Systems	Lawrence J. Epstein
2:35 - 3:05 PM	Successful Outcomes of Birmingham's Gulf War Veterans' Illness Demonstration Clinic	Michael P. Everson
3:05 - 3:35 PM	Brief Targeted Treatment Can Improve Health-Related Care Quality of Life in Symptomatic Gulf War Veterans	Dewleen G. Baker
3:35 - 4:05 PM	Case Management and Residential Rehabilitation for Gulf War Veterans	Gail Powell-Cope
4:05 - 4:30 PM	Wrap-up and Discussion	

Plenary Session Abstracts

Gulf War Illnesses Research: Science, Policy, and Politics

John R. Feussner, M.D., M.P.H.
Chief Research and Development Officer
Department of Veterans Affairs

First, I want to thank all the veterans, Veteran's Service Organizations, Members of Congress, experts, advisors, and other policy makers who have provided review, commentary, critique, and direction to our efforts to understand and treat the illnesses experienced by Gulf War veterans upon their return home after the War. Dr. Neal Lane, the former Special Assistant to the President for Science and Technology Policy, has spoken often about the responsibility of scientists to go beyond their own work and to get involved in teaching and explaining the excitement and promise of science to the non-scientist. Research on illnesses in Gulf War veterans exemplifies the interactions among science, policy, and politics. Insight and energy are generated at this volatile interface, and I would like to use my time this morning to draw contrasts between the differing perceptions, and at times the differing realities, among the science, policy, and politics of this issue.

There are a number of key questions and research issues for us to focus on. None of these issues is definitively resolved, but we are working diligently on all these areas:

- Is there a unique Gulf War syndrome?
- Are there specific diagnostic tests to guide clinicians?
- Are there possible causes of the veterans' illnesses?
- Are ill Gulf War veterans getting better, getting worse, or staying the same?
- Which treatment strategies are effective?
- What steps must be taken to prevent future war-related illnesses?

The first question asks whether illnesses in Gulf War veterans represent a new, previously unrecognized syndrome and has been a research focus since 1994. So far, five relevant reports have been published, based on different populations of veterans. One study concluded that there were six unique syndromes (Haley, 1997). Four other studies concluded that there is no unique syndrome. Data from these four studies demonstrated that Gulf War veterans and nondeployed veterans reported a similar pattern of symptoms (Fukuda, 1995; Ismail, 1999; Doebbeling, 2000; Knoke, 2000). What would one conclude from reviewing the growing body of scientific evidence concerning this key question? This conference includes a session later that highlights the results of these five studies, with participation of the study authors themselves!

Several policy documents, written by oversight groups and expert panels, have addressed this question formally. These have included the Presidential Advisory Committee on Gulf War Veterans' Illnesses *Final Report* (1996), the Senate Veterans Affairs Committee Report (1998), the Institute of Medicine Report (2000), the White House Report (2000), and the Presidential Special Oversight Board *Final Report* (2000). For example, the Institute of Medicine (2000) stated:

"Thus far, there is insufficient evidence to classify veterans' symptoms as a new syndrome. . . All Gulf War veterans do not experience the same array of symptoms. Thus, the nature of symptoms suffered by many Gulf War veterans does not point to an obvious diagnosis, etiology, or standard treatment."

As another example of a policy document, the White House Report (2000) stated:

“Several major studies have shown that Gulf War veterans do not suffer from a unique, previously unrecognized ‘syndrome.’ ”

This issue has not yet been resolved completely, despite five studies in two countries, performed by both university and government scientists. The lack of resolution is frustrating to the research community, as well as to veterans, health care providers, and members of Congress. This frustration was expressed recently by a member of Congress:

“If we say there is a Desert Storm syndrome, doesn’t that solve it? Can’t we say, OK, we now have a syndrome?”

However, just declaring it so, will not make it so. The research community responded to the congressional member’s statements with equally strong sentiments, in the British journal, *Nature* (2000):

“The Congress may wish to establish an administrative classification for the health problems afflicting veterans. But it should stop pressing scientists in effect to invent findings that would support its otherwise admirable impulse to assist them.”

Resolution of this issue will be more complex for Congress than it is for researchers and clinicians because of the need to factor in all three domains: science, policy, and politics.

Now, to focus on another question: Are there possible causes of the veterans’ illnesses? This is an extraordinarily complex question. In all its dimensions and ramifications, this question takes into account the large number of potential exposures or causes of illnesses, including the interaction among multiple possible exposures. Answers to this question require knowledge about the dose, duration, and periodicity of the possible exposures. Also, the research must consider the possible long-term consequences of low doses of exposures, in some cases, such low doses and short duration of exposures that soldiers experienced no noticeable, short-term symptoms.

One example of the complexity of this issue is exemplified by the controversy surrounding depleted uranium (DU) as a possible cause of the veterans’ illnesses. This issue has been in the news a lot in the past few weeks, not just related to the Gulf War, but also to deployments to Kosovo and Bosnia. We should review some scientific facts about DU, then consider the results of the ongoing research projects.

- Natural uranium is a low-level radioactive element.
- DU possesses only 60% of the radioactivity of natural uranium.
- No association has been demonstrated between occupational exposure to uranium and lung cancer or kidney disease.
- About 100 Gulf War soldiers were exposed to DU in friendly fire incidents, through wound contamination and inhalation.
- The Baltimore VA Medical Center longitudinal study of 63 veterans, who were wounded in friendly fire, has demonstrated no clinical evidence of illness associated with DU, other than traumatic injuries.

