GULF WAR VETERANS' ILLNESSES: THE RESEARCH AGENDA

HEARING

BEFORE THE

SUBCOMMITTEE ON HUMAN RESOURCES

OF THE

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT HOUSE OF REPRESENTATIVES

ONE HUNDRED FIFTH CONGRESS

SECOND SESSION

FEBRUARY 24, 1998

Serial No. 105–130

Printed for the use of the Committee on Government Reform and Oversight

U.S. GOVERNMENT PRINTING OFFICE

49–511 CC WASHINGTON : 1998

For sale by the U.S. Government Printing Office
Superintendent of Documents, Congressional Sales Office, Washington, DC 20402
ISBN 0-16-057235-5

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GULF WAR VETERANS' ILLNESSES: THE RESEARCH AGENDA

TUESDAY, FEBRUARY 24, 1998

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HUMAN RESOURCES,
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT,
Washington, DC.

The subcommittee met, pursuant to notice, at 10 a.m., in room 2154, Rayburn House Office Building, Hon. Christopher Shays (chairman of the subcommittee) presiding.

Present: Representatives Shays, Snowbarger, Towns, Kucinich, Allen, and Sanders.

Staff present: Lawrence Halloran, staff director; Robert A. Newman, professional staff member; and Cherri Branson, minority counsel.

Mr. SHAYS. I call this hearing to order and welcome our witnesses and our guests on this very important hearing, and welcome my colleagues, Mr. Towns and Mr. Sanders, as well.

In our oversight report on Gulf war veterans' illnesses, adopted without dissent by the full Government Reform and Oversight Committee in November, we found the Federal research effort had been blind to scientifically important but politically inconvenient, hypotheses about neurotoxic exposures. The committee recommended shifting control of the research agenda to an agency free of the institutional biases and doctrinal restraints we found hobbling the joint Veterans' Affairs and Defense Department program.

Today, we pursue and amplify that recommendation with an in-depth review of the Research Working Group of the Persian Gulf Veterans Coordinating Board, the interagency body now responsible for the evaluation and selection of the epidemiological, clinical and basic research critical to the health, and hopes, of sick veterans. The process and product of their work will tell us where we have been, where we are, and where we need to go in studying the causes and cures of Gulf war veterans' illnesses.

The issue today is not blame for false starts and past failures. The issue today, and every day until the discovery of effective treatments, is how to focus a 6-year-old, $115 million research program that appears to confuse motion for progress, quantity for quality, and breadth for depth. The current agenda, although lately pointed toward more probable and promising theories, still projects a diffused, confused path that stretches well over the millennial horizon.

Without that focus, without the discipline to ignore the deadening demands of institutional traditions and predispositions, we risk studying Gulf war veterans, literally, to death.

In looking for a sharper focus and a greater sense of urgency in Federal research, we are mindful of the incremental nature of the scientific inquiry. We share the inevitable frustration of researchers and patients as nature slowly yields her secrets. Many sick Gulf war veterans present complex, difficult to diagnose symptoms and disease states. Research into similar symptomatically described illnesses in the civilian population—fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity—appears as fragmented and inconclusive as Gulf war studies to date. But we are convinced the very intractability of the problem justifies, even demands, a more keenly concentrated approach.

For sick Gulf war veterans, the question is why private researchers appear to be making better progress than their Government in defining, and therefore understanding, their illnesses. They ask why studies are just beginning on wartime chemical exposures known to produce health effects at low levels in industrial settings. They ask why the starting point for so much research is psychological theory, stress, when their symptoms and pain are intensely physical.

To help answer these questions, we will hear testimony from members of the Research Working Group, the General Accounting Office, and researchers who have submitted proposals for evaluation and funding. We appreciate their time and expertise, and we truly look forward to their testimony.

Again, I would like to welcome our guests, those from the VA and the DOD and HHS as well as private researchers, and thank them all for being here.

At this time I would recognize my partner, Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman. Let me begin by saying I really, really appreciate the work that you have done in this area. You have really been involved, and I thank you and the staff for bringing us to this point in time. I think this is a very important hearing, and I again thank you.

Mr. Chairman, I want to also say to you that I think that we need to move in a very aggressive kind of way to make certain that the research that needs to be done is done. Anyone who follows this issue knows that this subcommittee's hearings and reports have led the way in examining the illnesses experienced by Persian Gulf war veterans.

Throughout this process, our ultimate goal has been to assure that veterans receive appropriate medical care at VA clinics and hospitals. Appropriate care requires effective treatment and competent practitioners. However, both the efficacy of the treatment and the capability of the professionals are jeopardized by ineffective or inappropriate research. Without proper research concerning the cause of illnesses and development of medicines to treat the disease, the practitioners and patients are left with few options and many frustrations.

Therefore, we are here today to assure that serious and substantial medical research is done to address the health problems faced by the Persian Gulf war veterans.

In previous hearings we have heard critiques and defenses of the research agenda. Out of those opinions, this subcommittee reached several conclusions. In our report we made several recommendations about the future research agenda and the coordination of research efforts by all agencies involved. Essentially, we are here today to determine whether the Research Working Group has implemented those recommendations and how we can help in assuring the implementation of our suggestions and the overall success of the research effort.

Mr. Chairman, I look forward to hearing from these outstanding witnesses about this very serious matter that we need to spend a lot of time on to make certain that we get to the bottom of it as fast as we possibly can. Thank you, and I yield back.

Mr. SHAYS. I thank the gentleman. At this time I recognize the gentleman from Maine. We are catching you just as you walk in here, but would you like to make a statement?

Mr. ALLEN. Very briefly, Mr. Chairman. I just want to say how much I appreciate your leadership on this particular issue.

This subcommittee reported last fall that, in our view, the Federal Government has failed to address the chronic ill effects which have disabled and compromised the health of thousands of our Gulf war veterans. A coordinated effort in addressing the neurological disorders afflicting a growing number of servicemen and women who served in the Gulf war theater is critical, and I look forward to today's testimony by the Research Working Group and the General Accounting Office on what measures the Federal Government has taken to coordinate research efforts and the effectiveness of those efforts. I am particularly interested in learning how the Research Working Group is responding to the recommendations made by this committee.

Thank you very much, Mr. Chairman. I yield back.

Mr. SHAYS. Thank you, Mr. Allen.

Just to get some housekeeping out of the way, I would ask unanimous consent that all members of the subcommittee be permitted to place any opening statements in the record and that the record remain open for 3 days for that purpose.

Without objection, so ordered.

I ask further that all witnesses be permitted to include their written statements in the record.

Without objection, so ordered.

At this time I will call on our panel: Dr. John Feussner, Chief Research and Development Officer, Department of Veterans Affairs, accompanied by Dr. Timothy Gerrity, Special Assistant to the Chief in the Research and Development Office, Department of Veterans Affairs. Second is testimony from Dr. Anna Johnson-Winegar, Director of Environmental and Life Sciences, Department of Defense. Dr. Drue Barrett from Environmental Hazards and Health Effects Division, Centers for Disease Control and Prevention. Also accompanied, not giving testimony but here to respond to questions in her soft voice, Dr. Sheila Newton.

So we will have testimony from three and we will have five participate in the dialog. I want to just call you all doctors now. Since my wife is seeking her doctorate, I know what it involves, and so

I am in awe of all of you for that. But if you would stand, I will swear you all in.

[Witnesses sworn.]

Mr. SHAYS. For the record, all of the witnesses have responded in the affirmative.

If we could go in the way I called you, Dr. Feussner, you are first and we look forward to your testimony. What I am going to do is, I am going to have a clock on and it will be on for 5 minutes, and then I will click it on for another 5, and if you could kind of finish up in that second 5, that would be great. So good to have you.

STATEMENTS OF JOHN FEUSSNER, M.D., CHIEF RESEARCH AND DEVELOPMENT OFFICER, DEPARTMENT OF VETERANS AFFAIRS, ACCOMPANIED BY TIMOTHY GERRITY, SPECIAL ASSISTANT TO THE CHIEF RESEARCH AND DEVELOPMENT OFFICER; ANNA JOHNSON-WINEGAR, DIRECTOR, ENVIRONMENTAL AND LIFE SCIENCES, DEPARTMENT OF DEFENSE; DRUE H. BARRETT, PH.D., DIVISION OF ENVIRONMENTAL HAZARDS AND HEALTH EFFECTS, NATIONAL CENTER FOR ENVIRONMENTAL HEALTH, CENTERS FOR DISEASE CONTROL AND PREVENTION, U.S. PUBLIC HEALTH SERVICE; AND SHEILA NEWTON, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. FEUSSNER. Good morning, Mr. Chairman, other members of the committee. Thank you for this opportunity to discuss the status of the Federal research program on Gulf war veterans' illness.

As you indicated, I serve as the Department of Veterans Affairs' Chief Research and Development Officer and chairperson of the Research Working Group of the Persian Gulf Veterans Coordinating Board. The primary charge to the Research Working Group is to assess the state and direction of research, identify potential new approaches, collect and disseminate scientifically peer-reviewed research information, and ensure that appropriate peer review and oversight are applied to research conducted and sponsored by us, the Federal Government.

The Research Working Group has guided the Federal research portfolio using a number of different sources of input. These sources include results from ongoing research; various expert panels and oversight committees, such as the Institute of Medicine, the Defense Science Board, the National Institutes of Health; several congressional committees, including this congressional committee; the Presidential Advisory Committee on Gulf War Veterans' Illnesses; independent scientists; and veterans. The Research Working Group, has synthesized this advice and information into a research strategy embodied in a working plan for research on Persian Gulf veterans' illness.

This morning I want to highlight three of the ongoing research efforts into Gulf war veterans' illness.

Shortly after the June 1996 announcement of events at Khamisiyah, the Research Working Group met and acted to recommend funding by DOD of three proposals that had previously been deemed scientifically meritorious. The three projects are valued at approximately $2.5 million and involve investigations con-

cerning sulfur mustard, the nerve agent VX, and the role of the genetic expression of cholinesterases in protecting against anticholinesterase nerve agents.

Subsequently, DOD published a four-part broad agency announcement called BAA to amplify research on low-level chemical warfare nerve agent effects, as well as research on the health effects of other exposures including insecticides, the nerve agent prophylaxis pyridostigmine bromide, and stress. The BAA resulted in funding recommendations for 12 new projects valued at approximately $12 million and covering such exposures as sarin, pyridostigmine bromide, insecticides, psychological stress and heat stress, alone and in various combinations.

In March 1997, the VA organized an international symposium in conjunction with the Society of Toxicology on the health effects of low-level exposure to chemical warfare nerve agents. Investigators from the United States and from Japan to Israel participated in that conference.

More recently, the sarin terrorist attacks in Japan have provided an opportunity to study the health consequences of a real-time, clearly confirmed sarin exposure. A VA investigator has been collaborating with Japanese investigators who have conducted follow-up studies on exposed individuals. These study subjects experienced acute, but mild, symptoms arising from the Tokyo subway sarin attack of 1995. Investigators have studied psychological, neurobehavioral, and neurophysiological outcomes in these subjects.

Three papers subsequently have resulted from this research and have been published. These papers provide new insight into the effects of clinical exposure to sarin 6 to 8 months following an acute attack. In comparison with matched controls, the exposed subjects manifest subtle neurophysiological effects that show that sarin may cause effects on the brain that are sustained for some time following clinical recovery from acute effects.

Second, although issues around the potential health impacts on our troops of potential low-level exposures to nerve agents are important, there are other health outcomes of concern as well. For example, the importance of musculoskeletal conditions among Gulf war veterans is clearly evident based on the prevalence of these conditions among veterans reporting to the VA and DOD registries and on results emerging from a number of research efforts.

Because of the obvious importance of ensuring appropriate and effective treatment of Gulf war veterans' illness, the Department of Veterans Affairs, Office of Research and Development, formed a planning group charged with developing a program announcement inviting proposals within the VA system, or in collaboration with DOD, for multicentered trials for candidate treatments of clearly defined medical syndromes or illnesses among subgroups of Gulf war veterans. The program announcement was issued in January 1998. In addition, VA and DOD are proceeding with the planning of a joint VA-DOD multicenter treatment trial for chronic fatigue syndrome and fibromyalgia in Gulf war veterans.

Third, both VA and DOD have undertaken new initiatives that are focused on neurobiology of stress and stress disorders. These new efforts include the following: VA and DOD have issued a re-

quest for intramural proposals valued at approximately $5 million for research on the neurobiology of stress, the neuroendocrine sequelae of stress, and immunologic consequences of stress.

In June 1997, VA funded a multicenter study examining the effectiveness of a computerized battery of neuropsychological testing that could improve the accuracy of the diagnosis of PTSD by enabling the clinician to rule out organic central nervous system dysfunction.

In July 1996, VA funded a new multicenter treatment trial investigating the efficacy of trauma-based group therapy in the treatment of post-traumatic stress disorder.

Finally, VA has issued a program announcement in August 1997, requesting proposals for additional multicenter trials of PTSD treatment. Treatment methodologies sought include novel, nonpharmacological approaches to treatment, with special emphasis on targeted subpopulations such as women and Gulf war veterans.

From 1994 to present, the Research Working Group has worked to coordinate and direct a diverse research portfolio consisting of 121 projects and a total cumulative investment of approximately $115 million. Of these 121 projects, 39 have been completed, 78 are ongoing, and 4 have been newly awarded and are awaiting startup. There are 14 identified research focus areas ranging from the effects of service in the Gulf war on the brain and nervous system to potential health consequences of low-level exposure to chemical warfare agents. Approximately one-third of the projects are epidemiological, one-third clinical, and one-third represent basic laboratory-based research.

As the research programs of the Federal Government continue to provide more results, we will increase our understanding of Gulf war veterans' illnesses, which will, in turn, enhance our potential ability to diagnose and treat them.

Mr. Chairman, I will conclude my testimony here and answer questions later.

[The prepared statement of Dr. Feussner follows:]

Statement of
John R. Feussner, M.D.
Chief Research and Development Officer
Veterans Health Administration
Department of Veterans Affairs
Before the Subcommittee on Human Resources of the
House Committee on Government Reform and Oversight

Research on Gulf War Veterans' Illnesses

February 24, 1998
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Mr. Chairman and members of the Subcommittee, thank you for this opportunity to discuss the status of the current and projected federal research program on Gulf War veterans' illnesses. I serve as the Department of Veterans Affairs' (VA) Chief Research and Development Officer and the Chairperson of the Research Working Group (RWG) of the Persian Gulf Veterans Coordinating Board. Today I will focus my presentation on the strategy and objectives of the RWG.

First, I would like to provide some history of the RWG. The federal research effort on Gulf War veterans' illnesses involves scientists in federal, academic, and private institutions, in the United States and abroad, whose research is sponsored by VA, the Department of Defense (DoD), and the Department of Health and Human Services (HHS). Each department has distinct, though complementary, capabilities for conducting and sponsoring research on Gulf War veterans' health issues. In addition, each department has its own appropriations for extramural and intramural general biomedical research.

The primary charge to the RWG is to assess the state and direction of research; identify gaps in factual knowledge and conceptual understanding; identify testable

hypotheses; identify potential new research approaches; review research concepts as they are developed; collect and disseminate scientifically peer-reviewed research information; and ensure that appropriate peer review and oversight are applied to research conducted and sponsored by the federal government.

The biomedical research programs in VA, DoD, and HHS have well established management structures for science policy formulation and the solicitation, scientific peer review, and funding of research projects. The coordination and management of this large research effort on Gulf War veterans' illnesses required the establishment of an overall research policy framework linking each Department's research management hierarchy. To provide this linkage, in 1993 VA, DoD, and HHS formed the "Persian Gulf Interagency Research Coordinating Council". By January 1994, when the Secretaries of VA, DoD, and HHS formed the Persian Gulf Veterans Coordinating Board (PGVCB), the Research Coordinating Council became the Research Working Group (RWG) operating under the auspices of the Coordinating Board. Because of the potential link between environmental factors and Gulf War veterans' illnesses, the Environmental Protection Agency was asked to be a member of the Research Working Group.

An important function of the RWG is programmatic review and recommendation to funding agencies of research proposals that have been competitively peer reviewed. The RWG works collectively with VA, DoD, and HHS to elucidate agency-specific funding mechanisms to support research in those identified areas. For a specific research funding activity, the responsible funding agency works with and through the RWG to develop a targeted solicitation for research. Proposals that are submitted to the funding agency in response to a solicitation are scientifically peer-reviewed using agency-specific peer-

review programs (e.g., DoD/Department of the Army uses a contract with the American Institute of Biological Sciences). Abstracts of peer-reviewed proposals, written reviews of the peer-reviewers, and the scientific merit scores assigned by the peer-reviewers, are provided to a subcommittee of the RWG charged with providing secondary review of proposals for relevance. The information provided is redacted for personal and institutional identifiers so that programmatic review is anonymous. Relevance determinations are guided by programmatic needs articulated through the RWG process. In its secondary review the RWG may re-rank proposals based on relevance, but it will not recommend non-meritorious proposals for funding to any agency.

The RWG continues to work diligently to foster the highest standards of competition and peer-review for all research on Gulf War veterans' illnesses.

As an operational policy, the Research Working Group works through the line management authority each department maintains over its intramural scientists, scientific program managers (responsible for extramural research), and budgets.

By drawing the three departments together, the RWG has been able to jointly develop a research strategy, jointly serve as a forum for researchers to present ideas and findings, and jointly respond to emerging research issues and problems. Through the priority setting processes carried on within the RWG, each department is able to independently develop approaches to addressing those priorities. These approaches are then returned to the RWG for joint discussion, resolution, and recommendations. The RWG has served as an umbrella under which the federal government has been able to respond to many research issues outside the context of the RWG's regular meetings. When emerging research issues arise within an individual department, the RWG is

engaged to ensure that each department participates in discussions on the issues. A specific example of this is when DoD made its determinations about the potential for exposure of troops to nerve agent at Khamisiyah. The determination was made through the work of DoD's Office of the Special Assistant for Gulf War Illnesses. However, DoD immediately engaged the RWG to develop a coordinated research response to this event. The RWG response was the development of an action plan that led in part to the development of DoD's 1997 Broad Agency Announcement requesting new research on the health effects of low-level exposure to chemical warfare agents and environmental toxins, alone and in combination with one another.

The RWG has guided the federal research portfolio using a number of different sources of input. These sources include results from ongoing research; various expert panels and oversight committees, such as the Institute of Medicine, the Defense Science Board, the National Institutes of Health; Congressional committees including the Human Resources Subcommittee; the Presidential Advisory Committee on Gulf War veterans' illnesses; independent scientists; and veterans. The RWG has synthesized the advice and information into a research strategy embodied in *A Working Plan for Research on Persian Gulf Veterans Illnesses* first released in August 1995 and revised in November 1996. The next revision will be available later in Spring 1998.

Other notable activities and accomplishments of the RWG include:

- Production and dissemination of Annual Reports to Congress on progress and results of federal research activities;
- Secondary programmatic review of research proposals submitted to funding agencies;

- Presentations by federal and non-federal researchers before the Research Working Group;
- Organization of meetings of federally-funded researchers;
- Organization of an international symposium in conjunction with the Society of Toxicology on the health effects of low-level exposure to chemical warfare nerve agents.
- Development of a strategy for research on the health effects of exposure to low-levels of chemical warfare nerve agents.
- Follow-up investigation of preliminary reports of positive experimental serological tests for leishmaniasis.

I want to highlight some of the ongoing research efforts on Gulf War veterans' illnesses.

Shortly after the June 1996 announcement of the events at Khamisiyah, the Research Working Group acted to recommend funding by DoD of three proposals that had been previously deemed scientifically meritorious but not funded. The three projects are valued at approximately $2.5 million and involve (1) dosimetry research on exposure to sulfur mustard that will enable quantitative determinations of sulfur mustard exposure at short and long-term intervals; (2) research on the toxicokinetics of the nerve agent VX in three species of animals. The results of this research will facilitate animal to human extrapolation of observed effects in animals resulting from controlled low-level nerve agent exposure; and (3) research on the role of genetic expression of cholinesterases in protecting against anticholinesterase nerve agents. Each of these are described in more

detail in the Annual Report to Congress on Federally Sponsored Research on Persian Gulf Veterans' Illnesses for 1996 released in the Spring of last year.

Subsequently, DoD published a four-part broad agency announcement (BAA) to amplify research on low-level chemical warfare nerve agent effects, as well as research on the health effects of other exposures including insecticides, the nerve agent prophylaxis pyridostigmine bromide (PB), and stress. The BAA resulted in funding recommendations for 12 new projects, valued at approximately $12 million, and covering such exposures as sarin, PB, insecticides, psychological stress, and heat stress, alone and in various combinations. Additional projects have been recommended for funding. DoD will announce these new projects at the time of final award.

As part of the BAA the scientific community was asked for proposals for a feasibility study on the conduct of epidemiological research on the possible health outcomes among troops potentially exposed to sarin at Khamisiyah, Iraq in March 1991. Unfortunately, there was no response to this request. The Department of Defense asked the Medical Follow-Up Agency (MFUA) of the Institute of Medicine (IOM) to develop a protocol for conducting such a study. MFUA designed a protocol that was peer-reviewed by a panel of experts assembled by the American Institute of Biological Sciences. The peer-review panel provided a scientifically meritorious score and the RWG recommended to DoD that this project be funded.

In early 1997 VA and DoD tasked the Medical Follow-up Agency of the Institute of Medicine to undertake feasibility studies on the long-term health effects of exposure to chemical warfare nerve agents. This work is focusing on MFUA's access to cohorts of veterans exposed at Aberdeen Proving Ground as a part of their research on the health

effects of low-level exposure to nerve agents dating back to the 1950s. The MFUA informed us that such a project is indeed feasible and they are currently preparing a full proposal for review.

Also in early 1997, the RWG established a small subgroup of experts on the health effects of nerve agents to develop a broad-based research strategy for investigation of the long-term health effects of low-level exposure to chemical warfare nerve agents. This plan will be published in an upcoming Annual Report to Congress on Gulf War veterans' illnesses research.

The sarin terrorist attacks in Japan provided an opportunity to study the health consequences of a real-life confirmed sarin exposure. A VA researcher, who is also the Director of the VA Boston Environmental Hazards Research Center, has been collaborating with Japanese investigators who have conducted follow-up studies on 18 exposed individuals. These subjects experienced acute (i.e. sudden onset), but mild, symptoms arising from the Tokyo subway sarin attack of 1995. Investigators have studied psychological, neurobehavioral, and neurophysiological outcomes in these subjects using up-to-date techniques. The outcome measures in each of the exposed subjects have been compared with matched non-exposed control subjects. Three papers resulting from this research have been recently published in the scientific peer-reviewed literature. These papers provide new insight into the effects of clinical exposures to sarin 6-8 months following the attack. In comparison with matched controls, the exposed subjects manifested subtle neurophysiological effects that, although they were not clinically significant, do show that sarin can cause effects on the brain some time following recovery from the acute effects.

Although issues around the potential health impacts on our troops of potential low-level exposures to nerve agents are very important to us, there are other exposures and health outcomes of concern as well. For example, the importance of musculoskeletal conditions among Gulf War veterans is clearly evident based on the prevalence of these conditions among veterans reporting to the VA and DoD registries, and on results emerging from a number of research efforts including the Iowa study of Gulf War veterans. The federal research portfolio contains significant research efforts to better clarify the pathophysiology and clinical significance of musculoskeletal conditions in Gulf War veterans. Of particular note are the efforts at the Portland VA Environmental Hazards Research Center investigating the pathophysiology of Fibromyalgia (FM) and the hypothesis that FM is a disease process that accounts for a significant amount of the musculoskeletal symptoms in ill Gulf War veterans. Also of note, the DoD BAA from 1995 provided funds for three new research programs that employ multi-disciplinary approaches to musculoskeletal function in the context of both pain and fatigue.

Because of the obvious importance of ensuring appropriate and effective treatment of Gulf War veterans' illnesses, the Department of Veterans Affairs, Office of Research and Development formed a Planning Group charged with developing a Program Announcement (a type of request for applications) inviting proposals within the VA system, or in collaboration with DoD, for multi-center trials for candidate treatments of clearly defined medical syndromes or illnesses among subgroups of Gulf War veterans. The Program Announcement was issued in January 1998. In addition, VA and DoD are proceeding with the planning of a joint VA/DoD multi-center treatment trial for Chronic Fatigue Syndrome and Fibromyalgia in Gulf War veterans.

