

**The Health Impact of Chemical Exposures During the Gulf War: A
Research Planning Conference**

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Acknowledgments

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Definition of Abbreviations

CARC	Chemical agent resistant coating
CDC	Centers for Disease Control and Prevention
CFS	Chronic fatigue syndrome
DoD	U.S. Department of Defense
DSM-IV	Diagnostic and Statistical Manual, version IV
FM	Fibromyalgia
HHS	U.S. Department of Health and Human Services
ICD-9	International Classification of Diseases, version 9
IOM	Institute of Medicine
MCS	Multiple chemical sensitivities
PRD	Presidential Review Directive
PPE	Personal protective equipment
PTSD	Post-traumatic stress disorder
QSAR	Quantitative structure-activity relationship
RADS	Reactive airways dysfunction syndrom
RWG	Research Working Group of the Persian Gulf Veterans Coordinating Board
SEER	Surveillance, Epidemiology and End Results
VA	U.S. Department of Veterans Affairs

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Executive Summary

On February 28 through March 2, 1999, the Centers for Disease Control and Prevention (CDC) and other agencies of the Department of Health and Human Services (HHS) brought together scientists, clinicians, veterans, veterans' service organizations, Congressional staff, and other interested parties to discuss and make recommendations regarding the direction of future research on undiagnosed illnesses among Gulf War veterans and their links with multiple chemical and environmental exposures. The format for the conference included plenary sessions, concurrent workgroups, and a veterans' forum. The plenary sessions were meant to provide background information and to stimulate dialog on research questions. The plenary sessions included an overview of research findings regarding the health impact of the Gulf War, a panel discussion of the experience of Gulf War veterans, a series of presentations on the possible health outcomes of low-level chemical exposures focusing on nervous system, immune system, and pulmonary system outcomes, a series of panel discussions on research and clinical findings regarding multiple chemical sensitivity among Gulf War veterans and civilian populations, a series of presentations on possible mechanisms of action of chemical exposures, and a panel discussion on methodological considerations in studying the health impact of chemical exposures during the Gulf War.

The concurrent workgroups were asked to develop research recommendations in four areas: pathophysiology, etiology, and mechanisms of action; assessment and diagnosis of illnesses; treatment; and prevention of illnesses in future deployments. Each workgroup was asked to develop research recommendations that addressed specific issues. For the pathophysiology workgroup, these issues included synergistic and subclinical effects of chemicals, genetic susceptibility, biomarkers of susceptibility and exposure, and appropriate study methods. The assessment and diagnosis workgroup was asked to focus on case definition, overlap of conditions, the role of chronic multi-system conditions, biomarkers of illness, optimal methods for assessment and diagnosis, and validation of assessment approaches. The treatment workgroup was asked to focus on appropriate treatment paradigms, rehabilitation approaches, health care opportunities, education of physicians, and appropriate study methods. The prevention workgroup was asked to focus on health education and risk communication, approaches to environmental assessment, biomonitoring, and health preparedness. The workgroups were free to use whatever approach they found useful for developing research recommendations. In some cases there was considerable disagreement among workgroup members on the direction of the recommendations. Thus, the final recommendations of the workgroups were not necessarily endorsed by all workgroup members.

This report summarizes the outcome of each of the four workgroup sessions. Chapters 2 - 5 present the recommendations as developed by the workgroups. Although the workgroups were asked to focus on research recommendations, some recommendations reflect clinical care, administrative, or policy issues. No attempt was made to filter non-research recommendations

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from this report. Chapter 6 provides a discussion of the workgroup deliberations and attempts to place the recommendations in the context of current Gulf War research activities.

The recommendations developed at this conference represent the deliberations of the workgroup participants and do not necessarily imply endorsement by the veteran or scientific community as a whole or by the federal government. While some of the recommendations could be implemented in the short-term, many of the recommendations reflect long-term goals requiring significant restructuring of current systems and are unlikely to be easily implemented, especially in the time frame requested by Gulf War veterans. Some of the recommendations may not be feasible, given current federal regulations. Other recommendations reflect initiatives that have already been instituted by federal agencies responsible for the care of veterans.

Pathophysiology Workgroup Recommendations

The pathophysiology workgroup made recommendations for a variety of human and animal studies. Recommendations for human studies include analysis of various deployment cohorts and other coalition partners, studies of chemical exposures in non-Gulf War settings (such as examination of the health effects of destruction of chemical warfare agents and pesticide exposures), susceptibility studies, and examination of chemically sensitive patients. Recommended animal research includes studies of synergistic, sub-clinical, low-level, and multi-generational exposures; studies to develop animal models for chemical sensitivity and other conditions; studies examining patterns of gene expression and delayed expression of effects of environmental exposures; and studies of sex differences in effects of chemical exposures. The pathophysiology workgroup also made recommendations regarding use of new methodologies and special needs. These include recommendations regarding biomarker research, new analytic technologies, use of environmental control units, establishment of a Gulf War research library, and need for research oversight.

Pathophysiology Workgroup Recommendations
I. Human Studies
1. Analysis of deployment cohorts
2. Analysis of exposed Gulf War veteran populations from other countries
3. Studies of potential health effects of destruction of chemical warfare agents in the U.S.
4. Studies of potential health effects of pesticide exposures
5. Susceptibility studies
6. Studies of chemical sensitivity

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II. Animal Studies
1. Studies of synergistic effects of exposures
2. Studies of subclinical effects of exposures
3. Studies of low-level, chronic exposures
4. Studies of multi-generational exposures
5. Studies to develop animal models for chemical sensitivity and other conditions
6. Studies to examine patterns of gene expression
7. Studies to evaluate delayed expression of effects of environmental insults
8. Studies of sex differences in effects of chemical exposures
III. New Methodologies
1. Quantitative Structure-activity Relationship (QSAR) modeling
2. Development of biomarkers of exposure, susceptibility, and effect
3. Use of anti-sense DNA technologies
4. Use of multifactorial statistical models
5. Use of transgenics and knockouts for studies of genetic susceptibility
6. Use of alternatives to animal systems
7. Use of imaging techniques
IV. Special Needs
1. Centralized Gulf War research library and data repository
2. Controlled-environmental medical unit
V. Establishment of a research oversight mechanism

Assessment and Diagnosis Workgroup Recommendations

The assessment and diagnosis workgroup developed research recommendations covering a wide range of issues including case definition, study of chronic multi-system conditions among Gulf War veterans (such as chronic fatigue syndrome, multiple chemical sensitivity, and fibromyalgia), and studies to examine the overlap of these conditions. The workgroup also made recommendations regarding optimal methods for assessment and diagnosis, and validation of assessment approaches.

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Assessment and Diagnosis Workgroup Recommendations
I. Case Definition
1. Establish methods for comparing case definitions for chronic multi-system conditions
2. Specify diagnostic criteria used in research studies
3. Subtyping of Gulf War related illnesses should be based on available data
II. Chronic Multi-System Disorders
1. Conduct research on the prevalence and overlap of chronic multi-system disorders
2. Conduct studies to assess multi-system disorders among Gulf War veterans
3. Use novel techniques to study chronic multi-system disorders
4. Examine barriers to diagnosis of chronic multi-system disorders
III. Well-Defined Disorders
1. Use well-established diagnostic coding systems
2. Document coexisting conditions
IV. Overlap of Conditions
1. Define exclusionary diagnostic criteria
2. Specify methods for assessing overlap in symptoms and diagnoses
3. Examine the role of treatment seeking
4. Examine the role of pre-existing disorders
5. Examine the role of gender status
V. Biomarkers
1. Develop biomarkers for past exposures
2. Use existing biomarkers on combinations of chronic multi-system disorders
VI. Assessment and Diagnosis
1. Assessment techniques should reflect specific hypotheses
2. Conduct behavioral or physiological challenge studies
3. Develop new laboratory tests of chemical effects
4. Use combinations of assessment and diagnostic techniques

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5. Use a comprehensive assessment approach
6. Consider using non-routine assessment approaches
7. Use assessment instruments that have established normative and validity data
8. Conduct research to assess longitudinal health changes in normal populations
9. Conduct studies that include careful assessment of confounders and effect modifiers
10. Conduct protocol driven autopsy studies following the death of a Gulf War veteran
VII. Conduct validation studies
VIII. Declassify and disseminate all relevant scientific field investigations and clinical studies

Treatment Workgroup Recommendations

The recommendations of the treatment workgroup emphasized the need for increasing current treatment options for Gulf War veterans, using research methods to assess treatment efficacy, and assessing veteran satisfaction with treatment. Recommendations were also made regarding the development of therapeutic options by controlled clinical trials, with evidence-based trials having the highest priority. In addition, the development of new strategies for physician education and the assessment of the effectiveness of the education were emphasized. The treatment workgroup made specific recommendations in four areas: pharmacologic therapy, non-pharmacologic approaches, treatment regimens based on chemical intolerance, and “macro” issues, such as the patient-physician relationship, the interrelation of the individual to the organization, veterans’ satisfaction with care, and education of physicians.

Treatment Workgroup Recommendations
I. Pharmacologic Therapy
1. Examine the efficacy of pharmacologic therapy to treat specific symptoms
2. Conduct studies to examine the role of neurally-mediated cardiovascular changes
3. Conduct trials to examine the role of sub-clinical hypothyroidism and hypoadrenalism.
4. Examine the benefits of nutritional supplements
II. Non-pharmacologic Therapies
1. Conduct pre-care needs assessment
2. Develop pre-care guidance on self-care strategies

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3. Use a primary care and collaborative primary care approach to treatment
4. Provide intensive specialized care for chronic symptoms of unclear etiology
5. Evaluate novel, new, or promising non-pharmacological treatment modalities
6. Develop a coordinated quality improvement program
III. Treatment Regimens Based on Chemical Intolerance
1. Conduct treatment trial to examine efficacy of detoxification approaches
2. Examine efficacy of a physician-directed, home-based chemical intolerance assessment and avoidance approach
3. Examine efficacy of a chemical detoxification, trial and error testing, and avoidance approach
4. Conduct a double-blinded placebo-controlled trial of drug elimination
5. If indicated by above studies, construct environmental control unit to diagnose and treat Gulf War veterans who have chemical intolerances
IV. Macro Treatment Issues
1. Establish a Logistics and Communication Network Center
2. Conduct focus groups to assess Gulf War veterans' health care needs and health care provider concerns
3. Develop protocols focusing on communication and education issues
4. Develop mechanisms to update primary care practitioners
5. Monitor the availability of effective treatments for compassionate use
6. Develop mechanisms to monitor quality of care
7. Create a virtual library of high quality patient information
8. Develop methods to increase patients' access to their medical records
9. Conduct research to enhance treatment of multi-system diseases in primary care

Prevention Workgroup Recommendations

The prevention workgroup focused on developing recommendations to reduce or eliminate health effects associated with future deployments. The workgroup relied on the occupational and public health concept of "hierarchy of control strategies." This concept emphasizes the importance of

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developing an ordered hierarchy of prevention and intervention strategies. Specific recommendations were made regarding interventions to reduce or eliminate environmental hazards, including use of engineering controls, examination of work practices, and modification of personal protective equipment. Recommendations were also made for improving health education and risk communication efforts, and for surveillance and biomonitoring initiatives.

Prevention Workgroup Recommendations
I. Substitution Approaches
1. Identify less toxic substances and their interactive effects
2. Restrict the need for use of multiple pesticides
3. Optimize vaccine potency, formulation, dose, and duration
II. Engineering Controls
1. Evaluate the current design and operation of equipment and material to reduce hazards
2. Design containment for transport of contaminated material
III. Administrative Controls - Health Education
1. Identify and segment key audiences
2. Determine appropriate instructional strategies
3. Identify barriers to understanding the importance and impact of health education messages on readiness
IV. Administrative Controls - Risk Communication
1. Develop and test message content and channels
2. Identify multiple audiences and information sources
3. Assess effective communication of scientific uncertainty and technical information
4. Assess comprehension, utility, and value of risk information
5. Identify methods to communicate comparative risk issues
V. Administrative Controls - Environmental Surveillance
1. Develop enhanced instrumentation for nuclear, biological, chemical, and environmental exposure assessment
2. Establish exposure limits that take into account multiple operating environments
3. Characterize the environment of deployment

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VI. Administrative Controls - Medical Surveillance
1. Develop a data gathering tool that spans the life of the service member
2. Validate self-reported environmental exposures
3. Develop an effective prospective surveillance system for multiple endpoints
4. Develop methods for surveillance of low level exposures
5. Develop methods for archiving biological specimens
VII. Work Practices
1. Evaluate existing health hazard protocols
2. Explore the impact of varied work organization structures on negative health outcomes
3. Develop mechanisms to insure implementation of management controls
VIII. Personal Protective Equipment (PPE)
1. Design protective clothing that is durable, viable, and ergonomically flexible
2. Develop and validate data/standards for PPE compliance

Summary

HHS convened this conference in order to further the dialogue between government officials, scientists, and veterans on issues of upmost concern to the veterans of the Gulf War. Despite considerable government and non-government sponsored research to address the health impact of the Gulf War, we have yet to find the scientific basis for these veterans' unexplained illnesses. This conference highlighted the importance of including veterans in the process of planning and implementing research. Veterans and scientists alike expressed that they found the process useful and that future similar efforts should be encouraged.

The recommendations developed at this conference represent the deliberations of the workgroup participants and do not necessarily imply endorsement by the veteran or scientific community as a whole or by the federal government. The purpose of this report is to document the conference workgroup deliberations and to form the basis for further discussions regarding the direction of research into illnesses among Gulf War veterans.

It is anticipated that this report will be of interest to a broad range of individuals and organizations and may encourage new research collaborations and exchanges. HHS has coordinated its Gulf War related research activities with those of the two principally responsible agencies, the

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Department of Defense and the Department of Veterans Affairs through the Research Working Group (RWG) of the Persian Gulf Veterans Coordinating Board. It is through the RWG that the federal research agenda is developed and coordinated. Recommendations for new research will need to be considered in light of the existing research portfolio of the RWG.

Chapter 1

Introduction

Since the end of hostilities, portions of the U.S. armed forces deployed to the theater of operations during Operations Desert Shield and Desert Storm have reported illnesses, some of which do not fall under the classic definitions of known diseases. The illnesses encountered by these individuals present with a variety of symptoms including fatigue, cognitive dysfunction, skin rash, sleep disturbances, musculoskeletal problems, diarrhea, and depression. For many Gulf War veterans, these symptoms have presented without objective signs of disease or laboratory findings.

The cause of the illnesses seen in Gulf War veterans has been the subject of much speculation, debate, and research since the end of Operation Desert Storm. Many groups have been brought together to shed light on the possible causes of these illnesses. These groups include committees and workgroups from the Defense Science Board, the National Institutes of Health, the Presidential Advisory Committee on Gulf War Veterans' Illnesses, and the Institute of Medicine. Many of the comments and recommendations from these groups have focused on the environmental and chemical exposures that occurred during the war and how these exposures may have contributed to the illnesses seen in veterans today.

Despite these review and research efforts, many questions regarding the nature of exposures encountered during the Gulf War remain. The etiologies of the illnesses facing these veterans are also still unknown. The relationship between these illnesses and other conditions, such as chronic fatigue syndrome and multiple chemical sensitivity, is not completely understood. Researchers and clinicians need ways to properly classify illnesses among Gulf War veterans. There is also need to investigate the synergistic effects of multiple chemical and environmental exposures and to identify the possible mechanisms leading from exposure to health outcomes.

From February 28 through March 2, 1999, the Centers for Disease Control and Prevention (CDC) and other agencies of the Department of Health and Human Services (HHS) brought together scientists, clinicians, veterans, veterans' service organizations, Congressional staff, and other interested parties to discuss and make recommendations regarding the direction of future research on undiagnosed illnesses among Gulf War veterans and the possible links between these illnesses and multiple chemical and environmental exposures. At this meeting, *The Health Impact of Chemical Exposures During the Gulf War: A Research Planning Conference*, participants worked together to address research needs in the areas of pathophysiology, assessment and diagnosis of illnesses, treatment, and prevention of illness in future deployments. Appendix A contains a list of all registered conference participants.

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This meeting was held in response to a Congressional request that HHS examine the role of chemical exposures in the illnesses being reported by Gulf War veterans (1). Specifically, Congress believed it would be useful to support research in the areas of multiple chemical sensitivity, the definition of individual genetic differences in the ability to metabolize environmental agents commonly encountered during the Gulf War, and the development of a better understanding of how multiple exposures of chemicals interact to exert their toxicity (2). In addition, Congress emphasized the need for treatment trials that use treatment approaches being developed in the public and private sectors for illnesses resulting from chemical and other environmental exposures.