The results of the Depleted Uranium Medical Follow-Up Program at the Baltimore VA Medical Center will be presented by its Director later at this conference. I would encourage you to review the research before you stake out your own position.

Several policy documents, written by oversight groups and expert panels, have addressed this question of DU as a possible cause of veterans' illnesses. These documents include the Presidential Advisory Committee on Gulf War Veterans' Illnesses *Final Report* (1996), the RAND Report (1999), the Agency for Toxic Substances and Disease Registry Report (1999), the General Accounting Office Report (2000), the Institute of Medicine Report (2000), the White House Report (2000), and the Presidential Special Oversight Board *Final Report* (2000).

For example, the Institute of Medicine (IOM) (2000) concluded:

There is limited/suggestive evidence that there is "no association between exposure to uranium and lung cancer and clinically significant renal dysfunction." Also, there is "inadequate/insufficient evidence to determine whether an association does or does not exist" for several other potential long-term health effects (e.g., lymphatic cancer or bone cancer).

The IOM conclusions are based on groups of miners and millers who had high-level uranium exposures for years to decades. However, the IOM conclusions reflect also the incomplete nature of the data for some long-term health effects that may result from low dose or short-term exposure to DU. Even with decades of data, there are uncertainties regarding dose, duration of exposure, and latency of onset of disease. The Chair of the IOM Committee will present the findings and conclusions of this report later at this conference.

As another example of a policy document, the White House Report (2000) stated:

"Other than injuries resulting from wounds, these reviews indicated that U.S. troops were unlikely to suffer any additional ill effects as a result of exposure to DU during their deployment."

In contrast to these scientific and policy statements, DU has been an inflammatory topic in the media for the past few weeks. There is great disparity in the risk assessments made by some scientists and some politicians. Here are some examples of recent headlines:

- "Radiation Sickness Scare Ignores Scientific Facts" (Los Angeles Times)
- "Fray in Europe over Uranium Draws Doubters" (New York Times)
- "Scare-Mongering Suspected as Uranium Fears Revive" (Environmental News Network)

Here are contrasting headlines that appeared the same week:

- "Hundreds Died of Cancer after DU Bombing" (Reuters)
- "Use of DU Weapons Could Be War Crime" (CNN)
- "Uranium Shells Held 'Cocktail of Nuclear Waste'" (The Sunday Times, London)

The continuing controversy on illnesses in Gulf War veterans was expressed succinctly in a CNN article about the Presidential Special Oversight Board *Final Report*, which was published in December 2000. The CNN headline consisted of two lines:

"Panel finds Pentagon 'diligent' on Gulf War illness issue
"It's a whitewash' veterans advocate says"

Keynote Address

As I indicated at the beginning of this presentation, there is both insight and energy at this volatile interface between science, policy, and politics. Let me conclude with some assessment about where we are and what we have learned to date from the research effort related to Gulf War Veterans Illnesses. Over the past decade, the Federal Government has supported 192 research projects at a cost of \$155 million. This research has been funded by the Department of Defense, Veterans Affairs, and Health and Human Services. So far, 83 (43%) projects are completed, and 109 projects are ongoing.

What have we learned from the completed research, in terms of general conclusions? Or, what do we *think* we have learned, as of January 2001?

- Gulf War veterans consistently report more symptoms than nondeployed veterans.
- There is little evidence for a unique “Gulf War syndrome.”
- There is no increase in mortality, except for motor vehicle accidents.
- There is no increase in hospitalizations, except for traumatic injuries.
- The rates and patterns of infectious diseases have been unremarkable.
- There is no increase in birth defects among offspring.
- No exposure has been shown conclusively to cause a particular individual symptom or combinations of symptoms.
- There is consistent evidence that pyridostigmine bromide does not cross the blood brain barrier; therefore, it is unlikely to cause changes in brain function.
- There is little evidence that uranium exposure is associated with adverse clinical outcomes.

As more research is completed, these conclusions may be revised. In addition, some scientists, some veterans, and some members of Congress probably disagree with these conclusions now.

Sometimes, it is hard to remember that the Gulf War was a tremendous success. There were only 148 combat deaths and 224 deaths due to diseases or non-battle injuries (DNBI). This was the lowest DNBI rate for any major U.S. conflict in history. However, let’s consider the post-war situation. In the decade since the war, 80,000 Gulf War veterans have received VA registry examinations. Over 250,000 veterans have received care in VA outpatient clinics, and over 26,000 have received care in VA hospitals. Approximately 143,000 Gulf War veterans’ claims for disability compensation have been granted.

Clearly, many veterans are ill. Clearly, their illnesses are real, not imagined. But this issue of Gulf War Veterans Illnesses is a difficult problem to address clinically. One goal of the research must be to identify treatments that will provide “victories” for our ill veterans, just as these veterans provided the “victory” for our country in the war.

In summary, most of the issues related to illnesses in Gulf War veterans sit at the interface of science, policy, and politics. Today’s conference focuses on the scientific information acquired to date. However, we scientists must remember that we do not work in isolation. We must be sensitive to the illnesses of our veteran patients, as well as their concerns and fears. We must know that science can influence policy. And the results of our research, whether preliminary or definitive, can create political opportunities or controversies. I close with a reflection from a former Secretary of State, Henry Kissinger, who noted that:

“Each success only buys an admission ticket to a more difficult problem.”

Thank you for your research efforts to clarify this difficult issue of Gulf War Veterans Illnesses.