Both VA and DoD have undertaken new initiatives that are focused on the neurobiology of stress and stress-related disorders. These new efforts include:

1. Part of the 1997 DoD BAA requested proposals for studies of post conflict illnesses that extend beyond the Gulf War. These studies have been requested to address aspects of the wartime experience that create a confluence of cognitive, emotional, and physical factors to produce chronic, non-specific symptoms and physiological outcomes. Proposals submitted in response to this part of the BAA have been reviewed for scientific merit and program relevance. The RWG made its funding recommendations to DoD and DoD expects to announce awards of selected projects soon. Results of this research are expected to provide new insight into the causes of stress-related disorders.
2. VA and DoD have issued a request for intramural proposals valued at $5 million for research on the neurobiology of stress. Proposals will undergo scientific review by a joint VA/DoD appointed panel of experts, and programmatic review by the RWG. Awards of projects by VA and DoD are expected by July 1, 1998.
3. In June 1997 VA funded a multi-center cooperative study examining the effectiveness of a computerized battery of neuropsychological tests that could improve the accuracy of the diagnosis of PTSD by enabling the clinician to rule out organic central nervous system dysfunction.
4. In July 1996 VA funded a new multi-center treatment trial investigating the efficacy of trauma-based group therapy in the treatment of PTSD.

5. VA issued a Program Announcement in August 1997 requesting proposals for additional multi-center trials of PTSD treatment. Methodologies sought include novel, non-pharmacologic approaches to treatment, with special emphasis on targeted subpopulations such as women and Gulf War veterans.

I will now provide you with an update of the VA National Survey of Persian Gulf Veterans authorized by Public Law 103-446. The Office of Research and Development has awarded funds for Phase III of the National Health Survey of Persian Gulf Veterans and preliminary site selection has begun. A subcommittee of the Cooperative Studies Evaluation Committee (CSEC, a federally chartered advisory committee), scientifically reviewed the protocol for Phase III.

It is expected that physical examinations will begin in the near future. As you may recall, the National Survey is designed to determine the prevalence of symptoms and illnesses among a random sampling of Persian Gulf veterans across the nation. The Survey is being conducted in three phases. Phase I was a population-based mail survey of the health of 30,000 randomly selected veterans from the Persian Gulf era (15,000 Persian Gulf veterans and 15,000 non-Persian Gulf veterans, males and females). The data collection phase is complete and analysis of the data continues. Phase II consisted of a telephone interview of 2,000 non-respondents from Phase I (1,000 from each group) to determine if there are any response differences between respondents and non-respondents. Additionally, 1,000 veterans from each group will be selected for a telephone interview to validate their responses from the mail survey. Phase II is nearing completion. In Phase III the 2,000 veterans who responded to the postal survey and underwent a telephone interview will be invited, along with their family members, to participate in a

comprehensive physical examination protocol. These examinations will be conducted at 18 VA medical centers nationwide and involve specialized examinations including neurological, rheumatological, psychological, and pulmonary evaluations. Completion of data collection is anticipated around mid-1999. When the National Survey is complete we will have a much clearer picture of the prevalence of symptoms and illnesses among Gulf War veterans.

The medical evaluations in Phase III are designed to determine whether or not:

1. Gulf War veterans have an increased prevalence of the following conditions frequently reported in the literature compared to a control group of non-deployed veterans: Chronic Fatigue Syndrome (CFS), Fibromyalgia (FM), neurologic abnormalities including peripheral neuropathy and cognitive dysfunction, post-traumatic stress disorder (PTSD), and measures of general health status.
2. The specific medical conditions of arthritis, dermatitis, hypertension, bronchitis, and asthma that have been reported as more frequent among Gulf War veterans compared to non-deployed veterans are of greater prevalence among deployed Gulf War veterans upon objective clinical examination.
3. The prevalence of any of these conditions is greater among the spouses of Gulf War veterans than among spouses of non-deployed veterans.
4. The prevalence of medical conditions and major birth defects found on a pediatric physical examination in the children conceived after the war is greater for Gulf War veterans than for non-deployed veterans.

We anticipate that the participating medical centers will enroll patients, spouses, and children by May 1, 1998. We are allowing 18 months for completion of all medical evaluations.

From 1994 to the present the RWG has worked to coordinate and direct a diverse research portfolio consisting of 121 projects and a total investment of approximately $115 million. Of these 121 projects, 39 have been completed, 78 are ongoing, and 4 have been newly awarded and are awaiting startup. Additional research projects are at various stages of planning. There are 14 identified research focus areas ranging from the effects of service in the Gulf War on the brain and nervous system to the potential health consequences of low-level exposure to chemical warfare agents. Approximately one-third of the projects are epidemiological, one-third are clinical, and one-third are basic research.

This research program, as well as research outside of the government, has yielded important new information. Some of the highlights of recent research findings include:

- Population-based epidemiological studies are showing that Gulf War veterans self-report more symptoms and exposures than non-deployed veterans of the same era. Currently it is not possible to identify a causal connection between the reported symptoms and exposures. However, ongoing and newly funded projects are directed toward determining whether such a connection may exist.
- Based on VA and DoD mortality studies there does not appear to be more deaths from disease-related causes among Gulf War veterans when compared to non-deployed veterans of the same era. VA plans to continue following the mortality experience of Gulf War veterans well into the future.

- A study of military hospitalizations has shown that, at least among active duty personnel, the rate of hospitalizations of Gulf War veterans did not exceed that of their non-deployed counterparts. This suggests that Gulf War veterans are not experiencing more illnesses of a severity that would lead to hospitalization. To account for potential bias from restricting this study to military hospitals, the investigators are extending their study to include civilian health care facilities.
- A substudy of the hospitalization study shows that infants of Gulf War veterans have not been experiencing a greater prevalence of birth defects compared to the infants of non-deployed era veterans. A more focused examination of the rare birth defect known as Goldenhar Syndrome also failed to find any statistically significant difference in prevalence in infants of Gulf War veterans compared to non-deployed era veterans. Further studies of birth outcomes continue to explore this concern.
- Recent research studies have provided important information on the interactions of neurotoxins and other exposures. A recent study indicates that stress can increase the penetration of PB across the blood-brain barrier suggesting the possibility that PB could cause a central nervous system effect. Another recently published study suggests that PB may decrease the levels of permethrin in the central nervous system, thus potentially mitigating against an adverse synergistic interaction between these two compounds. The federal government has increased its research investment in research on the toxicology of interactions.

- Neurobehavioral studies of Gulf War veterans and control populations suggest that Gulf War veterans have some brain function abnormalities in such areas as memory, cognition, and motor control in comparison to non-deployed era veterans. Some of these deficits can be accounted for by psychological factors.
- Two different research groups have independently found that health symptoms in Gulf War veterans may be associated with PTSD symptoms.
- A study conducted at the National Cancer Institute examined blood samples drawn from deployed veterans who went to the Gulf immediately after the end of hostilities. Blood samples were collected in Germany and in the Gulf and tested for a marker of exposure to polycyclic aromatic hydrocarbons (a carcinogenic product of partial combustion of petroleum products). The researchers found more markers for PAH exposure in the samples taken in Germany than in the Gulf.

As the research programs of the federal government continue to provide more results, we will substantially increase our understanding of Gulf War veterans' illnesses, which will, in turn, enhance our ability to diagnose and treat them. In addition, this newly gained knowledge will enhance prevention and intervention of illnesses in participants of future deployments.

I will conclude my testimony here and answer any questions you may have.

Mr. SHAYS. Thank you very much. We will go to Dr. Winegar.

Ms. WINEGAR. Thank you, Mr. Chairman, for the opportunity to review with you and the other members of your important subcommittee the current and projected DOD research program addressing multiple aspects of Gulf war veterans' illnesses.

As you indicated, I am currently the Director for Environmental and Life Sciences within the Office of the Director of Defense Research and Engineering. In this position I oversee all defense biomedical and medical science and technology programs. Today I will focus my comments on our efforts on Gulf war veterans' illnesses.

I want to emphasize at this point that the Department of Defense is committed to an aggressive, coordinated, well-focused, but broadly scoped and strong Gulf war veterans' illness research program that does the following.

One, furthers the fundamental understanding of the illnesses; two, provides enhanced diagnostic capabilities and efficacious treatment modalities for veterans; and, three, supports the establishment of policies and preventive measures that minimize the risk of such illnesses during future military operations.

Dr. Feussner has addressed the role of the Research Working Group, and therefore I shall now focus my comments on the DOD program and the procedures we use to implement that program.

The Department of Defense uses competitive procedures to solicit extramural proposals for scientific studies and research on Gulf war veterans' illnesses. This extramural research program is administered for the DOD by the U.S. Army Medical Research and Materiel Command at Fort Detrick. They possess unparalleled experience and have in place the contract clauses and review processes that are necessary for solicitation and selection of fully qualified proposals on merit factors of program relevance and scientific excellence; for resolving complex and difficult issues of regulatory compliance, such as the protection of human research subjects, ensuring the welfare of research animals, the safe use of high-hazard etiologic agents, research safety and surety for handling highly toxic chemical warfare agent materials; and for rapid program starts through application of streamlined extramural research acquisition processes.

As was mentioned, these research proposals are solicited through the use of either an open-ended broad agency announcement, BAA, or through BAAs announcing specific research opportunities. These announcements are formally made through publication in the Commerce Business Daily and may be accessed and downloaded from the Internet.

Extramural research awards on Gulf war veterans' illness may result from an investigator responding to the openended BAA which solicits medical and biomedical research ideas, with emphasis on those that are most relevant to ongoing medical research programs. In order to do so, an investigator submits a preproposal, usually 3 to 4 pages in length, which states the problem to be studied; the significance and/or uniqueness of the proposed effort; the relevance to the defense biomedical and medical research programs; some relative cost information; an overview description of any proposed use of animal or human subjects in the research; and

a brief curriculum vitae for the principal investigator and any key personnel.

Research program directors oversee the review of these proposals and look at several factors, including the following: No. 1, military and program relevance; No. 2, research objective; No. 3, scientific excellence; No. 4, qualifications; No. 5, facilities; and No. 6, budget. The final stage of the evaluation is the establishment of a relative order-of-merit list which is based both on military relevance and scientific merit evaluations.

The project officer and the contracting staff review the comments from the Research Working Group before they begin any negotiations with potential contractors.

In addition to full and open competition, as I have mentioned, there are occasions when noncompetitive awards may be made to support program administration and management, to fulfill sole-source requirements for unique capabilities, including those directed by the Congress, and to conduct intramural Federal laboratory research. Examples of such awards include using contract vehicles for study and management assistance, contracting with the National Academy of Sciences for assistance to the DOD, and the conduct of epidemiological studies of veterans who were in the vicinity of the Khamisiyah demolition, as well as studies in DOD facilities that have specialized containment facilities, equipment and standard operating procedures for work with chemical or biological warfare agents.

During this last year, the Director of Defense Research and Engineering took several actions to increase the visibility and oversight of all Department of Defense research efforts on Gulf war veterans' illnesses, as well as to facilitate program management and integration with the Research Working Group. These actions include, first, taking steps to establish a single Defense program element and project in fiscal year 1999 with 1998 being a transition year. Currently, defense research on Gulf war veterans' illnesses is supported under multiple Defense-wide and Army research development test and evaluation program elements. We feel that the establishment of a single Defense line for Gulf war veterans doing the specific research should improve DOD oversight and expedite congressional review, since all program accomplishments, plans and resource information will appear now as a single program on the RDT&E budget justification sheets.

Second, we chartered a Working Integrated Process Team on Deployment Toxicology in November 1997. The purpose of this team is to review current deployment toxicology initiatives and to develop a recommendation regarding appropriate DOD-level sponsorship and oversight of related policy issues, doctrinal matters and requirements generation.

Finally, we have incorporated a DOD-wide review of Gulf war Veterans' Illnesses research in our annual technology area research and assessment process. This review process is utilized by the Director of Defense Research and Engineering to obtain advice and recommendations from outside experts to help us guide our program.

Let me conclude my statement by noting that it has not yet been 5 years since the formation of the Research Working Group to co-

ordinate Federal research into the health consequences of service in the Persian Gulf war. The genuine concern and recognition of the magnitude and consequences of the challenges before us are reflected by our commitment to work in a productive and cooperative manner that will exploit our individual Department's scientific strengths and unify them into a productive, responsive and fully integrated research effort, the RWG's Working Plan.

As I have alluded, the path of science is difficult; it is challenging, expensive and time consuming. Easy and complete solutions to such complex health problems are very attractive, but are extremely rare. My written statement summarizes new directions and accomplishments for the DOD. I feel that the challenges are great. There are no quick solutions; however, we remain committed to the responsible and aggressive pursuit and resolution of these problems.

That concludes my statement, and I will be happy to answer any questions that you might have.

Mr. TOWNS [presiding]. Thank you very much, Dr. Winegar.

[The prepared statement of Ms. Winegar follows:]

CONGRESSIONAL TESTIMONY
GULF WAR VETERANS' ILLNESSES

Introduction

Mr. Chairman, thank you for the opportunity to review with you and the members of this important subcommittee the current and projected DoD research program addressing multiple aspects of Gulf War Veterans' Illnesses (GWVI).

I am Dr. Anna Johnson-Winegar, Director for Environmental and Life Sciences (DE&LS), Office of the Director of Defense Research and Engineering (ODDR&E). As the DE&LS, I oversee the Defense biomedical and medical science and technology program. Today, I will focus my testimony on GWVI research matters.

Department of Defense Oversight of GWVI Matters

In overseeing the Defense biomedical and medical science and technology program, I am accountable to the DDR&E. As you know, the DDR&E is the principal staff assistant and advisor to the Under Secretary of Defense for Acquisition and Technology (USD(A&T)) for DoD scientific and technical matters, basic and applied research, and advanced technology. Health policy issues and activities as they relate to the Department's readiness mission are the responsibility of the Assistant Secretary of Defense for Health Affairs (ASD(HA)). This mission includes providing medical services and supporting U.S. Forces during military operations, as well as providing medical services and support to U.S. Forces, their dependents, and others entitled to DoD medical care. The ASD(HA) reports to the Under Secretary of Defense (Personnel and Readiness) (USD(P&R)). The USD(P&R) is the principal staff assistant and advisor to the Secretary and Deputy Secretary of Defense for Total Force management as it relates to readiness; National Guard and Reserve Component affairs; health affairs; training; and personnel requirements and management. Operating independently of these USD(A&T) and USD(P&R) program responsibilities is the Office of the Special Assistant for Gulf War Illnesses (OSAGWI). The OSAGWI is developing case narratives, studies and models to better understand and resolve exposures during Gulf War service.

I also serve as the Chair of the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee. It is co-chaired by the Deputy Assistant Secretary of Defense for Health Services Operations and Readiness, Office of the ASD(HA). The ASBREM Committee provides centralized management for the Defense biomedical research, development and acquisition (RDA) program. This program includes medical chemical defense, medical biological defense, infectious diseases of military importance, military operational medicine, combat casualty care, and radiological defense, as well as congressional special interest biomedical RDA efforts. It involves the discovery, development and acquisition of the means–knowledge and technology–to prevent and treat disease and injury through biomedical solutions to operational health threats posed to U.S. Forces. Biomedical solutions include pharmaceuticals,

biologicals, preventive medicine guidance, standards, diagnostics, treatments, and devices that are provided to medical and non-medical users in various operational communities.

The ASD(HA) uses and applies results from this program to support doctrine development, force structure, training, and military operational considerations. The Defense biomedical RDA program is different from the ASD(HA) health care programs. Thus, the ASBREM Committee provides DoD with the capability for effective technology developer and health care provider interactions. This is important for resolving GWVI-related issues and other research and health care matters.

Purpose of GWVI Research Program

On August 2, 1990, Iraq invaded Kuwait. Within five days, the United States began to deploy troops to the Persian Gulf in Operation Desert Shield. In January, 1991, United Nations coalition forces began intense air attacks against the Iraqi forces (Operation Desert Storm). On February 24, a ground attack was launched, and within four days, Iraqi resistance crumbled. Almost 700,000 U.S. troops participated in the Gulf War. Most troops returned home and resumed their normal activities. However, a number of those who had been deployed to the Persian Gulf began to report health problems they believed to be connected to their deployment. These problems included symptoms of fatigue, headache, memory loss, depression, anxiety, mood changes, sleep disturbances, muscle and joint pain, and persistent rashes.

I want to emphasize that the Department is committed to an aggressive, coordinated, well-focused but broadly scoped and strong GWVI research program that does the following:

- furthers the fundamental understanding of the illnesses;
- provides enhanced diagnostic capabilities and efficacious treatment modalities for veterans; and
- supports the establishment of policies and preventive measures that minimize the risk of such illnesses during future military operations.

We also are committed to ensuring that our research program is of the highest quality. We use competition and independent peer review to secure the very best research performers, hypotheses, and experimental designs, from all possible sources, including the Federal, civilian, national and international communities. This commitment follows an appreciation at all levels within the Department of our responsibility to achieve an optimal investment of taxpayer dollars, to assist our Gulf War veterans secure diagnoses and treatments for their disabilities and illnesses, and to prevent such disabilities and illnesses as a consequence of future deployments.

Federal Interagency Participation in GWVI Research Program

As you are aware, our research program and findings on GWVI are coordinated and integrated with those of the Departments of Veterans Affairs (VA) and Health and Human Services (HHS) through the Research Working Group (RWG) of the Persian Gulf Veterans'

Coordinating Board (PGVCB). Because of possible links among environmental factors and GWVI, the Environmental Protection Agency provides a member on the RWG.

The Department of Veterans Affairs, the responsible agency for coordination of GWVI research for the Federal Government, submits an Annual Report to Congress on the results and progress of research activities undertaken or funded by the Executive Branch of the Federal Government on Persian Gulf veterans illnesses. The PGVCB-RWG has published two editions of "A Working Plan for Research on Persian Gulf Veterans' Illnesses" (1995, 1996), and a third addition (1997) is in press. In accordance with section 769 of the National Defense Authorization Act for Fiscal Year 1998, the Secretary of Defense will also submit a report on "Effectiveness of Medical Research Initiatives Regarding Gulf War Illnesses" to the Committee on National Security, House of Representatives, and the Armed Services Committee, U.S. Senate. These reports, collectively, represent the definitive sources of information on GWVI research, significant research findings, and recommendations for additional research.

I now wish to provide you with the Department's view of the operations strategy, objectives, and agenda of the PGVCB-RWG, as well as the status of current and projected Defense GWVI research program.

The PGVCB-RWG provides the overarching policy and guidance linking the overall research and management efforts by DoD, VA, and DHHS into a comprehensive and integrated national research program. The DoD supports the guidance, oversight, and assistance of the RWG. The research on GWVI is a complex and difficult undertaking that does not lend itself to simple or single-agency approaches. The lack of a yet defined causal relationship to the illnesses cannot be allowed to deter our national research effort to find solutions that will benefit afflicted veterans now, and minimize related illnesses during future military operations. The PGVCB -RWG strategy involves a multidisciplinary approach along many different and novel scientific lines by scientists and clinicians in Federal, academic, and private institutions.

The RWG is charged with:

- assessing the status and direction of research;
- identifying deficiencies in knowledge and concepts, testable hypotheses, and potential research approaches;
- reviewing research concepts and disseminating scientifically peer-reviewed research information; and
- ensuring that appropriate peer review and oversight are applied to GWVI research.

The RWG's operational approach has been to work collectively with the DoD, VA, and DHHS in assessing research priorities. The Federal investment in GWVI has been guided primarily through the coordinating efforts of the RWG as expressed in the "Working Plan." The major influences on this Plan and the reason for frequent updates are new research findings, emergent risk factors, recommendations of expert oversight groups, Public Law, and Congressional reports. These factors and the disciplined approach being followed have enabled the RWG to effectively assess and make sound recommendations to DoD, VA, and DHHS on the

programmatic relevance of research proposals that have been competitively and scientifically peer-reviewed

The guiding RWG goals for GWVI research are to: seek the causes (pathogenesis) of the unexplained illnesses of Gulf War veterans; use new knowledge of basic mechanisms to help veterans; and avoid or reduce such unexplained illnesses in future military deployments. Areas of medical research focus include assessing:

- environmental chemicals, prophylactic drugs, and military materiel for synergistic toxic interactions;
- the effect of exposure to subclinical levels of chemical warfare agents on long-term health consequences; and
- the confluence of cognitive, emotional and physical factors that produce chronic, nonspecific symptoms and physiological outcomes typical of the undiagnosed illnesses of some veterans of the Gulf War.

Other areas of medical research pursuit or interest include those on stress, reproductive outcomes, infectious diseases including mycoplasma and leishmaniasis, multiple chemical sensitivity, chronic fatigue syndrome, fibromyalgia, and epidemiological studies.

Research Operations

The Department of Defense uses competitive procedures to solicit extramural proposals for scientific studies and research on GWVI. This extramural research program is administered for the DoD by the U.S. Army Medical Research and Materiel Command (USAMRMC), Fort Detrick, Maryland. This Command was selected because its Headquarters staff and contracting activity, the U.S. Army Medical Research Acquisition Activity (USAMRAA), have a long history of providing responsive program execution support to the DoD on a broad spectrum of Congressional special interest, medical and biomedical science and technology programs. They possess unparalleled experience and have in place the contract clauses and review processes necessary for:

- solicitation and selection of fully qualified proposals on merit factors of program relevance and scientific excellence;
- resolving complex and difficult issues of regulatory compliance (e.g., protection of human research subjects, ensuring welfare of research animals, safe use of high hazard etiologic agents, research safety and surety for handling highly toxic chemical warfare agent materials); and
- rapid program starts through application of streamlined extramural research acquisition processes.

Solicitation. Research proposals are solicited through the use of either an open-ended Broad Agency Announcement (BAA) or through a BAA announcing specific research opportunities. These announcements are formally made through publication in the *Commerce Business Daily* and may be accessed and downloaded from the Internet (http://www-usamraa.army.mil/baa.htm).

Extramural research awards on GWVI may result from an investigator responding to the USAMRMC open-ended BAA. This open-ended announcement is the USAMRMC BAA 95-1 (http://www-usamraa.army.mil/baa95-1.htm). It solicits medical and biomedical research ideas, with emphasis on those that are most relevant to ongoing Army medical research programs. It has no specific closing date and investigators are encouraged to submit brief, three to four (3-4) page preproposals addressing:

- the problem to be studied;
- significance and/or uniqueness of the proposed effort;
- proposed relevance to Defense biomedical and medical research programs;
- relative cost information such as project duration, number and type of personnel as well as estimated levels of effort, and major equipment purchase requirements;
- overview description of any proposed use of animal or human subjects of research; and
- brief curriculum vitae for the principal investigator and any key personnel.

Review Process. Research program directors oversee the review of these preproposals and either encourage investigators to submit full proposals or dissuade submission of a full proposal. If an investigator desires, the preproposal route need not be followed and a full proposal may be submitted according to proposal preparation instructions provided in the BAA. Proposals submitted under the open-ended BAA are evaluated by in-house or by in-house and independent review committees for scientific merit and programmatic relevance against the following factors (in descending order of importance).

(1) Military and Program Relevance. Does the proposal clearly address a relevant and significant military related problem that can be solved by research and development studies? Does the proposed research meet current USAMRMC program needs and goals?

(2) Research Objective. Is the stated objective clear, valid, and logical?

(3) Scientific Excellence. Are the plans, methods, techniques and procedures feasible, clear, valid, adequately referenced, and state-of-the-art?

(4) Qualifications. Are the qualifications, capabilities, and experience of the proposed principal investigator and other key personnel sufficient to achieve the proposed objectives?

(5) Facilities. Are the proposed facilities and equipment, or unique combinations of these, adequate for the proposed objectives?

(6) Budget. Does the budget reflect the actual needs of the proposed work? Have the requests for personnel, equipment, supplies and travel been fully justified?

The final stage of the evaluation is the establishment of a relative order of merit list, which is based on military relevance and scientific merit evaluations. Awards depend upon:

- the relative order of merit;
- regulatory compliance;
- the availability of funds; and
- project affordability.

One of three different types of awards may be made. The most common is a cost-reimbursement type of contract that permits reimbursement for actual costs incurred in the accomplishment of the research. These contracts also permit some flexibility in the redirection of research effort as a result of research findings or changes in program emphasis. Grants and cooperative agreements may be used when the primary intent is to provide resources to support and stimulate research. Additionally, grants are used when involvement and interactions between Defense and the recipient are intended to be few; cooperative agreements are used when substantial involvement and interactions are anticipated. The normal period of performance for an award made under a BAA is 3 to 5 years.

GWVI Broad Agency Announcements. The majority of GWVI awards have resulted from DoD solicitations using specific purpose announcements. Special funding opportunities are normally announced by a BAA having specific closing dates for receipt of proposals and usually do not encourage use of the preproposal process. Proposals must be responsive to the USAMRMC BAA 95-1 requirements as well as to any special provisions of a specific announcement. The DoD, through USAMRMC, has advertised seven GWVI special topic BAAs since 1994. The most recent, FY98 Gulf War Illness Research Program, was announced on November 20, 1997 and closed February 4, 1998. To date, these seven announcements have resulted in 29 awards. The number of proposals and awards in response to BAA by year are as follows:

GWVI BAA SUMMARY (FY94 - Present)

Date of Announcement	Special Solicitation Topic	Proposals Received	Awards To Date
29 Apr 94	Low level chemical sensitivities	5	1
29 Apr 94	Depleted uranium	2	2
24 May 95	Gulf War Illness, 3 subtopics	117	14
10 Dec 96	Low-level chemical exposures	22	4
29 Jan 97	Gulf War Illnesses (non-Federal)	36	8
29 Jan 97	Historical War Syndromes	14	3 (pending)
20 Nov 97	Gulf War Illnesses (non-Federal, U.S. universities)	41	BAA closed on 4 Feb 98

Since 1994, the DoD has awarded funds for 35 (this includes both the open-ended and special funds BAAs) extramural projects intended to improve our knowledge and understanding of the pathogenesis of GWVI. At present, there are additional extramural projects undergoing review or negotiations for award.