An Executive Planning Committee, composed of representatives from CDC, HHS's Office of Public Health and Science, the National Institutes of Health, and the Agency for Toxic Substances and Disease Registry, was formed to oversee planning for the conference. Members of the Executive Planning Committee are listed in Appendix B. The Executive Planning Committee emphasized the importance of obtaining broad public input both during the planning process and during the actual conference. As part of this public outreach, on July 21, 1998, a public meeting was held to obtain individual input from veterans, advocates, and scientists regarding the format and agenda for the conference. More than forty individuals were brought together and asked to provide their opinion on the types of topics that should be discussed at the conference and to give their recommendations regarding potential speakers and conference participants. Participants in the public planning meeting are listed in Appendix C.

One recommendation made during the July planning meeting was that it would be useful to circulate, before the conference, a background document which would provide an overview of the research literature relating to Gulf War health issues. This background document was produced by an independent contractor, Syracuse Research Corporation, and provides an excellent resource on Gulf War health issues (3). It includes an overview of the exposures and health outcomes of concern to Gulf War veterans and reviews the research effort that has examined these health problems. This background document was distributed in advance of the conference to all persons who preregistered. Two additional documents were also distributed. These included a special issue of the journal *Environmental Health Perspectives* containing papers presented at the Workshop on Experimental Approaches to Chemical Sensitivity held September 20-22, 1995 in Princeton, New Jersey (4), and the Annual Report to Congress on Federally-sponsored Research on Gulf War Veterans' Illnesses for 1997 prepared by the Research Working Group (RWG) of the Persian Gulf Veterans Coordinating Board (5). The background document can be accessed on the Internet at <http://www.cdc.gov/nceh/meetings/1999/gulfwar/>. The current RWG's Annual Report to Congress can be accessed at <http://www.va.gov/resdev/pgulf98/gwrpt98.htm>.

Using feedback received during the July planning meeting, the Executive Planning Committee developed a format for the conference that included plenary sessions, concurrent workgroups, and

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a veterans' forum. The conference agenda is provided in Appendix D. The plenary sessions were meant to provide background information and to stimulate dialog on research questions. The plenary sessions included an overview of research findings regarding the health impact of the Gulf War, a panel discussion of the experience of Gulf War veterans, a series of presentations on the possible health outcomes of low-level chemical exposures focusing on nervous system, immune system, and pulmonary system outcomes, a series of panel discussions on research and clinical findings regarding multiple chemical sensitivity among Gulf War veterans and civilian populations, a series of presentations on possible mechanisms of action of chemical exposures, and a panel discussion on methodological considerations in studying the health impact of chemical exposures during the Gulf War.

The concurrent workgroups were asked to develop research recommendations in four areas: pathophysiology, etiology, and mechanisms of action, chaired by Dr. Barry Wilson of the University of California at Davis; assessment and diagnosis, chaired by Dr. Roberta White of the Boston Veterans Affairs Medical Center; treatment, chaired by Dr. Benjamin Natelson of the New Jersey Medical School and the East Orange Veterans Affairs Medical Center; and prevention, chaired by Dr. Melissa McDiarmid, of the University of Maryland and the Baltimore Veterans Affairs Medical Center. Additional workgroup members were selected to bring a variety of experience and expertise to the process of developing research recommendations and included scientists and non-scientists, government and non-government representatives, and U.S. and international researchers. Workgroup members are listed in Appendix E.

In developing the agenda, the Executive Planning Committee made a concerted effort to structure the meeting to allow for maximum public input and for interaction between veterans and scientists. An evening session, the veterans' forum, was held to provide an opportunity for veterans to discuss their concerns with the workgroup chairs. Veterans used this opportunity to present their individual health concerns and experiences in seeking treatment and their suggestions regarding research priorities and alternative treatment approaches. The workgroups were also structured to ensure audience participation. Each workgroup met four times. The first session focused on workgroup member presentations, while the second session was devoted to audience input. Research recommendations were developed during the third and fourth workgroup sessions. To foster the exchange of information outside of the plenary and workgroup sessions, conference planners set aside space in a central location for audience members to distribute information.

Each workgroup was asked to develop research recommendations that addressed specific issues. For the pathophysiology workgroup, these issues included synergistic and subclinical effects of chemicals, genetic susceptibility, biomarkers of susceptibility and exposure, and appropriate study methods. The assessment and diagnosis workgroup was asked to focus on case definition, overlap of conditions, the role of chronic, multi-system conditions, biomarkers of illness, optimal methods for assessment and diagnosis, and validation of assessment approaches. The treatment

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workgroup was asked to focus on appropriate treatment paradigms, rehabilitation approaches, health care opportunities, education of physicians, and appropriate study methods. The prevention workgroup was asked to focus on health education and risk communication, and to examine approaches to environmental assessment, biomonitoring, and health preparedness. The workgroups were free to use whatever approach they found useful for developing research recommendations. In some cases there was considerable disagreement among workgroup members on the direction of the recommendations. Thus, the final recommendations of the workgroups were not necessarily endorsed by all workgroup members.

This report summarizes the outcome of each of the four workgroup sessions. To develop this report, the Executive Planning Committee reviewed the transcripts of the conference. The transcripts from the conference are available on the Internet at <http://www.cdc.gov/nceh/meetings/1999/gulfwar/>. Chapters 2 - 5 present the specific research recommendations developed by each workgroup. The research recommendations included in these chapters represent the deliberations of the workgroup participants and do not necessarily imply endorsement by CDC or any other federal agency or endorsement by the veteran or scientific community as a whole. Although the workgroups were asked to focus on research recommendations, some recommendations reflect clinical care, administrative, or policy issues. No attempt was made to filter non-research recommendations from this report. Chapter 6 provides a discussion of the workgroup deliberations and attempts to place the research recommendations in the context of current Gulf War research activities. A summary of the workgroup members' presentations and a description of the highlights of audience input during the workgroup sessions are presented in Appendix F.

Chapter 2

Workgroup 1: Pathophysiology, Etiology, and Mechanisms of Action

Background:

The workgroup that convened to examine pathophysiology, etiology, and mechanisms of action as related to Gulf War veterans' health concerns established several objectives governing its recommendations for research. Research in this area should be focused on identifying the events or environmental agents precipitating Gulf War illnesses, identifying the biochemical and physiological bases of Gulf War veterans' symptoms, identifying the mechanisms leading from exposure to symptoms, and establishing the scientific bases for treatment strategies for Gulf War illnesses.

There are a variety of exposures recognized to have been encountered by individuals in the Gulf War theater. Many, if not most, of these exposures are already the subject of extensive study as potential contributors to the development of health effects in Gulf War veterans. It was emphasized by the workgroup that both individual exposures and interactions between various exposures need to be studied. The list of exposures of concern includes:

- ' Depleted uranium (chemical and radiological effects).
- ' Pyridostigmine bromide.
- ' Vaccines and experimental adjuvants.
- ' Nerve and blister agents, especially at low levels.
- ' Biological warfare agents.
- ' Heavy metals (e.g., lead).
- ' Pesticides (e.g., organophosphates, pyrethroids, lindane).
- ' Insect repellents (DEET).
- ' Petroleum (e.g., solvents, fuels, Kuwaiti crude).
- ' Oil fires (e.g., soot, oil rain; composition and concentration).

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- ' Carbon monoxide.
- ' Contaminated fine sand (bioactive properties).
- ' Chemical Agent Resistant Coating (CARC) paint.
- ' Heat, exertion, and other stresses.
- ' Infections (fungi, viruses, etc.).

To explore the most plausible etiological hypotheses concerning diagnosed diseases and unexplained multi-symptom illnesses noted among Gulf War veterans, the pathophysiology workgroup emphasized the need for multidisciplinary research efforts. The research recommendations include both short-term goals of immediate relevance to the understanding and treatment of unexplained illnesses of Gulf War veterans, and longer-term goals that include building a foundation of knowledge that can be used to understand and, hopefully, prevent environmental disorders in future generations.

Research Recommendations:

I. Human Studies:

Studies of veteran populations and other groups affected by similar exposures need to be continued and enhanced, to include, among other things, an examination of a wide range of physiological systems and endpoints to reflect the different symptoms reported by Gulf War veterans. The research effort should include neurological, central nervous system, neuromuscular, and aging studies; immunological and immunotoxicity studies; studies of the pulmonary and respiratory systems; circulatory and hematopoietic system studies; studies of dermal and gastrointestinal system involvement, especially as routes of exposure; and studies of birth defects (e.g. Goldenhar syndrome) and reproductive toxicity. Since many of the reported manifestations of illness are similar to conditions which appear to affect men and women differently in civilian populations, gender differences in these endpoints should also be examined. Exposure assessment in these studies will be a critical contribution to establishing a link between exposures and disease. Specific recommendations for human studies include:

- 1) *Analysis of deployment cohorts:* Future studies should examine the interaction of physical, chemical, and other stressors on multiple organ systems. This research should include an assessment of the proportion of cases of unexplained illness as a function of length of time spent (and possibly location) in the Gulf in order to segregate separate sets of exposures to chemicals, physical agents, and psychological or physical stressors and to

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determine the associations with health or disease. There should be a comparison of Desert Shield veterans, Desert Storm veterans, and troops that arrived after the cessation of hostilities.

- 2) *Analysis of exposed Gulf War veteran populations from other countries and related experiences:* There is little information on country-specific prevalence of unexplained illness among veterans and why such illness was not reported by some coalition partners. Little or no research has been undertaken among the communities directly affected by the Gulf War conflict, and no international public health research has been carried out in Iraq. For a clear picture of the relationship between the adverse health effects of environmental exposures in the theater-of-war, it is imperative that every conceivable opportunity is taken to collect and synthesize relevant exposure and health information from other nations, including both allied countries and Iraq. Because veterans of all countries participating in the Gulf War sustained exposures of concern, there is no scientific basis for the exclusion of one party from study. The medical doors of countries involved in the Gulf War conflict now appear to be opening to international medical scientists committed to finding answers to common health problems. Credible evidence of a rare disorder occurring in a high incidence among Iraqi veterans could greatly affect understanding of a comparable illness among veterans of coalition forces.
- 3) *Studies of potential health effects of destruction of chemical warfare agents in the U.S.:* Current plans call for controlled destruction of a stockpile of chemical warfare agents at seven sites in the U.S. One proposal is to undertake prospective health assessments of communities impacted by sarin and mustard incineration at these seven sites before, during, and after incineration.
- 4) *Studies of potential health effects of pesticide exposures:* Studies of populations exposed to organophosphate pesticides that have mechanisms of neurotoxicity similar to those of some chemical warfare nerve agents can shed light on those health effects.
- 5) *Susceptibility studies:* Besides exposure, the other key component that determines health is a person's individual susceptibility. In this context, susceptibility is a wide-ranging term, encompassing genetics, nutrition, gender, age, and other factors. Factors relating to susceptibility to any disease or exposure are still very poorly understood, but elucidating these factors may have the power to help us understand the incidence and distribution of illnesses among Gulf War veterans. Specifically, answering the question of whether low-level exposures lead to neurotoxic and other health effects will depend on our understanding of the intrinsic toxicity of the chemical, the presence of other exposures, and the susceptibility of the person who is exposed. Our knowledge of the possible exposures and the physiological mechanisms involved in metabolizing these chemicals can suggest candidate genes for study. We can develop the tools for genetic screening for

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polymorphisms among genes interacting with known risk factors (e.g., cholinesterases, porphyriopathy).

- 6) *Chemical sensitivity studies:* Studies should examine toxicant-induced loss of tolerance in susceptible individuals as a possible explanation for some Gulf War symptoms. Susceptible people, following an initial exposure event, may lose specific tolerance and become sensitive to low level exposures of many different foods and substances.

II. Animal Studies

Controlled studies of exposure under laboratory conditions are only possible with animal models. Under these conditions, we can refine our understanding of clues obtained from human studies and gain insights that will lead to more effective treatment strategies. The use of transgenic animals is also valuable for determining the genetic components of responses to some exposures of interest. With the right animal models and exposure measures, we can answer some questions that cannot be easily asked in human studies; for instance, we can examine the interactions of Gulf War exposures with physical stress (exertion). Specific recommendations for animal studies include:

- 1) Studies of synergistic effects of exposures.
- 2) Studies of subclinical effects of exposures.
- 3) Studies of low-level, chronic exposures.
- 4) Studies of multi-generational exposures.
- 5) Studies to develop animal models for chemical sensitivity and other conditions.
- 6) Studies examining patterns of gene expression.
- 7) Studies evaluating delayed expression of effects of environmental insults.
- 8) Studies of sex differences in effects of chemical exposures.

III. New Methodologies

New tools are revolutionizing biomedical science and toxicology. These tools should be brought to bear on the study of Gulf War veterans' illnesses. Recommendations regarding new

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methodologies include:

- 1) *QSAR approach to molecular interactions:* Studies should make use of quantitative structure-activity relationship modeling to predict chemical toxicity in relevant receptor systems (using combinatorial chemistry, computer/information technology, statistical modeling and biological information).
- 2) *Development of biomarkers of exposure, susceptibility, and effect:* Biomarker tools are needed for exposure assessment in human studies, for linkage of exposures to preclinical outcome measures, and for use in animal studies. Studies should be conducted to identify:
 - ' biomarkers of susceptibility to chemical sensitivity and other predispositions to disease.
 - ' biomarkers of stress, including physical exertion and heat stress.
 - ' biomarkers for chemical agent exposures.
- 3) *Anti-sense DNA technologies:* In cases where expression of a specific gene(s) is determined to be a necessary step for development of health effects, use of anti-sense DNA has potential as a novel treatment strategy (for instance against acetylcholinesterase).
- 4) *Other new methodologies:* Other approaches that should be explored include:
 - ' Multifactorial statistical models (gene-environment interactions, exposure confounders).
 - ' Transgenics and knockouts for studies of genetic susceptibility.
 - ' Alternatives to animal systems (cell and tissue culture)
 - ' Imaging techniques.

IV. Special Needs

- 1) *Centralized Gulf War research library and data repository:* The workgroup unanimously endorsed a recommendation for the establishment of a centralized research library and data repository that would collect research proposals and results and maintain them in a format that would be easily accessible and searchable electronically.

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- 2) *Controlled-environment medical unit(s)*: This proposal is for a controlled isolated hospital environment to reduce everyday exposures as low as practicable. Sensitive individuals can be placed in this environment and challenged with different substances.

V. Research Oversight

To ensure and enhance continuation of the present cooperation between health professionals and veterans, the workgroup recommends that a non-governmental national committee be established to advise on the selection and implementation of these research recommendations. This committee is not intended to replace the governmental interagency Persian Gulf Veterans Coordinating Board, but rather, to provide a mechanism by which the interests of Gulf War veterans can be heard on a continuing basis by a non-governmental group. A possible venue for this committee is the National Research Council (a non-governmental body with a reputation for independence), with joint participation among the National Academy of Sciences (Board on Toxicology and Environmental Health Hazards), the Institute of Medicine (including the Medical Follow-up Agency), and representatives of Gulf War veterans' organizations. Alternatively, a federally sanctioned committee could be established under which representation from the various interested parties would be mandated. This committee could be modeled on the advisory group that provided oversight to the Superfund Hazardous Substances Basic Research and Training Program.

Chapter 3

Workgroup 2: Assessment and Diagnosis

Background:

The assessment and diagnosis workgroup was charged with developing research recommendations covering a wide range of issues including case definition; chronic multi-system conditions, such as chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), and fibromyalgia (FM); overlap of these conditions among Gulf War veterans; optimal methods for diagnosis; and validation of assessment approaches.

The workgroup recognized that Gulf War veterans were presumed to be in better health than the general public and to be healthy before they were deployed. Veterans were exposed to a combination of wartime and environmental factors that are known to have health risks. In other occupational groups, such as firefighters, police, and miners, who have exposures to complex environmental hazards, it is often recognized that these exposures affect health. The workgroup recommended that an interim assumption of service connection be established pending better characterization of the illness so that veterans can obtain appropriate treatment and compensation.

Research Recommendations:

I. Case Definition

- 1) Case definitions for illnesses among Gulf War veterans must be developed in a way that allows comparison to case definitions already existing for chronic multi-system conditions. The establishment of methods for comparing case definitions would allow for identification of areas of overlap and possible new etiologies or conditions among this population.
- 2) All definitions for Gulf War illnesses should be described in detail in research studies so that all parties understand the criteria used in establishing conclusions from the work. Efforts should be made to examine and compare the methods used for diagnostic criteria within studies. Such efforts allow for development of the most robust case definition.
- 3) All subtypes of Gulf War related illnesses should be based on available data. If individual symptoms or symptom clusters cannot be placed into a diagnosis or disorder, these symptoms should be tracked with regard to relevant independent variables, such as exposure status.