LONGITUDINAL FOLLOW-UP OF GULF WAR VETERANS: THE DEVENS COHORT STUDY

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Introduction

The Devens cohort consists of a group of US Army military personnel (n=2,949) who have been studied since within five days of their 1991 return from the Gulf War (GW), before they returned to their families. The focus of the initial cross-sectional study was to examine psychological readjustment after GW deployment. Comparisons between this sample and data available for the Ft. Devens military population at large indicate that 1991 survey respondents are representative of the military population on that base and the New England area at that time. In 1991, the Devens cohort had a mean age of 30.2 years (SD=8.6) and 13.2 years of education (SD=1.8). The majority of the troops was Caucasian (87.4%) and had served as Reservists (52.2% National Guard; 19.9% Reserves) in the Gulf War. For this presentation and other subsequent discussions, we define the Devens cohort as the 2,709 men and 240 women who completed the Time 1 survey in 1991.

Objectives

Increasingly, there have been a number of studies undertaken and published that have demonstrated that GW-deployed veterans are reporting more health problems and symptoms compared to non-GW-deployed veterans. But, to date, no prospective cohort study has examined and published on whether the health status of GW veterans is changing over time and if so, how. The Devens cohort has and continues to represent a unique opportunity to examine the psychological and physical health consequences of GW deployment and changes in individual veterans' health over the years since the Gulf War. This presentation will focus on the examination of changes in physical and emotional health outcomes within the Devens cohort members.

Methods

The Devens cohort has been subsequently studied at several additional time points over the past nine years. All the 2,949 persons in the Devens cohort were targeted for re-survey between late 1992 and early 1993 (78.4 % response rate; *Time 2*). Then, a stratified, random sample of the cohort participated in an in-person assessment protocol (n=220) between late 1994 and early 1996 (*Time 3*). Subjects were asked to complete neuropsychological testing, clinical psychiatric interviews and environmental history interviews, and a series of questionnaires. And, in 1997-1998, the Devens cohort was recontacted and asked to complete a mail survey (44% response rate; *Time 4*). Thus, the Devens cohort study represents a panel study where the same group of individuals is followed over time. All the original cohort members have been targeted for each follow-up assessment wave unless they have indicated that they would like to be removed from our contact list. After the Time 4 survey, there were a total of 13 persons categorized as 'refusers' in the Devens cohort and 20 persons who had died.

Findings to Date

In this presentation, we will summarize the findings to date on the changes in psychological and physical health outcomes in the Devens cohort members. Analyses indicate that between Time 1 (1991) and Time 4 (1997-8) there have been significant increases in some health outcome measures (indicating higher levels of symptomatology), but decreases in others. We have examined changes in several reliable and validated psychological and physical health measures that have been collected at multiple time points (such as the Brief Symptom Inventory, the PTSD Checklist, and several health symptoms focusing on nervous system, gastrointestinal, and respiratory complaints). We will describe the results for those persons that completed the Time 1, 2, and 4 surveys.

In summary, significant increases in certain physical and psychological symptomatology in individuals between Time 1 and 2 and Time 1 and 4 are observed. However, there are indications that there has been some leveling off in depression symptomatology and in the number and types of health symptoms reported between Time 2 and 4. And, in some instances, significant improvements are noted between Time 2 and 4 (i.e., anxiety and certain health symptoms). Comparisons of the unadjusted scores over time for these measures of physical and psychological

symptomatology suggests that GW veterans' health is not consistently improving or declining and suggest that predictors of change (whether it is an improvement, persistence, or decline over time) may be multi-factorial.

Future Directions

Plans to conduct a Time 5 assessment of the Devens cohort are pending. Also, the application of longitudinal data analysis techniques to address the complex nature of changes in GW veterans' health over time and the potential contributing demographic and confounding factors is underway. An update of our progress in these areas will be presented together with a discussion of the strengths and limitations of this cohort study.

LONGITUDINAL EXAMINATION OF SYMPTOM PATTERNS AMONG GULF WAR REGISTRY VETERANS

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Introduction

We provide a preliminary report on the results of an in-progress follow-up study of symptom patterns among a sample of veterans drawn from the Gulf War Health Registry maintained by the Department of Veterans Affairs.

Procedures

Eleven hundred sixty-one (60%) of 1935 Gulf War veterans in seven states in the East, Northeast, and Mid-West, selected randomly from the "Gulf-War Health Registry" maintained by the Veterans Administration completed a mail survey in Fall of 1995 (Time 1). In the Fall of 2000 (Time 2), a random sample of 330 of these veterans completed a similar mail survey and were then interviewed by telephone within two weeks, using the same symptom questionnaire. An additional random sample of 257 veterans was interviewed by telephone only. Data collection is on-going.

Summary of Results

At Time 1, 81% of these respondents reported that they believed that they had medical problems as the result of their service in the Gulf. They reported an average of 22 symptoms (of 48 possible), 12 of which were endorsed as moderate or severe. An exploratory factor analysis of reported symptoms revealed four stable factors representing (1) mood, memory and fatigue problems, (2) musculoskeletal problems, (3) stomach and digestive (GI) problems, and (4) nose, throat and breathing problems. A K-means cluster analysis found two stable clusters. The first cluster (60% of sample) represents a group of veterans with few moderate or severe symptoms. The second cluster represents veterans who report being in the worst health, and whose symptoms are centered around moderate to severe musculoskeletal, mood, memory, and fatigue problems and mild to moderate problems with a large number of other symptoms including throat/respiratory and gastrointestinal problems. At Time 2, only 66% reported that they believe they have medical problems as the result of Gulf War Service. Those who responded by mail reported an average of 21 symptoms, 11 of which were moderate or severe. In their matched telephone interview, this same group reported only an average of 17 symptoms, 11 of which were moderate or severe. Those in the sickest cluster at Time 1 (Cluster 2) showed modest reductions in the severity of 24 of the 48 symptoms reported at Time 2. Factor analysis of the symptoms reported at Time 2 showed a similar factor structure as that found at Time 1. The results of a K-means cluster analysis at Time 2 was also similar to those found at Time 1, with 78% of those classified into the same groups across time.