Proposals submitted in response to BAAs for the GWVI program undergo a two-tiered, scientific-peer and programmatic relevance, review process. The review for scientific merit is conducted by an independent organization; the reviewers are non-DoD personnel who are experts in the appropriate biomedical disciplines.

The in-depth review for programmatic relevance is conducted by the RWG. This programmatic review is intended to identify those proposals which best fulfill research needs including program requirements, avoidance of unnecessary duplication, and are judged to possess the sound potential for advancing program goals and fulfilling research objectives. Blinded scientific critiques of each proposal that include summaries of the proposed effort, scientific merit scores, and detailed assessments of proposal strengths and weaknesses serve as the basis for the RWG programmatic review. The RWG recommends a slate of proposals for award and also provides recommendations on any adjustments to statements of work and any associated modifications to budget requests.

The project officer and contracting staff receive the RWG recommendations and begin development of essential information needed for ensuring regulatory compliance. This includes compliance with the National Environmental Policy Act (NEPA–40 CFR 1500-1508) requirement for integration of considerations of potential environmental consequences of the proposed action into the decision-making process. In most instances proposals qualify for a categorical exclusion and a Record of Environmental Consideration is prepared in accordance with Army Regulation 200-2, *Environmental Effects of Army Actions*, 23 December 1988 (32 CFR 651). If the proposed work does not qualify for a categorical exclusion then an environmental assessment is required. Individual offeror's certification of environmental safety and compliance must be included with the proposal (Attachment 1).

If the proposed work requires the study of etiologic agents as part of the biological defense program, then the provisions of 32 CFR 626 and 32 CFR 627 concerning biological defense research safety would have to be exercised. These include pre-award site visits and establishment of special safety provisions to ensure worker and environmental safety. Similarly, work requiring the use of chemical warfare agents must fulfill special safety and surety requirements depending on the type and quantity of agent required. Work with either biological defense categories of etiologic agent or chemical warfare agents necessitates implementation of special contract provisions and reporting requirements. Facility safety plans (Attachment 2) must be included with the proposal for work in laboratories that may pose special risks.

Proposed use of human subjects or of animals also requires special review requirements as well as implementation of special contract clauses and reporting requirements. Protection of human subjects is defined by 32 CFR 219 and implemented by Department of Defense Directive 3216.2 and in the Army by Army Regulation 70-25. Proposed protocols and informed consent forms are forwarded to the USAMRMC Human Use Review Officer, who reviews them for compliance with regulatory requirements and, after resolving any issues, forwards them to The Surgeon General Human Subjects Research Review Board (HSRRB) for review and approval. Awards based on the general proposal may be made and would carry the prohibition against proceeding with any research involving human subjects until specific protocol and informed

consent approvals are obtained from The Surgeon General HSRRB. Proposal requirements for studies involving human subjects are at Attachment 3. Similarly, use of animals in research is prohibited until protocols have been reviewed and approved and the regulatory requirements of the 1966 Animal Welfare Act (P.L. 89-544) as amended in 1976 (P.L. 94-279) and 1985 (P.L. 99-198) and as implemented through DoD Directive 3216.1, *The Use of Animals in DoD Programs*, 1995. Proposal requirements for studies involving animal subjects of research are shown at Attachment 4.

In addition to full and open competition, noncompetitive awards may be made to support program administration and management, fulfill sole source requirements for unique capabilities including those directed by the Congress, and to conduct intramural–Federal laboratory–research. Examples include awards under existing contract vehicles for studies and management assistance; contracting with the National Academy of Sciences for assistance to DoD in the conduct of epidemiological study of veterans who were in the vicinity of the Khamisiyah demolition; as well as studies in DoD facilities that have specialized containment facilities, equipment and standard operating procedures for work with chemical or biological warfare agents.

GWVI Investment and Accomplishments

The DoD's RDT&E funding for GWVI research from FY94 through FY97 totals $62.6M. From FY98 through FY02, the Department estimates investing approximately $20M per year in GWVI specific research and thereby bringing the total since FY94 to approximately $160.8M. This funding profile does not include related funds for health care delivery or our investments in highly relevant, core science and technology efforts (e.g., the medical chemical defense program) which are already established, continuing programs that will likely have direct benefits for the GWVI research program.

Reporting total Defense Department funding for the GWVI program (i.e., including related projects) is complicated and somewhat subjective since there is no bright line demarcation between GWVI-specific funded projects and those related projects embedded in the DoD core science and technology programs. As I will mention later, the DoD has established a separate Program 6 RDT&E program element and project for GWVI specific research beginning in FY99. Establishment of this program will facilitate Departmental (e.g., ASBREM, Technology Area Review and Assessment (TARA) and Defense Science and Technology Advisory Group (DSTAG)) and Congressional reviews of resource expenditures, programs and budgets, as well as program accomplishments and plans.

The investment in GWVI is providing new information on the impact of military service in the Gulf War on health-related problems, providing new areas of research exploration, and prompting new force protection initiatives that provide for medical surveillance during future operations. With specific reference to GWVI, the investment and findings have highlighted the need for improved prevention, intervention, and treatment approaches, and the national program has responded to these needs both in its approaches for veterans' health care and in the RWG emphasis on its research investment strategy.

Although the investment in GWVI has already provided some meaningful results, the full impact of research often cannot be fully assessed for years after awards are made. Funds appropriated for GWVI research are typically placed on contracts 9 to 12 months after appropriation. This reflects the average time to: complete the solicitation, advertise it to the scientific community, prepare research proposals, conduct independent peer review, develop an investment portfolio by the RWG, accomplish regulatory compliance review and negotiate awards. Once an award is made, studies usually take between 3 and 5 years to complete. The final results are normally published in the scientific literature several months after completion of the contract or grant. These individual studies eventually merge into a body of knowledge that may be used for the definitive prevention and treatment of an illness, as well as advancing scientific hypotheses.

The DDR&E took several actions during the past year to increase the visibility and oversight of Defense research efforts on GWVI, as well as to facilitate program integration with the RWG. These actions include:

- First, taking steps to establish a single Defense Program Element and project in FY99, with 1998 being the transition year, for a dedicated project for DoD GWVI-specific research. Currently, Defense research on GWVI is supported under multiple Defense-wide and Army RDT&E program elements. Establishment of a single Defense line for GWVI-specific research should improve DoD oversight and expedite Congressional review since program accomplishments, plans and resource information will appear as a single program on the RDT&E Budget Item Justification Sheet (R-2 Exhibit).

- Second, chartering a Working Integrated Process Team (WIPT) on Deployment Toxicology in November 1997. The purpose of the WIPT is to review current deployment toxicology initiatives and develop a recommendation for the ASBREM regarding appropriate DoD-level sponsorship and oversight of related policy issues, doctrinal matters, and requirements generation. This initiative complements, supports, and builds on DoD Directive 6490.2, "Joint Medical Surveillance," and DoD Instruction Number 6490.3, "Implementation and Application of Joint Medical Surveillance for Deployments," which were both issued in August 1997 by the Deputy Secretary of Defense and the Under Secretary of Defense (Personnel and Readiness), respectively. These initiatives are essential to provide the new technologies, doctrine, training and operational practices necessary for protecting the force during future deployments.

- Third, incorporating review of DoD–sponsored GWVI science and technology in the annual TARA process. This review is utilized by the DDR&E to obtain advice and recommendations and utilizes the expertise of outside reviewers and the DSTAG.

Summary of GWVI Research Results

The details of the RWG coordinated and integrated research efforts of DoD, VA, and DHHS will be provided in the DoD's Report to Congress and in the PGVCG-RWG's Annual Report to Congress that will be submitted by the Secretary of Veterans Affairs. At this point, I will simply

highlight important findings and initiatives resulting from the Federal GWVI program in 1997 and identify some of the key avenues that the DoD, VA and DHHS are pursuing in 1998. Importantly, we are trying to remain sufficiently flexible to be able to take advantage of new findings and scientific leads.

- Some groups of Gulf War veterans have an excess of self-reported symptoms in comparison with non-deployed veterans. Although no connection has been made between symptoms and specific disease pathology, ongoing and newly funded projects are being directed at determining whether such a connection exists.

- Published mortality studies through 1993 (and preliminary results through 1995) do not demonstrate any excess of disease-specific deaths of Gulf War veterans when compared to non-deployed veterans of the same era. The mortality rates of both veterans groups are about half the rate of the general U.S. population. The Department will continue to follow the mortality experience of veterans into the future.

- A study of military hospitalizations indicated that, at least among active duty personnel, the rate of hospitalizations of Gulf War veterans did not exceed that of their non-deployed counterparts. This suggests that Gulf War veterans were not experiencing an excess of illnesses of a severity that would lead to hospitalization.

- One focused study of a small cohort of Gulf War veterans and a study of military hospitalizations did not uncover an excess of birth defects among veterans' offspring. Another study examined the occurrence of Goldenhar Syndrome (a rare birth defect) among the offspring of Gulf War veterans and, in those born to Gulf War era veterans in military hospitals, found no statistically significant difference in the occurrence of Goldenhar Syndrome.

- There is some evidence that there are neuropsychological differences between veterans reporting symptoms of GWVI and in a control population. Although the clinical significance of these differences is unclear, research results suggest that the differences may be due to psychological distress and exposure to neurotoxins. It has also been shown that there is some attention and memory dysfunction in Gulf War veterans diagnosed with posttraumatic stress disorder (PTSD). These areas of research continue to be intensely pursued.

- There is recent indication from follow-up studies of the Tokyo sarin poisoning that sarin may have a subtle neurotoxic action that is unrelated to acute inhibitory action on brain cholinesterase or to PTSD, which had been reported in these victims. The Department is placing increased emphasis on assessing long-term effects of exposure to chemical warfare agents.

- There is indication that stress can lead to an increase in the penetration of pyridostigmine bromide across the blood-brain barrier, suggesting the possibility of central nervous system effects. However, another study provides data that pyridostigmine bromide

decreases the level of permethrin in the central nervous system. The importance of such interactions led the Department to solicit additional research proposals addressing the toxic effects of simultaneous exposure to different agents and prophylaxes.

Summary of Recent Recommendations for GWVI Research

I have already mentioned several areas of GWVI-specific research that we are executing. At this point I want to highlight for you recommendations regarding GWVI research that the Department is or will be pursuing. These include:

- GWVI-related research will focus on increasing the understanding of deployment-related risk factors known to be associated with GWVI. Studies are needed to identify the confluence of cognitive, emotional and physical factors that produce chronic, nonspecific symptoms and physiological outcomes typical of the undiagnosed illnesses of some Gulf War veterans.

- Research will continue to investigate persistent uncertainties related to long-term health consequences associated with exposure to subclinical levels of chemical warfare agents, and the toxicity and toxic interactions of environmental chemicals, prophylactic drugs, and military materiel. Clinical trials for assessing the effectiveness of treatments provided to Gulf War veterans are essential and are currently being planned.

- Additional research on appropriate treatments for GWVI will include clinical trials, in collaboration with VA, for assessing the effectiveness of medical therapies provided to Gulf War veterans. Such trials can be established for new proposed treatments as clearly defined, symptom-based medical syndromes are identified.

- Many of the health concerns identified after the Gulf War are similar to those associated with other deployments. Increased knowledge of the potential biological and toxicological associations between deployment-related exposures and health outcomes, relative to past, present, and future deployments, would be useful. Such knowledge could enhance the analysis of potential causes of illnesses; research and development on effective prevention, intervention, and treatment strategies; and development of an accurate and effective risk communication plan to inform troops about potential exposure risks. Comprehensive population-based troop health assessments and exposure monitoring data and data systems will enable epidemiological researchers to define the potential associations between exposures and outcomes during future military operations.

- Thus, a coordinated capability is needed to apply epidemiological research to determine whether deployment-related exposures are associated with post-deployment health outcomes. A balanced research program targeted at improved prevention, intervention, and treatment strategies for priority health risk factors and exposures and improved biologically based dose-response models is also needed. A methodology needs to be developed to systematically collect population-based demographic and health data to enable evaluation of the health of all Service personnel throughout their military careers

and after leaving military service. These data could be used to detect the appearance of novel or unanticipated health risks and to quickly deploy assets to collect and assess data relevant to any newly identified threats.

Conclusion

Let me conclude by noting that it has not yet been 5 years since formation of the PGVCB-RWG to coordinate Federal research into the health consequences of service in the Persian Gulf War. The genuine concern and recognition of the magnitude and consequences of the challenges before us are reflected by our commitment to work in a productive and cooperative manner that exploits our individual Department's scientific strengths and unifies them into a productive, responsive and fully integrated research effort, the RWG *Working Plan*. As I have alluded, the path of science is difficult, challenging, expensive and time consuming. Easy and complete solutions to complex health problems are exceptionally attractive but extremely rare. This truth is especially obvious to those who suffer the consequences of prolonged, often incapacitating, illnesses of uncertain or unknown origins and for whom medical science offers little in the way of long-lasting relief or a cure.

We are committed to sustaining a sound and responsive RWG *Working Plan* against which scientifically meritorious proposals will be evaluated for relative programmatic merit. Historically, the match of scientific merit and program needs has been the foundation upon which our National leadership in medical science has been built. I am unaware that there are either reliable alternative means or compelling reasons for risking our potential for meaningful progress by challenging or changing that proven formula for success.

I have summarized our success and findings to date and highlighted new directions the DoD and our Federal partners are taking to resolve GWVI and prevent similar illnesses among our service men and women as a consequence of future deployments. The challenges are great and while there may be no quick solutions, we are committed to responsible and aggressive pursuit and resolution of these problems.

ATTACHMENT 1

CERTIFICATE OF ENVIRONMENTAL COMPLIANCE[1]

CERTIFICATE OF ENVIRONMENTAL COMPLIANCE

The offeror currently ____IS ____IS NOT in compliance with applicable national, state, and local environmental laws an regulations. *[If not in compliance, attach details and evidence of approved mitigation measures.]*

The offeror has examined the activities encompassed within the proposed action entitled " " *[enter title and/or Solicitation number and Principal Investigator's name]*, for compliance with environmental laws and regulations. The offeror states that the conduct of the proposed action ___ WILL ___ WILL NOT violate any applicable national, state, or local environmental law or regulation. *[If a violation will result, attach details describing the nature of the violation and evidence of approved mitigation measures.]*

The offeror agrees that if the work required under the proposed action at any time results in a violation of any applicable environmental law or regulation, the offeror will immediately take appropriate action, to include notifying the Contracting Officer, and coordinating with the appropriate regulatory agencies.

(Name of Official Responsible for Environmental Compliance)

Signature
(Title)

Date

(Name of Organization)

USAMRMC FORM 65-R
1 Oct 94

[1] From U.S. Army Medical Research and Materiel Command Broad Agency Announcement 95-1

ATTACHMENT 2

FACILITY SAFETY PLAN (FSP)[2]

Laboratory research may pose special risks to the safety and health of personnel and to the environment. Law and USAMRMC policies governing workplace safety and occupational health (analogous to Federal and state regulations) require that research be conducted safely and in an environmentally responsible manner. Offerors notified that their proposal is being considered for award shall provide the information identified below, as applicable to the type of research proposed, either in the form of existing organizational documentation or by preparation of a Facility Safety Plan addressing each of these points.

1. Facility Description:

    a. Describe the facility where work will be performed (e.g., engineering controls and relevant building/laboratory ventilation features, special containment features, fire suppression systems, etc.).

    b. Describe the surrounding environment (e.g., urban, rural, single or mixed-use building, number of employees, size of adjacent populations, etc.).

2. Safety and Occupational Health Programs:

    a. Describe the organizational safety program, to include inspections, standing operating procedures, personal protective equipment, and safety committees, and identify the document(s) that codify the program. Describe discrete program elements such as biological, chemical and radiation safety programs.

    b. Identify existing Federal, state or local documents, permits, or certifications (e.g., building use permits, hazardous materials use permit, JCAHO, GLP, etc.) that relate to the proposed research or facilities proposed for use.

    c. Describe the safety program for use of hazardous materials (e.g. HAZCOM, Laboratory Standards (29 CFR 1910.1450), permitting, internal regulations, etc) by which compliance with Federal, state and local regulations pertaining to hazardous materials transportation, handling, storage, and disposal is accomplished.

    d. Provide a complete listing of all hazardous, radioactive, chemical, and/or biological substances to be used in the conduct of the proposed research. Proposals to use these materials must include, as a minimum, an organizational license or approval (e.g. Nuclear Regulatory Commission for use of radioactive materials) and approval by the organizational committee for the PI to use material in the proposed manner (e.g., Radiation Protection Committee, Institutional Biosafety Committee, etc.).

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[2] From U.S. Army Medical Research and Materiel Command Broad Agency Announcement 95-1

3. Safety and Occupational Health Programs for Specific Research Areas:

a. Recombinant DNA. Research involving recombinant DNA must meet or exceed NIH Guidelines for Research Involving Recombinant DNA Molecules, latest edition. The proposal should discuss these requirements, as appropriate. The PI must have written approval from the organizational Institutional Biosafety Committee prior to the proposed DNA work.

b. Chemical Surety Materiel (neat and dilute) and Chemical Warfare Agent Analogs. A facility safety and security plan (FSSP) is required for all facilities using chemical agents for research. Initial and recurring inspections by government safety personnel are required. A Chemical Warfare (CW) agent analog is a compound which structurally resembles that of a CW agent and exhibits similar chemical properties and pathophysiological effects. Use of CW agent analogs will not be used in USAMRMC sponsored medical chemical defense research except by special approval in rare instances. Full justification, including special safety provisions, is required for the proposed use of CW agent analogs.

c. Infectious Disease Safety Program. Research involving biological or infectious disease agents must demonstrate compliance with CDC/NIH Guidelines and OSHA regulations for universal precautions and safety in blood-borne pathogens.

d. Medical Biological Defense Research Safety Program. Research performed for biological defense must meet requirements of 32 CFR 626 and 627 and USAMRMC policy. Provide the following information:

(1) List of the etiologic agents (including microorganisms, toxins, toxoids, etc.) to be used in the proposed research.

(2) Recommended biosafety level appropriate for safe conduct and biocontainment.

(3) Describe special laboratory features and/or procedures that ensure personnel and environmental safety.

(4) Describe the organizational biological safety program, including safety committee reviews, inspections, and standing operating procedures for the safe use, handling, transportation, storage, and disposal of potentially hazardous biological materials.

(5) Formal agreements documenting coordination with local (community outside the organization) emergency authorities (including fire, health, and police officials) are required for research funded by the Biological Defense Research Program (BDRP). The documentation from the organization must include information such as potential hazards that may be encountered, symptoms of exposure, recommended treatment of exposure, and personal protective equipment required for responders. The formal agreement must be signed by each community official (fire, health, and police) official.

4. Medical Support:

a. Identify (name and address) the emergency medical care facility that provides local support to the organization, and describe any specific treatment resources for hazards unique to the proposed research. Identify organizational personnel (office and title(s)) who have been designated as points of contact for advanced treatment resources and consultation.

b. Describe the routine medical monitoring/occupational health program and process by which the results of the program are reviewed. Identify the program provider (office and individual's official title) and frequency of monitoring.

c. Describe any immunization program required in association with the proposed research.

5. Loss Control: Describe the security provisions, access restrictions, and/or administrative controls for the materials involved in the proposed research.

DATE OF PREPARATION:

PREPARED BY:

ATTACHMENT 3

RESEARCH INVOLVING HUMAN SUBJECTS/ANATOMICAL SUBSTANCES[3]

1. The USAMRMC policies and procedures governing the use of human subjects parallel those of the Department of Health and Human Services (DHHS) as contained in the Code of Federal Regulations, Title 32 Part 219 (32 CFR 219) and Title 45 Part 46 (45 CFR 46) Subparts B, C and D. Assurance of compliance with USAMRMC policy must be documented by submission of a completed Optional Form 310 (Protection of Human Subjects Verification Identification/ Certification/Declaration). This form is attached. This form must be completed by the Chairperson of the Institutional Review Board. If the study is exempt, it should be noted in the appropriate exemption blocks. The level of risk that has been assigned to the protocol (exempt, minimal, greater than minimal) must be indicated in the comments block. This form is required for all studies funded by USAMRMC (to include those studies only using anatomical substances). If such documentation is not available, a statement from an approved institutional official indicating full compliance with 32 CFR 219 and 45 CFR 46 may be used, after review by the USAMRMC, to negotiate a special assurance regarding the use of human subjects in the research project.

2. Informed Consent Statements for the proposed research shall include those details described in 32 CFR 219 and 45 CFR 46, and in addition the special DA provisions listed in paragraph 3 below. The protocol, consent form and the advertisement used to recruit subjects, if applicable, should be provided with the proposal. Paragraph 4 below contains the suggested elements of informed consent which should be followed when constructing the consent form. Paragraph 5 contains guidance for constructing the advertisement notice.

3. Special Human Use Provisions in DOD Funded Research

a. Title 10, U.S.C., Section 980, Requirement for Obtaining Informed Consent states that funds appropriated to the DOD may not be used for research involving a human being as an experimental subject unless:

(1) The informed consent of the subject is obtained in advance; or

(2) In the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subject is obtained in advance.

In essence, if an individual cannot give specific consent, the person cannot be entered into a study unless the prospective subject will receive some definitive benefit as a result of participation. This is legally binding and there will be no exceptions.

[3] From U.S. Army Medical Research and Materiel Command Broad Agency Announcement 95-1

b It is DA policy that the contractor must make provision for all necessary medical care of research subjects for injury or disease which is the proximate result of participation in the research.

c. Department of Defense Directive 6465.2, dated 19 April 1984, stipulates that organs, tissues, or tissue fluids obtained from an autopsy shall not be used for research or investigational purposes without the expressed consent of the next of kin. It should be noted that a general autopsy consent may not, in itself, be sufficient. If autopsy tissue is to be used, the protocol should include a copy of the consent form used to obtain the tissue. All studies involving the use of anatomical substances must include a completed Optional Form 310 and documentation of Institutional Review Board review and approval to conduct the study. This documentation must include the level of risk assigned to the study. If the Institutional Review Board determines the study to be exempt from human use regulations, a letter signed by the Institutional Review Board Chairperson must be included stating the study is exempt.

d. It is the policy of the USAMRMC that organs, tissues, or tissue fluids obtained from a surgical procedure shall not be used for research or investigational purposes without the expressed consent of the patient or the patient's legal representative. It should be noted that a consent to perform surgery may not, in itself, be sufficient. If excised tissue is to be used, the protocol should include a copy of the consent form used to obtain the tissue. All studies involving the use of anatomical substances must include a completed Optional Form 310 and documentation of Institutional Review Board review and approval to conduct the study. This documentation must include the level of risk assigned to the study. If the Institutional Review Board determines the study to be exempt from human use regulations, a letter signed by the Institutional Review Board Chairperson must be included stating the study is exempt.

e. It is the policy of the USAMRMC that any anatomical substance (organs, tissues, or tissue fluids) linked by identifiers to a particular person and used for research under a USAMRMC sponsored contract shall be donated for the purpose of research or investigation. The donor shall be the person from whom the substance is removed or, in the event of death or legal disability of the person from whom the substance is removed, the next of kin or legal representative of such person. Donation shall be made by written consent and the donor shall relinquish all ownership and/or rights to the substance. All human anatomical substances used in research under contract shall be lawfully acquired. It should be noted that a general autopsy consent form or a consent to perform surgery in and of themselves, may not be adequate. If excised or autopsy tissue is to be used, the protocol should include a copy of the consent form used to obtain the tissue. All studies involving the use of anatomical substances must include a completed Optional Form 310 and documentation of Institutional Review Board review and approval to conduct the study. This documentation must include the level of risk assigned to the study. If the Institutional Review Board determines the study to be exempt from human use regulations, a letter signed by the Institutional Review Board Chairperson must be included stating the study is exempt.

f. Prisoners of War shall not be used as research subjects.

g. The USAMRMC may inspect contractor records concerning the use of humans as research subjects.

h. The Human Use Review and Regulatory Affairs Division (HURRAD) is the office to which principal investigators are to report any research related illnesses or injuries which have occurred as a result of a subject's participation in an investigational drug/device study sponsored by the USAMRMC.

i. It is the policy of the USAMRMC that whenever the use of volunteers exists in USAMRMC sponsored research, data sheets are to be completed on all volunteers for entry in the USAMRMC's Volunteer Registry data base. The intent of the data base is twofold: first, to readily answer questions concerning an individual's participation in research conducted or sponsored by the USAMRMC; and second, to ensure that the USAMRMC can exercise its "duty to warn." The "duty to warn" is an obligation to ensure that research volunteers are adequately informed concerning the risks involved with their participation in research, and to provide them with any newly acquired information that may affect their well-being when that information becomes available. The duty to warn exists even after the volunteer has completed his or her participation in research. To accomplish this, a system must be established which will permit the identification of volunteers who have participated in research conducted or sponsored by the USAMRMC. The data base must contain items of personal information, for example, name, Social Security Number, etc., which subjects it to the provision of The Privacy Act of 1974. References: Federal Acquisition Regulation (FAR) Protection of Privacy and Freedom of Information at Part 24; Privacy Act clauses of the FAR, Privacy Act Notification at 52.224-1, and the Privacy Act at 52.224-2. For each subject enrolled in a USAMRMC-sponsored study, a Volunteer Registry Data Sheet (USAMRMC Form 60-R, attached), is to be completed. The principal investigator is to complete Part A of Form 60-R; after which, Form 60-R is to be provided to volunteers for completion at the time of consent. The information collected is then sent to the Human Use Review and Regulatory Affairs Division (HURRAD) upon completion of the research or upon expiration/termination of the contract, whichever occurs first. Data sheets collected on volunteers participating in task orders or subelements of the overall effort are to be submitted to the HURRAD upon completion of each task order or subelement. The information is stored in the USAMRMC Headquarters data base for a minimum of 75 years. Information stored in the Volunteer Registry data base will be disclosed in accordance with Army Regulation 340-21 (the Army Privacy Program), and the Privacy Act of 1974. Upon written or oral requests, persons on whom data is collected, or a specific designated agent or legal guardian may have access to the record pertaining to that individual contained in the Volunteer Registry data base. Only authorized staff of the HURRAD may have access to information entered in and information selected from the Volunteer Registry data base.