II. Chronic Multi-System Disorders

Many of the symptoms reported by Gulf War veterans overlap with other chronic multi-system disorders such as MCS, FM, and CFS. Recommendations of the workgroup included some specifics on these disorders which should be explored in connection to Gulf War veterans in particular.

- 1) Research is needed to examine the prevalence and overlap of a number of conditions which resemble the illnesses of Gulf War veterans. These conditions include CFS, FM, MCS, somatization disorder, post-traumatic stress disorder, sick building syndrome, and neurasthenia. The prevalence of these conditions should also be determined in other relevant populations. Such populations might include indigenous populations of the area, other coalition forces, and active duty personnel who prepared for deployment but never actually deployed.
- 2) Case-control studies should be carried out among Gulf War veterans to better assess the occurrence of multi-system disorders in this population. These studies should include the examination of field data on casualties and illnesses affecting soldiers in the theater of operation. While much of these data may be lost, certain data, such as some inpatient records, may be retrievable.
- 3) Novel techniques, such as laboratory models (e.g., environmental control units), functional imaging techniques, and development of biomarkers in exposed populations, need to be explored in an effort to understand the illnesses experienced by Gulf War veterans. Currently there are no animal models to study these chronic multi-system disorders. The workgroup encourages the development of novel animal models to study issues pertinent to these disorders. Examples of possible animal models may include the development of new animal strains to express unique polymorphisms which may be relevant to exposure effects.
- 4) Investigations should be conducted into barriers that may exist within the Department of Veterans Affairs (VA) which may deter physicians from using the diagnosis of chronic multi-system disorders with patients under their care. These investigations should include an assessment of the reliability of the VA application of chronic multi-system diagnoses and the potential for training physicians in the proper application of new diagnostic methods and procedures.

III. Well-Defined Disorders

The workgroup put forth a number of recommendations encouraging the use of well-defined criteria when investigating and assessing conditions among Gulf War veterans. Any diagnosis for research purposes, as much as possible, should be achieved through use of accepted gold standard evaluations.

- 1) Medical disorders should be classified by International Classification of Diseases, version 9 (ICD-9) criteria; psychiatric disorders should be classified by Diagnostic and Statistical Manual of Mental Disorders, version IV (DSM-IV) criteria. All adverse reproductive outcomes should fall under the Centers for Disease Control and Prevention (CDC) classification of birth defects, and all cancer diagnoses should be made according to appropriate Surveillance, Epidemiology, and End Results (SEER) classification.
- 2) Research studies should document the existence of multiple disorders using standard criteria to characterize coexisting conditions. These conditions could include, but may not be limited to, physical trauma, infectious diseases, autoimmune disorders, vocal chord dysfunction, reactive airways dysfunction syndrome (RADS)/asthma, rhinitis, and mortality. Any research on MCS should consider overlap with other disorders which have well-defined ICD-9 criteria.

IV. Overlap of Conditions

The workgroup realized the tremendous potential of overlap in chronic multi-system conditions and recommended careful study design when diagnosing such disorders.

- 1) When assessing overlapping conditions, investigators should define the exclusionary criteria used for labeling subjects with each condition, and use standard criteria for diagnosing the condition whenever possible (clearly indicating the criteria that were used). Researchers must evaluate the overlap between specific chronic multi-system conditions and other such conditions as well as well-defined conditions.
- 2) Investigators should develop and specify the methods by which they handle overlap in symptoms and overlap in diagnoses.
- 3) Investigators should explore the determinants of patient treatment-seeking and assess the impact of treatment-seeking on the characteristics of study populations. Researchers are encouraged to explore characteristics of patients seeking care at different types of health care facilities. Additionally, it is important to carry out studies on non-treatment seeking populations. Such groups may be important in the determination of prevalence and may

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have profound effects on conclusions of research into Gulf War illnesses.

- 4) Studies should be conducted to examine the role of pre-existing disorders. Data need to be collected for the study of relationships between pre-existing disorders (both well-defined and chronic multi-system disorders) and the expression of chronic multi-system disorders after Gulf War service. These data would help physicians better understand the influence of pre-existing conditions in the initiation or propagation of the disorders seen in Gulf War veterans.
- 5) An additional area of research to be studied and evaluated is the role of gender in the development of disorders among Gulf War veterans. Some observations have shown that there is a higher rate of some conditions among males in the Gulf War veteran population than in other populations. Studies could be developed to investigate how these observations relate to current knowledge regarding disorders such as CFS and MCS.

V. Biomarkers

Biomarkers need to be studied in relation to both the illnesses among Gulf War veterans and other chronic multi-system disorders such as CFS, FM and MCS.

- 1) Due to the long period of time which has passed since the Gulf War, particular emphasis should be paid to the development of biomarkers for past exposures.
- 2) The study of existing biomarkers should continue and new research should be performed using existing biomarkers on combinations of chronic multi-system disorders.

VI. Assessment and Diagnosis

The workgroup had very specific recommendations related to the assessment and diagnosis of disorders when performing research on illnesses affecting Gulf War veterans. All of the recommendations for assessment and diagnosis would be considered long-term efforts due to the significant amount of time and amount of resources necessary to bring the recommendations into practice.

- 1) Assessment techniques employed in research should reflect specific hypotheses about relationships between chemical exposures and structural changes or functional abnormalities.
- 2) Behavioral or physiological challenge studies that allow expression of pathology in well-

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compensated subjects should be conducted.

- 3) Development of new laboratory tests of chemical effects is recommended. In order to be applicable, new tests must meet rigorous standards and studies should include evaluation of reliability, repeatability, validity, and specificity.
- 4) Combinations of assessment and diagnostic techniques aimed at evaluation of the same organ structures should be employed in research. For example, a study of the central nervous system might include structural imaging, neuropsychological testing, neurophysiologic measures, and functional imaging.
- 5) Comprehensive assessment may be required to accurately measure variables of interest, to evaluate confounders, and to assess the same domains in different ways. Since there is the possibility of significant overlap in the disorders affecting Gulf War veterans, care needs to be taken when assessing patients. Thorough examination and accurate testing of variables will help eliminate problems when identifying illnesses in this veteran population.
- 6) Clinically non-routine assessment probes are recommended for consideration in research. This would include such procedures as use of environmental control units, carbon dioxide challenges, blind olfactory challenges, and autonomic nervous system assessment.
- 7) Use of tests for which there are normative and validity data for the general U.S. population or carefully matched control groups is recommended.
- 8) A research project assessing longitudinal health changes across time in a normal population is suggested. The illnesses facing Gulf War veterans are not unlike disorders in the general population and studies looking at the changes in health over time in normal individuals would provide a valuable basis for comparison.
- 9) Careful assessment of confounders and effect modifiers is necessary. (For example, research should control for medication history.) Assessment of family members and significant others is recommended for independent verification of partner health outcome and risk factors in order to both ascertain whether there is a biological basis for symptom transmission and explore environmental exposure histories at home.
- 10) Assessment of events following the death of a Gulf War veteran is suggested in order to track factors that might influence mortality and the death certificate diagnosis. The workgroup was not aware of any autopsy studies examining causes of death in Gulf War veterans. Therefore, protocol driven autopsy studies are recommended following the death of a Gulf War veteran.

VII. Validation

The workgroup recognized the importance of validation of study results and recommended that the identification of appropriate populations for validation and cross validation of study results on Gulf War populations should consider groups deployed elsewhere, non-deployed military personnel, and other exposed populations. It should be recognized that military controls may not always be appropriate because the controls may have the same exposures as deployed veterans. Care should be taken to identify the appropriate control group when designing research protocols.

Many instruments are available for investigating illnesses among Gulf War veterans, but most of these were not designed specifically for this purpose. It is recommended that standardized instruments revised for use in Gulf War populations be re-validated. Additionally, while the use of convenience samples to develop hypotheses about Gulf War related disorders is appropriate, the findings from these studies should be validated using larger representative samples if provocative results are obtained.

Validation of a case definition can be carried out at three levels (from lowest to highest):

- ' derivation on a single Gulf War population.
- ' replication in a second Gulf War population.
- ' association of findings with appropriate biomarkers.

VII. Other

Lastly, the workgroup made a general recommendation. Since it is necessary to use the most current and relevant information, the Department of Defense should continue to declassify and disseminate all relevant classified scientific field investigations and clinical studies to enable a better understanding of Gulf War veterans' illnesses and their possible causes.

Chapter 4

Workgroup 3: Treatment

Background:

The treatment workgroup was asked to address five areas: appropriate treatment paradigms, approaches to rehabilitation, healthcare opportunities for veterans of the Gulf War, education of physicians, and appropriate study methods for treatment trials. The workgroup emphasized the need for increasing current treatment options for Gulf War veterans, using research methods to assess treatment efficacy, and assessing veteran satisfaction with treatment. The workgroup developed additional long-term recommendations focusing on development of therapeutic options by controlled clinical trials, with evidence-based trials (hypothesis-based ideas with supporting data) having the highest priority. In addition, the need for new strategies to educate physicians and to assess the effectiveness of the education was emphasized by the workgroup.

The treatment workgroup developed recommendations in four areas: pharmacologic therapy, non-pharmacologic approaches, treatment regimens based on chemical intolerance, and “macro” issues (the patient-physician relationship, interrelation of the individual to the organization, veterans’ satisfaction with care, and educating physicians). The workgroup members attempted to focus on treatment approaches that were evidence-based and could be tested with appropriate research designs.

Research Recommendations:

I. Pharmacologic Therapy

There is an urgent need for research concerning treatment approaches for Gulf War veterans. Several potentially promising approaches to treatment are not supported by the degree of empiric support or pilot data that is typically required. When such proposals are being considered for funding, special peer review panels should be assembled that understand these unique circumstances. Funding should be considered for well-conceived, scientifically sound proposals that may lack empirical supporting data. As research progresses, if a subset of Gulf War veterans is identified that has a specific cause for their symptoms and an appropriate treatment, then this testing should be considered for all symptomatic veterans.

- 1) Studies should be conducted to examine the efficacy of pharmacologic therapy to treat specific symptoms of Gulf War veterans. Assessment of treatment efficacy should include measures of symptom severity, quality of life, and veteran satisfaction. Subjects still

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experiencing significant symptoms at the end of trials should be considered for subsequent treatment trials using other available medications. Examples for treatment of pain and cognitive dysfunction include the following (other focused symptoms should be treated using a similar approach):

- ' Pain – An open trial aimed at veterans with untreated pain to sequentially examine the efficacy of low doses of medications that have been found to be effective in reducing pain among other patient populations. Examples include low dose antidepressants (e.g., venlafaxine) and analgesics (e.g., tramadol).
 - ' Cognitive symptoms – A trial examining the efficacy of bupropion (a selective dopamine-reuptake inhibitor) and pemoline (a psychostimulant) in improving cognitive symptoms in persons with these conditions.
- 2) Studies should be conducted to test the hypothesis that neurally-mediated cardiovascular changes may be responsible for symptoms of some Gulf War veterans. Therapeutic considerations for such a trial include fluid and sodium repletion, beta-blockers, mineralocorticoids, and calcium channel blockers.
 - 3) Since sub-clinical hypothyroidism and hypoadrenalism may occur in patients with fibromyalgia and chronic fatigue syndrome, trials examining the efficacy of low-dose replacement of these hormones among Gulf War veterans with unexplained symptoms are recommended.
 - 4) Nutritional supplements and vitamins are purported to be effective for a number of the conditions and symptoms affecting Gulf War veterans. Governmental agencies should form a committee to examine which nutritional interventions would be most likely to be of benefit, and then fund pilot studies to examine the effectiveness of these therapies.

II. Non-pharmacologic Therapies

Some of the major challenges faced when attempting to maximize the use of effective non-pharmacological therapies include matching therapies to the specific needs of the veteran, and ensuring that a wide range of therapies is available and consistently and appropriately implemented in the course of routine health care delivery. The usual structure of primary care and specialty care features a 10-15 minute acute care visit with a physician. The prudent clinician rapidly narrows the focus of the visit to one or two “chief complaints.” Often, physicians target a certain area of the veteran’s health concerns and prescribe one or more pharmacological treatments, which sometimes cause unexpected side-effects. For veterans with complex health needs, this approach is unsatisfying at best and disabling at worst. The workgroup recommends

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that, rather than focus on specific non-pharmacological therapies, clinicians and researchers should develop a more comprehensive and population-based approach to non-pharmacological care.

- 1) *Conduct a pre-care needs assessment:* This assessment should target all Gulf War veterans, including active duty members and reservists not currently covered in either the Department of Veterans Affairs (VA) or the Department of Defense (DoD) health care systems. The needs assessment could be completed using some combination of paper and pencil survey, semi-structured telephone interview, and/or clinician administered systematic assessment. Needs assessments must emphasize the veteran's perspective. Areas of inquiry should include current communication modalities available for veterans and their health care systems to exchange information (e.g., Internet access, personal computer, current and permanent address, other available points of contact); perceived need for health information; need for assistance with activities of daily living; need for specific types of health care; access to care; barriers to care (including the benefits assistance process); recent levels of fatigue, pain, sleep, and cognitive difficulties, physical health concerns, health-related quality of life, satisfaction with care, and illness-related psychosocial distress; need/desire for specific non-pharmacological therapies not currently available; and suggestions for improvement in current health care.
- 2) *Develop pre-care guidance on self-care strategies:* Gulf War veterans should be targeted in a population-based fashion for mailed self-help guides. All veterans should receive either standard self-help literature focused on common veteran health concerns and needs, or literature tailored to their needs as identified on the needs assessment. The added benefit of the tailored literature would be estimated using reassessments of all or some of the areas of inquiry described in the pre-care needs assessment.
- 3) *Use a primary care and collaborative primary care approach to treatment:* Gulf War veterans responding to the needs assessment should be given membership in the primary care practice team's patient panel for routine primary care follow-up. The practice team would clinically assess, discuss together, and plan the short- and long-term care of responding veterans. Level of care should be matched to each veteran's needs. For those veterans with complex health care needs or for those whose health concerns persist in spite of primary care follow-up and implemented medical strategies, collaborative efforts involving combinations of health information materials (brochures, books, tapes), and non-pharmacological strategies implemented by clinicians other than physicians on the primary care practice team (e.g., nurses, occupational therapists, physical therapists, social workers, psychologists) would be emphasized in a planned, explicit, and structured delivery approach. This level of care should be compared to usual VA and DoD care or other less intensified or coordinated approaches to VA and DoD primary care. Outcomes assessed should include those described for the pre-care intervention.

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- 4) *Provide intensive specialized care for chronic symptoms of unclear etiology:* When disability persists despite these previous elements of care, more intensive programs emphasizing rehabilitative measures should be tested, such as the current VA exercise/behavioral treatment trial. Other models may be borrowed from efforts currently being successfully used for individuals with chronic illnesses (e.g., fibromyalgia, chronic fatigue, chemical sensitivity and related syndromes, and head injury).
- 5) *Evaluate novel, new, or promising non-pharmacological treatment modalities:* Pilot studies followed by single center and multi-center randomized clinical trials should be used to evaluate novel, new or promising non-pharmacological modalities. Some modalities of interest include acupuncture, chiropractic, modified psychosocial interventions such as cognitive-behavioral therapies used for other physically symptomatic illnesses, sauna, dietary, and creative arts approaches.
- 6) *Develop a coordinated quality improvement program:* This program should encourage health services research and research into innovative efforts to integrate non-pharmacological treatments into the usual provision of VA and DoD primary and specialty care.

III. Treatment Regimens Based on Chemical Intolerance

Anecdotal evidence suggests that detoxification-based treatment programs have been effective in reducing symptoms of some Gulf War veterans. Detoxification is a treatment involving sauna baths, stringent exercise, and vitamin therapies. Other veterans report that trial and error testing has revealed intolerance to chemical inhalants, foods, and drugs. Further, veterans report that avoiding these substances improves their symptoms. This elimination routine has been advocated by some practitioners for more than fifty years. Other veterans report that a combination of these therapies increases their health and well-being. The enthusiasm shown for these therapies by veterans who have undertaken them suggests that controlled trials should be conducted to determine their efficacy. Criticism has been made of the practice of prescribing multiple drugs for symptomatic relief of Gulf War veterans with unexplained illnesses, and some have suggested that adverse reactions to multiple drugs is a factor in these illnesses. This hypothesis is easily tested by a drug avoidance protocol.