Conclusion

There was stability in the number of symptoms endorsed at Times 1 and 2 when reported by mail survey. When reporting by telephone interview at Time 2, respondents reported 4 fewer symptoms on average, than when they reported by mail. Mild symptoms seem to be under-reported in the telephone interview. Some modest reductions in symptom severity are evident at Time 2, especially among those who were sickest at Time 1. However, this may represent regression toward the mean and the small improvements suggest that the veterans may be "slightly better, but not well." The stability in the number of symptoms reported, the similar factor structures and results of the cluster analyses suggest few changes in symptoms have occurred over time.

Time 1 research was supported by The Department of Veterans Affairs. Time 2 research and additional analyses were supported by the Centers for Disease Control under Cooperative Agreement U50/CCU214463-03-02.

SOLVING CHALLENGES IN LONGITUDINAL RESEARCH ON GULF WAR ILLNESSES

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Introduction

Cross-sectional, case-control and other research designs have contributed substantially to the understanding of Gulf War (GW) Veterans' health problems. However, to fully appreciate the consequences of service in the Gulf requires longitudinal follow-up. Assessment of individuals over time allows estimation of disease incidence rates, and provides insight to the course of illness and prognostic factors. In addition, the time between exposure and disease can be substantial for many chronic conditions. Because of the aging process; it is imperative to include both exposed and nonexposed individuals. A notable advantage of following a cohort is the opportunity for nested case-control studies. The Iowa Gulf War Cohort, which includes Gulf War deployed (GWD) and Gulf War-era (GWE) military personnel residing in the Midwest, is an excellent population for such studies. Here we discuss several of the challenges encountered in our ongoing follow-up study. Assessments began 3/99, 480 were completed as of 12/12/00.

Case Validation Study Design

We conducted a population-based telephone survey of GWD (N=1,896) and GWE, (N=1,799) personnel in 1995-96 (*JAMA*, 1997). In an ongoing nested case-validation study, a sample of participants from the earlier survey are being contacted to come to The University of Iowa General Clinical Research Center for an in-person clinical evaluation, entailing an approximately eight-hour assessment. The assessment includes a physician evaluation, which consists of a medical history and a thorough physical exam. The assessment also includes a battery of questionnaires and interviews assessing occupational and exposure history, risk factors, current function and health status (e.g., SF-36 and the HUI-III), psychological functioning, and current symptomatology. All participants undergo the Structured Clinical Interview for DSM-IV disorders (SCID-IV) and subsets of symptomatic subjects (and randomly-selected controls) undergo extensive neuropsychological, neurophysiologic and neuromuscular evaluation. Blood samples are being collected from all participants and stored at -70°C; a subset of symptomatic GW veterans undergo lab tests.

The 1995-96 telephone survey employed a two-stage sampling approach; our case validation study used a similar approach. Initially, approximately 1000 subjects were randomly selected from a pool of the original participants who reside in Iowa or a surrounding state. Sampling was stratified by Gulf War deployed status and to include appropriate numbers of symptomatic and nonsymptomatic participants. Recruitment was initiated and after 10 months we assessed participation by relevant strata to prepare for a second-stage sampling. The number of completed assessments to date were compared with the sampling plan target within strata to reveal the number of additional assessments needed. To estimate the number of subjects to select in the second-stage sample, we adjusted this number based on stratum specific participation rates and the number of potential participants remaining. Since women comprise a small proportion, the decision was made to attempt to recruit all women within the sampling frame.

Case Validation Study Field Methods

During the planning phase, the project team met on a biweekly basis to discuss theoretical, methodological and practical issues, especially study recruitment. This is a multidisciplinary team with expertise in medicine, neurology, psychiatry, psychology, epidemiology, and biostatistics. This group continues to meet regularly to resolve questions, assess study progress, and plan analyses. The expertise the study group has brought to the planning and implementation phases has resulted in a number of innovative solutions to the challenges that have arisen.

Nine subjects were recruited and assessed to pilot and refine the study assessments. The pilot subjects were recruited from a local Army National Guard unit and included those deployed during Operation Desert Shield/Desert Storm, and those not deployed. Telephone survey participants were not eligible to serve as pilot subjects. This “dress rehearsal” was a valuable step in fine-tuning the assessment – a handful of unanticipated problems arose and were resolved. In addition, the pilot subjects provided critique of the assessment, such as useful input on terminology.

Locating Subjects

High participation rates are important in any health study. Loss to follow-up is of particular concern with longitudinal research, and locating and tracking strategies are key. Participants in the 1995-96 telephone survey were the potential sampling frame for the follow-up study. However, we expected a sizeable proportion of a young, employed population would have moved from the region after nearly five years. The sampling frame was thus limited to subjects who currently reside in Iowa or a surrounding state due to the travel time to Iowa City. To date, 93% of our follow-up study participants have been Iowa residents.