4. Elements of Informed Consent. In seeking informed consent, the following information shall be provided to each subject:

a. State the title of the study and location (specify address) where it is to be conducted.

b. List the name of principal investigator and associate(s), if applicable, conducting the study.

c. Include a statement that the study involves research and an explanation of the purposes of the research. In general, the structure of the informed consent form:

(1) Should be readable (written in 8th grade reading level language).

(2) Should contain, when feasible, non-medical language that is easily understood by the subject. One must take into consideration the age group, reading level, and education of the prospective subject.

(3) Should be translated if a subject enrolled in a study does not comprehend English. The following statement and additional information must be on the English version of the consent form "I certify that this is an accurate and true translation." The translator's signature, typed name, address, phone number and TELEFAX number should also be included.

(4) Should speak to the research subject in the first person singular "I" and/or second person "you."

(5) Subjects are to be told, within the consent document, that they will receive a copy of the consent form. A copy of the consent form must be provided to subjects.

d. Include a statement indicating the expected duration of the subject's participation (e.g., the number of hours, days, weeks, months).

e. Provide a description of the procedures to be followed and identify any procedures which are experimental.

(1) Briefly explain the study design relative to what will be done to the subject (in blind or double-blind studies, subjects must be informed that they may receive either the experimental modality or a placebo). If a placebo is used, its contents should be described.

(2) Specify what is required of the subject (hospital visits, blood donation, etc). The amount of blood should be expressed in lay terms, e.g., teaspoonsful.

(3) When experimental procedures, pharmaceuticals, or devices are to be used, an Investigational New Drug/Investigational Device Exemption (IND/IDE) approval must be obtained from the FDA. The subject should be advised that the IND/IDE is permission for the study to be undertaken but does not indicate the FDA approval for the routine use of the drug or device in the method stated in the protocol or proposal. If a drug or device covered under an IND or IDE is involved, it must be clearly indicated in the consent form that it is investigational for the purpose of this research.

(4) Although subjects may be familiar with procedures, never assume that he or she comprehends everything.

f. Provide a written description of any reasonably foreseeable risks or discomforts to the subject.

(1) For studies of potential subject benefit, describe risks unique to the study, estimate their severity and likelihood, and/or compare these risks with the risks which the subject may encounter in the course of daily activities and include any possible risks to pregnant women, if applicable. If similar research has been conducted in the past, describe the incidence of adverse effects or injuries which have occurred in previous subjects.

(2) For studies of no potential benefit to the subject, list all risks which are more than "minimal" (risks which are greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine medical tests).

(3) Where applicable, the subject will be advised:

(a) that a certain treatment of procedure to be used may involve risks that are currently unforeseeable; and,

(b) of any precautions which are to be observed by the subject before and after the study.

g. Provide a written description of any benefits to the subject or to others which may reasonably be expected from the research (mention remuneration if any). It should be noted that for studies in which a considerable sum will be paid, that payment should be prorated and not paid in a lump sum, or a disproportionately large sum, at the completion of participation.

h. Provide a written disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject, e.g., whether treatment is available outside of the protocol/proposal.

i. Provide a statement to the subject describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. The possibility should also be noted that representatives from the FDA, DOD, e.g., USAMRMC, may inspect the research records. For studies utilizing military personnel, the following statement must be included: All data and medical information obtained about you as an individual will be considered privileged and held in confidence; you will not be identified in any presentation of the results. Complete confidentiality cannot be promised, particularly to subjects who are military personnel,

because information bearing on your health may be required to be reported to appropriate medical or command authorities.

j. The following statement must be incorporated into the consent form: You are authorized all necessary medical care for injury or disease which is the proximate result of your participation in this research. The U.S. Army requires that this institution provide such medical care when conducting research with private citizens. Other than medical care that may be provided (and any other remuneration specifically stated in this consent form), there is no other compensation available for your participation in this research study; however, you understand this is not a waiver or release of your legal rights. (This statement must be in all consent forms, regardless of risk level of the study.)

k. Provide the subject an explanation of:

(1) Whom to contact for answers to pertinent questions about the research, and whom to contact to report research related injuries. The principal investigator should be listed as the contact. This information should include complete telephone number(s) and address(es).

(2) Whom to contact to answer questions about research subject's rights. The Institutional Review Board (IRB) chairman and/or the legal office of the contracting organization should be listed as the contact. This information should include telephone numbers and addresses.

l. Include a statement that explains that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

m. If blood, tissue or body product samples will be drawn in the study for the express purpose of storing for possible future use in another protocol, the following statement must be included "I understand that there is a possibility that the [blood, tissue, body fluids<specify what type] which I am providing under this study may also be used in other research studies and could potentially have some commercial applicability." If, indeed, it is anticipated that the samples donated by the subject will be used in other studies, an additional consent form must be prepared for signature by the subject which states "I voluntarily and freely donate any and all [blood, tissue, body fluids<specify what type] to the U.S. Government and hereby relinquish all right, title and interest to said items." The title of the study should be inserted at the top of the form.

n. Any additional costs to the subject must be clearly indicated.

o. If applicable, the following must be included "In order to participate in this study, you should have avoided becoming pregnant from the first day of your most recent menses. A negative pregnancy test does not absolutely prove that you are not pregnant. Regardless of

the results of the pregnancy test which you were administered as part of the screening for this study, you should not participate if you think there is a possibility that you might be pregnant." Also, a statement should be included which directs the volunteer to notify the principal investigator if she becomes pregnant while enrolled in the study. If women will be withdrawn from the study should they become pregnant, that should be clearly indicated.

p. For all USAMRMC-sponsored studies, the following statement must be included in the consent form: It is the policy of the U.S. Army Medical Research and Materiel Command (USAMRMC) that data sheets are to be completed on all volunteers participating in research for entry into the USAMRMC's Volunteer Registry Data Base. The information to be entered into this confidential data base includes your name, address, social security number, study name and dates. The intent of the data base is two fold: first, to readily answer questions concerning an individual's participation in research sponsored by the USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

q. Provide a space for subject's typed/printed name and permanent address as well as space for date and signature of witness and typed/printed name of witness.

5. In accordance with 21 CFR 56.111(a)(3), IRBs are responsible for reviewing the methods used by investigators to recruit subjects. One method of recruiting subjects is through advertisements which should be seen as an extension of the informed consent (see 21 CFR 50.20, 21 CFR 50.25). IRB review of advertisements is necessary to ensure that the information is not misleading to subjects. The FDA recently established guidelines on advertisement for research subjects. Generally, the FDA believes that any advertisement to recruit subjects should be limited to:

a. The name and address of the principal investigator.

b. The purpose of the research and, in summary form, the eligibility criteria that will be used to admit subjects into the study.

c. A straightforward and truthful description of the benefits (e.g., payments or free treatment) to the subject from participation in the study.

d. The location of the research and the person to contact for further information.

Provision of the advertisement used by the investigator to recruit research subjects must be included with the protocol/ proposal submission.

6. The USAMRMC Human Use Review and Regulatory Affairs Division should be contacted should a principal investigator have questions concerning these provisions or if the principal

investigator would like a copy of the Human Use Protocol Review Checklist. Inquiries may be forwarded in writing to

Commander

U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ
Fort Detrick
Frederick, MD 21702-5012
or by TELEFAX (301) 619-7803.

ATTACHMENT 4

RESEARCH INVOLVING ANIMALS[4]

Each of the items listed below must be addressed in a proposal appendix entitled "Research Involving Animals." If an item has been fully covered in the proposal, reference the page number and section. Questions concerning animal use should be directed to the USAMRMC Animal Use Review Office, in care of Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, Fort Detrick, Frederick, MD 21702-5012, Telephone (301) 619-2144.

1. Alternatives Search: Identify the services (computer databases, literature searches, etc.) that were used to obtain information on alternatives to painful procedures and to the use of live animals. It is USAMRMC policy that alternatives to the use of animal models be thoroughly investigated prior to submission of any protocol involving animals. The USAMRMC reserves the right to request evidence that a search for alternatives was performed.

2 Species Identification: Identify the species of animal to be used and the estimated number of each species to be used in the proposed study.

3 Rationale: Provide a statement of the rationale for using animals, for the species proposed, and for the number of animals to be used in the proposed study.

4. Animal Use: Provide a complete description of the proposed use of animals. Describe what anesthetics, tranquilizers and analgesics will be used. If none, why?

5. Euthanasia: Describe the euthanasia methodology. Approved methods are listed in the "1993 Report of the American Veterinary Medical Association Panel on Euthanasia." If animals are not euthanized, state final disposition of the animals.

6. Accreditation: Provide one of the following:

a. Evidence that the contractor's facility is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC).

b. A copy of the contractor's Institutional Letter of Assurance of Compliance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals, revised September 1986.

c. A statement signed by an official of the contractor's Animal Care and Use Committee that the care and use of animals will be done according to NIH 86-23, 1985 Edition, "Guide for the Care and Use of Laboratory Animals," or other applicable Federal permits and regulations.

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[4] From U.S. Army Medical Research and Materiel Command Broad Agency Announcement 95-1

7. IACUC Approval: Provide evidence that the protocol was reviewed and approved by the principal investigator's Institutional Animal Care and Use Committee (IACUC). If it was not possible to have the protocol reviewed by the Committee prior to submission of the proposal, then so state. Evidence of Committee review can follow but must be provided prior to award. RESEARCH WILL NOT BE FUNDED WITHOUT EVIDENCE OF APPROVAL OF THE ANIMAL CARE AND USE COMMITTEE.

8. USDA Inspection Report: Include a copy of the most recent U.S. Department of Agriculture's APHIS Form 7008, Inspection of Animal Facilities, Sites or Premises.

9 Assurances: Provide a signed statement from the principal investigator for the following:

a. I assure that discomfort, pain, and injury to animals will be limited to that which is unavoidable in the conduct of scientifically valuable research, and that analgesic, anesthetic and tranquilizing drugs will be used where indicated and appropriate to minimize discomfort and pain to animals.

b. I assure that the animals authorized for use in this protocol will be used only in the activities, the manner, and quantities described herein, unless a deviation is specifically approved by my IACUC and the USAMRMC Animal Use Review Office.

c. I accept full responsibility for the proper care and use of the animals during the conduct of research outlined in the proposal.

d. I verify that I have made a reasonably good faith effort to ensure that this protocol is not an unnecessary duplication of previous experiments. (The USAMRMC reserves the right to ask for evidence that a thorough literature search was performed.)

e. I verify that the personnel performing the animal procedures/manipulations described in this protocol are technically competent in those procedures, and have received their training on the use of animals in research, as required by the Animal Welfare Act of 1985.

For proposals which require the use of non-human primates, companion animals, marine mammals, or protocols deemed sensitive by USAMRMC, a site visit shall be conducted as necessary by the Contracting Officer and the USAMRMC Animal Use Review Officer, or designees.

Mr. TOWNS. Dr. Barrett.

Ms. BARRETT. Thank you for the opportunity to review the Department of Health and Human Services involvement in the coordinated effort to address the health concerns of Gulf war veterans.

As you indicated, I am Dr. Drue Barrett. I am Chief of the Veterans' Health Activity Working Group of the National Center for Environmental Health at the Centers for Disease Control and Prevention. I serve as CDC's liaison to the HHS on Gulf war issues, and I am a member of the Research Working Group of the Persian Gulf Veterans Coordinating Board.

Through its membership in the Research Working Group, HHS has been involved in providing guidance and coordination for DOD, VA, and HHS research activities relating to Gulf war veterans. Specifically, this has included assessing the state and direction of research, review of Government research concepts as they are developed, identification of gaps in factual knowledge and conceptual understanding, and providing recommendations regarding research direction.

When the input of experts on a specialized research topic is needed, HHS scientists who are not regular members of the Research Working Group have provided consultation and have participated on special subcommittees managed by the Research Working Group. Through participation on the Subcommittee for Project Funding Recommendations, HHS has provided input into the programmatic review and funding recommendations of the Research Working Group. The process that is involved is reviewed in my written testimony.

HHS believes that the Research Working Group has developed an appropriate and scientifically rigorous agenda for addressing the health concerns of Gulf war veterans. This research agenda includes an important balance of clinical studies, epidemiologic investigations, and basic research.

Now I would like to briefly review CDC's current research activities relating to Gulf war veterans and how these activities were selected and funded.

In 1997, CDC developed a request for proposals which focused on two programmatic priority areas: one, research that enhanced the understanding of conditions and symptoms reported to be more prevalent among Gulf war veterans; and two, research that added to the scientific knowledge needed to develop a case definition of illness among Gulf war veterans.

CDC convened a Special Emphasis Panel, known as SEP, composed of 17 experts from outside CDC to review and rate the scientific merit of the proposals received. In addition, a subcommittee of the Research Working Group reviewed proposal abstracts and SEP summary statements to determine the relevancy to the Federal research goals.

Based on the results of the SEP and the Research Working Group reviews, two new studies were selected for funding. The Boston University School of Public Health will conduct a study examining "Cognitive Function and Symptom Patterns of Persian Gulf Veterans." Robert Wood Johnson Medical School will conduct a study comparing various case definitions for unexplained illness

among Gulf war veterans. Specifics regarding these two studies are detailed in my written testimony.

Besides these two new studies, CDC continues to work with the Iowa Department of Public Health and the University of Iowa to collect additional data to validate health outcomes reported by participants of the Iowa study. A followup study focusing on the self-report of asthma symptoms will be conducted.

The University of Iowa has also been funded by DOD to conduct additional validation studies on other health outcomes, including depression, cognitive dysfunction and multisystemic conditions. An interagency agreement is currently being developed that will enable CDC investigators to provide technical assistance to DOD and the University of Iowa for this study.

Finally, HHS has developed a research strategy for addressing health effects of exposure to multiple chemicals. The principal goal for fiscal year 1998 is to develop a 5-year research plan. This will include joint sponsorship by CDC and the National Institute for Environmental Health Sciences of a consensus-building conference. In addition, HHS will augment funding for an existing NIH grant announcement calling for research projects on the health effects of chemical mixture exposures.

Together with research sponsored by VA and DOD, HHS's past research efforts have added new or confirming information to the growing knowledge base managed by the Research Working Group. Our new research activities will continue to contribute to a better understanding of illnesses among Gulf war veterans and will assist in providing new information to guide the collaborative planning process of the Federal Government.

HHS is proud to serve along with the other two principally responsible departments on the Persian Gulf Veterans' Coordinating Board. This board has provided a necessary forum for the exchange of information within the Government and for the development of interdepartmental relationships, which have fostered greater understanding and cooperation. We look forward to continuing collaboration of this type.

That concludes my statement.

Mr. TOWNS. Thank you very much, Dr. Barrett.

[The prepared statement of Ms. Barrett follows:]

Mr. Chairman, thank you for the opportunity to review with the Committee the Department of Health and Human Services' (HHS) involvement in the coordinated Federal effort to address the health concerns of Gulf War veterans and our corresponding research activities in this area. I am Dr. Drue Barrett, Chief of the Veterans' Health Activity Working Group in the Division of Environmental Hazards and Health Effects, National Center for Environmental Health (NCEH), Centers for Disease Control and Prevention (CDC). I serve as CDC's liaison to HHS on Gulf War issues and I am a member of the Research Working Group of the Persian Gulf Veterans Coordinating Board.

NCEH has been designated as the lead Center at CDC for addressing Gulf War veterans' health concerns, however other Centers within CDC have also been involved in this effort, including the National Center for Infectious Diseases, and the National Institute of Occupational Safety and Health (NIOSH). Besides CDC, other agencies within HHS have also contributed to addressing the health concerns of Gulf War veterans, including the National Institutes of Health (NIH) and the Agency for Toxic Substances and Disease Registry (ATSDR).

Coordination of Federal Research Efforts:

There has been HHS representation on the Research Working Group since its inception. In addition to CDC, the Office of the Secretary and NIH are represented. Through its membership, HHS has been involved in providing guidance and coordination for the Department of Defense (DoD) , the Department of Veterans Affairs (VA), and HHS research activities relating to Gulf War veterans. Specifically, this has included assessing the state and direction of research, review of government research concepts as they are developed, identification of gaps in factual knowledge and conceptual understanding, and providing recommendations regarding

research direction. When the input of experts on a specialized research topic is needed, HHS scientists who are not regular members of the Research Working Group have provided consultation on specific projects and have participated on special subcommittees managed by the Research Working Group. Examples of this include the involvement of a CDC scientist with particular expertise in chemical warfare agents on a subcommittee addressing low level nerve agent exposure health effects, involvement of CDC, NIH, and Food and Drug Administration scientists with expertise in parasitic diseases on a subcommittee regarding serological testing for detection of leishmania infection, and consultation of CDC and NIH infectious diseases experts on mycoplasma infection issues. NIOSH and ATSDR have also been involved in providing consultation to the Persian Gulf Veterans Coordinating Board on health risk communication issues.

Through participation on the Subcommittee for Project Funding Recommendations, HHS has provided input into the programmatic review and funding recommendations of the Research Working Group. Specifically, this has involved a process where DoD, VA, and HHS representatives review abstracts of peer-reviewed proposals along with written reviews of the peer-reviewers and their scientific merit scores. The submitting investigator's names and institutions are removed form these abstracts and peer reviews in order to minimize any potential bias. The Subcommittee is charged with reviewing this information in order to rate the proposals for relevance to the programmatic needs as outlined in the Research Working Plan. This process was used to rate the relevance of proposals submitted in response to recent DoD Broad Area Announcements and to a CDC program announcement. Only proposals that receive scientifically meritorious ratings through the peer review process are recommended for funding.

The Research Working Group also serves as a forum for research data exchange among the three departments and among federally funded investigators. This includes the maintenance of a research database on all VA, DoD, and HHS research activities. VA, DoD, and HHS share in the responsibility for tracking research projects and updating the research database, which is maintained at the VA Office of Research and Development. The Research Working Group also sponsors an annual investigators meeting where new research results are shared. HHS participates on the planning subcommittee for this effort.

CDC Gulf War Research Activities:

Now I would like to review CDC's research activities relating to Gulf War veterans, with a special focus on our current activities and how these activities were selected and funded. Our involvement in this research effort began not long after the cessation of hostilities when in May 1991 researchers from NCEH and several other Federal agencies conducted cross-sectional surveys of workers in Kuwait City and of firefighters in the oil fields in October 1991. Since this initial research effort, CDC has continued to contribute to our understanding of the health effects of military service in the Gulf War through a variety of studies. Besides studies on the health effects of exposure to oil well fire smoke, CDC researchers have conducted studies addressing the prevalence of birth defects among Gulf War veterans, and have completed two large epidemiologic studies documenting the prevalence of symptoms and conditions among Gulf War veterans in comparison to Gulf War era controls, the Iowa and Pennsylvania Air National Guard studies.

Our involvement in the Gulf War research effort has been initiated through a variety of mechanisms. For example, the Iowa study was conducted in response to a Congressional request

to assess the prevalence of illnesses among Gulf War veterans from Iowa. The Pennsylvania Air National Guard Study was conducted in response to a request by the Department of Veterans Affairs in conjunction with DoD, and the Pennsylvania Department of Health to investigate a reported cluster of illnesses among members of a specific Air National Guard unit. More recently, NCEH directly provided funding to expand on the findings of the Iowa and Pennsylvania studies

The Iowa study was one of the first population-based epidemiologic studies to document that Gulf War veterans are reporting more medical and psychiatric conditions than their nondeployed military peers. The study, conducted in collaboration with the Iowa Department of Public Health and the University of Iowa, identified several medical and psychiatric conditions that need to be studied in more detail. These conditions include fibromyalgia, cognitive dysfunction, depression, chronic fatigue, post-traumatic stress disorder, and respiratory illness (asthma and bronchitis). The conditions identified in this study appear to have had a measurable impact on the functional activity and daily lives of these Gulf War veterans. However, these conditions may not be unique to Gulf War veterans and may be similar to the experience of veterans in other wars.

Dr. William Reeves will be providing you with information regarding the Pennsylvania study. But briefly, the results of this study found that Gulf War Veterans were more likely to report a variety of symptoms including fatigue, diarrhea, joint pain, nasal or sinus congestion, muscle pain and memory difficulty. This investigation also addressed the development of a research case definition for illness among the Gulf War veterans studied.

The results of the Iowa and Pennsylvania studies established the need to investigate

further the causes, clinical nature, and public health implications of the higher rates of self-reported health problems of Gulf War veterans. In this regard, in 1997, NCEH investigators developed a request for proposals which focused on two programmatic priority areas: (1) research that enhanced the understanding of conditions and symptoms reported to be more prevalent among Gulf War veterans, and (2) research that added to the scientific knowledge needed to develop a research case definition of illness among Gulf War veterans. Specifically, for programmatic priority area 1, we asked for research on conditions found to be more prevalent among Gulf War veterans in the Iowa study. We asked that these studies include appropriate clinical evaluation in order to validate the diagnosis, assessment of the course of the illness among Gulf War veterans, assessment of risk factors, and assessment of the impact of the illness on functional status. For programmatic priority area 2, we called for studies focusing on development of a case-definition for illness among Gulf War veterans. We asked that these studies evaluate whether symptoms reported among Gulf War veterans represent a unique illness or are better characterized by existing clinical entities. We also asked for a comparison of data driven case-definitions and use of known clinical diagnoses in order to determine the best way to characterize illness among Gulf War veterans or for a validation of previous data driven case definitions of illnesses among Gulf War veterans.

Eligible applicants included all nonprofit and for-profit organizations. Thus, State and local health departments, State and local governmental agencies, universities, colleges, research institutions, hospitals, other public and private non-profit organizations were eligible to apply.

CDC convened a Special Emphasis Panel (SEP) composed of 17 experts from outside CDC to review and rate the scientific merit of the proposals received. The SEP was

composed of federal, state, and private members with expertise in public health issues, epidemiology, environmental and occupational medicine, research methodology, and Gulf War health issues. In addition, representatives from two national Veterans' Service Organizations served as members on this panel. Members were also selected in order to ensure adequate geographic, racial, and gender diversity. SEP members were provided with clear criteria for evaluating the proposals (these criteria were also included in the request for proposals). These criteria including ratings of the significance, originality, and adequacy of the proposed research plan; the inclusion of clear, measurable objectives; the adequacy of the proposed evaluation plan; and the degree of the investigators' understanding of the problem and ability to conduct the proposed work.

In addition to the review by the SEP, as described above, a subcommittee of the Research Working Group, composed of representatives from DoD, VA, and HHS, reviewed proposal abstracts and summary statements from the SEP review. All abstracts and summary statements were redacted so that the Research Working Group subcommittee was blinded to the institutions and investigators associated with each proposal. The subcommittee was asked to review the proposals for relevancy to the research goals identified by the Research Working Group. The subcommittee's recommendations corresponded with the scientific merit scores.

Based on the results of the SEP and Research Working Group reviews, two new studies were selected for funding, one study addressing each of the programmatic priority areas. Both of these studies were funded at $600,000 per year for a three year period.