In order to rule out potential biases, these studies should be conducted in a controlled and blinded fashion. In addition, patients with possible infectious disease, specific toxicological syndrome, or other well-defined medical illnesses that would explain symptoms should be excluded. Pre-, post-, and intra- treatment assessments should be conducted. Evaluation procedures should include self-assessment instruments, including instruments designed to assess the severity of

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illness, quality of life, and neuropsychiatric symptoms. For the detoxification protocols, there should be monitoring of levels of chemical in adipose tissue, serum, urine, sweat, and any abnormal body secretions. Specific chemical intolerance study recommendations include:

- 1) Conduct a treatment trial to examine the efficacy of a detoxification routine consisting of saunas, stringent exercise, and vitamin therapies at a clinic specializing in this technique.
- 2) Examine the efficacy of a physician-directed, home-based trial of testing of intolerance to chemical inhalants, foods, and drugs, followed by avoidance of those chemicals to which there is sensitivity in order to evaluate if health is substantially improved.
- 3) Conduct a treatment trial to examine the effectiveness of a program combining detoxification with trial and error testing of intolerance to chemical inhalants, foods, and drugs, followed by avoidance of those chemicals to which there is sensitivity in order to evaluate if health is substantially improved.
- 4) Conduct a double-blinded, placebo-controlled trial of drug elimination with veterans who are taking multiple drugs for symptomatic relief of unexplained symptoms. Clearly, this study should exclude all veterans taking essential medications for conditions such as diabetes, heart disease, and hypertension.
- 5) Depending on the efficacy of the pilot studies described above, one or more environmental control units should be constructed to diagnose and treat Gulf War veterans who may have multiple intolerances to those foods, chemicals, and inhalants found to exacerbate symptoms. These studies should integrate detoxification regimes as appropriate.

IV. Macro Treatment Issues

The effectiveness of Gulf War related treatment trials and other research programs would be maximized by establishing a central body to coordinate communication, education, and outreach efforts and to ensure that Gulf War veterans are being treated with dignity and respect. This body should facilitate communication channels among veterans, health care professionals (especially VA or DoD Gulf War coordinators), researchers, and administrators. Information should be used to expedite the identification, dissemination, and implementation of therapies that are effective in order to match veterans with specialized care centers for specific conditions, and to ensure that health care providers are aware of the most current information on Gulf War related illnesses.

- 1) *Establish a Logistics and Communication Network Center:* This center should consist of appropriate parties (e.g., researchers, health care providers, veterans, and members of

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advocate groups) committed to enhancing communication, outreach, and education between groups. To support the concept and the adoption of this recommendation, the center may be modeled in a manner similar to the National Center for Posttraumatic Stress Disorder. This center should maintain a central data bank of completed and ongoing research protocols and establish an Internet Website and newsletter.

- 2) *Conduct focus groups:* Focus groups should be conducted at VA and DoD sites to assess Gulf War veterans' health care needs and health care provider concerns. Gulf War coordinators should interface between the focus groups and the Logistics and Communication Network Center.
- 3) *Develop, evaluate, and implement protocols focusing on communication and education issues:* These protocols should include education of veterans, family members, and veterans' advocates, as well as VA, DoD, and other appropriate health care providers, staff, and administrators. The effort should address issues such as needs assessment of potential patients, identification and recruitment of candidates for study, communication through newsletters and Internet sites to update veterans and health care providers on effective treatment protocols and other Gulf War related information, development of self-help education for veterans and family members, development of outreach programs for multi-disciplinary teams of health care providers, and examination of administrative processes that may be stumbling blocks for high-level quality of health care delivery.
- 4) *Other macro treatment issues:* Other macro treatment recommendations include:
 - ' Develop mechanisms to update primary care practitioners so they are knowledgeable about emerging exposure information.
 - ' Monitor the availability of effective treatments/drugs to be considered for compassionate use.
 - ' Develop mechanisms to monitor the quality of care of Gulf War era veterans.
 - ' Create a virtual library of high quality patient information.
 - ' Develop methods for patients to have greater access to their medical records.
 - ' Conduct research to enhance the treatment of multi-system diseases in primary care settings.

Chapter 5

Workgroup 4: Prevention

Background:

The prevention workgroup was asked to focus on four areas: health education and risk communication, approaches to environmental assessment, biomonitoring, and preparedness against chemical exposures. The workgroup relied on basic public health principles to develop recommendations and to establish priorities. That is, in structuring an approach to identifying prevention research needs, the workgroup considered the severity of the hazard, the number of people potentially exposed, the availability and feasibility (technical and economic) of interventions, and chances for success with existing interventions. The workgroup also emphasized the importance of relying on well-tested models and research tools, such as those currently used in occupational settings. Most important to the deliberations was the occupational and public health concept of "hierarchy of control strategies." This concept emphasizes the importance of developing an ordered hierarchy of prevention and intervention strategies. The implementation of these strategies should move from lower order items to higher order items with each step providing additional levels of protection. The prevention workgroup used the following elements of the hierarchy of control strategies as a framework for specific research recommendations:

Hierarchy of Controls

1. Substitution
2. Engineering Controls
3. Administrative Controls
 - A. Health Education
 - B. Risk Communication
 - C. Surveillance
 - a. Environmental
 - b. Medical/Biomonitoring
4. Work Practices
5. Personal Protective Equipment

Research Recommendations:

General Prevention Principles To Be Considered When Formulating a New Research Agenda

Three key prevention messages should be considered when formulating a new research agenda: assess what has already been done, examine exemplary models of prevention strategies and outcomes, and identify data gaps for future prevention research approaches.

- 1) *Assess what has already been done:* A critical first step is to evaluate previous efforts to determine the effectiveness of what has already been done. Such outcome research should focus on lessons learned, best practices, and evaluation research. Several interventions are already in place. The Department of Defense (DoD) and Department of Veterans Affairs (VA) must thoroughly assess these efforts when formulating policies and procedures for future deployments and follow-up strategies. For example, DoD maintains a central database repository, the Defense Medical Surveillance System, which consists of a system of linked databases containing medical information, personnel data, and deployment rosters. This system presents a key data source that would permit objective analysis to identify problem areas and critical needed improvements. However, collection of such data without attempts to assess and analyze the information will not lead to the necessary short-term and long-term prevention strategies that are possible.

- 2) *Examine exemplary models of prevention strategies and outcomes:* The second key approach is to assess other exemplary national and international models of strategies and outcomes. An issue that has hampered professionals in public health is lack of record linkage. The United Kingdom and Canada, because of their health care systems, can use record linkage to strive toward better health outcomes. Such basic structural record linkage creates possibilities that allow epidemiologic studies to be done. While operating in a different health care environment than either of these two countries, the U.S. will continue to have problems accessing critical health information until the record linkage issue is fully addressed.

Other existing comprehensive safety and health management programs can suggest a framework for analysis. Existing programs in the military can be compared with other programs in occupational health in an effort to implement best practice standards or to use them as a marker for developing new programs. Well-implemented plans with defined procedures and internal audit systems to assess the deficiencies and limitations of the procedures are essential.

- 3) *Identify data gaps for future prevention research approaches:* In formulating future directions, prevention research should include identification of data gaps and measurement of effectiveness of assessment strategies. One approach is to stratify effectiveness by

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content and process end points. A classic example is the development of vaccines that protect against debilitating disease. A content endpoint for effectiveness would be the basic laboratory and clinical research that identifies the best way to formulate vaccines. A process end point would be the outcome research that identifies the most acceptable way to administer vaccines to prevent illness in populations.

Specific Recommendations Based on Hierarchy of Control Strategies

I. Substitution

If exposure to certain toxicants (or other hazards) can be eliminated or other less hazardous substitutes provided to protect the service member, then other interventions would not be necessary. Research is needed to:

- 1) Identify less toxic substances and their interactive effects.
- 2) Restrict the need for use of multiple pesticides.
- 3) Optimize vaccine potency, formulation, dose, and duration.

Research to examine the interactive effects of environmental exposures is critical and a fruitful area for laboratory research. In addition to lowering potential health risks, limiting exposure to environmental hazards, such as restricting the number of pesticides that are in use, would simplify the gathering of exposure histories. Improvements in vaccines may reduce service members' concerns about potentially negative effects sometimes associated with vaccinations.

II. Engineering Controls

Engineering controls are applied when the hazard cannot be substituted or removed. A physical barrier protects service members with design features that do not require the physically exposed person to consciously do something to protect him or herself. There is a built-in presumption of protection because the situation itself is engineered to eliminate the hazard. While the unique nature of military operations makes this aspect difficult, preplanning in design of equipment and of weapon systems can help. Research is needed to:

- 1) Evaluate the current design and operation of equipment and material in order to reduce hazards to service members.
- 2) Design containment for transport of contaminated material.

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Human factors need to be considered when designing effective engineering controls. Additional research is needed to better understand how humans cognitively process and act upon objective information under normal conditions and under conditions of high stress. Such knowledge is essential for effective design of human-machine or human-instrument interfaces.

III. Administrative Controls - Health Education

Research is needed to improve the delivery and effectiveness of health education in military settings. This should include research to:

- 1) Identify and segment key audiences.
- 2) Determine appropriate instructional strategies.
- 3) Identify barriers to understanding the importance and impact of health education messages on readiness.

Health education efforts should focus on identifying the various populations for outreach. In the military setting, there are much larger audiences than just the service member, including family members and other potentially affected people. From a readiness point of view, the importance of preparing service members and their families needs to be recognized. For example, information on reproductive health issues is one content area where health information should be enlarged. Another major issue is determining the best channels for transmitting health education information, including identifying the types of information sources that are credible to specific audiences. Knowledge regarding effective instructional strategies is important for decision-makers like field commanders, who have to make strategic decisions. These should be informed strategic decisions, especially if there must be tradeoffs between military strategy and exposure to hazardous conditions. Theoretically, during the Gulf War, health information was to have been communicated. However, clearly there were problems with this health education effort. Prevention research is needed to identify the barriers to veterans' understanding of health education messages and the impact of such barriers on readiness.

IV. Administrative Controls - Risk Communication

Providing effective communication of scientific uncertainty is extremely difficult. With the reality that nothing is assured and experience is not the same from person to person, complex uncertainties arise when information on health risks is communicated. Research is needed to:

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- 1) Develop and test message content and channels.
- 2) Identify multiple audiences and information sources.
- 3) Assess effective communication of scientific uncertainty and technical information.
- 4) Assess comprehension, utility, and value of risk information.
- 5) Identify methods to communicate comparative risk issues.

It is important to provide information on real versus perceived risks. A significant example of this is the communication of information on reproductive health issues. It is also important to identify the channels through which people are obtaining information: print media, broadcast media, fact sheets, Internet sources, or other electronic media. What are the key concepts or principles that should be conveyed in a message? What is the individual to do about behavior as well as intent? Much important research can be done around these questions.

V. Administrative Controls - Environmental Surveillance

Exposure limits are an important aspect of environmental issues. In the military, there are at least three major environments: the theater of war, operations other than warfare, and in garrison. In a conflict situation, protection might not be as absolute as it is in the civilian environment. It must be considered that individuals are actually living where they are working and the usual exposure limits of eight hours a day, forty hours a week, are no longer germane. The real limits are twenty-four hours a day, 168 hours a week. Distinguishing non-combat from combat effects also requires an understanding of the limits of the instrumentation and a knowledge of factors influencing false positives, false negatives, sensitivity, and specificity. Prioritization of high hazards and low hazards is essential. Chemical and biological warfare exposures would usually be of higher concern than exposure to industrial chemicals. However, in certain theaters, there may be exposure to large quantities of toxic industrial chemicals. Research is needed to:

- 1) Develop enhanced instrumentation for nuclear, biological, chemical, and environmental exposure assessment.
- 2) Establish exposure limits that take into account the multiple operating environments.
- 3) Characterize the environment of deployment.

VI. Administrative Controls - Medical Surveillance and Biomonitoring

A current problem of considerable magnitude is the difficulty of linking medical information and tracking an individual's health records from civilian life, into the military arena, and back into civilian life. Without such systems, long-term follow-up and retrospective examination of health records remain almost impossible tasks. A major point that must be considered is privacy of the data, and there should be an organized effort to attend to this issue. First, a way of managing the data could be developed that would allow both DoD and VA use of information for various purposes, while simultaneously preserving the privacy of the data. A second area of concern is that if there is not adequate privacy of the data, the validity of the self-report data will be seriously compromised. Critical research is needed to:

- 1) Develop a data gathering tool that spans the life of the service member, that accompanies the person from DoD to VA to civilian life, and that links both exposure information and health outcomes.
- 2) Validate self-reported environmental exposures.
- 3) Develop an effective prospective surveillance system for multiple endpoints.
- 4) Develop methods for surveillance of low level exposures.
- 5) Develop methods for archiving biological specimens.

Current surveillance instruments and questionnaires do not employ language that can unequivocally avoid ambiguous answers. For example, a question such as "Were you ever . . ." does not help retrospectively to put together an exposure assessment. Following military personnel forward into future life, presumably civilian life, is problematic. Low-level exposure assessment also presents difficulties. There is need to define what low-level exposure is, but the definition would depend on the toxicant under scrutiny. If specimens were stored and retrievable, making comparisons for end points identified in future research would be possible. Such specimen archiving is being done with high risk civilian occupation groups and with other groups that are at high-risk for developing certain types of diseases.

VII. Work Practices

Consideration must be given to safety and health management in civilian life, often termed comprehensive safety and health plans, which incorporate built-in audit or outcome assessment components. More reservists and National Guard members were used during the Gulf War than in previous conflicts. A key work practice issue is how such part-time military service members

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are integrated with full-time service members into functional units. Should reservists and National Guard members be organized alongside full-time personnel, or should there be separate units of full-time and part-time military personnel? This work organization issue might be a focus for future research efforts. Research strategies can be developed to:

- 1) Evaluate existing health hazard protocols and develop metrics to compare work practice risk.
- 2) Explore the impact of varied work organization structures on negative health outcomes.
- 3) Develop audit and investigation systems to insure implementation of management control efficiencies.

VIII. Personal Protective Equipment (PPE)

DoD should more aggressively utilize existing expertise in the civilian sector for such items as chemical protective clothing and respiratory protection. Research needs should focus on projects to:

- 1) Design protective clothing that is durable, viable, and ergonomically flexible.
- 2) Develop and validate data/standards for PPE compliance that strive to adhere to the existing regulatory standards, such as those of the Occupational Safety and Health Administration and the Mine Safety and Health Administration.

Clearly, in the warfare arena, there are situations with extenuating circumstances that would preclude full adherence to these standards. However, there remains much opportunity in the near term to implement the same types of classical, good occupational health practices regarding PPE as exist in the civilian sector.

High Priority Recommendations

In the short-term, prevention research approaches can be initiated immediately in the following five areas, as much background data and information already exist.

- 1) Assessment of what has already been done since 1991.
- 2) Comprehensive safety and health management program.

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- 3) Metrics for implementation and effectiveness.
- 4) Personal protective equipment.
- 5) Optimization of vaccine safety and efficacy.

Chapter 6

Discussion

An intensive research effort to address Gulf War veterans' health concerns has been mounted by federal agencies and non-governmental scientists. As of 1999, there have been 145 federally-funded research projects on Gulf War veterans' illnesses with a cumulative expenditure of \$133.5 million for research from FY94 through FY99 (6). These projects represent a broad spectrum of research efforts, ranging from small pilot studies to large-scale epidemiology studies addressing mechanistic, clinical, and epidemiological issues. Similar efforts have been initiated in other coalition countries, most notably in the United Kingdom and Canada. In addition, numerous review panels and expert committees have evaluated the available data on Gulf War veterans' illnesses (7-10). Despite these extensive research and review efforts, many questions remain regarding the health impact of the Gulf War and the health of troops in future deployments.

The purpose of the Centers for Disease Control and Prevention (CDC) sponsored conference, *The Health Impact of Chemical Exposures During the Gulf War: A Research Planning Conference*, was to bring together scientists, veterans and their representatives, patient advocates, and other interested parties to obtain broad public input on the development of future research priorities for addressing the relationship between chemical exposures during the Gulf War and illnesses affecting Gulf War veterans. Veterans have often felt left out of the research planning process and thus have become mistrustful of government efforts to address their health concerns. This conference highlights the usefulness of establishing an ongoing dialog among veterans, scientists, and government officials.

The recommendations developed at this conference include suggestions for research across many different areas of concern to Gulf War veterans and reflect the combined input of the veteran, medical scientist, and patient advocate participants. While some of the recommendations could be implemented in the short-term, many of the recommendations reflect long-term goals requiring significant restructuring of current systems and are unlikely to be easily implemented, especially in the time frame requested by Gulf War veterans. Some recommendations reflect initiatives that have already been instituted by federal agencies responsible for the care of veterans. Still other recommendations may not be feasible. For example, a study of Iraqi soldiers conducted or supported by U.S. researchers or the federal government may not be possible due to prohibitions on travel and the transfer of funds to Iraq. It will be necessary to compare these research proposals with previous recommendations made by numerous review groups and with ongoing research to determine areas that are newly identified. It should also be noted that these recommendations have not been endorsed by the veteran and scientific community as a whole nor by the federal government. The purpose of this report is to document the deliberations of the workgroups in order to further dialogue among government officials, scientists, and veterans on

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the future direction of Gulf War illnesses research.