The initial contact letter explained the study and included a copy of the IRB-approved informed consent document. “Address Service Requested” was included on envelopes so that an updated address would be returned whenever a forward mail order was in effect. A postage-paid return postcard was included for corrections to their name, address, and telephone number; and to list a convenient time for phone contact to answer questions and schedule an appointment. Subjects were asked to return the postcard, regardless of their participation plans, in order to obtain updated contact information.

A secured relational database is used to maintain and track subject information and recruitment. Subjects were classified in this database according to the response our initial letter generated – an undeliverable letter would lead to a “tracking” categorization, a postcard expressing interest in participating would lead to a “contact: interested in participating” categorization, etc. The database is continually updated based on telephone calls and returned postcards and letters. Recruiting and participation is reviewed in weekly meetings.

Search Process

Nearly half (45%) of the selected subjects had relocated since 1995-96. In these instances the subject was categorized as “tracking – need to locate” and a search algorithm was initiated. This search algorithm consisted of the following steps: contact the person identified in the telephone interview as someone who will always know the subject’s whereabouts, ask for the subject’s current address and telephone number; use web-based directories to search for the subject in their last-known location; use telephone directory assistance to search for the subject in their last-known location; expand search nationwide; use a variety of directories; outsource the search to a credit agency/address search firm.

The contact person identified during the telephone interview (usually parents, siblings or other family members) has been the most consistently successful method for tracking. The utility of obtaining such a contact person, even if no follow-up study is currently planned, cannot be overstated. Web-based search engines are becoming more powerful, but often they fail to produce “hits” (or produce an unmanageable number of hits for common names). Directory assistance is useful if the subject has relocated in the same community, but is often not fruitful for subjects who have moved any distance. Credit agency searches have been useful, but the results are costly and of variable quality and assistance.

Subject location efforts have benefited from an interagency agreement between NIOSH and the Internal Revenue Service. Despite assistance from DoD personnel, there were much longer delays (approximately 11 months) in obtaining permission to obtain this data than we experienced in the original study funded by CDC. Under the terms of this agreement, the IRS provided for us the most recent address in its files for the study cohort. These data have provided new addresses on over 200 subjects that had not been otherwise locatable. It also allowed us to identify potential participants who had returned to the Midwest since 1995-96. In many cases the IRS did not have any address listed for an individual, and most often, the IRS address matched the address in our database. Data on last known address is provided, but a telephone number is not included. Nevertheless, this search has been one of the most valuable tools we have utilized for tracking subjects.

Enhancing Participation

Many subjects have been quite motivated to participate, likely due to the nature of the illness under study and our prior relationships with participants; in fact, at least one subject has refused reimbursement for participating. However, since participation consists of an all-day on-site assessment, and most of our subjects have to drive some distance to participate, we have implemented several provisions to make participation less burdensome and to encourage participation.

First, an easy-to-remember toll-free telephone number was obtained for use when contacting us. We monitor this line throughout normal business hours, and the line has voicemail for off-hour calls. We reimburse for mileage, parking charges, and time (\$100/day). Overnight room and board for subjects and a companion is covered.

Many subjects have expressed an interest in participating but have been unable to do so because of work schedules or other responsibilities during the week. We thus implemented a limited number of Saturday appointments, which have proven extremely popular.

The daylong assessment involves the scheduling and coordination of a number of study personnel and assessments; thus, it is important that scheduled appointments be kept. To facilitate this, when a subject schedules an appointment, a confirmation letter is sent to the subject, complete with maps and directions. We also place a reminder call a few days prior to the appointment. Despite these efforts, no-shows occur with some regularity. When a subject fails to show for an appointment, we immediately contact the subject to determine the reason for the no-show and to reschedule. In some cases the subject is able to come in yet that day for a late start. In other cases a new appointment is scheduled. In still other cases, subjects express concerns or worries that led them to fail to show for their appointment – in these instances an attempt is made to address these concerns and find the soonest possible time to reschedule.

Finally, goodwill toward the study has been nurtured through a respectful attitude toward participants, opportunities for participants to describe their illnesses and experiences in an open-ended interview format, assessments of subject satisfaction, and mailings to participants informing them of the study findings and progress. This also has helped to maintain valid address information. A public advisory committee and a scientific advisory committee were implemented in 1995-96; it is likely that the enhancement of study quality and a voice for concerns these committees provided have resulted in increased participation.

Conclusions

In sum, this project has exhibited all the classic challenges inherent in longitudinal research. Recruitment efforts are ongoing, and in light of the burdens of subject travel and the daylong assessment, to date we have achieved an acceptable participation rate (estimated 63-65%).

VIEW FROM THE UNITED KINGDOM

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There is no UK data on the outcome of gulf related illness. However, the King's College group are commencing a follow up of the original cohort (Unwin et al, 1999), which will provide the first such information. Pilot data suggests that some service personnel who were symptomatic six years after the conflict have now recovered, and that a smaller number have changed from being well to sick. It remains to be seen whether or not these results will be replicated in the larger sample. At the same time opportunity will be taken to follow up the Bosnia control group, who were well in 1998/1999. It is hoped that they will still be well in 2001.