Addressing priority area 1, Dr. David Ozonoff of the Boston University School of Public Health will conduct a study entitled "Cognitive Function and Symptom Patterns in Persian Gulf

Veterans." This investigator and his collaborators have been following cohorts of Gulf War veterans and Gulf War-era veterans for several years and have shown higher prevalences for a variety of symptoms in veterans who were deployed to the Gulf as opposed to those deployed only as far as Germany. This has included pilot data showing poorer neuropsychological test scores in Gulf-deployed versus non-Gulf-deployed veterans.

In this study, functional magnetic resonance imaging (fMRI) will be used with 120 subjects to examine possible differences in brain activation within specific neuroanatomical areas between Gulf-deployed and non-Gulf-deployed subjects with different levels of symptoms. Patterns of activation of fMRI in Gulf War veterans challenged with a test of working memory will be compared to veterans not deployed to the Gulf (n=40); and between high symptom Gulf deployed veterans (n=40) and low symptom Gulf-deployed veterans (n=40).

In addition, a new data-driven mathematical technique, Logical Analysis of Data, (LAD) will be used to examine previously collected symptom data (n=300) to see if there is a set of complaints characteristic of service in the Gulf region useful for determining etiology or for case definition. This component of the study will be used to identify the most significant items or patterns of items for discriminating deployed and non-deployed subjects.

Finally, neuropsychological test results and symptom prevalence measures will be replicated and verified in a cohort of Danish armed forces. The Danish forces arrived after the cessation of hostilities. This component of the study will compare neuropsychological function in Danish troops deployed to the Gulf (n=200) and a comparison sample of non-deployed Danish troops (n=200); relate neuropsychological test results in the Danish deployed cohort to self reported exposures while in the Gulf; compare neuropsychological test scores in the Danish and

US cohorts; compare symptom prevalences in the Gulf-deployed Danish troops and those not deployed; and test the validity of the LAD findings with the Danish subjects.

For Priority Area 2, Dr. Howard Kipen of the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School will conduct a study entitled " Defining Gulf War Illness." The purpose of this study is to characterize and compare alternative classifications for symptoms and functional disability which remain medically unexplained in Gulf War veterans. This will be accomplished in three phases. Phase I will assess persistence and stability of symptoms over time, as well as compare the performance of data-driven case definitions derived from two samples: 1) the New Jersey Center for Environmental Hazards Research sample of Gulf War veterans participating in the Department of Veterans Affairs Gulf War Registry (N= 1,161), and 2) a cohort of Air Force members from a previous CDC study of Gulf War veterans and Gulf War-era controls from Pennsylvania and Florida (N=3,723). All subjects from the previously studied New Jersey cohort and a sample of the CDC Air Force cohort (N= 1,400) will be administered a symptom questionnaire. In addition to assessing data-driven case definitions for illness among Gulf War veterans, existing definitions for medically unexplained symptoms, such as chronic fatigue syndrome, multiple chemical sensitivity, and fibromyalgia will be evaluated. Phase II will attempt to assess the generalizability of both derived and existing case definitions in a National random sample of deployed and non-deployed Gulf War era veterans (N=3,000). Phase III will consist of a standardized telephone interview for the assessment of psychiatric conditions. This will be administered to a sample (not to exceed 600) of Phase I and Phase II participants who are identified through their responses to paper-and-

pencil questionnaires as having high levels of psychologic distress.

Besides these two new studies, CDC continues to work with the Iowa Department of Public Health and the University of Iowa to collect additional data to validate health outcomes reported by participants of the telephone survey component of the Iowa study. Collection of these data is vital to address the limitations of the self-report telephone information. A follow-up study focusing on the self-report of asthma symptoms will be conducted with carry over funds from the original telephone survey.

A sample of 50 Gulf War and 50 non-Gulf War military personnel who completed the initial telephone survey and met pre-defined criteria for asthma will be invited to participate in the asthma follow-up study. Additionally, a sample of 100 telephone survey participants who did not meet criteria for any of the conditions assessed in the survey will be selected from among persons deployed and not deployed to the Persian Gulf to serve as controls. Subjects will receive a detailed clinical evaluation which will include physical examination, medical history, tests of lung functioning, occupational and exposure history, assessment of functional status and quality of life, assessment of psychiatric history and personality functioning, history of major mental disorders in first-degree relatives, assessment of social support, and questions about significant life stressors in the six months prior to the Gulf War. All exams will be conducted at the University of Iowa Hospitals and Clinics in Iowa City, Iowa. In addition, a review of medical records for the last 10 years will be completed on a sub-sample of persons who complete the asthma follow-up study.

Subjects will be classified on the basis of the initial telephone interview as screening positive or negative for asthma. Subsequent in-person objective testing will classify the

screening results as true positive, true negative, false positive, or false negative. Three hypotheses will be tested: (1) the rate of false positives of the Gulf War military personnel self-reports of asthma are the same as the rate of false positives of the non-Gulf War military personnel self-reports of asthma; (2) the self-report of asthma among Gulf War and non-Gulf War military personnel is accurate and correlates with objective measures of asthma; and (3) among the Gulf War military personnel, there is no association between exposures in the Gulf War and the subsequent occurrence of asthma. Comparison of the false positive and false negative rates for self-reported asthma between Gulf War and non-Gulf War military personnel will allow us to estimate the degree of over-reporting of symptoms potentially attributable to publicity associated with service in the Gulf War.

The University of Iowa has also been funded by DoD to conduct validation studies of additional health outcomes among participants of the telephone survey. These include validation of depression, cognitive dysfunction, and multisystemic conditions. An interagency agreement is currently being developed that will enable CDC investigators to provide technical assistance to DoD and the University of Iowa for this study.

Finally, in response to House Report 105-205, HHS developed a research strategy for addressing the health effects of exposure to multiple chemicals. The principal goal for FY'98 is to develop a five-year research plan to investigate the relationship between possible biological and chemical exposures in the Gulf War and subsequent illnesses among Gulf War veterans. This will include joint sponsorship by CDC and the National Institute for Environmental Health Sciences (NIEHS) of a consensus-building conference. The conference will strive to fully characterize the nature of multiple chemical exposures within the Gulf War veteran population

and to relate this characterization to what is known about multiple chemical sensitivity (MCS) and related conditions and disorders within civilian populations. The goal of the workshop is to develop a research plan that builds upon existing efforts to understand MCS and related conditions within the context of the known environmental exposures during the Gulf War. It is expected that the plan will focus on individual factors that could affect susceptibility to low-level chemical exposures, and on the development of acceptable case criteria for MCS that can be used in future clinical and epidemiological research. The plan will also set forth a multi-year program for the development of biomarkers that can be used to document chemical exposure.

Attendees to this conference will include those in the public and private sectors who are most engaged in and affected by the multiple chemical exposure problem and whose personal experience and/or profession expertise would add new information regarding the health effect of multiple chemical exposures relevant to the Gulf War experience. These would include scientists with recognized expertise in the area of MCS and related disciples of neurobiology, immunology and endocrinology; prominent advocacy/treatment consumer group representatives and other stakeholders; research scientists and policy makers from appropriate government agencies, including State health departments, HHS, DoD, VA, and the Environmental Protection Agency (EPA).

In addition, in FY'98, HHS will augment funding for an existing NIH Grant Announcement, entitled "Chemical Mixtures in Environment Health" (RFA:ES-98-002, NIH Guide, Volume 26, Number 38, November 21, 1997). This announcement is a joint effort of NIEHS and EPA. The announcement seeks to fund research projects that will expand our knowledge of the health effects of chemical mixture exposures, including an exploration of the

mechanisms of action as they relate to human health.

Together with research sponsored by VA and DoD, HHS's past research efforts on the health effects of Gulf War service have added new or confirming information to the growing knowledge base managed by the Research Working. Our new research activities will continue to contribute to a better understanding of illnesses among Gulf War veterans and will assist in providing new information to guide the collaborative planning process of the Federal government. HHS is proud to serve along with the other two principally responsible Departments on the Persian Gulf Veterans Coordinating Board. This Board has provided a necessary forum for the exchange of information within the government and for the development of interdepartmental relationships, which have fostered greater understanding and cooperation. We look forward to continuing collaboration of this type, not only for addressing the important concerns of Gulf War veterans, but also for helping to properly prepare the Nation for future conflicts and peacekeeping missions.

Mr. TOWNS. Dr. Gerrity.

Mr. GERRITY. I don't have a prepared statement.

Mr. TOWNS. No prepared statement. Thank you.

Let me begin then by asking, can you tell us what kind of coordination efforts are in place for research, as well as funding, at this particular time?

Dr. FEUSSNER. You mean the process that is involved from soup to nuts, the identification of a part, or all the way through?

Mr. TOWNS. All the way through.

Mr. FEUSSNER. Yes, sir.

Typically what happens when inputs are received or are offered to the Persian Gulf Research Working Group, one of the departments will take a lead in developing some ideas about how the research is to be approached. Then that is discussed during the committee meetings. BAAs, broad area announcements, are made. Then, DOD releases the request. In the VA, these are called requests for applications, RFAs. Both BAAs and RFAs are typically time-limited requests so that you might announce one of these at time X and then have the proposals submitted within 90 to 120 days.

There is another mechanism that is used. DOD has used BAAs that are open-ended. The VA has yet another mechanism called program announcements, which are open-ended announcements in priority research areas.

Once the nature of the research solicitation is clear, discussed among VA, DOD, NIH, CDC, et cetera, the programs are officially announced. Investigators then may respond to those announcements with written grant proposals. Then those proposals are reviewed and the review, a scientific review, is nested within the originating department, so that DOD would assume responsibility for having proposals submitted to DOD externally reviewed; VA, the same; CDC, NIH, likewise.

After the external peer review, the grants are rank-ordered in terms of priority, the best score being one, so that a grant proposal that would be rank-ordered on scientific merit as one would be virtually perfect, through a score of five, which would be very imperfect. Then the approved proposals with high-priority scores undergo a secondary review by a subcommittee of the Persian Gulf Research Working Group for relevance to see if the prioritization needs to change for the scientifically approved research projects. That again gives a chance for combined and coordinated input from the several membership groups in the Research Working Group. Then, recommendations are made back to the originating department for funding decisions.

Mr. TOWNS. Thank you. The reason I mentioned this is because we have asked about the inclusion of members of the medical community who may have unorthodox or, for lack of a better word, novel theories. Have you managed to include those views in the Research Working Group?

Dr. FEUSSNER. The answer to that question is yes. In addition to the standing memberships of the Research Working Group that we alluded to earlier, the Research Working Group has had on the order of 80 to 85 additional ad hoc members called in at various times to provide their expertise. Over the course of the last several

years, the RWG has had 12 to 14 presentations, including scientific presentations, frequently from investigators who are not funded through traditional Federal Government mechanisms.

Mr. TOWNS. I know it is difficult to predict exactly when we will have information. Let me ask, can you give us some sort of estimate about the amount of additional time we may expect these research efforts to continue before we have some concrete answers? I know you can't be specific, but we are asked this question all the time out there.

Dr. FEUSSNER. Yes, I am asked that question very frequently. I don't know the answer to that question. I view the research effort as open-ended. Many of the research projects have only begun in 1993–1994, 1995–1996 timeframe. The research will not be coming due until the turn of the century, 2000 and upwards. It really depends on how insightful or how important the research findings may be. A breakthrough could be discovered, or we may have to stay at this research activity for decades.

I mean, there are analogies with other equally difficult clinical problems. You probably don't know, but insulin was discovered in the decade of the 1920's, and while we have been treating diabetes aggressively with insulin, we, as yet, have no cure for that disease.

When my patients ask me why they have hypertension, I don't know in most cases what the cause of their hypertension is, although I do have effective treatments. And in 1972, President Nixon declared war on cancer, and a lot of research has been done, a lot of progress has been made, but few cures pertain.

So I don't know the answer to your question. We continue to conduct research today, for example, on Agent Orange exposures during the Vietnam conflict. Our sense is that this is an open-ended commitment.

Mr. TOWNS. Mr. Chairman, just one quick, last question.

Mr. SHAYS. Sure.

Mr. TOWNS. I think it was in September or October, the Food and Drug Administration issued a notice requesting comments about the advisability of the use of investigational drugs in a theater of war. Did any of the agencies here submit written comments? What was the essence of those comments, if you did; and will you submit a copy of those comments to the committee, as briefly as possible?

Ms. WINEGAR. Yes. The Department of Defense did submit written comments to that announcement, and we will be happy to make a copy of those comments available to this committee also. Basically, our concern dealt with issues that we would be faced with should the interim rule be revoked, as has been suggested by the FDA, and some of those deal specifically with the details of administering those drugs by the Code of Federal Regulations requirements, which include such things as obtaining written, informed consent from each individual who would be receiving that product and putting those in the context of a military operation.

We consider that the use of some of these materials is not really a research project, because we are not there to actually gather data; rather, we are there to provide these investigational materials as we believe that they are the best medical countermeasure

in light of the threat that has been described to us.

Mr. TOWNS. And you will submit a copy of that for the record?

Ms. WINEGAR. Yes, we will.

Dr. FEUSSNER. Yes, we will, sir.

[The information referred to follows:]

THE ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, D. C. 20301-1200

HEALTH AFFAIRS

OCT 29 1997

Michael A. Friedman, M.D.
Lead Deputy Commissioner
Food and Drug Administration
Department of Health and Human Services
Rockville, Maryland 20857

Attn: Documents Management Branch (HFA-305)
Re: Docket No: 90N-0302

Dear Dr. Friedman:

This letter provides Department of Defense (DoD) comments on the July 31, 1997, Federal Register notice soliciting comments on the Interim Final Rule of December 21, 1990, authorizing the Commissioner of Food and Drugs to determine that obtaining informed consent for the use of investigational new drugs in certain military combat exigencies is not feasible. We feel the prime objective should be to allow medical personnel to use the best prophylactic and therapeutic products available to protect military members against chemical and biological weapons and other operational medical threats and to protect disaster response personnel and the public in the event of domestic terrorism use of chemical and biological weapons We offer three primary points in support of maintaining the "military combat exigency" rule.

1. We must keep faith with the President's commitment that "we will always, always do everything we can to protect our own."

Consideration of the military combat exigency rule should be guided primarily by the need to protect military forces. There are undoubtedly numerous compliance issues concerning "investigational new drug" (IND) rules in military combat operations, and many of these are indeed important. But they are secondary to the primary issues of the life and health of military members in high threat situations. The review of the interim final rule should start with a commitment to allow medical personnel to use the best prophylactic and therapeutic products available to protect military members against chemical and biological weapons and other operational medical threats.

2. The need to "protect our own" extends to the threat of foreign and domestic terrorism involving use of chemical or biological weapons against military personnel or civilians.

Khobar Towers, the World Trade Center, Oklahoma City, and the Tokyo Subway are reminders of the need for preparedness against terrorism. The DoD is

required by Presidential Decision Directive 39 to support the Department of Health and Human Services in making available DoD stockpiles of unique medical products in the event of a domestic terrorism use of chemical or biological weapons. The medical response to such an event – whether against military or civilian targets – may include the treatment use of products not approved by the FDA for general commercial marketing. The ability to use these "investigational new drugs" in this context may be critical to saving lives, perhaps many, many lives. In a large emergency response operation, as in a large military combat operation, compliance with all of the normal FDA rules for INDs – rules designed primarily for clinical research trials – may be quite infeasible. If the best treatment available to save lives is an IND product, use should not be hindered by non-feasible regulatory compliance requirements. The responsible Federal agencies should be guided by the prime objective of allowing medical personnel to use the best prophylactic and therapeutic products available to protect military members against chemical and biological weapons and other operational medical threats and to protect disaster response personnel and the public in the event of domestic terrorism use of chemical and biological weapons.

3. The ability to "protect our own" requires a range of viable options for the President and other senior officials to consider in a military or civilian emergency, including the option of determining that informed consent and other normal IND requirements are infeasible.

How the responsible agencies achieve the prime objective of allowing medical personnel to use the best products available depends on the circumstances of the exigency presented. There needs to be a range of potentially viable options that can be considered by the President, Secretary of Defense, Secretary of Health and Human Services, and other officials to meet the prime objective in military or civilian terrorism exigencies that may arise. For particular scenarios, options might include: use of approved products only; use of IND products under all IND rules; use of IND products with waivers of many IND rules; and perhaps special product approvals for emergency uses only. One of the options that should remain available is the use of an IND product under a determination that normal IND rules, including informed consent, are infeasible. DoD would prefer, as FDA undoubtedly would, that this option not be used. However, we strongly believe the authority of the current rule must be maintained as an option.

Finally, we look forward to the results of our joint FDA/DoD/OEP working group charged to develop a range of potentially viable options for achieving the prime objective of allowing medical personnel to use the best prophylactic and therapeutic products available to protect military members against chemical and biological weapons and other operational medical threats and to protect disaster response personnel and the public in the event of domestic terrorism use of chemical and biological weapons. This is a difficult challenge, one not likely to produce in the near term an "perfect solution." Therefore, we suggest the work group concentrate on developing a range of potentially viable options that could be considered by the President, Secretary of Defense, Secretary of Health and Human Services, and other officials to meet the

Secretary of Health and Human Services, and other officials to meet the prime objective in military or civilian terrorism exigencies that may arise in the near term.

Attached are DoD responses to the questions posed in the Federal Register notice. Also, to supplement the public record, we resubmit our comments of September 13, 1996, and enclose a copy of the 1996 testimony of Dr. Edmund Howe to the Presidential Advisory Committee on Gulf War Illnesses concerning the ethics of the military combat exigency rule.

Thank you for your assistance in these matters over the past few months and for your consideration of DoD comments on this important national security issue.

Sincerely,

Edward D. Martin

Edward D. Martin, M.D.
Acting Assistant Secretary of Defense

Attachments:

1. DoD comments on questions posed in Federal Register notice.
2. DoD letter to FDA of September 13, 1996.
3. PACGWI 1996 testimony of Dr. Edmund Howe.

Department of Defense Comments
on FDA Questions Regarding Interim Final Rule

Issue A: Questions regarding the interim rule.

A.(1) Should the agency revoke the interim rule? If so, why?

The Department of Defense considers it a national defense requirement that the authority of the military combat exigency rule be maintained.

A.(2) Are there circumstances under which use of the interim rule would be justified? If so, what are those circumstances?

The circumstances under which use of the military combat exigencies rule is both justified and required are that based on the best evidence of safety and efficacy of a drug or vaccine, the degree of peril posed by the threat for which the drug or vaccine is indicated, and the absence of a satisfactory alternative therapy, failure to use the drug or vaccine will, regardless of the personal preferences of the military member, be contrary to the best interests of the member, endanger other personnel in the unit, and risk failure of the military mission.

Implicit in this answer are three points which, at the risk of redundancy, bear explicit underscoring. First, the military purpose is force protection, not data collection. Stated another way, it is medical treatment, not medical research. Second, the drugs and vaccines involved will be safe. The evidence of safety will be comparable to that for drugs and vaccines approved by FDA for general commercial marketing. They are not exotic, experimental drugs. Third, the reason these products are classified as "investigational new drugs" -- i.e., the reason they have not been approved by FDA for general commercial marketing -- is that efficacy has not been proven in controlled human clinical trials, which is the normal FDA standard for drug approvals. But apparent efficacy will be established by results of animal trials and other means. Stacked against the degree of peril and absence of an alternative, the evidence of safety and efficacy -- even if less than that necessary for FDA approval for general commercial marketing throughout the United States -- is sufficient for FDA approval for standardized use in the military combat exigency.

A.(3) The interim rule is based on the premise that informed consent is not feasible in military combat exigencies because if a soldier were permitted to say "no," this could jeopardize the individual soldier's life, endanger other personnel in his or her unit, and jeopardize the accomplishment of the combat mission. DoD has alleged that it is not an option to excuse a nonconsenting soldier from a military mission. Given the experience in the Gulf War, does this rationale still hold?

The use of the military combat exigencies rule during the Gulf War was to help protect American military personnel from the enemy's horrific arsenal of chemical and

biological weaponry. The most important "experience in the Gulf War" was that the enemy chose not to use this arsenal. If there is a basis for confidence that every potential adversary in the future would also not use such weapons, then the rationale for the military combat exigencies rule would not "still hold."

The problem is that the world community has clearly documented very aggressive chemical and biological weapons programs in North Korea, China, Iran, Iraq, Libya, Russia, and possibly other countries. In a future conflict, the United States will have four options:

> Option 1: To assume the enemy will not use chemical or biological weapons, and, therefore, to eschew medical countermeasures.
>
> Option 2: To excuse military personnel who chose not to use the medical protection, both respecting their individual choice and saving them from danger.
>
> Option 3: To allow individual military members to decide on the use of medical countermeasures, but with the selection having no impact on the individual's responsibility for the mission.
>
> Option 4: To make standardized use of a drug or vaccine, when indicated by the best evidence of its safety and efficacy, the degree of peril posed, and the absence of a satisfactory alternative therapy.

The respective risks of each option must be considered. If option 1 is chosen, and the assumption turns out to be wrong, there could be horrendous consequences. Under option 2, the predictable consequences in any major scale military operation, are a large number of abstentions, grave danger for remaining members who choose to carry out the mission, and military failure. If option 3 is chosen and the enemy uses chemical or biological weapons, those who declined medical protection will be at great risk, as will others in their units who rely on them and the accomplishment of the aspects of the mission for which they were responsible. If option 4 is followed, and it turns out that the enemy does not use the weapons, the drugs or vaccines would have been received unnecessarily.

At this juncture, it is not necessary for the Secretary of Health and Human Services to decide that option 4 is the most prudent course -- only that it should be *an* option; that it *might be* the best option under *some* circumstances that *might* arise. For it to be *an* option, the military combat exigency rule must be maintained.

A.(4) Instead of waiving the requirement for informed consent, is it feasible to obtain anticipatory consent from military personnel during peace time for the future use of investigational products during a military conflict? If it is feasible, would such consent be valid as "informed consent"? What would be the needed consent algorithm to make it valid and feasible?

It is unclear what "anticipatory consent" means. For example, is it a subset of option 2 or option 3, as described in the comment to the previous question? The primary issue is not the proximity of the consent to the use of the drug or vaccine, but whether the military command authority can order military personnel to use a drug or vaccine under the extremely limited circumstances described in the comment to question 2, above, and covered by the current military combat exigency rule. If the concept of "anticipatory consent" means providing information and training to military personnel in advance of contingency operations, this is very desirable.

A.(5) Instead of waiving the requirement for informed consent, is it feasible to obtain anticipatory consent from military recruits (prior to their recruitment into the military) for the future use of investigational products during a military conflict? If it is feasible, would such consent be valid? What would be the needed consent algorithm to make it valid and feasible?

Again, the meaning of "anticipatory consent" is not clear. In a very real sense, under the all-volunteer military force, the act of volunteering for military service is consent to be subject to command authority for the conduct of military operations. It is well understood that this command authority can order an individual to do things that may result in the loss of the individual's life. It is also well understood that the autonomy enjoyed by civilians in American society is significantly sacrificed in the specialized society of the military. To the extent the conduct of military operations includes requirements to take drugs or vaccines when indicated by the best evidence of safety and efficacy, the degree of peril posed, and the absence of a satisfactory alternative therapy (whether or not those products have been approved for general commercial marketing in the United States), this is subsumed by the obligation freely accepted -- legally, ethically, and practically -- by every military member.

If the point of the question is whether informed consent similar to that under 21 CFR Part 50 is feasible, the answer is that it is not. Among the reasons is that the regulations disallow any penalty for declining to use an IND product, as well as assure the right to withdraw consent at any time. If declining means the individual who wants to join the military will not be accepted, the "voluntariness" of the consent will not meet the regulatory requirement, nor would irrevocable consent. In addition, providing detailed information regarding a variety of possible threats and medical countermeasures a recruit might face during a period of military service is not feasible.

A.(6) If the interim rule is needed, are there changes that should be made to it based on experiences during and following the Gulf War? If so, what are these changes and why should they be made.

The Department of Defense has no changes to recommend based on experiences during and following the Gulf War, but welcomes the opportunity to consider changes suggested in the public comment process.

A.(7) Can or should the interim rule be narrowed in scope? If so, how?

The scope of the rule should not be narrowed. It should be broadened in two ways. First, it should be explicit that military operational exigencies other than combat are covered within the scope of the rule. For example, protection against a terrorist attack, such as that at Khobar Towers last year, or an endemic disease threat in a peacekeeping or humanitarian operation might meet the criteria of the rule and should be covered. Second, the issue of medical countermeasures against the threat of domestic terrorism involving chemical or biological weapons should be considered.

A.(8) If the rule were to be re-proposed:

(a) Should there be a requirement that DoD's proposed use of investigational products(s) be approved by an IRB that is independent of DoD? If so, why should DoD be held to a requirement not imposed on other institutions, and what should be the requirement for that independent IRB? Can this be accomplished without compromising military or national security?