One clear recommendation from the conference is the need to involve veterans in the process of planning and implementing research. Congress has also emphasized the need for veterans' input. Section 104 of Public Law 105-368 directed the Secretary of Veterans Affairs to establish a public advisory committee on Gulf War veterans' illnesses research. In response to this legislation, the Department of Veterans Affairs (VA) is in the process of forming the Research Advisory Committee on Gulf War Veterans' Illnesses which will be composed of veterans, veterans' representatives, and non-governmental scientists. This committee will provide advice and make recommendations to the VA Chief Research and Development Officer in his capacity as Chairperson of the interagency Research Working Group (RWG) of the Persian Gulf Veterans Coordinating Board, to the Under Secretary for Health, and to the Secretary for Veterans Affairs on research relating to Gulf War veterans' illnesses. Members for the advisory group will be selected based on their ability to represent the broad health concerns of Gulf War veterans or to provide scientific expertise in the areas of basic biomedical research, epidemiologic research, clinical research, environmental and health research, and mental health and behavioral research.

Conference participants also emphasized the need for a central body to coordinate and disseminate information. Suggestions were made that a data coordinating center be established and that it be modeled after the VA Cooperative Trials Network or the National Center for Post-Traumatic Stress Disorder. Congress has also made recommendations in this area. The Defense Authorization Bill for Fiscal Year 1999 authorized the Secretary of Defense to establish a center for evaluation of the health of those serving in the armed forces upon return from deployment. In response to this legislation, the Department of Defense (DoD) has proposed to build upon existing programs to develop Centers for Deployment Health that will focus on force health protection, surveillance, clinical care, and research.

Section 103 of Public Law 105-368 required the Secretary of Veterans Affairs to enter into an agreement with National Academy of Sciences' Institute of Medicine (IOM) to develop a plan for the establishment of a VA national center on war-related illnesses and post-deployment health issues. In December 1998, VA contracted with the IOM to assist in developing a plan for the establishment of this new center. In late 1999, the IOM Committee on a National Center on War-Related Illnesses and Postdeployment Health Issues issued a report containing recommendations regarding the scope, focus, organizational structure, and funding for a National Center for Military Deployment Health Research (11). The committee specifically recommended that VA model the Deployment Health Center on VA's Geriatric Research, Education, and Clinical Centers. The Center should focus on the health of active, reserve, and National Guard forces, and on veterans and their families. The IOM committee recommended that the Center establish a broad research agenda that addresses conditions that emerge both during and following deployment, including diagnosable conditions, medically unexplained symptoms, effects on health-related quality of life, family impacts, and sequelae of combat injuries. Furthermore, the

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committee recommended that the governing board for the Center should include representatives from VA, DoD, and HHS; representatives from the research community; and representatives from the community at large, including veterans and their families and the general public.

Another point emphasized in this conference is the need for improved coordination and oversight of both Gulf War related research and future research on deployment health issues. This need for improved coordination has been previously noted by several oversight committees (10,12). To ensure that a coordinated research effort was developed to longitudinally follow up on the health status of Gulf War veterans, VA contracted with IOM to make recommendations regarding a systematic research approach to monitoring the ongoing health status of Gulf War veterans. The IOM Committee on Measuring the Health of Gulf War Veterans issued a report in September 1999 containing suggestions for a research portfolio and core set of data elements that would facilitate linkages across studies (13). The IOM committee specifically recommended that population studies, health services research studies, and biomedical and clinical investigations be conducted and that all studies include measures reflecting core health concepts (death and duration of life, impairment, functional status, health perceptions, and health opportunity), and individual and environmental correlates of health. Furthermore, the committee recommended that a prospective cohort study of the population of Gulf War veterans be conducted in order to assess the health status of Gulf War veterans, changes in health over time, how Gulf War veterans health compares to other veteran and civilian groups, and the individual and environmental characteristics associated with health status. The IOM committee anticipated that this prospective cohort study would serve as the foundation for the entire portfolio of research activities.

VA also contracted with IOM to conduct a review of the scientific and medical literature regarding adverse health effects associated with exposures experienced during the Gulf War. This committee will review information on a broad range of exposures and health outcomes and will make recommendations for additional scientific studies to resolve areas of continued scientific uncertainty related to the health consequences of Gulf War service.

To address the issue of health outcomes in future deployments, a Presidential Review Directive (PRD) was issued directing the National Science and Technology Council to oversee the development of an interagency plan for minimizing or preventing post-conflict health concerns in future deployments. *PRD-5, Planning for Health Preparedness for and Readjustment of the Military, Veterans, and Their Families after Future Deployments*, was released in November 1998 (14). In this plan, specific recommendations are made regarding improving service members' understanding of health risk information, improving medical and non-medical countermeasures, enhancing government collection of health and exposure data, improving linkages among health information systems, coordinating agency research activities, and improving delivery of health care services to veterans and their families.

As recommended in PRD-5, VA, DoD and the Department of Health and Human Services (HHS)

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will be co-chairing a permanent interagency coordinating board, the Military and Veterans' Health Coordinating Board. This board will be responsible for ensuring coordination of federal clinical, research, and health risk communication efforts related to the health of military service members and veterans during and after deployments. The board will provide recommendations for deployment health and research activities, as well as for outreach and health risk communication efforts with veterans, the public, other federal government entities, military and veterans' service organizations, health professionals, scientific professional societies, the media, and state, county, and local governments.

Despite these current initiatives, additional research can add useful information on Gulf War veterans' illnesses and assist in efforts to prevent illness among military personnel and their family members after future deployments. This report outlines recommendations for this future research based upon input by scientists, veterans, and other interested parties. In responding to these recommendations, funding agencies should be guided by sound scientific methodology and ethical principles established to protect research participants.

Pathophysiology Recommendations:

An overarching theme that arises from the recommendations of the pathophysiology workgroup is the synergy and benefits that result from interactive research among medical and basic research scientists and veterans. To maximize the chances for success, scientists must listen to the experiences of the veterans and attend to their needs. In order to enhance communication between veterans and scientists, the workgroup unanimously endorsed a recommendation for the establishment of a centralized research library and data repository that would collect research proposals and results and maintain them in a format that would be easily accessible and searchable electronically.

The research agenda, whenever possible, should be interdisciplinary since the combined activity of both the basic and the clinical scientist is required in order to move from the bedside to the bench and from the bench to the bedside. The workgroup strongly emphasized that research should focus on unifying mechanisms that have the potential to explain the multi-system symptoms of Gulf War veterans.

The workgroup recognized that the immediate needs of Gulf War veterans are important and pressing; however, the group also emphasized the value of investing a portion of available research funds in developing new methodologies through basic research. Chemical and biological weapons have emerged from being anecdotes in the history of human warfare to being pressing current environmental hazards in both military and civilian sectors. The importance of research on the mechanisms of action and the short- and long-term adverse health effects of acute, low-level and sub-lethal exposures has been recently recognized.

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Of the areas identified by the participants as promising avenues for research, some of the research efforts already undertaken include the establishment of a number of epidemiologic studies, both in the U.S. and in the United Kingdom. In an effort to begin surveillance and determine prevalence information, the Naval Health Research Center in San Diego is establishing a birth defects registry. A five-year follow-up is underway of Army personnel exposed to chemical warfare agents at Khamisiyah. Much work is being done on the pharmacokinetics, pharmacodynamics, and central nervous system responses to pyridostigmine bromide in humans and animal models. A number of studies are focusing on effects of mixtures of chemicals: prophylactic drugs and pesticides with each other, with jet fuel, with sunlight, and with stress. Other studies seek to identify sites and pathophysiologic mechanisms of neurological damage specific to symptoms experienced by Gulf War veterans, both to provide a means for identifying patients needing treatment and to provide a basis for the development of new treatments.

The need for research among coalition partners was strongly recommended by the pathophysiology workgroup. Some of this work has already been initiated. For example, an interagency effort between the Office of the Special Assistant on Gulf War Illnesses, the Uniformed Services University of the Health Sciences, the Naval Health Research Center, and CDC is currently in process. This study will examine health outcomes among members of the Saudi Arabian National Guard.

As the level of knowledge of the pathophysiology and etiology of Gulf War veterans' illnesses continues to increase, researchers hope that new insights will emerge which will lead to efficacious treatment for veterans, to a broader understanding of potentially similar conditions in civilian populations, and to effective prevention of disease in the future.

Assessment and Diagnosis Recommendations:

The issues involved in assessment and diagnosis include problems with case definition, proper identification of disease, and the nature of overlapping disorders which involve multiple organ systems. Primarily the symptoms are self reported and clinicians and researchers lack the proper measures to define unexplained illnesses affecting Gulf War veterans. The workgroup felt that the development of biomarkers to properly assess overlapping disorders, such as chronic fatigue syndrome (CFS), multiple chemical sensitivities (MCS), and fibromyalgia (FM), is extremely important so that a proper identification of disease can be made. The development of case definitions will be aided by the existence of specific biomarkers that are available in appropriate biological matrices, such as blood or urine. The proper application of unique biomarkers in the investigation of disorders such as the illnesses in Gulf War veterans is valuable and will enhance the assessment, diagnosis, and treatment of these disorders. In order to study biomarkers of illness in Gulf War veterans, researchers may need to identify and characterize those parameters that have a biological half-life long enough to remain with the individual. Development of such

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markers may have implications in many situations where the identification of a hazardous exposure comes years after the exposure occurred. Identification of versatile biomarkers will serve to protect troops in future deployments.

CDC's Division of Environmental Health Sciences in the National Center for Environmental Health has taken the lead in the development of biomarkers for environmental exposures. CDC scientists are developing technology that will rapidly assess a battery of 150 chemical agents in biological samples (blood and urine). This technology will allow for a determination of individual human exposure (including exposure level) to the targeted agents. Categories of chemical agents to be tested include chemical warfare agents, heavy metals, dioxins, and pesticides. This technology has the potential to be beneficial for both military and civilian populations because of its ability to rapidly address health concerns regarding environmental exposures.

Recommendations from the workgroup also place a strong emphasis on the proper design of studies. Protocols relating to MCS, CFS, and FM must be designed so as to take into account the multifaceted nature of the disorders. There needs to be a critical evaluation of any study design in order to assure that proper measures are being used and that confounders are limited as much as possible. With respect to chemical interactions, care must be taken to study the appropriate combinations of chemicals using well-defined criteria so as to be able to draw reasonable conclusions from the study.

Additional work should be done on developing a validated case definition. Problems have arisen in the past due, in part, to the lack of a proper case definition. While case definitions exist for research purposes, a validated case definition has not been developed. Although no universal case definition has been determined, many of the studies surrounding Gulf War illnesses have focused on the identification of a case definition and the assessment of the illnesses using a variety of approaches. Included in these are a number of studies which have put forth research case definitions which have been used in the evaluation of specific groups of veterans. These include studies of members of the Pennsylvania 193rd Air National Guard (15) and the 24th Reserve Naval Mobile Construction Battalion (16).

There are several ongoing studies that are attempting to address the issue of case definition. CDC is funding the University of Medicine and Dentistry of New Jersey to investigate the stability of Gulf War veterans' symptoms over time and to compare previously derived data-driven case definitions with existing definitions for chronic multi-system illnesses. The study will assess the generalizability of derived and existing case definitions in a new random sample of Gulf War veterans and will also assess the role of psychiatric conditions in the illnesses affecting Gulf War veterans. DoD is currently funding the University of Iowa School of Medicine to conduct a study on case validation of illnesses among Gulf War veterans from Iowa in order to compare rates of medically validated illnesses among deployed and non-deployed veterans. This study also attempts to compare risk factors for validated illnesses in a series of case-control studies for each

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illness outcome.

The workgroup made two general recommendations regarding the importance of continued declassification and dissemination of relevant scientific field investigations and clinical studies and the usefulness of adopting an interim assumption of service connection pending better characterization of Gulf War veterans' illnesses. These two recommendations highlight the interaction of public policy and science. Clearly, recommendations regarding service connection and declassification of documents reflect policy decisions rather than research issues. However, if possible, the best science should be brought to bear on this decision making.

Treatment Recommendations:

The deliberations of the treatment workgroup highlighted the need to move quickly to provide treatment options to Gulf War veterans. However, this need for swift action must be balanced with the equally important requirement that all treatment recommendations be based upon rigorous scientific methods with careful attention given to protecting the rights of patient participants. Anecdotal findings may provide fruitful avenues for innovative treatment approaches; however, these alternative treatment modalities will require scientific assessment to determine their efficacy prior to being implemented with large numbers of Gulf War veterans. This effort to provide effective treatment to Gulf War veterans will be hastened by examining and utilizing interventions that have been proven to be effective with other populations with similar overlapping conditions. This would include using interventions that have been proven to be effective for coping with pain, improving sleep quality, and minimizing memory deficits. For example, cognitive behavioral therapy techniques have been found to be effective in these areas (17-19).

Significant progress in initiating treatment trials for Gulf War veterans was made in 1999. VA and DoD initiated two clinical treatment trials which should assist in the search for effective treatment regimens for Gulf War veterans. One study, the exercise/behavioral therapy trial, will focus on aerobic exercise and behavioral therapy to reduce the severity of chronic symptoms among Gulf War veterans who report pain, fatigue, and/or cognitive difficulties. More than 1,300 veterans will be enrolled at VA and DoD medical centers across the U.S. The trial will assess whether exercise and cognitive behavioral therapy, separately or in combination, improve physical function.

The second treatment trial will focus on assessing the effectiveness of antibiotic treatment in reducing Gulf War veterans' chronic symptoms. This will be a multi-site, 30-month, double-blind clinical trial of antibiotic treatment of symptomatic patients with positive findings for mycoplasma infection. The trial will identify 450 Gulf War veterans who are experiencing at least two of three chronic symptoms (fatigue, musculoskeletal pain, and neurocognitive dysfunction) and who test

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positive for the microorganism *Mycoplasma fermentans*. Subjects will be randomly assigned to 12-month treatment with either 300 mg doxycycline per day or placebo. Outcome measures will include assessment of physical function, pain, fatigue, and cognitive functioning.

Despite these current activities, there is considerable dissatisfaction among veterans regarding the availability of treatment options. The recommendations of the treatment workgroup represent a broad range of approaches which may offer promise for addressing the treatment needs of Gulf War veterans. The deliberations of the treatment workgroup emphasized the need for expanded clinical options, including clinical trials to examine the efficacy of alternative treatment approaches using sound scientific methods. The workgroup also emphasized the importance of expanding current outreach efforts to assess the needs of Gulf War veterans and to ensure that they and their health care providers are informed of the latest developments on Gulf War related research and clinical information.

Prevention Recommendations:

The prevention workgroup emphasized the importance of first assessing the steps that have been taken by DoD since the Gulf War to protect troop health. While a number of interventions are already in place, the workgroup noted that DoD and VA should significantly enhance their efforts to foster objective and thorough examination of the Gulf War experience (and subsequent deployments) in accord with widely accepted principles of public health. Lessons learned from the Gulf War (as well as from deployments in Bosnia, Haiti, and Somalia) include the need to correct deficiencies in record keeping, poor understanding of the relationship between exposure and response, and inadequate health risk communication. Valuable work and knowledge resides in the civilian sector. These sources have much to contribute to improvement of the overall health status of service members deployed in a wide range of environments.

Several major efforts to protect the health of deployed U.S. forces have been initiated since the Gulf War. DoD has initiated a force health protection strategy to provide maximum health protection to service members throughout their military service. This strategy includes components to achieve a healthy and fit force, to enhance casualty prevention, and to improve casualty care and management. DoD, HHS, and VA jointly developed a strategic plan for improving the health of military veterans and their families. *The Presidential Review Directive on Planning for Health Preparedness for and Readjustment of the Military, Veterans, and Their Families after Future Deployments* (14) includes recommendations for improving deployment health, record keeping, research, and health risk communication. More recently, IOM issued a report on strategies to protect the health of deployed U.S. forces (20). This report contains detailed recommendations regarding medical surveillance, post-deployment reintegration, medical record keeping, risk communication, and strategies to address medically unexplained symptoms and to improve force health protection in reserve military components.