CDC AIR FORCE STUDY: DEVELOPMENT OF A WORKING CASE DEFINITION

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Background

Soon after the cessation of hostilities, anecdotal reports of illnesses among Gulf War veterans and speculation over environmental, biological, and chemical hazards led to concerns about a "Gulf War syndrome." Subsequent studies have documented that Gulf War veterans report numerous chronic nonspecific symptoms, such as fatigue, neurocognitive problems, and musculoskeletal pain, significantly more often than their non-deployed peers.⁽¹⁻³⁾

In December 1994, the U.S. Secretary of Defense, the Secretary of Veterans Affairs, and the Commonwealth of Pennsylvania asked the Centers for Disease Control and Prevention (CDC) to investigate a "mystery illness" reported among Gulf War veterans from an Air National Guard (ANG) unit in Lebanon, Pennsylvania. This illness was reported to be characterized by irritable bowel syndrome, large joint polyarthralgia, pustular dermatitis, splenomegaly, nasal ulcers, ear infections, bleeding gums, and alopecia.

CDC conducted a three stage investigation.^(4,5) Stage 1 consisted of an evaluation of a sample of the reported cases in order to verify and characterize the illness. Stage 2 involved a survey of the index unit and three comparison units to determine if there was a cluster of illness in the index unit, to determine if deployment to the Gulf War was a risk factor, and to develop a working case definition. Stage 3 consisted of an evaluation of Gulf War veterans from the index unit in order to characterize clinical features of the illness defined in Stage 2 and to identify risk factors.

This presentation focuses on Stage 2 and the development of a working case definition.

Methods

From January through March 1995, a cross-section survey was administered to members of the index unit and three additional control units. The three control units included another ANG unit in Pennsylvania, a US Air Force Reserve unit in Florida, and an active-duty Air Force unit in Florida. The questionnaire was administered anonymously in small groups and inquired about demographic and military characteristics, 35 symptoms, health status, and potential risk factors. All members of the unit who were on base at the time of the survey were eligible to participate. Thus, both deployed and non-deployed and ill and non-ill personnel were included. In all 3,927 military personnel completed the questionnaire. Of these 1,164 had deployed to the Persian Gulf during the Gulf War and 2,763 were not deployed. Response rates per unit ranged from a low of 35% to a high of 73%.

Two approaches were considered for developing a working case definition, a clinical and a statistical approach. In addition, within the statistical approach, two different strategies were compared, one based on factor scores and one based on symptom categories. The clinical approach involved identifying case defining symptoms based on the following decision variables: the symptom had to be reported as chronic (present for 6 months or long), it had to be reported by at least 25% of the Gulf War veterans, and it had to be reported at least 2.5 times more frequently by Gulf War veterans than by non-deployed personnel. The statistical approach involved using factor analysis to identify symptom clustering. The sample was randomly divided into two subsamples of 1,631 and 1,624 subjects. The first sample was used for exploratory principal components analysis and the second sample was used for confirmatory factor analysis. All 35 symptoms were used in the exploratory principal components analysis. We used promax rotation, retaining factors with an eigenvalue >1. Symptoms with factor loadings greater than 0.40 were kept for the confirmatory factor analysis.

Results

As has been found in other studies, Gulf War veterans reported all symptoms, except hay fever and other allergies, significantly more often than non-deployed subjects. The five most frequently reported symptoms were sinus congestion (reported by 52% of Gulf War veterans and 39% of non-deployed personnel), headaches (50% and 41%), fatigue (43% and 17%), joint pain (36% and 13%), and difficulty remembering or concentrating (34% and 9%).

The clinical approach identified six case defining symptoms: fatigue, difficulty remembering or concentrating, moodiness, difficulty sleeping, joint pain, and joint stiffness.

The exploratory factor analysis yielded 10 components. The first (feeling depressed, feeling anxious, feeling moody, difficulty remembering or concentrating, trouble finding words, difficulty sleeping, and fatigue) accounted for 16.8% of the variance. The second component (joint stiffness, joint pain, and muscle pain) accounted for 11.9% of the variance. The third component (wheezing shortness of breath, coughing, and chest pain) accounted for 10.4% of the variance. The remaining components each contributed less than 10% of the total variance.

Only symptoms from the first three principal analysis components were used in the confirmatory factor analysis. Confirmatory factor analysis identified two factors: mood-cognition-fatigue (feeling depressed, feeling anxious, feeling moody, difficulty remembering or concentrating, trouble finding words, difficulty sleeping, and fatigue) and musculoskeletal (joint stiffness, joint pain, and muscle pain). The 10 symptoms identified by the confirmatory factor analysis included all six symptoms identified by the clinical approach.

Using the symptoms identified by the factor analysis, we derived two possible working case definition. In the first definition, the confirmatory phase factor analysis model was fit to the participants' symptom data and a total factor score was calculated for each participant by adding the scores of the factors. A case was defined as having a combined factor score in the top 25th percentile. In the second definition, we grouped the symptoms into three categories: fatigue, mood-cognition, and musculoskeletal. We separated chronic fatigue even though it did not load as a separate factor because of the central role of fatigue in previous studies of Gulf War veterans.

Forty-seven percent of Gulf War veterans and 15% of non-deployed personnel were classified as cases by the factor score definition. Forty-five percent of Gulf War veterans and 15% of non-deployed personnel were classified as cases based on the symptom category definition. There was substantial overall agreement between the working case definitions (k statistic = 0.79).

As both case definitions were comparable, we chose the symptom category approach as it would be easier to apply in a clinical setting. Thus, we defined a case as having one or more chronic symptoms (present for 6 months or longer) from at least 2 of the following categories: fatigue; mood and cognition (symptoms of feeling depressed, difficulty remembering or concentrating, feeling moody, feeling anxious, trouble finding words, or difficulty sleeping); and musculoskeletal (symptoms of joint pain, joint stiffness, or muscle pain). We sub-classified a case as severe if each case-defining symptoms was rated as severe; otherwise, we considered the case to be mild-to-moderate.