Under the law, the chain of command for military operations "runs – (1) from the President to the Secretary of Defense; and (2) from the Secretary of Defense to the commander of the combatant command." 10 U.S.C. § 162. The Department of Defense does not support the diversion of command responsibility to a review board. It should be noted that the use of the military combat exigency rule requires a determination by the Commissioner of Food and Drugs, who is independent of DoD.

(b) Should the authority to make the "feasibility determination" (i.e., whether obtaining informed consent is "not feasible") under the interim rule be vested in persons or entities other than the Commissioner of FDA?

The Commissioner of the FDA is the appropriate official for the feasibility determination.

(c) Should the rule be more specific in describing the information that must be supplied to military personnel, or should FDA have wide latitude to make such determinations on a case-by-case basis?

The items of information to be provided to military personnel should be agreed upon by the DoD and the FDA on a case-by-case basis. Information should address: the nature and degree of peril against which the drug or vaccine is designed to protect; safety and efficacy of the drug or vaccine; contraindications and side-effects; and alternatives treatments.

(d) Should additional measures be taken to insure that information required by FDA is effectively conveyed to the affected military personnel? If so, what should these measures be?

No changes to the regulation are required in this regard. At the time the determination is requested that informed consent is not feasible in a particular military combat exigency, DoD should provide its plan for the dissemination of information.

(e) Should the rule address what constitutes adequate record-keeping and adequate long term follow-up of individuals who receive investigational products? If so, in what way?

The rule need not more specifically address record-keeping for the use of investigational products. Issues of record-keeping and follow-up are already covered in existing FDA regulations and guidelines, including the rules for the treatment use of INDs. DoD and FDA should work toward a mutually satisfactory resolution of feasible record keeping requirements. This work can take account of ongoing DoD initiatives to develop automated record keeping and immunization tracking systems. These should facilitate record keeping and follow-up for approved products and INDs, even in operational settings.

(f) Should the rule contain additional procedures to enhance understanding, oversight, and accountability? If so, what are these procedures?

DoD believes internal military procedures for understanding, oversight, and accountability have been and will continue to be strengthened. These matters, however, are separate from the decisive factors pertinent to the issue of the feasibility of informed consent under certain military combat exigencies.

(g) Should the rule contain additional procedures to track noncompliance?

Validation of compliance is an important matter for DoD to assure. However, no changes in the regulation are needed concerning this matter.

Issue B: When is it ethical to expose volunteers to toxic chemical and biological agents to test the effectiveness of products that may be used to provide potential protection against those agents?

The products under development are to be used to protect service members against lethal exposure to chemical and biological warfare agents. It is never ethical to expose volunteers to such lethal amounts of these agents in order to test the potential effectiveness of pre-treatment, treatment or prophylactic products.

Dose or concentration ranging studies are normally required for new or new-indication studies of drugs or biologics. Because response to treatment of sub-lethal doses of chemical or biological agents (weapons) could not be extrapolated to predict response to higher doses, a lethal dose would be necessary to test the efficacy of the protective drug or biologic. If lethal doses were given to volunteers, a 100% effective

rescue agent would need to be available, in case the protective agent failed and a potentially fatal toxicity had to be reversed. Antidotes to probable threat agents do not currently exist.

Issue C: If products that may be used to provide potential protection against toxic chemical and biological agents cannot be ethically tested in humans, what evidence would be needed to demonstrate their safety and effectiveness?

C(1). Should FDA identify the evidence needed to demonstrate safety and effectiveness for drugs that cannot ethically be tested on humans to demonstrate efficacy when such tests would involve administering a severely toxic substance to human volunteers? If yes, what should constitute the evidence needed to demonstrate safety and efficacy?

Safety and efficacy data from well-controlled animal studies can serve as the basis for approval of certain drugs or biologics for humans. Four requirement categories for generating safety and efficacy data are provided.

1. Animal studies should clearly show efficacy. A validated animal model should be selected which has biological and mechanistic relevance to humans for the toxicology of the compound and the pharmacology of the antidote.

2. Animal studies should show a functional relationship between a surrogate marker and efficacy. A change in the surrogate marker should reflect a change in efficacy.

3. The surrogate marker needs to reflect the pathophysiology of the toxic process.

4. The surrogate marker should be measurable in humans. The drug or biologic agents should produce in humans the surrogate endpoint that would indicate detoxification of the chemical or biological weapon. The kinetics and/or pharmacodynamics of the drug or vaccine should be sufficiently understood to allow estimation of an effective dosing regimen in humans.

In addition, other information should be obtained in order to better understand and perhaps predict the reactions of the drug or vaccine when given to a large group of DoD personnel. These might include metabolic and disposition pathways in both the animal model and in humans and population studies in humans to understand clinical covariates to predict response ranges in very large groups.

C(2) If the agency were to identify the evidence needed to demonstrate safety and effectiveness of these products, would this preclude the need for the interim rule? What specific advantages would this offer over the interim rule?

Not completely. There will always be a requirement for the interim rule. Even if safety and efficacy benchmarks were identified by the agency for the products under development today, until these products were actually licensed or approved, they would still be investigational. The clear threat of new chemical and biological weapons being developed makes the search for protective agents a continuous process. In the DoD's efforts to continually improve medical care and to counter new chemical and biological threats, there will always be products in development which will not have yet reached sufficient maturity to be licensed or approved. These products may still require use while they remain in an IND status, in which case use in connection with military combat exigencies may raise an issue regarding the feasibility of informed consent.

C(3) Civilian populations may require products used in the prevention or treatment of the serious or life-threatening effects from exposure to toxic chemical or biological agents, e.g., in the event of exigencies such as the release of toxic chemical agents in the Tokyo subway system. Thus, should the agency consider identifying the evidence needed to demonstrate safety and effectiveness for these products which would apply to both civilian as well as military populations?

The Office of Emergency Preparedness, DoD, and the FDA should work together to assure that medical personnel can use the best prophylactic and therapeutic products available against chemical and biological weapons in both the military and civilian contexts. This should be an urgent priority.

THE ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, D. C. 20301-1200

HEALTH AFFAIRS

SEP 13 1996

Honorable David Kessler, M.D.
Commissioner of Food and Drugs
Department of Health and Human Services
Rockville, Maryland 20857

Dear Dr. Kessler:

On behalf of the Department of Defense, I submit comments on the petition filed May 7, 1996, by Public Citizen Litigation Group requesting that the FDA repeal 21 CFR § 50.23(d), which allows the Commissioner of Food and Drugs to determine that obtaining informed consent for the use of an investigational new drug is not feasible under certain military combat exigencies.

Granting this petition would jeopardize the lives and health of military personnel and weaken national defense. The Department of Defense urges that it be denied.

The DoD comments are set forth in the attachment. To briefly summarize, when the President orders the deployment of U.S. military forces, the U.S. Government has a duty to take all reasonable precautions to bring about a successful completion of the mission and a safe return of the forces. In today's world, that duty must include a recognition of the startling proliferation of chemical and biological weapons among potential adversaries and terrorist organizations and an obligation to implement the best possible medical countermeasures. Implementation of the best possible medical countermeasures may require the standardized treatment use of an investigational new drug or vaccine for all personnel at risk in a military combat exigency. The current rule's authority to do this is extremely limited, available only under extraordinary circumstances and explicitly restricted to advancing the best interests of the military personnel concerned. The current regulation fully complies with applicable law and governing ethical standards.

Overall, notwithstanding some difficulties in carrying out the designed treatment protocols, the uses of the current rule during the Persian Gulf War clearly support the rule's

Encl 2

continuation. It was used only twice, both times for well established drugs about which very strong evidence of safety and efficacy was documented. It was never used for exotic or "experimental" drugs. Finally, DoD initiatives since the Gulf War, including those taken for Operation Joint Endeavor in Bosnia, have improved our ability to implement medical countermeasures under the authority of the current rule, should that become necessary in the future.

It has been nearly six years since the current rule was approved by the Secretary of Health and Human Services in anticipation of imminent hostilities in the Persian Gulf War. The rule was accepted by the courts, by Congress, by the press, and by the public. Remaining dissenters are few, and are unencumbered by any responsibility for the lives and safety of the personnel sent by the President into military operations. Even with critical hindsight, the interim final rule stands today as a scrupulously limited, well justified authority. DoD remains quite interested in working with the FDA on possible refinements to the rule and improvements in implementation procedures, as well as on methods to expedite approval of appropriate drugs and vaccines needed for military operations.

We cannot predict the next occasion on which the President will determine that the national interest requires the deployment of U.S. military personnel, nor the exact threats they will face. We can, however, predict that the best medical countermeasures may well include the treatment use of an investigational new drug. And we can be certain of our duty to provide the best medical countermeasures available. For these reasons, the Department of Defense believes it is a national defense requirement that the authority of the current rule be maintained.

We urge that the petition be denied.

Sincerely,

Stephen C. Joseph, M.D., M.P.H.

Attachment

DEPARTMENT OF DEFENSE COMMENTS ON PUBLIC CITIZEN LITIGATION GROUP'S PETITION TO REPEAL INTERIM RULE ON THE TREATMENT USE WITHOUT INFORMED CONSENT OF INVESTIGATIONAL NEW DRUGS IN MILITARY COMBAT EXIGENCIES

The Department of Defense respectfully submits the following statement of reasons for urging that the petition to repeal the interim final rule be denied.

1. When the President commits U.S. military forces to a combat, peacekeeping, or humanitarian deployment, the U.S. Government has a duty to take all reasonable precautions to bring about a successful completion of the mission and a safe return of the deployed forces.

Following the terrorist bombing in June at the U.S. facility in Dhahran, in which 19 were killed, many critical questions have been asked of senior government officials about whether adequate precautions had been taken to protect these military members. It is predictable that such questions will be asked any time there are deaths and injuries that appear in hindsight to have possibly been preventable. This arises from the duty felt by the people to support deployed military forces whose responsibility it is to carry out missions ordered by the President. That support includes an expectation that the Department of Defense and other agencies of the U.S. Government recognize their duty to take all reasonable precautions to promote the successful completion of the mission and the safe return of the military members.

A vital part of that duty falls to the medical establishment of the Government. In preparing to meet that duty, scenarios involving hundreds or thousands of potential casualties and the precautions that should be taken must be considered. This responsibility to consider threats and precautions is not exclusive to the Department of Defense. Expertise and authorities of other agencies are often implicated, and when they are, these agencies share in the Government's duty to the military forces. Any breach of that duty by DoD or any other involved agency invites a potential calamity.

2. The Government's duty to take all reasonable precautions to preserve the fighting force must include recognition of the startling proliferation of chemical and biological weapons among potential adversaries and terrorist organizations and an obligation to implement the best possible medical countermeasures.

In a recent report[1] on the proliferation of weapons of mass destruction, Secretary Perry wrote:

> We received a wake-up call with Saddam Hussein's use of SCUD missiles during Operation Desert Storm and new information on his ambitious nuclear, biological, and chemical weapons programs. The proliferation of these horrific weapons presents a grave and urgent risk to the United States and our citizens, allies, and troops abroad. Reducing this risk is an absolute priority of the United States.
>
> * * * * *
>
> . . . . . The bad news is that in this era the simple threat of retaliation that worked during the Cold War may not be enough to deter terrorists or aggressive regimes from using nuclear, biological, and chemical weapons. . . . The bottom line is that, unlike during the Cold War, those who possess nuclear, biological and chemical weapons may actually come to use them. The increase in the likelihood of regional war in today's world raises the risk.
>
> This new danger requires new thinking and new leadership on how to prevent, deter and, if necessary, respond to the threat. . . .

This Report goes on to document very aggressive chemical and biological weapons programs in North Korea, China, Iran, Iraq, Libya, Russia, and possibly other countries. In addition, there have been warning signs regarding activities of terrorists and insurgents, including the 1995 nerve gas attack in Japan. The

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[1] "Proliferation: Threat and Response," Office of the Secretary of Defense, April 1996.

Report concludes:

> The character of warfare has changed. Just as military planners must assume that antagonists may have armored forces and combat aircraft, planning for major regional conflicts must give consideration to the possibility that adversaries may have NBC [nuclear, biological and chemical] weapons and the means to deliver them.

When such consideration is given to this possibility, attention must be focused on identifying the best possible medical countermeasures to the biological and chemical weapons threat.

3. Implementation of the best possible medical countermeasures may require the standardized treatment use of an investigational new drug or vaccine for all personnel at risk in a military combat exigency, including those personnel who, for whatever reason or no reason at all, would prefer an alternate treatment or no treatment.

The need to determine the best possible medical countermeasures may lead in any of a number of directions. Most likely, the medical community will recommend reliance on well established preventive or treatment approaches using approved drugs and licensed vaccines. However, in some cases, there may be no such option available. In this regard, the development of prophylactic or therapeutic modalities for chemical and biological weapons threats is severely hindered by an inability to carry out human clinical trials of efficacy. Nonetheless, sufficient evidence of efficacy may be present using a combination of animal model trials and surrogate endpoint data on humans. When justified by the safety and efficacy data, DoD strongly favors approval of a New Drug Application and continues to believe that the FDA's accelerated approval process, including the option of marketing limitations, is an appropriate mechanism for addressing these special military needs.

In still other cases where the best possible medical approach includes the use of an investigational new drug, it may not be necessary, depending upon the nature of the risk and other factors, to use the investigational product on a standardized basis. For example, in the current Bosnia deployment, military

members are given the option of receiving tick-borne encephalitis vaccine; members are free to decline the vaccine.

However, it is also possible that the best medical countermeasures are products not approved by FDA for general commercial marketing for the specific purpose involved, that approval under the accelerated process is not practicable, and that because of the nature of the threat and the lack of alternatives, a failure to use a drug would endanger individual members, others who rely upon them to carry out their respective tasks, and the mission. The question becomes: what should be done in such cases? In the preamble to the interim final rule, the FDA answered the question:

> . . . . DoD has the right and responsibility to make command decisions that expose troops to the possibility of combat and has the concomitant responsibility to protect the welfare of these troops both individually and as a group. . . . FDA respects DoD's obligation and commitment to do everything possible to protect military personnel who may be exposed to potentially hazardous conditions. FDA further appreciates that this protection may include medical treatment or prevention with an investigational drug considered necessary to protect not only the health of individual soldiers but to ensure the welfare of the remaining forces. . . . Since these individual soldiers may be required to be exposed to combat, permitting them to choose whether to receive an investigational product that is the only available satisfactory protection against life-threatening conditions, is contrary to their individual best interests and to the welfare of the other soldiers involved. [Emphasis added.]

One might ask: why would military members decline recommended drugs or vaccines under these circumstances? The answer is that there could be many, many reasons. Individuals might decide that it is unlikely that chemical or biological weapons will be used, or that, if they are, protective gear will be sufficient. They might have heard rumors of side effects or "mystery illnesses" attributed to the drugs or vaccines. They might not believe information from command authorities based on disenchantment with circumstances particular or general. They might have seen media coverage of statements from "public

interest" advocates back home inappropriately accusing the military of wrongs comparable to Nazi medical experiments. They might be getting erroneous medical advice from friends or family. They might be confused by the first-time experience of having a choice regarding combat medical care. They might put off a decision until a later possible time or event. Moreover, if the choice is truly voluntary, they do not need a reason and may not have one. The fact is that there is no basis to assume that, among a group of many thousands of people presented with complicated medical information, most will chose the course all knowledgeable medical people would consider the only wise one. And in the middle of large-scale combat operations or preparations, communication and decision making processes are anything but ideal.

As an illustration of the problem, assume a deployment for a major regional conflict, such as the Persian Gulf War, involving 500,000 U.S. troops. Assume further a very good response rate of 80% of these troops providing voluntary informed consent for, to select an example, botulinum toxoid vaccine. If botulinum toxin weapons are used in large scale by the enemy, we will have 100,000 troops at considerable risk of fatal injury, with no alternative treatment available. This far exceeds the total number of U.S. forces killed in the entire Vietnam War. Failing to prevent preventable casualties of even a small fraction of this magnitude would be a human tragedy, a military disaster, and a national scandal of historic dimensions.

4. The current rule is an extremely limited authority, requiring case-by-case justification, available only under extraordinary circumstances, and explicitly restricted to advancing the best interests of the military personnel concerned.

As the FDA stated in the preamble to the current regulation:

> . . . . Because of the paramount importance of informed consent, only the narrowest exceptions to this requirement are consistent with FDA's responsibilities and consistent with the best interests of human subjects. Nevertheless, FDA has determined that, in the special circumstance that may be created by the use of troops in combat and consistent with its obligations under sections 505(i) and 507(d) [of the Federal Food, Drug and Cosmetic Act], FDA may narrowly

> expand the circumstances in which the Commissioner may determine that obtaining informed consent is not feasible.

Consistent with this policy, the current rule is an extremely limited authority. First, it does not waive informed consent for the military, nor allow the military to do so. It does not even indicate that the Commissioner of Food and Drugs is inclined to find that informed consent is not feasible in military combat situations. It stands only for the proposition that it might be necessary under certain extraordinary circumstances to exercise the statutory authority to find that informed consent is not feasible because of military combat exigencies.

Secondly, quoting from the regulation (21 CFR § 50.23(d)(1)):

> [DoD's] request must also include a written justification supporting the conclusions of the physician(s) responsible for the medical care of the military personnel involved and the investigator(s) identified in the IND that a military combat exigency exists because of special military combat (actual or threatened) circumstances in which, in order to facilitate accomplishment of the military mission, preservation of the health of the individual and the safety of other personnel require that a particular treatment be provided to a specified group of military personnel, without regard to what might be any individual's personal preference for no treatment or for some alternative treatment.

Third, a duly constituted Institutional Review Board must have reviewed and approved the use of the investigational drug without informed consent. Id.

Fourth, the Commissioner must specifically find that "there is no available satisfactory alternative therapy." Id.

Fifth, the rule requires consideration of the "extent and strength of the evidence of the safety and effectiveness of the investigational drug for the intended use." § 50.23(d)(2)(i).

Sixth, the context in which the drug will be administered must be considered. § 50.23(d)(2)(ii). A context involving one-

on-one treatment of an injured or sick patient by a physician is quite different from the administration of large-scale prophylactic treatment.

Seventh, consideration must be given to the "nature of the disease or condition for which the preventive or therapeutic treatment is intended," such as whether it is fatal. § 50.23(d)(2)(iii).

Eighth, the Commissioner will consider the nature of the information to be provided "concerning the potential benefits and risks of taking or not taking the drug." § 50.23(d)(2)(iv). Even if consent is not required, comparable information will be provided.

Ninth, determinations that informed consent is not feasible because of military combat exigencies are time-limited, and may be revoked. § 50.23(d)(4).

Tenth, and most importantly, the "Commissioner may find that informed consent is not feasible only when withholding treatment would be contrary to the best interests of military personnel." § 50.23(d)(1) (emphasis added).

To repeal the regulation, as urged by the petitioners, would be a declaration that informed consent is never infeasible under military exigencies, including actual, effective use of weapons of mass destruction, which will have fatal effects, for which no alternative therapy is available, and in connection with which withholding the IND would be clearly contrary to the best interests of the troops.

5. The current rule is fully consistent with law and ethics.

The legality of the interim final rule was challenged in court by the same group that has now filed the current petition. The courts ruled that the rule is fully consistent with law. The District Court held:

> The DoD's use of unapproved drugs does not involve the type of scientific investigation under controlled circumstances that "research" connotes. On the contrary, the DoD has

> responded to very real circumstances and chosen what it views as the best alternative given current knowledge. The primary purpose of administering the drugs is military, not scientific. The fact that the DoD will collect information on the efficacy of the drugs does not transform the strategic decision to use the unapproved drugs in combat into research. Furthermore, the FDA has interpreted the FDCA to permit using unapproved drugs in a "treatment-investigational setting" in the past. . . . The FDA, therefore, does not view every use of unapproved drugs as research, and nothing in the DoD Act [10 U.S.C. 980, requiring informed consent in DoD "research"] suggests that Congress intended the term to have such a broad meaning.

Doe v. Sullivan, 756 F. Supp. 12, 15-16 (D.D.C. 1991).

The Court of Appeals for the District of Columbia affirmed this decision in favor of the Government. The Court ruled:

> While it is true that the FDA's prior interpretation of the words "not feasible" [in section 505(i) of the Act] focused on the subject's condition, the agency here has not reversed course. It has simply added a tightly circumscribed set of urgent circumstances in which the main rule of informed consent, with fidelity to the statute's terms, can be displaced. . . .

Doe v. Sullivan, 938 F.2d 1370, 1382 (D.C. Cir. 1991) (opinion by Judge Ruth Bader Ginsburg).

Not only was the regulation fully upheld by the courts, it is also consistent with ethical standards. The primary issue in the ethical analysis is: Does the use of INDs by the military in the circumstances of the interim final rule constitute "research" in the context of ethical standards which prohibit nonconsensual research on human subjects? The Belmont Report[2] discussed the distinction between research and treatment:

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[2] The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects in Research, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, OPRR Reports, April 18, 1979.

> It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects in research. . . .
>
> For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge. . . .
>
> When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research.

The rule itself makes clear that the only purpose is treatment, and that there is no research purpose in the use of INDs in military combat exigencies. Again quoting the primary standard in the regulation:

> The Commissioner may find that informed consent is not feasible only when withholding treatment would be contrary to the best interests of military personnel and there is no available satisfactory alternative therapy.

21 CFR § 50.23(d)(1). Nothing in the regulation even hints that the special authority is available if the military's purpose is to conduct research. One might suggest that the use of an IND for treatment purposes constitutes what the Belmont Report refers to as a departure from accepted practice. The same might be said for the common physician practice of off-label prescribing. But as the Belmont Report makes clear, this does not, as an ethical matter, convert a treatment purpose and effect into a research purpose or effect.

Another example in which a significant departure from standard clinical practice is not considered "research" is the

FDA's Accelerated Approval regulation, 21 CFR § 314.500, *et seq.* Under that regulation, an IND can be approved for marketing, and thus widespread treatment use, even if there is "uncertainty" as to clinical benefit, contingent on further post-marketing studies to follow. § 314.510. Post-marketing restrictions on distribution, labeling, and advertising may also be imposed pending additional evidence of safety and efficacy. §§ 314.520, 314.550, 314.560. However, during this process of conducting additional studies and collecting additional evidence, general uses of the drug are not considered to be research, nor are they subject to the protection of human subjects regulations. Additionally, FDA regulations also allow "treatment uses" of INDs, separate from ongoing research trials. 21 CFR § 312.34.

Once it is recognized that the use in a military combat exigency of drugs not yet approved by the FDA for general commercial marketing for the particular clinical indication is not "research" under law or ethical standards, the ethical justification for the mandatory use of protective drugs is not seriously debatable. Military members must make many sacrifices that in the civilian world would be considered intolerable. The Supreme Court has said: "The essence of military services is the subordination of the desires and interests of the individual to the needs of the service."[3] Although military members do not give up their interest in not being nonconsensual research subjects, they must subordinate many individual interests to the needs of the military to complete successfully the mission. Among these is to accept preventive or therapeutic medical care that command authorities decide is necessary for the preservation of the fighting force.

Those who refuse to acknowledge legal and ethical justifications for the interim final rule rely essentially on a single semantical argument: that anything categorized by the FDA as an "investigational new drug" is an "experimental drug," which cannot be used for anything except "research." But this semantical argument is not based on any meaningful analysis of the Food, Drug and Cosmetic Act, FDA regulations, the Common Rule for the Protection of Human Subjects in Research, the Belmont Report on which the Common Rule was based, or any other

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[3] *Goldman v. Weinberger*, 475 U.S. 503, 507 (1986).

persuasive source. Perhaps most importantly, the superficial semantics do not attempt to address what the interim rule does and does not do, and how that relates to the legal and ethical standards applicable to research and treatment. The rule does not authorize a determination that informed consent is not feasible in connection with any military undertaking that fits the legal, ethical, or clinical description of "research." The rule allows such a determination only when, based on the nature of the disease threat, the evidence of safety and efficacy of the drug to counteract that disease threat, and the lack of a satisfactory alternative, "withholding the treatment would be contrary to the best interests" of the military members.

6. Overall, notwithstanding some problems in carrying out the designed treatment protocols, the two uses made of the current rule during the Persian Gulf War support the rule's continuation.

Essentially, during the Persian Gulf War, DoD and FDA collaborated to do three significant things. One was to promulgate the rule authorizing a determination by the Commissioner that informed consent is not feasible in certain military combat exigencies. This rule was accepted by the courts and Congress and remains in effect today. The other two significant actions were the adoption, using the authority of the rule, of treatment protocols for the use of two IND products as medical countermeasures against certain suspected chemical or biological weapons threats. It is important to restate the facts with respect to these two actions.

With respect to the adoption of a treatment protocol for pyridostigmine bromide as a pretreatment antidote to nerve agent poisoning, the FDA thoroughly reviewed the issue through the Informed Consent Waiver Review Group (ICWRG), which included senior officials of the FDA, plus the Director of the Office for Protection from Research Risks (OPRR), HHS. In recommending approval of the DoD requested determination, these ICWRG members made the following findings:[4]

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[4] Memorandum to the Commissioner of Food and Drugs from Informed Consent Waiver Review Group, Subject: IND 23,509 - Pyridostigmine Bromide 30 mg Tablets - Action, January 8, 1991.