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Clearly, considerable steps have been taken to develop strategies to prevent illness in future deployments. However, continued vigilance is needed to ensure that these “lessons learned” are put into practice in ways that are compatible with military service. Reliance upon basic public health principles and well-tested models and research tools, such as those currently used in occupational settings, will enhance our efforts to protect the health of military personnel throughout their life-cycle.

Summary:

HHS convened this conference in order to further the dialogue among government officials, scientists, and veterans on issues of upmost concern to the veterans of the Gulf War. Despite considerable government- and non-government-sponsored research to address the health impact of the Gulf War, we have yet to find the scientific basis for these veterans’ unexplained illnesses. This conference highlighted the importance of including veterans in the process of planning and implementing research. Veterans and scientists alike expressed that they found the process useful and that future similar efforts should be encouraged.

The recommendations developed at this conference represent the deliberations of the workgroup participants and do not necessarily imply endorsement by the veteran or scientific community as a whole or by the federal government. The purpose of this report is to document the conference workgroup deliberations and to form the basis for further discussions regarding the direction of research into illnesses among Gulf War veterans.

It is anticipated that this report will be of interest to a broad range of individuals and organizations and may encourage new research collaborations and exchanges. HHS has coordinated its Gulf War related research activities with those of the two principally responsible agencies, DoD and VA, through the RWG of the Persian Gulf Veterans Coordinating Board. It is through the RWG that the federal research agenda is developed and coordinated. Recommendations for new research will need to be considered in light of the existing research portfolio of the RWG.

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Appendix A

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CDR Patrick McNeilly - Deputy Director, Office of Military Liaison and Veterans Affairs, Office of Public Health and Science, Office of the Secretary, Department of Health and Human Services, Washington, DC

Moiz Mumtaz, PhD - Science Advisor, Research Implementation Branch, Division of Toxicology, Agency for Toxic Substances and Disease Registry, Atlanta, Georgia

Sheila Newton, PhD - Director of Policy, Planning, and Evaluation, Office of the Director, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina

Phillip Talboy, PHA (Co-Chair) - Deputy Chief, Veterans' Health Activity Working Group, Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia

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Appendix C

Participants at July 21, 1998 Public Planning Meeting

Steven Adams, PHA - Meeting Moderator, Radiation Studies Branch, Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia

Drue H. Barrett, PhD - Chair, Executive Planning Committee, Chief, Veterans' Health Activity Working Group, Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia

Kelley Brix, MD, MPH - Medical Staff, Office of the Special Assistant for Gulf War Illnesses, SRA, Inc., Falls Church, Virginia

Stuart M. Brooks, MD - Professor, Colleges of Medicine and Public Health, Director, Sunshine Education and Research Center, Department of Environmental and Occupational Health, College of Public Health, University of South Florida, Tampa, Florida

Roger Burns (Observer) - Editor, CFS-NEWS Newsletter, Washington, DC

Janice Elaine Chambers, PhD - William L. Giles Distinguished Professor, Director, Center for Environmental Health Science, College of Veterinary Medicine, Mississippi State University, Mississippi State, Mississippi

Donna J. Dean, PhD - Member, Executive Planning Committee, Senior Advisor to the Deputy Director, National Institutes of Health, Bethesda, Maryland

Albert H. Donnay, MHS - Director, MCS Referral and Resources, Baltimore, Maryland

Asaf Durakovic, MD, PhD, FACP - Professor, Georgetown University, Department of Nuclear Medicine, Washington, DC

CDR David Edman (Observer) - Staff Director, Persian Gulf Veterans Coordinating Board, Interagency Support Office, Washington DC

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COL Edward Elson - Medical Director, Persian Gulf Veterans Coordinating Board, Interagency Support Office, Washington DC

Henry Falk, MD - Director, Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia

COL John Graham, MSc, MB, FFPHM - British Liaison Officer (Gulf Health), British Embassy, Washington DC

Robert W. Haley, MD, FACE, FACP - Director, Division of Epidemiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas

Thomas Michael Hennessy, Jr. - RESCIND, Inc., Potomac, Maryland

Anne Houser (Observer) - Office of Legislative Policy and Analysis, National Institutes of Health, Bethesda, Maryland

CAPT G. Bryan Jones - Emergency Coordinator, Office of Emergency Preparedness, Region 3, Philadelphia, Pennsylvania

Howard Kehrl, PhD - Medical Officer, Human Studies Division, U.S. Environmental Protection Agency, Human Studies Facility, Chapel Hill, North Carolina

Howard Matthew Kipen, MD, MPH - Director, Division of Occupational Health, Environmental and Occupational Health Sciences Institute, UMDNJ-Robert Wood Johnson Medical School, Piscataway, New Jersey

Andras L. Korenyi-Both, MD, PhD - Medical Director, Clinical Laboratories, Comprehensive Medical Network, Old Forge, Pennsylvania

John Kraemer (Observer) - Senior Staff Analyst, Environmental Agents Service, Department of Veterans Affairs, Washington DC

Chas. J. Lamielle (Observer) - National Center for Environmental Health Strategies, Inc, Voorhees, New Jersey

Mary Lamielle - Director, National Center for Environmental Health Strategies, Inc., Voorhees, New Jersey

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Brian J. Malkin, JD - Associate Director for Patents and Hearings, Office of Health Affairs, Office of the Commissioner, Food and Drug Administration, Rockville, Maryland

CAPT Peter Mazzella - Member, Executive Planning Committee, Director, Office of Military Liaison and Veterans Affairs, Office of Public Health and Science, Office of the Secretary, Department of Health and Human Services, Washington DC

John McNeill - Assistant Director for Veterans Benefits, Veterans of Foreign Wars, Washington, DC

LCDR Patrick McNeilly - Member, Executive Planning Committee, Deputy Director, Office of Military Liaison and Veterans Affairs, Office of Public Health and Science, Office of the Secretary, Department of Health and Human Services, Washington DC

William Joel Meggs, MD, PhD - Associate Professor of Emergency Medicine, Vice-Chair for Clinical Affairs, Chief, Division of Toxicology, Department of Emergency Medicine, East Carolina University School of Medicine, Greenville, North Carolina

Claudia S. Miller, MD, MS - Associate Professor, Department of Family Practice, Environmental and Occupational Medicine, University of Texas Health Science Center. San Antonio, Texas

John Muckelbauer (Observer) - Veterans of Foreign Wars, Washington DC

Andre A. Muelenaer, Jr., MD - Director, Pediatric Pulmonology, Carilion Medical Center for Children at Community Hospital of Roanoke Valley, Roanoke, Virginia

Moiz Mumtaz, PhD - Member, Executive Planning Committee, Science Advisor, Research Implementation Branch, Division of Toxicology, Agency for Toxic Substances and Disease Registry, Atlanta, Georgia

Frances Murphy, MD - Director, Environmental Agents Service, Public Health and Environmental Hazards Office, Department of Veterans Affairs, Washington DC

Sheila Newton, PhD - Member, Executive Planning Committee, Director of Policy, Planning, and Evaluation, Office of the Director, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina

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Deborah O. Norris, PhD - Neurotoxicologist, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC

Lawrence A. Plumlee, MD - President, Chemical Sensitivity Disorders Association, Corresponding Secretary, National Coalition for the Chemically Injured, Bethesda, Maryland

Matthew L. Puglisi - Assistant Director, Gulf War Programs, The American Legion, Washington, DC

Cindy Lynn Richard, CIH - Senior Scientist, Environmental Sensitivities Research Institute, Columbia, Maryland

Jonathan Silver Rutchik, MD, MPH - Medical Director, Division of Occupational and Environmental Neurology, Occupational Health and Rehabilitation, Inc., New York, New York

Ronald Simon, JD - Simon and Associates, Washington, DC

Lester Smith, PhD - Environmental Health Scientist, Executive Secretary, Interagency Work Group on Multiple Chemical Sensitivity, Office of the Assistant Administrator, Agency for Toxic Substances and Disease Registry, Atlanta, Georgia

Terry D. Spittler, PhD - Associate Director, Cornell Analytical Laboratories, Senior Research Associate, NYS Agricultural Experiment Station, Cornell University, Geneva, New York

William A. Suk, PhD - Chief, Chemical Exposures and Molecular Biology Branch, Division of Extramural Research and Training, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina

Paul Sullivan - Executive Director, National Gulf War Resource Center, Washington, DC

Phillip Talboy, PHA - Co-Chair, Executive Planning Committee, Deputy Chief, Veterans' Health Activity Working Group, Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia

James J. Tuite, III, MA - Director, Interdisciplinary Science, Chronic Illness Research Foundation, Annandale, Virginia

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Robert F. Vogt, PhD - Research Chemist, Clinical Biochemistry Branch, Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia

Note: Affiliations represent status at the time of the meeting.

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Appendix D

The Health Impact of Chemical Exposures During the Gulf War: A Research Planning Conference

Final Agenda

Day 1 (Sunday, February 28, 1999)

8:00 - 8:10 Welcome

Richard Jackson, MD, MPH - Director, National Center for Environmental Health, Centers for Disease Control and Prevention

Ruth Kirschstein, MD - Deputy Director, National Institutes of Health

CAPT Peter Mazzella - Director, Office of Military Liaison and Veterans Affairs, Office of Public Health and Science, Department of Health and Human Services

8:10- 8:30 Opening Remarks

The Honorable Bernard Sanders (I-Vermont) - U.S. House of Representatives

Session I - Background: Gulf War Chemical Exposures and their Health Impact

8:30 - 9:15 Key Note Address - The Gulf War Experience: Current Findings and Future Directions

G. Marie Swanson, PhD, MPH - Professor of Family Practice; Director, Cancer Center, Michigan State University

9:15 - 10:00 The Experience of Veterans (Panel Discussion)

Moderator: Donald Edwards - Major General, United States Army (Ret.); Special Projects Coordinator for Congressman Bernard Sanders

Anthony Hardie - President, Gulf War Veterans of Wisconsin; National Secretary, National Gulf War Resource Center

Rick Hirst - Training and Quality Control Specialist, Veterans of Foreign Wars

Debbie Judd, RN, MPA/HSA - President, Northern California Association of Gulf War Veterans; Board Member, National Gulf War Resource Center

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L. A. McClure - Referrals Coordinator, Alaska Gulf War Syndrome

Ronald Murray - President, Gulf War Veterans of Georgia; Board Member, National Gulf War Resource Center

Denise Nichols, RN, MSN, MAJ, USAFR (Ret.) - Vice-Chair, National Vietnam and Gulf War Veterans Coalition; President and Founder, Desert Storm Veterans of the Rocky Mountains

Matthew Puglisi - Assistant Director, Gulf War Programs, The American Legion

Victor Silvester - International President, Operation Desert Shield/Desert Storm Association

David Smith - State Commander, Idaho Desert Storm Justice Foundation

Debra Smith - Vice President, National Gulf War Resource Center

Joseph Violante - National Legislative Director, Disabled American Veterans

Session II - Possible Health Outcomes of Low Level Chemical Exposures: What Do We Know From the Civilian Literature?

Moderator: David Schwartz, MD, MPH - Professor of Medicine, University of Iowa College of Medicine

10:15 - 10:40 Health Effects of Chemicals on the Immune System

Noel Rose, MD, PhD - Professor of Pathology and Professor of Molecular Microbiology and Immunology, Johns Hopkins University

10:40 - 11:05 Health Effects of Chemicals on the Nervous System

Peter Spencer, PhD, FRCPath - Professor and Director, Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University

11:05 - 11:30 Health Effects of Chemicals on the Pulmonary/Respiratory System

Stuart Brooks, MD - Professor, Colleges of Medicine and Public Health; Director, Sunshine Education and Research Center, Department of Environmental and Occupational Health, College of Public Health, University of South Florida

11:30 - 12:00 Panel Discussion

Stuart Brooks, MD; Noel Rose, MD, PhD; David Schwartz, MD, MPH; Peter Spencer, PhD

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Session III - Multiple Chemical Sensitivity (MCS): Research and Clinical Findings among Gulf War Veterans and Civilian Populations

Moderator: Claudia Miller, MD, MS - Associate Professor, Department of Family Practice, Environmental and Occupational Medicine, University of Texas Health Science Center

1:30 - 2:15 Research on MCS and Gulf War Veterans (Panel Report on Current Research)

Iris Bell, MD, PhD - Staff Physician, Department of Psychiatry, Tucson Veterans Affairs Medical Center

Donald Black, MD - Professor of Psychiatry, University of Iowa College of Medicine

Daniel Clauw, MD - Associate Professor of Medicine and Orthopaedics, Chief, Division of Rheumatology, Immunology, and Allergy, Georgetown University

Nancy Fiedler, PhD - Associate Professor, Department of Environmental and Community Medicine, UMDNJ-Robert Wood Johnson Medical School

Susan Proctor, DSc - Associate Professor, School of Public Health, Boston University; Assistant Director, Boston Environmental Hazards Center, Boston VA Medical Center

2:15 - 3:00 MCS in Civilian Populations (Panel Discussion)

Iris Bell, MD, PhD - Staff Physician, Department of Psychiatry, Tucson Veterans Affairs Medical Center

James Cone, MD, MPH - Acting Chief, Occupational Health Branch, California Department of Health Services

Richard Graveling, PhD - Head, Department of Ergonomics, Institute of Occupational Medicine, United Kingdom

William Meggs, MD, PhD - Associate Professor of Emergency Medicine, Vice-Chair for Clinical Affairs, Chief, Division of Toxicology, Department of Emergency Medicine, East Carolina University School of Medicine

Anne Solomon, PhD, MA - Research Fellow, Department of Medicine, Pennsylvania State College of Medicine

Roberta White, PhD - Director, Boston Environmental Hazards Center, Boston VA medical Center

3:00 - 3:45 MCS: The Experience of Patients and Physicians (Panel Discussion)

Rebecca Bascom, MD, MPH - Professor of Medicine, Pennsylvania State College of Medicine

Leslie Israel, DO, MPH - Medical Director, UCSF-Stanford Employee and Occupational Health Services; Assistant Clinical Professor, Department of Medicine, University of California, San Francisco

Mary Lamielle - Executive Director, National Center for Environmental Health Strategies, Inc.

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William Rea, MD, FACS - Director, Environmental Health Center-Dallas
Cynthia Wilson - Executive Director and Chairman of the Board, Chemical Injury Information Network and Environmental Access Research Network

Session IV - Concurrent Workgroup Panels: Review of Major Research Issues

- 4:00 - 5:45 Workgroup 1: Chemical Exposures and Illnesses among Gulf War Veterans: Pathophysiology, Etiology, and Mechanisms of Action
- 4:00 - 5:45 Workgroup 2: Assessment/Diagnosis of Illnesses Associated with Chemical Exposures
- 4:00 - 5:45 Workgroup 3: Treatment of Gulf War Veterans
- 4:00 - 5:45 Workgroup 4: Prevention

7:30 - 9:00 Veterans Forum: Open Discussion Regarding Research Priorities

Facilitator: Michael Sage, MPH - Acting Deputy Director, Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Centers for Disease Control and Prevention

Day 2 (Monday, March 1, 1999)

Session V: Chemical Exposures: Possible Mechanisms of Action

Moderator: Timothy Gerrity, PhD - Special Assistant Chief Research and Development Officer, Office of Research and Development, Department of Veterans Affairs

- 8:00 - 8:20 Role of Susceptibility

Hermona Soreq, PhD - Professor of Molecular Biology, Head, Life Sciences Institute, Hebrew University

- 8:20 - 8:40 Synergistic Effects of Chemical Combinations

Mohamed Abou-Donia, PhD - Professor, Department of Pharmacology, Duke University Medical Center

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8:40 - 9:00 The Olfactory System: An Overview

Richard Doty, PhD - Director, Smell and Taste Center, Professor of Otorhinolaryngology, University of Pennsylvania Medical Center

9:00 - 9:20 Toxicant-Induced Loss of Tolerance and Masking

Claudia Miller, MD, MS - Associate Professor, Department of Family Practice, Environmental and Occupational Medicine, University of Texas Health Science Center

9:20 - 10:00 Panel Discussion

Mohamed Abou-Donia, PhD; Richard Doty, PhD; Claudia S. Miller, MD, MS; Hermona Soreq, PhD

Session VI: Concurrent Workgroup Panels: Opportunity for Public Input Regarding Research Recommendations

10:15 - 12:00 Workgroup 1: Chemical Exposures and Illnesses Among Gulf War Veterans: Pathophysiology, Etiology, and Mechanisms of Action

10:15 - 12:00 Workgroup 2: Assessment/Diagnosis of Illnesses Associated with Chemical Exposures

10:15 - 12:00 Workgroup 3: Treatment of Gulf War Veterans

10:15 - 12:00 Workgroup 4: Prevention

Session VII: Studying the Health Impact of Chemical Exposures During the Gulf War: Methodological Considerations