In all, 3,675 subjects provided complete data on the 10 case defining symptoms. Among the 1,155 Gulf War veterans, 6% were classified as severe cases and 39% as mild-to-moderate cases compared with 0.7% and 14%, respectively, among the 2,520 non-deployed personnel. Deployment to the Gulf War was the most important risk factor for illness. Multivariate analyses showed that illness was associated with Gulf War service, enlisted rank, female sex, and smoking. Illness was not associated with the number of deployments, the month or season of deployment, duration of deployment, location in the Persian Gulf, military occupational speciality, or direct participation in combat. Results from the Stage 3 evaluation of Gulf War cases and controls from the index unit found that illness was associated with a significant decrease in functioning and well being. However, the illness was not associated with any physical examination or laboratory abnormalities and was not associated with known infectious agents.

Conclusions

The results from this study clearly document that Gulf War veterans are more likely than non-deployed personnel to report a chronic multi-symptom illness that is associated with a significant decrease in functioning and well being. However this illness is not unique to Gulf War veterans. Questions remain regarding how this multi-symptom illness may or may not differ from other symptom based conditions.

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CRITERIA FOR A VALID CASE DEFINITION

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Why do we need a case definition?

The first step in the investigation of a new epidemic disease is to develop a case definition. And if you can't, then develop a case definition. Failure to do so means that you will not solve the epidemic problem; you have given up before you began. In the investigation of Gulf War syndrome, many years and tens of millions of dollars have been wasted by failing to pose one or more provisional case definitions to test in epidemiologic and clinical research studies.

Comparing large, potentially exposed and non-exposed populations is not useful without a case definition. This is because the small segment with the illness is obscured in the population mean, and differences in the prevalence of individual symptoms between exposed and non-exposed populations may suggest that a new disease is present but does not help to define it. Likewise, if medical examinations of sick volunteers by clinical doctors do not solve the problem after the first 50-100 patients, examinations on tens of thousands more, without control groups and epidemiologic or clinical research designs, are not likely to help. As long as research is confined to these global approaches without a case definition, history shows that no progress will occur.

What form should a case definition take?

Ideally a case definition is a simple sentence listing several clinical characteristics required to designate a case and differentiate individuals with the condition from those with similar illnesses and from well populations. When a simple list has not proved sufficient, however, case definitions taking more complex forms have proved useful, for example, dichotomized weighted scales of major and minor criteria developed from discriminant analysis, or a dichotomized factor scale developed from exploratory factor analysis.

How should a case definition be derived?

General approach. In most epidemic investigations, case definitions were derived by clinical intuition of one or two medical epidemiologists after examining, or reviewing the medical records of, a few typical cases (e.g., Legionnaire's disease, toxic shock syndrome). They proved so obvious, that they were widely accepted from the first. Where case definitions were not so obvious, provisional case definitions for research have been developed by consensus of experts with experience examining and studying patients (e.g., rheumatoid arthritis, amyotrophic lateral sclerosis, chronic fatigue syndrome). Provisional case definitions have also been derived by exploratory factor analysis of clinical data in moderate-sized samples of subjects with the illness. Ultimately, however, the objective is to move beyond consensus-based and factor-derived case definitions to simple, objectively defined ones.

What clinical characteristics do you measure? Ideally, a case definition is composed of objective clinical signs and laboratory markers, but when they are not available for a new disease, symptoms may have to suffice. In the debate over Gulf War syndrome, the idea of symptom-based definitions has been denigrated by the charge of "only self-reported symptoms." All symptoms, however, are by definition self-reported, and many recognized diseases are usefully defined mainly by symptoms (e.g., schizophrenia, depression, somatoform disorder). The fact that symptoms are self-reported does not diminish their usefulness for case definitions. The clinical building blocks (e.g., symptoms, signs, laboratory tests) used in a case definition must be typical of the disease, and at least their combination must be unique to the disease. In most epidemic investigations this is ensured by the medical epidemiologists examining a small number of typical cases (N=5-50) and enumerating the characteristics that distinguish the new disease from other, possibly similar, conditions.

When dealing with a controversial, difficult-to-define illness, some investigators have adopted blocks of questions from questionnaires previously validated for detecting other, apparently similar diseases. This is tempting because of the expectation that others will generalize the validation imprimatur of the original validated instruments to the measurements of the new disease under investigation. If symptoms are taken from questionnaires developed to measure diseases which occur commonly in every population (e.g., depression, mild aches and pains), however, it is likely that the case definition will detect those rather than the new disease of interest.

A major problem in developing a case definition for controversial, difficult-to-define illnesses is the *ambiguity of symptom measures*. If the words commonly used to describe a symptom unique to a new disease are the same words used by people with a different symptom that is common in people without the disease, failure to differentiate the two symptoms will defeat efforts to develop a case definition that differentiates the new disease. This is the case with some of the main symptoms of Gulf War syndrome. For example, •chronic fatigue• may mean excessive daytime sleepiness, premature muscle weakness after exertion, general weakness or shakiness or lack of motivation. •Tingling• and •numbness• have different pathophysiologic implications depending on their anatomic distribution. •Joint pains• may mean arthritis, arthralgias, periarticular inflammation, myalgias, neuritis, abnormalities in sensing pain (central pain), or simply the aches and pains of everyday life. Consequently, the wording of questions in symptom questionnaires must distinguish the various meanings of symptoms if the case definition is to discriminate the disease effectively.