- The use of pyridostigmine pretreatment, in conjunction with atropine and pralidoxime treatment, improved survival or animals exposed to soman. Limited human evidence suggests that the proposed dose of pyridostigmine will provide a level of enzyme inhibition in humans comparable to that achieved in animals which were protected from soman-induced mortality.

- There is extensive experience in humans with myasthenia gravis using doses of pyridostigmine much greater than those proposed in this treatment protocol, and we have no specific safety concerns with the proposed military dose.

- We agree with DoD that withholding treatment from an individual, based on personal preference not to receive the pretreatment with pyridostigmine, could jeopardize the health and safety of that individual or other military personnel in the event of a chemical attack.

Although the implementation of the approved treatment protocol for pyridostigmine was not problem free, no such implementation difficulties meaningfully call into question any of these determinations made by the ICWRG.

Similarly, the proposed treatment protocol for pentavalent botulinum toxoid vaccine also was thoroughly reviewed by the FDA. In adopting the staff recommendation, the Commissioner responded to DoD:[5]

> Based on your assessment of the military operation, I find that there is no available satisfactory alternative therapy for the prevention of botulism, and I concur with your assessment that informed consent is not feasible and that withholding treatment would be contrary to the best interests of military personnel.

When the vaccine, which was in very limited supply, and the

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[5] Letter to Assistant Secretary of Defense (Health Affairs) from Commissioner of Food and Drugs, December 31, 1990.

approved treatment protocol reached the Gulf, the Central Command changed the protocol. It was modified (without notice to the Pentagon, as far as can be reconstructed, until after the fighting stopped) to permit members the choice of declining the vaccine. The Central Command Surgeon recently explained the change as being based on three primary factors:[6] 1) very limited vaccine supply; 2) the lack of intelligence reports that would have allowed prioritized use of the limited supply based on some judgments that certain personnel are more at risk than others; 3) Command concerns about rumors arising from a Stars and Stripes article reporting on allegations back home about requiring troops to take "experimental vaccines." Anecdotal reports leave somewhat unclear whether, in actual use throughout the theater of operations, the vaccine was uniformly administered in accordance with the Central Command's revised protocol or was sometimes given consistent with the original protocol.

The Central Command's revision to the protocol was a surprise to the DoD officials with whom the FDA was dealing. But, in retrospect, it was quite proper to give the responsible military command the option to decide whether actual military circumstances unfolding in the theater of operations truly required the standardized use of the vaccine. Had intelligence reports changed or had the timetable for combat operations allowed for procurement of additional supplies, implementation of the original protocol might have been necessary after all. It was not unreasonable to give the Central Command that option. However, there was a breakdown in communications that prevented a common understanding among all involved officials. Had communications been better, the determination that informed consent was not feasible could have been contingent upon a final Command decision confirming the existence of, in the words of the rule, "special military combat (actual or threatened) circumstances" which "require that a particular treatment be provided to a specified group of military personnel, without regard to what might be any individual's personal preference for no treatment or for some alternative treatment."

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[6] Testimony of Brigadier General Robert Belihar before Presidential Advisory Committee on Gulf War Veterans' Illnesses, Public Meeting, Kansas City, Missouri, January 12, 1996.

There were also implementation difficulties in connection with the uniform provision of information to personnel regarding pyridostigmine and the preservation of records in connection with botulinum toxoid vaccines. Efforts to carry out the planned distribution of revised information packets on pyridostigmine to the hundreds of thousands of troops deployed throughout the theater of operations were frustrated by the limited time between the FDA approval of the protocol January 8, 1991, and the beginning of Operation Desert Storm a couple of weeks later. With respect to record keeping and reporting on pyridostigmine, normal IND record keeping and reporting requirements had been waived by the FDA in recognition of the logistical realities and the reliance on self administration of the tablets. After the cessation of hostilities, several surveys were conducted, with results reported to the FDA. With regard to botulinum toxoid vaccine, appropriate record keeping and retention were frustrated by the Central Command's determination of the need for security classification regarding biological warfare defense vaccines (including both the licensed anthrax vaccine and the IND botulinum toxoid vaccine).

These several implementation problems establish the need for improvements, at least some of which have already been made in the implementation systems and procedures DoD relies upon in operational deployments. Perhaps most importantly, the treatment protocol development process needs to include people who are closer to the reality of the battlefield. However, none of these implementation difficulties during the Gulf War changes the fundamental fact that had the enemy used its apparent capability to deliver chemical or biological weapons, based on the available evidence of the safety and efficacy of these two IND products and the lack of an effective alternative treatment, the best medical countermeasures, as far as the medical establishment of the Government could determine, clearly included the treatment use of these products. And, in the context of the pending petition, nothing that happened during the Gulf War even remotely supports the argument that military personnel or the Government or the nation would be better off with the repeal of the current rule.

Some of the other criticisms of DoD and/or FDA actions during the Gulf War are without foundation. For example, evidence supporting the safety of pyridostigmine and botulinum toxoid was and still is quite solid. Pyridostigmine has been

used safely for more than 40 years as the principle treatment for myasthenia gravis at much higher doses over much longer periods than the regimen used in the Gulf. The drug does have side effects, but these are relatively mild. The evidence does not suggest a difference in safety between use by men and women. The recently published studies conducted by Moss and by Abou-Donia in cockroaches and chickens, respectively, used extraordinarily high dosages and routes of administration that differed from the route of administration used by Service members in the Gulf. Although providing potentially valuable preliminary scientific information, these data cannot be generalized to a human population. Similarly, decades of experience with botulinum toxoid vaccine provide a clear basis for confidence concerning safe use. The overwhelming weight of evidence continues to support the safety of these two IND products.

The efficacy of pyridostigmine has been questioned based on an Army study suggesting that it decreases the effectiveness of atropine and pralidoxime chloride against nerve agents sarin and VX. Pyridostigmine is used to counter soman poisoning based on evidence that it substantially enhances the effectiveness of the post exposure treatments against soman. Although it does decrease somewhat the effectiveness of atropine and pralidoxime against sarin and VX, the two treatments are so highly effective against sarin and VX, that any negative interaction of pyridostigmine and the nerve agent would be overwhelmed by the atropine/pralidoxime therapy. Thus, in predicted clinical outcome, pyridostigmine substantially improves medical protection against soman and does not affect medical protection against sarin and VX. In preparing medical countermeasures against the possibility of chemical weapons attack using any of these nerve agents, as was necessary in the Gulf War, predicted clinical outcome clearly calls for the use of pyridostigmine.[7]

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[7] The results of the sarin/VX study were reported to the FDA by the Army component responsible for administration of the pyridostigmine IND in full compliance with 21 CFR § 312.33. The study, conducted under a different Army command element, was unknown to the IND investigators until it was published. In any event, the results of the study do not affect the DoD or FDA conclusions regarding the evidence of efficacy of pyridostigmine for this clinical purpose.

7. Initiatives since the Gulf War, including current operations in Bosnia, have improved DoD's ability to implement medical countermeasures under the authority of the current rule, should that become necessary in the future.

Since the Gulf War, the Department has significantly improved its capability to monitor the health of military personnel deployed by the President to hazardous areas, such as the current Operation Joint Endeavor in Bosnia. As part of the "lessons learned" from the Gulf War, DoD has assigned a high priority to improved documentation of health information, including administration of medications and vaccines. A number of initiatives are in progress to enhance capabilities to manage medical information under field conditions. DoD has established a task force to address the issue of medical records in a military theater of operations. Records pertaining to the results of pre-and post-deployment health screening will be captured in an automated data base. DoD is expanding the automated Composite Health Care System (CHCS) medical record system to include a module for medical records of a deployed force. Attention is being directed toward developing a mechanism for computerizing medical data (including classified information, if and when it is needed) in the field to ensure standardized record keeping.

In May of 1994, DoD initiated an aggressive, clinical diagnostic plan, the Comprehensive Clinical Evaluation Program (CCEP) to offer intensive examinations to Gulf War veterans. The CCEP has provided an in-depth medical evaluation to eligible Service members concerned about their health. The CCEP provides an integrated system to evaluate the health status of service members who participate in deployments in the future. Modifications of the program will allow DoD to administer health questionnaires and conduct medical examinations of groups of deployed personnel, and collect the information through an automated process for entry into a centralized data base for subsequent analysis and interpretation.

Earlier this year, DoD released the *Medical Surveillance Plan for U.S. Ground Forces Deploying to Bosnia*, which has improved significantly the capability to monitor the health of the deployed force. The plan provided guidance, in conjunction

with directives from the Joint Chiefs of Staff, regarding implementation of a standardized medical surveillance program. The program expands capabilities in a number of areas including: health education, risk communication, standardized medical screening pre and post deployment, health hazards assessment, and in-theater medical surveillance. Upon return from the deployment, each service member will undergo health screening with the results annotated on standardized forms for entry into a central data base. In addition, DoD has established a telemedicine network within Bosnia that allows the projection of specialized diagnostic care and consultation forward to the patient.

As an aside, DoD efforts to provide effective countermeasures against medical risks in Bosnia include very careful planning regarding the use of two INDs. Tickborne Encephalitis (TBE) and Hemorrhagic Fever with Renal Syndrome (HFRS) are two infectious diseases which present serious potential health risks to U.S. forces operating in Bosnia. The Department through the Army Surgeon General filed INDs to use ribavirin as a treatment for HFRS and the Austrian TBE vaccine for immunization of military personnel. Medical staff have been notified that informed consent is required to administer these pharmaceuticals. In both of these cases, DoD determination that informed consent is feasible was based on a thorough analysis of the nature and extent of the health risk presented, the treatment context, the military situation, available alternatives, and, most importantly, the best interests of the members.

CONCLUSION.

For the reasons stated above, the Department of Defense urges that the petition be denied.

STATEMENT BY

EDMUND G. HOWE, M.D., J.D.

PROFESSOR OF PSYCHIATRY; DIRECTOR OF PROGRAMS IN MEDICAL ETHICS

(UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES)

BEFORE THE

PRESIDENTIAL ADVISORY COMMITTEE

ON GULF WAR VETERANS' ILLNESSES

USE OF INVESTIGATIONAL DRUGS AND VACCINES IN THE GULF WAR

ETHICAL CONSIDERATIONS IN WAIVING INFORMED CONSENT FOR MILITARY EXIGENCIES

JANUARY 12, 1996

NOT FOR PUBLICATION
UNTIL RELEASED BY
PRESIDENTIAL ADVISORY COMMITTEE
ON GULF WAR VETERANS' ILLNESSES

USE OF INVESTIGATIONAL DRUGS AND VACCINES IN THE GULF WAR

ETHICAL CONSIDERATIONS IN WAIVING INFORMED CONSENT FOR MILITARY EXIGENCIES

Mr. Chairman, distinguished Members of the Committee, I am Edmund G. Howe, M.D., J.D., Professor of Psychiatry and Director of Programs in Medical Ethics at the Uniformed Services University of the Health Sciences. I appreciate the opportunity to discuss with you today the exceedingly difficult ethical questions which arose in regard to the use of protective agents in the Persian Gulf. When the DOD first anticipated that Iraq might use chemical and biological weapons, the DOD was aware of the profound ethical dilemmas this situation posed. Consequently, the DOD immediately sought consultation from other governmental agencies and civilians outside the DOD with special expertise in medical ethics.

One of the parties with whom the DOD conducted extensive discussions was the Office for Protection from Research Risks (OPRR/NIH). The OPRR is responsible for monitoring and protecting the health and welfare of humans and animals when they are used as research subjects in behavioral and biomedical research supported by the Public Health Service. Guidance from the OPRR was particularly valuable to the DOD's understanding of the ethical issues involved pertaining to research. The OPRR pursued extensive ethical discussions with civilian ethicists throughout the process

of providing ethical input to the DOD. This process consisted of many hours of discussion at multiple meetings held by the DOD with the OPRR and other experts, including those from other governmental agencies such as the FDA. I was fortunate enough to be one of the civilians asked to participate in this process.

The ethical questions posed were of enormous significance because in addition to servicepersons' autonomy, tens of thousands of servicepersons' lives were potentially at stake. It was known that certain agents would help protect servicepersons from the harmful effects of these weapons if Iraq chose to use them. Thus the use of these agents, literally, might have been lifesaving. Yet, these agents had not been tested for this particular use on humans. It would, in fact, have been unethical to subject humans to the effects of chemical or biological weapons to determine the extent to which these protective agents would be effective. Thus, two unprecedented ethical questions arose: Should these agents be used at all? And if they should be, should servicepersons be given the opportunity to withhold consent?

The ethical justification of the military's giving servicepersons these agents without obtaining their consent is as follows: For the sake of this discussion, it must be assumed that this war was both necessary and just. If this is assumed to be true, servicepersons have unique obligations during war both to their country and to other servicepersons with whom they risk their lives during combat. That is, servicepersons agree to sacrifice their lives if necessary to further the military's mission or to

benefit the servicepersons serving with them. Servicepersons understand that they may have to sacrifice any number of personal interests during combat and, implicitly, they agree to make such sacrifices if this is necessary when they enter the military.

This shift from the usual ethical priorities adopted by civilians during peacetime is exemplified by the principle of military medical triage. Normally during emergency situations medical careproviders give highest priority to saving the lives of those patients who are worst off. During combat, military physicians are expected under extremely rare circumstances to do the opposite. Namely, they are expected to shift priorities and treat servicepersons who are better off and can return to battle if and when this seems necessary to further the likelihood of success of the military's mission. In actuality, this hardly ever occurs. In principle, however, this shift is radical. It is this same kind of shift in regard to the use of protective agents which was necessitated by the threat of Iraq's using chemical and biological warfare against our troops.

The underlying ethical justification for this rare and radical shift in priorities is that unless the customary values are sacrificed, far greater wrongs may occur: these may include one country taking over another and harming its people, genocide, and even the destruction of this nation and its people. The different priorities in the military during combat, accordingly, are not established by the military but are established by and represent the country whose interests it serves.

Servicepersons' priorities differ, then, from civilians' in

that their individual interests are subordinated to those of the mission and their unit. Thus, although it would be in servicepersons' individual best interests to not fight when they are ill, as from malaria or dysentery, commanders may send them to the front, regardless of their illness, if this is necessary to benefit the mission or other servicepersons. Similarly, if an individual serviceperson did not want to carry a canteen, wear protective clothing, or be vaccinated against an endemic disease, the commander could not permit this serviceperson to exercise autonomy in this manner since this would unnecessarily endanger the serviceperson and, consequently, the mission and other servicepersons in the unit.

Servicepersons are aware that as they approach actual fighting, their autonomy dramatically may decrease. They understand that their commander may order them to enter life-threatening situations under enemy fire, and make any number of other decisions to benefit the mission or the unit. These may include their commanders requiring them to make use of protective devices during combat.

As I already have stated, when servicepersons join the military, they agree to subordinate their own interests and autonomy to the military when necessary for the mission or their unit. This promise is also reciprocated, however, by the military. The military, in turn, promises all servicepersons that it will protect their lives during combat to the maximal degree that this is possible, contingent, of course, on its fulfilling the needs of the mission.

Ethically, there are basically four arguments that servicepersons should take protective agents without being given the opportunity to refuse to consent: First, this is necessary to maximize the likelihood that the US military effort will succeed. As stated, if US troops were decimated after Iraq used chemical or biological weapons, hardly imaginable harms to persons in other countries and this one could occur. Second, this is necessary to protect inordinate numbers of servicepersons' lives which would be lost if Iraq used these weapons. Third, this is necessary for all servicepersons to fulfill the implicit promise they have made to other servicepersons that they will sacrifice their lives if necessary for the mission or their benefit. In this case, of course, the sacrifice required to save the mission or other servicepersons is not their lives but their autonomy to refuse to consent to taking these protective agents. Fourth, this is necessary for the military to fulfill its promise to all servicepersons to do everything possible to protect their lives.

What are the opposing arguments? First, it can be argued that protective agents which have not been fully tested should not be given at all. Whether these agents should be given should depend primarily on whether these agents most likely would save large numbers of servicepersons' lives if Iraq used chemical or biological weapons, but do little harm if Iraq did not. As stated, when the possible need for protective agents initially became apparent, medical experts in the DOD and FDA reviewed the available data on the effects of these agents on humans in other contexts and on animals. On the basis of this review, the DOD determined that

for the agents considered, the probable benefits were overwhelming and the expected adverse risks, minimal. If this had not been the case or if the benefit/risk ratio had even been significantly closer to marginal, the justification for using these agents would have been, of course, increasingly problematic.

Second, it can be argued that even if these agents should be available, servicepersons should be able to refuse to take them. If servicepersons could refuse consent, this would respect their autonomy, but several important values would be violated. That is, if servicepersons were permitted to refuse to consent, two options would be possible: Servicepersons who refused consent could be excused from combat altogether or they could remain in combat without their being protected by these agents.

If servicepersons were excused from combat, this could result in US troops becoming significantly depleted. This could jeopardize the success of the mission and increase the danger to servicepersons who remained in combat. Further, if consenting servicepersons remained in combat, this would violate the ethical principle of justice or equity. That is, those who took the agents would still risk being killed during combat by normal weapons; those who did not take these agents and, therefore, were removed from combat would not.

If, on the other hand, servicepersons who refused consent remained in combat without these protections and Iraq used chemical or biological weapons, the servicepersons without protection would be much more vulnerable to illness and death. Again, as a result of the depletion in their numbers, the success of the mission could be

threatened and servicepersons taking protective agents more greatly endangered. They would be additionally endangered if they attempted to help these servicepersons.

Fortunately, the degree to which these agents would protect servicepersons from the effects of chemical and biological weapons was never tested in the Persian Gulf. Yet, investigations following the war have indicated that Iraq had these weapons ready for use. It may have been only because Iraq falsely believed that the US would retaliate with nuclear weapons that Iraq decided not to use them. Our information regarding the weapons Iraq could have used was accurate. For example, Iraq was prepared to deliver botulism, a highly lethal disease, by missile attack. Botulism vaccine was one of the protective agents given to servicepersons.

Thus, this chilling question remains. What would have happened if Iraq had used these weapons and U. S. forces had not had as much protection as possible? The grim outcome which can be imagined supports the wisdom of the ethical judgements actually made. It suggests as well, several new needs, such as to insure that servicepersons are protected as much as possible in the future and to establish means by which other countries' forces, captured enemy servicepersons and civilians can be protected as well. These initiatives may go beyond the scope of this discussion, but, hopefully, will be among the ethically important outgrowths of this meeting.

Mr. TOWNS. Mr. Chairman, I yield back.

Mr. SHAYS. Thank you.

Mr. Snowbarger.

Mr. SNOWBARGER. Thank you, Mr. Chairman. I apologize to you and also to the witnesses that I was not able to be here for most of your testimony. So I apologize if I am asking questions that you feel like you have already answered, but if you would bear with me, I would appreciate it.

One of the problems that has faced this panel and faces you in this issue is the question of information that is available to you, particularly exposure information; and it seems that without that exposure information, at least accurate exposure information, that we are spending millions of dollars on research here, and I am just not confident that I know whether or not we are going to be able to produce any results, much less accurate results.

I guess, Dr. Feussner, if I could ask you, could you tell me what studies are under way that you think are going to produce valid definitions of what Gulf war veterans' illnesses are all about?

Dr. FEUSSNER. Well, that is a difficult question. I think your assertion is correct. Highly problematic is the observation that there are multiple potential exposures that occurred at multiple potential times and in multiple potential combinations. It is not—I do not believe it is possible to specify who was exposed to what with any precision. That causes difficulty in doing the research on two fronts. Less desirable definitions of exposure must be used, for example, in the VA mortality study, deployment to the Gulf versus being active duty and not deployed to the Gulf.

That level of imprecision introduces noise into the assessment and that requires large sample sizes of study patients followed for a long duration of time to try to detect differences in those groups.

For example, I believe that, the mortality study that has now had 4 years of followup may present useful information about whether survival is different, whether disease-specific survival is different in deployed versus nondeployed study subjects.

The other way I think that we can approach that, short of human studies, is to look at animal studies where a research project, for example, showed that pyridostigmine bromide does not cross the blood-brain barrier, but when animals were exposed to stressful situations, the stress modified the permeability of the blood-brain barrier and that chemical was able to get across the blood-brain barrier.

I think opportunistic efforts, for example, the collaboration with the Japanese where they have known exposures and they can study those exposures soon after they occurred, may provide us some insights, but saying what causes this, how do we fix this, as opposed to merely treating this are very nettlesome issues.

Mr. SNOWBARGER. Well, I guess the reason for my question is, we are 3 years down the road from the time the initial studies were begun. I mean, the problem showed up earlier than that, but we didn't start until 1994, or somewhere in that neighborhood; and here we are almost 4 years later, and I am not getting any sense of confidence that we are going to be able to do the studies that are going to lead us to the right answers.

Let me followup with a question on animal studies. I found this one rather fascinating.

Dr. Winegar, if you could help me with this one, there is a Defense Department study that was approved by the Working Group, and it has spent about $262,000 to date. It doesn't look like it is using money in fiscal year 1998, so perhaps this study is done at this point. But the hypothesis that it was testing was that, "In the final analysis, there would be no differences in the diagnosis between the Gulf military working dogs cohort and the comparison group of dogs which never deployed to the Gulf War."

According to public reports, the dogs no longer in active service are being observed and posthumously examined. First of all, what is the status of that study?

Ms. WINEGAR. I don't have the details as to whether that study has been completed or not, or whether we have received a final report, but I will be happy to provide that information to you.

Mr. SNOWBARGER. OK. The report that we have indicates that it is ongoing, but again, without any expenditures expected in fiscal year 1998, so I am presuming all the research has been done; it is a matter of analysis at this point, I would presume.

Ms. WINEGAR. That could be, but I will have to verify that.

Mr. SNOWBARGER. Well, OK.

[The information referred to follows:]

FACT SHEET

DOD Military Working Dog Evaluation

Indicators of Human Disease from Persian Gulf War Service: A Study of Military Working Dogs Deployed in Operations Desert Shield/Storm

The Department of Defense (DOD) is conducting a comprehensive evaluation to determine if any diseases exist in Military Working Dogs (MWDs) deployed during the 1990-91 Persian Gulf War that do not exist in non-deployed dogs. Both populations of animals will be evaluated following completion of a working career. No dogs have been or will be euthanized because of this evaluation. MWDs die of natural medical causes following a working service that usually lasts 10-12 years or are euthanized, based on the clinical judgement of a veterinarian, due to debilitating and incurable diseases that occur in all aged dogs.

MWDs with Persian Gulf War service inhabited similar environments as U.S. Armed Forces service members. At the Armed Forces Institute of Pathology, the American Registry of Pathology funded a pilot protocol in 1994 enabling the early implementation of a data collection system that will include pathologic, demographic, temporal and clinical findings from initially identified PG MWD cohort and matched comparison MWDs. This pilot protocol expired in 1995. The current protocol title is: Indicators of Human Disease from Persian Gulf War Service: A Study of Military Working Dogs Deployed in Operations Desert Shield/Storm. The hypothesis (null) to be tested is that in final analysis, there will be no significant differences in clinical or pathologic diagnoses between the Persian Gulf War cohort and the comparison group.

Methodology: This evaluation includes retrospective and prospective components. Retrospectively, the medical and training records of the 118 MWDs that deployed to the Persian Gulf, and 472 non-deployed MWDs matched four to one based on age, gender and breed, will be abstracted for the following variables: animal identification; age at death; date of death; breed; gender; location during the time frame 1 August 1990 to 31 December 1991; and duration of deployment. Parameters being assessed include: clinical, clinicopathological, autopsy findings, histopathological, toxicological (if indicated) and epidemiological.

Prospectively beginning in 1996, those 39 Persian Gulf cohort dogs, which remained on active service, and comparison cohort of 156 non-deployed MWDs will be relocated to DOD Military Working Dog Veterinary Service (DODMWDVS), Lackland AFB, TX, when the attending veterinarian determines these animals are unable to perform military missions. This process was initiated in order to conduct comprehensive physical, neurological, behavioral, radiographic, clinicopathological, electrodiagnostic, autopsy and histopathological examinations in a standardized methodology. The above 39 dogs and the matched comparison group are expected to complete active service within the next 12-18 months.

This evaluation has not had any impact on the operational readiness of the DOD working dog program. The only change has been the administrative procedures to relocate dogs to Lackland, AFB, TX when these animals are unable to perform military missions.

Generation of data: All MWDs receive semi-annual physical examinations that include panels of hematologic, selected serologic, and blood chemical analyses. The results are posted in the medical record. Complete medical records from all deceased MWDs in the Department of Defense are archived at DODMWDVS, Lackland Air Force Base, Texas. Following the completion of a working career with death from natural causes or euthanasia for medical reasons, complete autopsies are performed in accordance with a standard protocol. Histopathological assessment and archival of military working dog tissues are completed at the Armed Forces Institute of Pathology, Washington, DC.