Moderator: Stephen Thacker, MD, MSc - Director, Epidemiology Program Office, Centers for Disease Control and Prevention

1:30 - 2:00 Current Status of Gulf War Exposure Data

Jack Heller, PhD - Senior Scientist, Deployment Environmental Surveillance Program, United States Army Center for Health Promotion and Preventive Medicine

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2:00 - 3:00 Research Strategies (Panel Discussion)

Rebecca Bascom, MD, MPH - Professor of Medicine, Pennsylvania State College of Medicine

John Feussner, MD - Chief Research and Development Officer, Office of Research and Development, Department of Veterans Affairs

Gary Gackstetter, DVM, MPH, PhD - Colonel, United States Air Force, Biomedical Sciences Corps; Assistant Professor and Deputy Director, Division of Epidemiology and Biostatistics, Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences

Robert Haley, MD, FACE, FACP - Director, Division of Epidemiology, Department of Internal Medicine, University of Texas Southwestern Medical Center

David Ozonoff, MD, MPH - Chair, Department of Environmental Health, Boston University School of Public Health; Medical Director, Boston Environmental Hazards Center, Boston VA Medical Center

Session VIII: Concurrent Workgroup Panels: Finalization of Research Recommendations

3:15 - 5:30 Workgroup 1: Chemical Exposures and Illnesses Among Gulf War Veterans: Pathophysiology, Etiology, and Mechanisms of Action

3:15 - 5:30 Workgroup 2: Assessment/Diagnosis of Illnesses Associated with Chemical Exposures

3:15 - 5:30 Workgroup 3: Treatment of Gulf War Veterans

3:15 - 5:30 Workgroup 4: Prevention

Day 3 (Tuesday, March 2, 1999)

Session IX: Concurrent Workgroup Panels: Finalization of Research Recommendations (Continued)

8:00 - 9:30 Workgroup 1: Chemical Exposures and Illnesses Among Gulf War Veterans: Pathophysiology, Etiology, and Mechanisms of Action

8:00 - 9:30 Workgroup 2: Assessment/Diagnosis of Illnesses Associated with Chemical Exposures

8:00 - 9:30 Workgroup 3: Treatment of Gulf War Veterans

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8:00 - 9:30 Workgroup 4: Prevention

Sesion X - Research Recommendations

Moderator: Drue Barrett, PhD - Chief, Veterans' Health Activity Working Group, National Center for Environmental Health, Centers for Disease Control and Prevention

9:45 - 11:45 Report from Workgroups and Discussion

11:45 - 12:00 Closing Remarks and Adjournment

Henry Falk, MD MPH - Director, Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Centers for Disease Control and Prevention

Appendix E

Workgroup Members and Facilitators

Pathophysiology Workgroup:

Members

Mohamed Abou-Donia, PhD - Professor, Department of Pharmacology, Duke University Medical Center

David Ashley, PhD - Chief, Air Toxicants Branch, Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention

Iris Bell, MD, PhD - Staff Physician, Department of Psychiatry, Tucson Veterans Affairs Medical Center

COL Andras L. Korenyi-Both, MD, PhD - United States Army National Guard; Medical Director and Director of Clinical Laboratories, Comprehensive Medical Network, Pennsylvania

Claudia Miller, MD, MS - Associate Professor, Department of Family Practice, Environmental and Occupational Medicine, University of Texas Health Science Center

Deborah Norris, PhD - Neurotoxicologist, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics

Arnold Peckerman, PhD - Assistant Professor, Department of Neurosciences, University of Medicine and Dentistry of New Jersey; Director, Psychophysiology Laboratory. Gulf War Research Center, East Orange VA Medical Center

Satu Somani, PhD - Professor of Pharmacology and Toxicology, Department of Pharmacology, Southern Illinois University School of Medicine

Hermona Soreq, PhD - Professor of Molecular Biology, Head, Life Sciences Institute, Hebrew University

Barbara Sorg, PhD - Assistant Professor, Program in Neuroscience- VCAPP Department, Washington State University

Peter Spencer, PhD - Professor and Director, Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University

*Barry Wilson, PhD - Professor, Department of Animal Science and Department of Environmental Toxicology, University of California, Davis (**Workgroup Chair**)*

Facilitators

Sheila Newton, PhD - Director of Policy, Planning, and Evaluation, Office of the Director, National Institute of Environmental Health Sciences, National Institutes of Health

William Suk, PhD - Chief, Chemical Exposures and Molecular Biology Branch, Division of Extramural Research and Training, National Institute of Environmental Health Sciences,

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National Institutes of Health

Assessment and Diagnosis Workgroup:

Members

Maria Rosario Araneta, PhD, MPH - Epidemiologist, Emerging Illness Research Team, Naval Health Research Center

Lawrence A. Bradley, PhD - Professor of Medicine, Division of Clinical Immunology and Rheumatology, University of Alabama, Birmingham

James Cone, MD, MPH - Acting Chief, Occupational Health Branch, California Department of Health Services

Albert Donnay, MHS - Director, MCS Referral and Resources

Gary Gackstetter, DVM, MPH, PhD - Colonel, United States Air Force, Biomedical Sciences Corps; Assistant Professor and Deputy Director, Division of Epidemiology and Biostatistics, Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences

Robert Haley, MD, FACE, FACP - Director, Division of Epidemiology, Department of Internal Medicine, University of Texas Southwestern Medical Center

Howard Kipen, MD, MPH - Associate Professor, Director, Division of Occupational Health Environmental and Occupational Health Sciences Institute, UMDNJ-Robert Wood Johnson Medical School

Linda McCauley, PhD - Associate Professor, Oregon Health Sciences University, Center for Research on Occupational and Environmental Toxicology

Karen Schmaling, PhD - Associate Professor of Psychiatry and Behavioral Sciences, University of Washington

Edward Shorter, PhD - Professor, History of Medicine, Faculty of Medicine, University of Toronto

Terry Spittler, PhD - Senior Research Associate, Center for the Environment and Department of Food Science and Technology, Cornell University

Robert Vogt, PhD - Research Chemist, Clinical Biochemistry Branch, Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention

*Roberta White, PhD - Director, Boston Environmental Hazards Center, Boston VA medical Center (**Workgroup Chair**)*

Facilitators

CDR Patrick McNeilly - Deputy Director, Office of Military Liaison and Veterans Affairs, Office of Public Health and Science, Office of the Secretary, Department of Health and Human Services

Moiz Mumtaz, PhD - Science Advisor, Research Implementation Branch, Division of Toxicology,

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Agency for Toxic Substances and Disease Registry

Treatment Workgroup:

Members

Rebecca Bascom, MD, MPH - Professor of Medicine, Pennsylvania State College of Medicine
Stuart Brooks, MD - Professor, Colleges of Medicine and Public Health, Director, Sunshine Education and Research Center, Department of Environmental and Occupational Health, College of Public Health, University of South Florida
Daniel Clauw, MD - Associate Professor of Medicine and Orthopaedics, Chief, Division of Rheumatology, Immunology, and Allergy, Georgetown University
Kirstina Dahl, MD - Clinical Instructor, Department of Neurosciences, University of Medicine and Dentistry of New Jersey
LTC Charles Engel, Jr. MD, MPH - Chief, Gulf War Health Center, Walter Reed Army Medical Center
Nancy Fiedler, PhD - Associate Professor, Department of Environmental and Community Medicine, UMDNJ-Robert Wood Johnson Medical School
Victor Gordan, MD - Staff Physician, Outpatient Service, Manchester VA Medical Center
Leslie Israel, DO, MPH - Medical Director, UCSF-Stanford Employee and Occupational Health Services; Assistant Clinical Professor, Department of Medicine, University of California, San Francisco
Mary Lamielle - Executive Director, National Center for Environmental Health Strategies, Inc.
William Meggs, MD, PhD - Associate Professor of Emergency Medicine, Vice-Chair for Clinical Affairs, Chief, Division of Toxicology, Department of Emergency Medicine, East Carolina University School of Medicine
*Benjamin Natelson, MD - Professor, Department of Neuroscience, New Jersey Medical School; Medical Director, Center for Environmental Hazards Research, East Orange VA Medical Center (**Workgroup Chair**)*
Michael Sharpe, MA, MB, MRCP, MRCPsych - Senior Lecturer in Psychological Medicine, University of Edinburgh, Royal Edinburgh Hospital
Anne Solomon, PhD, MA - Research Fellow, Department of Medicine, Pennsylvania State College of Medicine

Facilitators

Edwin Kilbourne, MD - Senior Medical Officer, Office of the Director, Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Centers for Disease Control and Prevention
Mitchell Wolfe, MD, MPH - Epidemic Intelligence Service (EIS) Officer, Surveillance and Programs Branch, Division of Environmental Hazards and Health Effects, Centers for Disease Control and Prevention

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Prevention Workgroup:

Members

Henry Anderson, MD - Environmental/Occupational Epidemiologist, Division of Public Health, Wisconsin Department of Health and Family Services

Lt Col Philip Bolton - Medical Advisor, Gulf Veterans Illnesses Unit, Ministry of Defence, Whitehall, London

Larry Edmonds, MSPH - Acting Chief, State Services Branch, Division of Birth Defects and Pediatric Genetics, National Center for Environmental Health, Centers For Disease Control and Prevention

Timothy Gerrity, PhD - Special Assistant Chief Research and Development Officer, Office of Research and Development, Department of Veterans Affairs

Jack Heller, PhD - Senior Scientist, Deployment Environmental Surveillance Program, US Army Center for Health Promotion and Preventive Medicine

CAPT Michael Kilpatrick, MD - Director, Medical Outreach and Information, Office of the Special Assistant for Gulf War Illnesses

Max Lum, EdD, MPA - Associate Director for Health Communication, National Institute of Occupational Safety and Health

*Melissa McDiarmid, MD, MPH - Assistant Professor of Medicine, University of Maryland; Director, VA Depleted Uranium Program, Occupational Health Project, Baltimore VA Medical Center (**Workgroup Chair**)*

James Pirkle, MD, PhD - Assistant Director for Science, Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention

Douglas Rokke, PhD - Assistant Professor, Department of Physical and Earth Science, Jacksonville State University

COL Ken Scott, MD - Assistant Chief of Staff, Health Support Operational Training Units Canadian Forces Medical Group - Headquarters

LT COL Bob Thompson, Preventive Medicine Action Officer, Logistics Directorate, Medical Readiness Division, The Joint Staff

James Tuite, III, MA - Director, Interdisciplinary Science, Chronic Illness Research Foundation

Facilitators

Donna Dean, PhD - Senior Advisor to the Deputy Director, National Institutes of Health

Timothy Tinker, DrPH, MPH - Chief, Communications and Research Branch, Division of Health Education and Promotion, Agency for Toxic Substances and Disease Registry

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Appendix F

Summary of Workgroup Members' Presentations and Highlights of Audience Input

Pathophysiology Workgroup:

Workgroup Member Presentations

Dr. Mohamed Abou-Donia raised three questions that he thought would be important for the workgroup to consider: 1) What is the effect of low-level exposures, that is, exposures below a threshold level that would cause acute effects? 2) What is causing the delay period between time of exposure and onset of clinical signs? 3) What is the prognosis for those who have been exposed and who report illnesses?

Dr. David Ashley emphasized the importance of recognizing and studying the role of genetic susceptibility in influencing health outcomes in Gulf War veterans.

Dr. Iris Bell posited that a substantial subset of Gulf War veterans' illnesses could be explained by chemical sensitization or chemical intolerance. She also suggested avenues for study of factors that may render individuals more susceptible to chemical sensitization, including parental genes or exposures, earlier stresses in an individual's life, use of addictive substances, and either peak acute chemical exposures or repeated chemical exposures at lower levels.

COL Andras Korenyi-Both drew the panel's attention to the role of sand as a common denominator. He described his chemical investigations on sand content and his work on Al Eskan Disease, involving an immune reaction to the properties of sand located in the central and eastern region of the Arabian Peninsula. COL Korenyi-Both suggested that low level chemical warfare agents saturated sand particles and entered the blood stream, resulting in a variety of clinical symptoms. He recommended studies of sand samples to detect chemical warfare agent contamination and studies of the neuromuscular junction by muscle biopsies of symptomatic Gulf War veterans to detect signs of low density exposure to cholinesterase-inhibiting chemicals.

Dr. Claudia Miller discussed a theory of disease involving loss of specific tolerance for previously tolerated exposures, including environmental chemicals, foods, and drugs. She described how a controlled-exposure hospital unit could be used for studies of people affected with this loss of tolerance to determine specific disease mechanisms.

Dr. Deborah Norris pointed out that assessing human health risk from exposure to a mixture of chemicals, as opposed to basing assessments on information for individual chemicals, is important to the understanding of illnesses among Gulf War veterans. However, it is a methodology that is still developing. Environmental Protection Agency risk assessment and testing guidelines on

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interactions of chemical exposures can provide some insights toward the development of a research program for Gulf War veterans' illnesses.

Dr. Arnold Peckerman reported results from his studies on altered immune function in sick versus healthy Gulf War veterans, looking at the relationships between self-reported exposure to chemicals, post-traumatic stress disorder (PTSD), and levels of cytokines. In his analyses, veterans who reported a low level of chemical exposures showed no relationships between their PTSD scores and two cytokines (interleukin-2 and tumor necrosis factor-alpha); however, in veterans who reported moderate to high levels of chemical exposures, there was a positive relationship between the present PTSD scores and those two cytokine levels. These studies suggest that Gulf War veterans have altered immune function and that the combination of chemical exposure (as self-reported by veterans at this time) and stress levels experienced by troops during the war predicts some immune functions currently measurable.

Dr. Satu Somani is studying neurotoxic effects of interactions of pyridostigmine, sarin, and physical exertion. He reported results suggesting that physical stress enhances the delayed effects of pyridostigmine in mice, possibly due to oxidative damage from the generation of free radicals.

Dr. Hermona Soreq described the use of molecular biology to develop rapid, accurate tests for exposure and risk assessment and also to help identify those who might be at greatest health risk from exposure. She also described gene manipulation studies using transgenic animals in order to study the mechanisms of delayed pathology resulting from exposures.

Dr. Barbara Sorg described studies testing the sensitization hypothesis and developing a rat model for multiple chemical sensitivity, using responses to cocaine or amphetamine as a measure of brain changes. In her studies, exposing these animals to formaldehyde caused them to show a sensitized response to cocaine.

Dr. Peter Spencer discussed approaches that could be used in order to differentiate and to compare the health effects of groups of veterans who had different sets of exposures in the various deployment phases of the Gulf War.

Dr. Barry Wilson described the charge of the workgroup and the importance of the deliberations as a "two-way street" between workgroup and audience members. He suggested a process for developing a list of research recommendations which involved focusing on the important unfulfilled directions of research. He also emphasized that the best science must drive the effort and that the recommendations should be based on testable hypotheses and relevance to veterans. Dr. Wilson described several paradigms for conducting research, including population level, individual level, organ level, cell level, and molecular level research. He suggested that single level research will not provide answers regarding the mechanisms responsible for illnesses of Gulf War veterans.

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Audience Input

The final research recommendations proposed by the pathophysiology workgroup reflect the many comments made by audience members during the workgroup sessions. Some points raised by audience members were:

- ' Include studies of effects of vaccines and physical exposures (such as electric and magnetic fields) as well as chemical exposures.
- ' Make sure of the consistency of case definitions in studies of veterans.
- ' Exercise care in study design to facilitate the extrapolation of results from animals to humans.
- ' Include neurological studies of larger groups of veterans.
- ' Conduct more studies on the synergistic effects of pesticides and other exposures.
- ' Try to get more veterans under study by using wider recall techniques.
- ' Look at cellular energetic deficiencies and blocks as a mechanism behind many or all symptoms of Gulf War illnesses.
- ' Do more lymphocyte testing and testing for EEG abnormalities.
- ' Measure levels of toxic chemicals in various body tissues and fluids before, during, and after detoxification in order to verify the chemical etiology of illness.
- ' Examine pre-morbid indicators of delayed neurological deficits (like Parkinson's or Alzheimer's diseases), especially interactive factors.
- ' Disseminate the results of epidemiologic studies more widely.
- ' Consider the need for a Gulf War library or bibliography.

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Assessment and Diagnosis Workgroup:

Workgroup Member Presentations

Dr. Happy Araneta presented a short discussion of chemically induced adverse reproductive and perinatal outcomes. She stressed the importance of the paternal contribution in adverse reproductive outcomes since the majority of Gulf War veterans are males. Dr. Araneta described the need for proper exposure measurements and identification of confounding variables.