How do you translate factor scales into a simple case definition? Exploratory factor analysis yields a continuous factor scale for each potential syndrome identified. A simple case definition can be extracted either by arbitrarily dichotomizing the continuous factor scales, or by identifying a small, discreet number of symptoms that are demonstrated analytically to explain much of the predictive information in the factor scales. One important study of Gulf War veterans, however, performed an exploratory factor analysis and then arbitrarily selected some symptoms that loaded strongly on the factors and others that did not, and proposed a combination of them as a case definition. It is not surprising that the resulting case definition did not very precisely discriminate the new disease from functional complaints of a normal population.

How do you know whether a proposed case definition is a good one?

In most new disease investigations, the case definitions were clinically obvious (had compelling face validity), and widespread acceptance occurred without formal validation. Where validity is not obvious, as for example when a case definition has been developed by consensus of a committee or by factor analysis, the following steps, listed in order of increasing strength, determine its validity.

1. *Does the case definition identify a substantially higher rate of cases in an exposed population than in a presumed non-exposed population?* In an epidemic situation with an abrupt rise in a new illness, it has not been common to compare incidence rates in the epidemic population with rates in a remote uninvolved population. Generally this would be considered superfluous. In a controversial, difficult-to-define illness, however, such a comparison may be necessary to satisfy skeptics. If done, it should only take place late in the investigation after the case definition has been thoroughly worked out. If done sooner, the use of a non-discriminatory case definition might obscure the difference.
2. *Is the case definition replicable in different samples of the affected population?* Early in development of a case definition by exploratory factor analysis, the factor model should be tested in an independent sample to ensure that the factor structure replicates (is not just capitalization on chance in the developmental sample). Replication in large random samples would be powerful where feasible and affordable, but factor analytic models are satisfactorily replicated in convenient samples of sufficient size ($N \geq 250$). Replication of factor analytic models is done by *confirmatory factor analysis with structural equation modeling*, using goodness of fit measures that are sensitive to lack of fit, but not by repeating the exploratory factor analysis.
3. *Does the case definition predict a pathologic or pathophysiologic abnormality that can be confirmed by objective tests?* Before a case definition can be accepted as a disease definition, it must prove to predict objective abnormalities, of tissue damage or dysfunction. This is generally demonstrated by performing tests on small numbers ($N=20$ or so) of cases and controls that confirm tissue damage or dysfunction in organs hypothesized to be the origin of the symptoms. Finding such an association substantiates the case definition as a predictor of disease. If the tests show no association, the provisional case definition is shown to be useless, and a new case definition should be sought.
4. *Does the case definition identify risk factors that point to causal mechanisms that can be demonstrated in laboratory experiments in animals, microbiological systems, genetic models, etc.?* The case definition is traditionally analyzed against responses from cases and controls on a questionnaire of self-reported risk factors for environmental exposures occurring before the onset of illness. Although self-reported risk factors have recently been denigrated, they have been the mainstay of successful epidemic investigations for decades even though objectively measured risk factors are often unavailable. In addition to high relative risks (>3 is suggestive and >5 is strong), dose-response effects, and synergistic effects, demonstrating the biological

plausibility of the identified risk factors in laboratory experiments has generally been accepted as confirmation of a causal link. In ongoing epidemics, cessation of new cases after removal of the risk factor is further convincing evidence.

5. *Does the case definition identify a group with a relatively homogeneous illness pattern who generally respond to a specific treatment?* The ability to identify cases that respond to a treatment is the ultimate goal of a case definition, but this is a late development in disease definition.
6. *Can each of these steps be replicated by others using the same approach?* Replication is the ultimate proof of the usefulness of a case definition. For a controversial, difficult-to-define illnesses, however, replication studies must be examined as closely as the original studies. A replication study employing different methods from the original may replicate it successfully, and that is a powerful validation. But for a study to conclude a lack of replication, it must have used the same methods as the original study or demonstrate how methodologic variations did not account for the failure to replicate.

In what kind of sample should a case definition be developed and validated?

Size. In general, investigations that have been successful in defining new epidemic diseases, their causes and pathophysiology have been small, generally fewer than 200 subjects. Most commonly epidemic investigations have initially studied 15-50 cases meeting the case definition and 50-200 controls, often follow by laboratory testing in subsamples of approximately 20 and 20 controls.

Neither national surveys in large population random samples (N=thousands) nor computerized analyses of an entire population (N=hundreds of thousands) have ever proved useful in initially investigating a new disease, although once the nature, causes and pathophysiology are worked out in small studies, large surveys may be very useful in replicating the initial findings or for estimating the magnitude of the problem. The problems that prevent large surveys and computer analyses of administrative databases from being useful include 1) the difficulty of designing formal surveys before the disease is understood, 2) the laboratory tests necessary to demonstrate the disease are too expensive to apply on large samples, 3) it is usually not possible to construct a case definition in an administrative database, and 4) administrative databases may not include important the right subjects.

Selection. Small case-control studies must contain subjects with typical illness, selected by the study investigators. Generally selection bias is not an issue in a case-control study as long as the cases are reasonably typical and the controls are well matched by demographic characteristics. Problems have arisen in Gulf War syndrome research, however, when samples were confined to soldiers remaining on active duty years after the Gulf War after the real sick veterans had left the service. In such cases, all, or most, with typical illness were excluded, leaving only only the mildest cases or functional illness.

Conclusion

The proven method of investigating epidemics, involving a case definition, should be more widely used in studying the epidemic in Gulf War veterans. Different case definitions should be tried.