Dr. Lawrence Bradley discussed the lack of standardization in the methods for assessment and diagnosis of chronic fatigue syndrome (CFS), fibromyalgia (FM), and multiple chemical sensitivities (MCS). He emphasized the need both for clarity in the criteria used in making diagnoses and for the ability to rule out competing sources of variance in research findings.

Mr. Albert Donnay summarized published information on MCS over the years and the evolution into its present day definition. He also submitted to the workgroup a list of criteria that he proposed would be useful for defining MCS.

COL Gary Gackstetter briefly described his early work addressing the health concerns of Gulf War veterans. Originally, researchers assumed that an answer should be easy to find; it would just involve establishing a tight case definition and quantifying exposures. However, researchers soon realized that the problem was much more complex.

Dr. Robert Haley presented a discussion in support of the theory that the illnesses affecting Gulf War veterans are a common-source epidemic and proposed that the study of the illnesses should be done in the same manner as studies for other epidemics. Dr. Haley emphasized that a case definition needs to be derived and that the next step would be to do a case control study using that case definition. He continued with a brief description of the work he is doing with a group of Seabees in an effort to develop a case definition.

Dr. Howard Kipen discussed the problem of observing patients with no physical signs but who are sensitive to chemicals. He pointed out that unexplained symptoms are common in the general population without identifiable organic cause. These symptoms need a systematic investigation to adequately identify an underlying disorder. Dr. Kipen also described the confounding of symptoms in patients with psychiatric disorders.

Dr. Linda McCauley provided background on a case control study involving a case definition that consisted of five major areas: musculoskeletal pain, fatigue, cognition problems, gastrointestinal complaints, and skin rash. She described how some symptoms (e.g., rashes and gastrointestinal complaints) did not appear to affect patients in the study and a revised case definition was derived without these factors.

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Dr. Karen Schmaling discussed areas of importance when dealing with CFS patients, including precise determination of confounding psychiatric disorders and elimination of interviewer bias. Dr. Schmaling also suggested looking at factors that might still be sustaining the illness and increase efforts to identify clusters of symptoms using factor analytic techniques.

Dr. Edward Shorter provided a history of somatization disorders which throughout the years have presented in various forms. He emphasized the role of the media and the loss of prestige of the medical profession as factors influencing the epidemic spread of illness attribution.

Dr. Terry Spittler provided some insight on additional avenues leading to information related to exposures in Gulf War veterans. He emphasized that reviewing inventories and interviewing veterans regarding their practices with environmental hazards might yield additional information on exposures.

Dr. Robert Vogt described his work at the Division of Laboratory Sciences at the National Center for Environmental Health looking at populations for new markers. He emphasized the importance of examining the role of the immune system in illnesses affecting Gulf War veterans and the need for collecting standardized data. He also stressed the importance of conducting case-control studies.

Dr. Roberta White presented comments relating to the experience of war and the overlap of variables that produce symptoms in individuals. Such factors include climate and geographic conditions, infectious disease, as well as individual factors that may play a role in the overall response of people following exposure to chemicals. Dr. White described the charge of the workgroup and gave the operative directions for the group.

Audience Input

The audience input emphasized the importance of proper diagnosis and assessment of Gulf War veterans. Participants strongly pointed to the need for a case definition to correctly diagnose the illnesses faced by veterans and separate definable disorders (e.g., PTSD) from undiagnosed illnesses in Gulf War veterans. They also expressed concern that efforts need to be expanded in the areas of diagnosis and treatment of veterans with undiagnosed illnesses and that it should be recognized that although these patients do not present with an easily definable disease, treatment may still be necessary. Furthermore, the audience emphasized the importance of physicians and other health care workers listening to veterans so that they may properly identify problems and determine possible exposures that may have an impact on the patient's condition. Other members of the audience were concerned about the role that multiple chemical sensitivities may play in illnesses affecting Gulf War veterans, and specifically about the impact of fragrances.

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Specific areas that the audience recommended for inclusion in the research agenda included:

- ' Investigation of the role of autoimmunity in Gulf War illnesses.
- ' Comparisons of Gulf War veterans with other populations presenting with similar symptoms (e.g., Chernobyl liquidators) to identify relationships between exposures and symptoms that may provide insight into the problems seen in Gulf War veterans.
- ' Studies of the role of depleted uranium in the illnesses faced by veterans.
- ' Investigations into the cause of deaths of Gulf War veterans (e.g., studies done at autopsy) to assess physiologic and morphologic changes that may result from exposures during the conflict.

Treatment Workgroup:

Workgroup Member Presentations

Dr. Rebecca Bascom discussed the importance of including in treatment research an assessment of issues of importance to the patient, such as the patient's view of what constitutes an adverse health event. Quality of life instruments can serve this purpose and should be used as an outcome measure for any proposed treatment trial.

Dr. Stuart Brooks emphasized that, although research has been unable to identify an etiological cause for the unexplained illnesses of Gulf War veterans, there are existing treatment protocols that can be evaluated without knowing the specific etiologic factors of the illnesses. Treatment protocols such as cognitive therapy, wellness protocols, exercise programs, and others should be tested as soon as possible.

Dr. Dan Clauw suggested that treatment regimens that have been used successfully for FM and CFS should be used to treat Gulf War veterans. In treating Gulf War veterans, clinicians must pay attention to the physiology of the illness(es) and the consequences of illness. Examples of consequences of illness include de-conditioning, loss of function, and mood disorders. Dr. Clauw suggested that initial low doses followed by gradually increased doses of medications, such as tricyclic anti-depressants and beta blockers, may be effective in reducing Gulf War veterans symptoms, which will then make adherence to cognitive-behavioral treatments more likely.

Dr. Kristina Dahl discussed research on the role of cardiovascular dysregulation and war time stress in illnesses among Gulf War veterans. The research suggests that Gulf War veterans with chronic fatigue may have inadequate cardiovascular responses to stressful behavioral activities, a

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condition which could have metabolic consequences consistent with fatigue. Cardiovascular dysregulation seen in those with chronic fatigue is worsened by PTSD. Dr. Dahl suggested that these effects are surprising as previous research has found that PTSD is associated with an autonomic over-reactivity. The fact that cardiovascular hypo-reactivity was correlated with poor clinical status suggests that treating cardiovascular hypo-reactivity may result in clinical improvement. The orthostatic hypotension seen in the patients with chronic fatigue and PTSD suggests that treatment with vasoconstrictors and agents that increase blood volume may be beneficial.

LTC Charles Engel recommended that evidence-based treatments that have been applied to other populations with physical symptom-based disorders be evaluated to determine their effectiveness when used with Gulf War veterans. LTC Engel described the Gulf War treatment program at Walter Reed Army Medical Center. The important components of this treatment include collaboration among medical disciplines and between the veteran and the health care provider, a focus on disability rather than disease, and education of both patient and significant others about the patient's health conditions. The major goals of the treatment are to improve health and overall quality of life and diminish distress about symptoms. Three-month data from the Walter Reed program indicate modest improvements in quality of life, distress, and symptom reports.

Dr. Nancy Fiedler discussed the importance of clinical decision-making regarding appropriate treatments to offer Gulf War veterans. Clinicians should use a single case research design to evaluate the impact of their interventions. Interventions should be multi-modal in nature and problem-focused. The strategy should be first to assess what the primary problems are, and then to put people in groups according to those primary problems, gear interventions towards those problems, and evaluate them.

Dr. Victor Gordan described his experience in evaluating over 650 Gulf War veterans. He has had disappointing results when focusing treatment on relief of individual symptoms. Dr. Gordan hypothesized that illness among Gulf War veterans may involve widespread inflammation which affects many organ systems. He suggested that treatment which focuses on reducing inflammation should be tried. Dr. Gordan also emphasized the importance of spending time with and listening to the patient.

Dr. Leslie Israel discussed clinical management options that are effective with chemically sensitive patients. These include non-judgmental supportive treatment; reduction of odors and irritants, and importantly, enhancement of the patient's control over his or her environment; behavioral desensitization, which can be done through bio-feedback and other rehabilitation approaches; treatment of co-existing illnesses; and pharmacologic treatment for symptomatic relief. Dr. Israel also emphasized that training of physicians should begin during residency training and should include occupational and environmental medicine training.

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Ms. Mary Lamielle discussed her work with civilian populations with MCS. She suggested that Gulf War veterans might benefit from changing their behavior to reduce or avoid intake of tobacco, caffeinated beverages, high-fat foods, and prescription and over-the-counter medications. She suggested that research should be conducted to determine the effectiveness of minimizing or avoiding exposures using an environmental medical unit and imaging techniques. Ms. Lamielle also emphasized the importance of educating individuals with chemical sensitivities about government protections (i.e., Department of Housing and Urban Development policies) and the need for more research on the social consequences of illness.

Dr. William Meggs discussed the need for avoidance research to determine the role of low-level chemical exposures in chronic conditions. He also referred to hypotheses regarding the role of neurogenic inflammation in MCS and suggested that pharmaceutical research should focus on development of a Substance P inhibitor. Finally, he suggested that controlled trials should be completed to evaluate the effectiveness of detoxification regimens.

Dr. Natelson reviewed results from his research on exercise treatment for CFS. The study found that minor fatigue symptoms were reduced among patients in the exercise group, but fatigue remained unchanged.

Dr. Michael Sharpe described his experience treating CFS in the United Kingdom using a 16 session cognitive-behavioral treatment approach. He emphasized the importance of treatment being multi-modal, addressing not only the patient's beliefs, fears and concerns, but also their mood, their coping skills, and their behavior, particularly avoidant behavior, with the assumption that this will influence physiological processes. Dr. Sharpe has found that the maximum treatment effect was seen at one year post-treatment. He speculates that the treatment alters the way the patient thinks about his or her problem, increases active problem-solving and activity levels, and decreases avoidance. Dr. Sharpe acknowledged that using a multi-modal treatment approach does not allow for an assessment of whether one component is more effective than other components. Another approach is to use a single modal therapy, such as exercise treatment. He suggested that this approach is more effective if used on homogenous subgroups of patients who have limited comorbidity. Dr. Sharpe concluded that in order for treatment to be effective, it needs to be acceptable to the patient and intensive.

Dr. Anne Solomon described her experience using a desensitization treatment model that focused on visual tasks (i.e., art therapy). She suggested that specific types of art and music therapy be evaluated for their effectiveness with Gulf War veterans.

Audience Input

The audience input emphasized the need for the immediate provision of treatment to Gulf War

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veterans. Audience members suggested that the focus of further Gulf War related research efforts should be placed on clinical trials rather than on basic research. Novel or alternative treatment approaches that have anecdotal evidence of efficacy were strongly encouraged by audience members. The audience also strongly recommended that a veterans' advisory group oversee the research effort and that status reports on the effectiveness of the treatment should be provided to the advisory group in a timely fashion. Results of research should be integrated into the overall treatment of veterans as soon as possible. Establishment of a central effort to communicate information to veterans, physicians, and other researchers was recommended. It was suggested that this outreach effort could be accomplished through the Internet. The Website needs to allow for feedback through a question and answer feature that can be used to communicate with researchers. In addition, clinicians and researchers need to work in collaboration with veterans and their spouses/partners and do a better job of assessing what is important to the veterans.

Specific treatment approaches recommended or discussed by audience members included:

- ' Treatment that focuses on removing chemical toxins from the body. Examples provided included using enzymes, liposomes, or other carrier systems to remove chemicals from the body.
- ' Use of vitamin, mineral, and/or protein supplements.
- ' A detoxification program of exercise, sauna, and supplements.
- ' Treatment with calcium channel blockers, Gabitril®, full laboratory work-ups with lymphocyte profiles, fungal and viral panels and antibodies to screen for myelin, smooth and striated muscle antibodies, and stomach and thyroid antibodies.
- ' Treatment that focuses on decreasing inflammation and infection rather than altering neurotransmitters (e.g., use of Depakote®, Wellbutrin®, and antibiotics)
- ' The combined use of cognitive enhancers, anxiolytics, sleep medication, anti-depressants, beta blockers, and Modafinil®.
- ' Use of kinesiology and nutrition to treat chemical sensitivities.
- ' Use of median regulatory acupuncture.
- ' Use of glucosamine chondroitin, vitamin B1, thiamin, and methadone, for the treatment of pain.
- ' Use of medications (e.g., Aricept®) that have been found to be effective in improving

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cognitive symptoms among patients with Alzheimer's disease.

- ' Use of fish oil, lecithin, vitamin E, selenium, and raw oatmeal.
- ' Use of hyperbaric oxygenation and plasmapheresis.
- ' Use of medications to influence the immune system.

In addition to being interested in specific treatment recommendations, the audience expressed interest in a number of issues relating to diagnosis and assessment. Specifically, audience members expressed concern that proper testing of Gulf War veterans was not being done. Many audience members were interested in increasing the availability of a variety of imaging techniques. They also recommended wider testing for a variety of environmental exposures, especially testing for exposure to depleted uranium and mycoplasma infection. In addition, assessment of bipolar disorder was recommended, especially when anti-depressant medications are used. Specific assessment measures recommended included the Neuropsychological Impairment Scale and the Multi-dimensional Pain Inventory.

Prevention Workgroup:

Workgroup Member Presentations

Dr. Henry Anderson highlighted the importance of pre-screening efforts in identifying individuals who may be at increased risk for adverse health outcomes in deployments. He emphasized the critical need for training and education, both of the individual service member and at the unit level.

LT COL Philip Bolton described the National Health Service in the United Kingdom, especially its ability to conduct disease surveillance and to maintain central records. He included an overview of the United Kingdom's experience in the Gulf War and the lessons learned.

Mr. Larry Edmonds focused on the need to collect standard reproductive and fertility history from all personnel entering military service, and added that this information should be updated periodically. He also asserted the importance of collecting biological samples and storing blood specimens for subsequent use in clarifying medical histories of military personnel.

Dr. Timothy Gerrity presented an overview of risk assessment/risk management paradigms included in the National Science and Technology Council/Presidential Review Directive 5, "A National Obligation: Planning for Health Preparedness for and Readjustment of the Military, Veterans, and Their Families after Future Deployments." He identified points at which

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prevention, intervention, and treatment strategies can be applied, and discussed how these principles might be applied in improving health outcomes from deployments.

Dr. Jack Heller discussed concepts that are important to the development of better methods for environmental exposure assessment, particularly for those exposures of long duration at low-levels. He emphasized the importance of assessing synergistic and antagonistic interactions, and correlating these data with those obtainable from general exposure data and troop movement data.

CAPT Michael Kilpatrick discussed the difficulties facing the practicing military physician, particularly those problems related to communication of risk and effective prevention strategies.

Dr. Max Lum emphasized the importance of health education efforts, particularly those to be drawn from the experience of federal, state, and county public health officials in the civilian sector. He emphasized that risk communication strategies for the deployed service member require careful study.

Dr. McDiarmid reviewed general principles of public health medicine and related how these principles would be applicable to the workgroup's task of identifying fruitful new research directions. She presented a framework of control strategies which formed the context for the group's subsequent recommendations.

Dr. Douglas Rokke discussed procedures for identifying and handling toxic materials in the Gulf War theater and the role of mitigation efforts and criteria in limiting extent of exposures. He highlighted the need to recognize and select appropriate courses of action against various threats in the military arena.

COL Ken Scott described Canadian experiences, both in pre- and post-deployment surveillance activities of service members and in education of care givers.

LT COL Robert Thompson identified the key facets of the force health protection program, which brings a life cycle management approach to dealing with service members from recruitment through active duty, to subsequent civilian life. The key roles of health surveillance and ongoing health assessments were addressed, both for individual exposures and for unit exposures.

Mr. James Tuite highlighted elements of occupational safety programs that are suitable for military use and are adaptable for both peacetime and wartime environments. Hazard communication strategies, training at all levels, accountability for collection of baseline data, and maintenance of exposure records (including medical practices) were deemed critical.

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Audience Input

The audience members emphasized the core importance of analyzing the effectiveness of new or updated prevention strategies put in place by the Department of Defense since 1991. They also strongly affirmed the central importance of transmitting accurate, timely, and complete information to veterans and their physicians. The audience focused on two central questions regarding future research efforts: (1) What research should be done? and (2) How is that research going to effect change to protect service members in the future? Key areas of concern for audience members were:

- ' Defining levels of risk, both in the short-term and in the long-term.
- ' Developing effective risk communication strategies.
- ' Identifying metrics that can measure effectiveness of prevention strategies.
- ' Creating ways to effectively link the military health sector to the civilian health sector.
- ' Engineering protective equipment and gear to be used in environments of potential exposures.
- ' Improving nutritional content of food provided to service members in deployment arenas.
- ' Standardizing medical surveillance throughout the service member's life, both military and civilian.
- ' Including input from veterans throughout the process of developing prevention strategies.