The clinical and pathological information generated from this effort will be electronically stored in a database for comparison of these two animal populations and statistical analysis.

Mr. SNOWBARGER. Let me ask——

Mr. SHAYS. Excuse me. Dr. Gerrity, do you have something you can add to this?

Mr. GERRITY. No. I just said that when you said that your records indicated zero funding for 1998, that it is not going on. I was just commenting that that is not necessarily the case, because sometimes moneys are put into projects that are then funded out of that initial pot of money over several years.

Mr. SNOWBARGER. OK. Thanks for that clarification.

Did you get further information, Dr. Winegar?

Ms. WINEGAR. No, I don't have any further information at this point, but I will provide that to you.

Mr. SNOWBARGER. OK.

[The information referred to follows:]

PERSIAN GULF VETERANS HEALTH RESEARCH
PROJECT UPDATE SHEET

PROJECT STATUS: Ongoing

PROJECT ID: DOD-13 **DATE OF UPDATE**: 30 September 1997

AGENCY: Department of Defense

PROJECT TITLE: Effects of Persian Gulf War Service on Military Working Dogs. (Indicators of Human Disease from Persian Gulf War Service: A Study of Military Working Dogs Deployed in Operations Desert Shield/Storm)

PRINCIPAL INVESTIGATOR(S): Armed Forces Institute of Pathology (AFIP); DOD Military Working Dog Veterinary Services (DODMWDVS); Walter Reed Army Institute of Research; (listed by Institute because individuals have and will change with the military)

Agency: DoD **Location**: AFIP, Washington, DC **Status**: Ongoing

Contact Name: LTC Robert Moeller **Contact Phone** : 202-782-2600

Contact Email: moeller@email.afip.osd.mil **Contact Fax**: 202-782-9150

RESEARCH TOPIC: Outcome **RESEARCH SUBTOPIC**: Epidemiology

OVERALL PROJECT OBJECTIVE: The possibility of exposure to environmental factors and endemic diseases exist for the population of military working dogs (MWDs) that deployed to the Persian Gulf (PG) theater of war. The question to be answered is: In the final analysis, what are the differences in diagnoses between the PG MWD cohort and a matched (on the basis of age, sex and breed) comparison group which never deployed to Southwest Asia (SWA).

SPECIFIC AIMS: The (null) hypotheses to be tested is that in the final analysis there will be no differences in the diagnoses between the PG MWD cohort and the comparison group which never deployed to SWA. Should this hypothesis not be supported: 1) the possibility exists that differences in diagnoses between the two groups may be the result of deployment to SWA; and 2) dates of deployment and location in theater will be compared among the PG MWDs, and conceivably to those of PG veterans.

METHODOLOGY:

The PG MWD cohort was identified after the cessation of hostilities and subsequent redeployment. The inclusive deployment dates for this population are 1 August 1990 to 31 December 1991.

MWDs receive semi-annual physical examinations throughout their active duty lives, which include clinical evaluations and routine panels of hematologic, serologic, and blood chemical analyses. The results of these tests are recorded in the animal's medical record. Those MWDs that are euthanized will have peripheral blood samples collected prior to euthanasia for the above tests. When natural death occurs, the most recent blood test will be used. Test results are to be included in the dog's permanent medical record. Necropsies are performed in accordance with a standard protocol contained in TB Med 283. Medical records from all deceased MWDs in the Department of Defense are archived at the DODMWDVS, Lackland AFB, Texas.

Based on the assumptions of a condition with 10% prevalence in the population, looking for a relative risk of 2.5 in the exposed group, setting the alpha level at 0.05 and the beta level at 0.2, a minimum of 112 animals of each group must be included in the study. Therefore, the medical and training records of those 118 MWDs which deployed to the Persian Gulf, and 472 non-deployed MWDs matched four to one based on age, gender and breed, will be abstracted during the study period for the following variables: animal identification; age at death; date of death; breed; gender; location during the time frame 1 August 1990 to 31 December 1991; duration of deployment; neurologic illness; orthopedic illness; dermatological illness; gastrointestinal illness; infectious diseases; parasitism; neoplasms; behavioral changes after 1 August 1990; pathologic diagnoses of biopsy specimens and pathologic diagnoses of autopsy specimens. These data will be electronically stored in a database for statistical analysis using the $SPSS_R$ analysis program.

Those 30 Persian Gulf deployed MWDs still living, and 120 age, gender, breed matched non-deployed control MWDs will be transported to the DODMWDVS, Lackland AFB when the responsible Veterinary Corps officer has determined the animal is no longer physically fit for duty and in need of humane euthanasia. Upon arrival, the medical record will be screened to determine the cohort of assignment. The MWD will receive a complete physical exam, to include the following: CBC; serum chemistry panel; serum acetylcholinesterase activity levels; urinalysis; fecal exam for parasites; canine thyroid hormone measurements (T_4, cTSH); electrocardiography; radiography; a neurologic examination and a behavioral assessment.

The MWD will be anesthetized according to a standard approved protocol. Radiographs of elbows, stifles, coxofemoral joints and spine will be obtained if not present in the record. Electromyograms and nerve conduction studies will then be conducted on the anesthetized dog, to determine neuromuscular function.

Euthanasia of the dog will be completed with a standard approved injectable euthanasia agent (Beuthanasia) and immediately necropsied in accordance with the TB Med 283. At necropsy, gross changes are described and an extensive set of tissues collected and forwarded to the Department of Veterinary Pathology, Armed Forces Institute of Pathology, Washington, D.C. Muscle biopsies of the biceps femoris and triceps brachii; and nerve biopsies of the tibial and radial nerves will be collected for analysis at Auburn University. Additionally, 6 gram samples of liver, kidney, lung, brain and fat will be collected for ultra low temperature freezing and stored at the AFIP or DoD Veterinary Laboratory until toxicological procedures may be performed, if indicated. Formalin fixed tissues will be processed for histopathologic examination resulting in a detailed final pathology diagnostic case report consisting of a list of

pathologic findings and an interpretation of these findings. Remaining wet tissues, paraffin blocks, microslides and case folder materials will be archived. The pathology report will be forwarded to the DODMWDVS, Lackland AFB, TX for inclusion in the MWD's medical record.

All clinical and pathological information collected during the final examination procedures will be electronically stored in a database for statistical analysis using the SPSS® statistical program.

Upon completion of initial data and records collection data , a multivariate analysis of collected variables will be accomplished to determine the effects of age, gender and breed on those conditions commonly occurring in the entire population of MWDs. Odds ratios and ninety-five percent confidence intervals will be calculated on all conditions occurring more frequently in one cohort to determine the effects of the exposure status on those conditions. Fishers's exact p values will be calculated to determine statistical significance of any conditions occurring more frequently in one cohort.

STATUS/ RESULTS TO DATE: Ongoing. We have identified one hundred eighteen MWDs that deployed to various locations in the PG Theater in support of operations within the inclusive dates listed above. The AFIP funded a pilot protocol enabling the early implementation of a data collection system that includes pathologic (including surgical and post-mortem morphologic changes), demographic, and clinical findings from initially identified PG MWD cohort and matched comparison MWDs. The pilot protocol funding expired in 1995.

The collection and analysis of epidemiological data is the primary responsibility of the US Army Veterinary Corps Officer currently stationed at the DODMWDVS, Lackland AFB, TX. Records have been collected and reviewed on 78 Persian Gulf cohort animals and approximately 400 additional dogs that will serve as a comparison group.

In January 1997, a panel of civilian veterinary medical experts from eight different academic and industrial institutes met, as an advisory body, with investigators from the DODMWDVS and AFIP to discuss the project.

The Department of Veterinary Pathology, Armed Forces Institute of Pathology, along with a database management consultant with expertise in SNOWMED International is near completion of the database system. This database system should be completed and ready for data entry in February 1998. Computer software and hardware have been obtained to support this process. The AFIP and the DOD Veterinary Laboratory at Fort Sam Houston ,TX are storing MWD tissue specimens for toxicological analysis, if indicated. Electrophysiological myoneural diagnostic evaluation is ongoing in cohort animals already at DODMWDVS. Muscle biopsies of the biceps femoris and triceps brachii; and nerve biopsies of the tibial and radial nerves are currently being collected for electron microscopic analysis at Auburn University. Approximately 75 % of the PG MWD cohort are deceased; however, information and records must be collected, collated and abstracted. Clinical and pathological findings must be entered into the database management system and analyzed in order to draw conclusions and compare the two cohorts.

PUBLICATION: None

START DATE: Summer 1994 **EXPECTED COMPLETION DATE**: 12/30/2001

LEVEL OF EFFORT TO DATE:

	To Date:	Projection to Completion
FTEs	2.5-3.5	9.5-10
Funding	214,500	165,000 (FY 97)

FUNDING SOURCE: AFIP; USA MEDCOM

FUNDING TYPE: Intermural; P-8

GRANTEE OR CONTRACTOR: NA

Mr. SNOWBARGER. Let me ask the more disturbing question. It is not whether or not you are studying dogs or not whether or not the tests are ongoing, but the hypothesis in general.

Are we studying military dogs to prove that Gulf war veterans are not sick?

That seems to be the hypothesis of this particular study and, again, it says to me that we are not giving much credence to those men and women who came back and are sick; and they are telling us that the illness began to manifest itself after their service in the Gulf.

Ms. WINEGAR. I believe that the work to be done under this project is but one small piece of an overall program, and I think that to say that we are studying dogs to prove that veterans aren't sick is a real extrapolation of one piece of information.

I think it is incumbent upon us to look into a number of different possibilities, and clearly in a controlled study such as this where we have, you know, good access to the information about the military dogs should provide one more piece of information to us as we try to unravel what I believe we all understand to be a very complex problem.

Mr. SNOWBARGER. Dr. Feussner, let me ask you to followup on that, if you would. I mean, it is the Working Group that approved that study and approved that hypothesis for a study.

Dr. FEUSSNER. Yes. I think that one of the persistent confusing features about science is that hypotheses are posed as the null; that is to say, that there is no association. The research is then carried out to reject the null hypothesis, such that it can accept the alternative hypothesis.

That is quite confusing and gives the impression that when you state the hypothesis as the null that is what you believe. It sometimes leads to the misgiving that, how do you ever prove a negative? It is impossible to prove a negative. That is a convention of science that is confusing. The goal of the research is to state the null and then reject it.

It would be simpler if the hypothesis were simply stated as a positive statement and then the research would either prove that the association is correct or not.

I have had a chance to explain many research projects. It is not something that I think we will ever get around, but I think it does mislead and give the impression that the scientist believes the null hypothesis, as stated. That's usually not the issue. That's the best I can tell you.

Mr. SNOWBARGER. Well, I guess I can't argue with convention in the scientific community other than to tell you it is pretty stupid. And when Federal dollars are involved on a general basis and when the health of servicemen is involved in this particular question, we would like to think that—this gives the impression that we don't believe our servicemen coming back and saying that there is a problem that was related to their service. And it sets up the—it sets up the wrong impression about how we feel about our veterans and their service and puts us, obviously, in a very awkward position, when it seems to me it is just as easy to set out the—not the null hypothesis, but I guess the positive hypothesis and prove or disprove that.

Mr. Chairman, I would yield back.

Mr. SHAYS. Thank you.

Mr. Sanders.

Mr. SANDERS. Thank you very much, Mr. Chairman. I am delighted to see our guests here today.

What I would like to do, with your support, is just to wander a little bit through the very fine report that this committee published in November, which I thought is the outstanding—it is the best piece of work I have seen in trying to understand the cause of—or at least what has been going on with research and so forth.

As members of the committee may know, and let me quote from the report, "This committee reluctantly concludes that responsibility for Gulf War illness, especially the research agenda, must be placed in a more responsive agency independent of the DOD and the VA." And I strongly agree with that conclusion.

This is not a personal criticism, but if I went to a physician for 6 years, and I said, Doctor, I am very, very sick, maybe I can't go to work, I have memory losses, I constantly am suffering from fatigue, I have rashes, et cetera, and after 6 years that doctor told me, I don't understand what the cause of your problem is and I have no treatment for you, I would say to that doctor, thank you very much for your help, I am going elsewhere.

I think that's probably the attitude of most members of the veterans community and many Americans. And I think it is not good enough to say it is a difficult problem. We recognize that it is a difficult problem. But I think today—and maybe in a moment you will answer this question—if I were to say to you, where are we now that we weren't 6 or 7 years ago? What is the cause of Gulf war illness? Don't know. What treatments do you have? Don't know.

And that's not good enough, it seems to me. And I think we have got to understand that.

No. 2, picking up on a point that Mr. Snowbarger made a moment ago, amazingly enough—and I would like you to address this as well—there was a program—Mr. Chairman, you may have seen it—Frontline, a couple of months ago, and Frontline on PBS is a pretty good program, pretty respected. Their conclusion was basically—and I would like you to tell me whether you agree with it—that there really is no Gulf war illness, that what we are suffering from—that the problem is still stress and that this happens after every war.

Nothing new here. It happened after the Civil War, World War I, World War II. When people come home from the war, they are sick, and there ain't no cause for the problem.

I think when Mr. Snowbarger asked his question, basically the thesis of that program, supported by former people in the VA, high-ranking physicians, was there is no problem; that much of what the chairman and I, Mr. Towns and others are trying to do is really a waste of time and maybe we are opportunists, politicians, trying to exacerbate fears among veterans and so forth. And maybe you will comment on that.

But now I want to ask you some—getting away from Washington, back home, let me tell you a few experiences I have had; and I see everybody here is a physician, so maybe you can help me with some answers.

A couple of months ago I was at a meeting with veterans in Springfield, VT, in southern Vermont, and on Saturday, just this week, I was in a meeting with veterans in Burlington, VT—the first meeting, about 20 veterans; the second meeting, about 50 veterans. I talked to the veterans and said, How are things going?—they were all from the Gulf war—and this is what they told me: In Springfield, sitting around the room with 20 people, I said, Tell me about memory loss, short-term memory loss. Everybody in the room started laughing, they started chuckling, because almost without exception every one of these people who were between 35 and 45, hard-working Vermonters, every one of these people were suffering from short-term memory loss.

So I want you to tell me whether you think it is a natural thing for people that age, who are healthy enough to get into the National Guard, should be suffering from that?

Then another funny thing happened. We were talking about other problems that people have, and a lot of guys were saying, you know, I go into a supermarket and I walk past the detergent section—you know how they have that funny smell from detergents—and they said, When I smell that, I get sick. Then they were talking about those scented candles, you know about scented candles, and they were all laughing about that. When they are around scented candles, they get sick. When their wives wear perfume, they get sick.

Now, let me read you just some testimony from the committee report, and this comes from Sergeant Martin, who testified before our committee. He said, "I suffer from excruciatingly painful headaches, memory loss and severe diarrhea, mood swings. I violently vomit if I smell perfumes, vapors or chemicals. I get lost and forget where I am sometimes."

In Burlington, in the meeting 2 days ago, we talked about short-term memory loss; almost every hand in the room went up. Now, I have a hard time understanding how healthy people 35 to 40 years old suffer from short-term memory loss.

A guy who is in a car, he says, with his family, they are out on a vacation having a great time, wife and two kids, suddenly he cannot remember where he was going. People cannot remember the simplest things.

Now, I want you to tell me about your views and whether you have done any work or you believe even in the concept of multiple chemical sensitivity. Throughout the testimony and in my own experience with Vermont vets, we hear things like, this is from Michael Donnelly, a major who is now very, very ill, he says and I quote, "I was exposed to malathion fogging, an organophosphate pesticide used for mosquito control, while jogging in the evenings. I started to have serious health problems."

In other words, time after time, we are hearing people—automobile mechanics no longer can deal with gas fumes, can't deal with oil fumes. A guy was telling me the other day in Vermont, who works in the forest, he cannot deal with the odor of trees, if you can believe it.

I want you to tell me what you have learned. Is this true? Is there any work that you have been doing on this? I would like you to tell us whether at this point in time you believe in the concept

of multiple chemical sensitivity, which seems to me an important aspect of this whole discussion; people are overladen with chemicals, who respond negatively.

What are we telling 70,000 vets about possible food—exposures to chemicals that might be in their food? What should they stay away from?

Furthermore, after 7 years, what kind of treatment protocols have you developed? If I am a Persian Gulf vet and I have memory loss, I have—one guy was telling me he sleeps 14 hours a night and still doesn't feel refreshed. What treatment do we have? After 7 years, is there any treatment?

Now, second of all, with regard to that, there are some people in the outside world who are trying to develop treatments. We have heard from a few physicians here. There were some physicians in the VA who did not seem to be able to stay in the VA for a very long time.

We heard from Dr. Nicholson, who has an idea. Is he right? I don't know if he is right, but how are we responding to his thoughts, to other people's thoughts?

So I would like you maybe to respond to some of those concerns. And I have gone on too long and thank you, Mr. Chairman.

Mr. SHAYS. No, you haven't gone on too long, and maybe, just to followup to make sure the different parts are answered, we have simply for all of you—if you can't remember all of his questions, but I would like you to try to go down them so we will use the time to do that.

Mr. SANDERS. Thank you, Mr. Chairman.

Mr. SHAYS. Except the part about whether people are being opportunistic, we will leave that out.

Dr. FEUSSNER. Well, I would say that it is not my perception that you are opportunistic.

You asked a lot of questions, and I tried to track them. I will go down the list and do the best I can.

Mr. SANDERS. Thank you.

Dr. FEUSSNER. The first issue you have asked me before, regarding turning the research effort over to an independent agency, and I think you know that my own perspective is different from yours. I view our research program as vigorous. I believe that we have gotten inputs from the best scientists in the United States. I believe that we have solicited inputs and have funded scientists from the international community as well.

It is a broad research effort, and so it can be viewed as diffuse, but I don't think so. I think we are trying to cover all the reasonable bases.

We have made critical observations, yes, and this committee has heard those before—about mortality, about hospital use, about birth defects. You have not heard any definitive information about what the cause of this is; and that is correct, I do not know what the cause is.

As I said earlier, I don't know what the cause of hypertension is in most of my patients, but I have very effective treatment for that illness; and I take your point on that as well, and we will get to that.

Some of the newer discoveries that the research has produced you are aware of. For example, the PB story, when stressful situations are overlaid on the administration of that drug, the blood-brain barrier may be modified so that the drug can get across.

The Japanese have made observations that there are brain abnormalities noticed that persist long after the acute exposure, months after the acute exposure. Those abnormalities may not be explainable on the basis that the nerve agent blocks acetyl cholinesterase. There may be other actions of that chemical.

The methodological issues and the causation issues are problematic, and you know that.

I feel that if we had some definitive treatments, we would become less concerned about cause because at least we could do something better for the patients. I actually did not see Frontline personally, but I do not believe that all of these various complaints fit neatly under one diagnosis of stress. I think that much of the research has shown that this is more complicated than that.

So I would be reluctant to blame stress as an explanation for all of this, on the one hand.

On the other hand, our patients think of stress or stress-related diseases as mental illnesses; they are diseases of the brain and the brain is a physical entity. Some of our research on the neurobiology of stress, the neuroendocrinology of stress, the effect of stress hormones on the immune system, provide mechanisms for more traditional disease situations to arise.

You asked about treatments. Now, we don't have definitive treatment protocols. What the Department has done is tried to treat patients symptomatically. I think that we have been fussing over trying to come up with a case definition so we can study Persian Gulf veterans' illness, and we can't come up with a case definition so we don't generate treatment protocols.

What we have done recently, in part in response to this committee's criticism, is to try to take parts of the larger problem, fibromyalgia, chronic fatigue syndrome, for example, and craft treatment trials for those conditions. We are in the midst of planning a trial that involves cognitive behavioral therapy and exercise therapy for chronic fatigue and fibromyalgia respectively.

Dr. Nicholson proposes a hypothesis that this condition—at least part of the Persian Gulf veterans' illness—is related to infections with an unusual mycoplasma organism. I think that is a tractable problem, and I think that Dr. Nicholson has been working with Walter Reed and investigators there, and at our last meeting we discussed the possibilities that we could actually plan an antibiotic treatment trial.

Mr. SANDERS. Let me, with your permission, Mr. Chairman, and for the record—you see, this is the problem that we have. This is a letter—I spoke to Dr. Nicholson. I happened to be in California last week. This is to Congressman Filner of California.

Nancy and I enjoyed meeting with you and Congressman Sanders on Sunday, February 14th, in Chula Vista. We were disturbed to find out that the Veterans Administration indicated to your committee that we are fully funded by the DOD for our work on identifying mycoplasmal infections of Gulf war illness patients. This is not true. We do have a pending contract with the U.S. Army Medical Research and Acquisition Command at Fort Detrick, but this has not yet been approved or funded. We did receive some small funds, $40,900, from the U.S. Army to train DOD person-

nel in the types of diagnostic tests that we employed to identify mycoplasmal infections of Gulf War patients . . .

et cetera.

In other words, it never ends.

What you are saying is, this guy may have a hypothesis. I think what everybody here understands, we are not saying he is right, we are not saying he is wrong, but for God's sake the guy is on to something. Are you going to come back next year and say, well, we are going to continue to work with him?

We are spending millions and millions of dollars. He has a hypothesis. Other people have hypotheses. They are people in the VA.

Now I would like to get on to this issue. Tell me, you are a doctor, why would people—in terms of the whole issue of multiple chemical sensitivity, do you believe in that?

Dr. FEUSSNER. Well, I don't think it is an issue of belief. What I will tell you is that I am very allergic to many of those things personally, so that my wife does not wear perfume, my daughter does not wear perfume, because I have a low tolerance for those things.

What I will say is, as a very allergic individual, that I have reactions to things that other people don't. I treat that with avoidance. I have treated that with immunotherapy in the past, and I am better.

At any rate, I don't know if that speaks to the issue of belief or not.

Mr. SANDERS. I have taken too much time. My last question, Mr. Chairman.

What would it tell you if you are sitting around a room of people, all of whom were over in the Gulf war, and they all respond—they get sick if they are around scented chemicals or they are around perfume? Don't you think there is a hypothesis there that we might explore that suggests that these people have a chemical problem?

I failed biology actually in college, I must confess. I am not a doctor, but it doesn't take a genius to suggest that there may be a problem here, that it is not an accident that so many people are responding that way.

Dr. FEUSSNER. I think it is not an accident, and we are funding research to further understanding in this area, yes.

Mr. SANDERS. You didn't tell me whether you believe in the concept of multiple chemical sensitivity.

Dr. FEUSSNER. Well, what I told you is that I get sick around these things. What I am really interested in doing is not inflicting my personal beliefs on others. I would like to generate some scientific information that will convince my colleagues, who may or may not be skeptical about this, that this is a reasonable consideration. I think there are many examples of individuals who are allergic.

Mr. SHAYS. Do you think it is a reasonable consideration?

Dr. FEUSSNER. Yes, sir.

Mr. SHAYS. I didn't have my mic on, but the question was, "Do you believe it is a reasonable consideration," and the answer was "Yes"?

Dr. FEUSSNER. That's correct.

Mr. SHAYS. Let me tell you the intention of the Chair here. Mr. Towns has to go somewhere. I would like to call on him. I am going to take 10 minutes, as well, and then we are going to take 10 minutes with you, Mr. Allen, if that's all right. And then we are going to come back.

Mr. Sanders, if you are going to be around, we are going to come back.

Mr. SANDERS. I am sorry, Mr. Chairman.

Mr. SHAYS. No apology is necessary.

Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman.

After listening to the questions and the comments made, I have a question. Based on—and it came out of that. Based on your research efforts to date, what you have done up to this point, are you in a position to recommend that we do something different if this situation presents itself again?

Dr. FEUSSNER. Yes. I think that information obtained in a base state—and what I mean by that is information that would be obtainable before one would be exposed to the consequences of war—would help clarify subsequent research issues as illness develops after other conflicts. So, yes, I think that the situation can be improved.

Some of our research is also focusing on trying to identify markers, sometimes somewhat retrospective markers. For example, with exposure to chemical weapons—some of the investigators in the Netherlands are investigating biomarkers whereby the binding of the chemicals to one enzyme is different and longer than it is to another enzyme. So if we could study people in a short period of time, days, we might be able to detect exposures.

We are doing research on emerging pathogens—new infections and new germs, trying to develop skin tests for leishmaniasis, for example. So I think that part of the research effort is looking to the future. The neurobiology of stress and how those hormones impact on the expression of disease, the genetics of the enzymes that are affected by chemical weapons, to be able to explain why most of the soldiers who maybe were exposed to a chemical don't have illnesses but a few might, because the enzyme involved is different in some subsets of subjects.

So I think several of those things could be done to help in the future.

Mr. TOWNS. Thank you very much, Mr. Chairman. I yield back. Thank you for allowing me the additional time.

Mr. SHAYS. Any time.

We had 11 hearings on Gulf war illnesses, and we know it is—we believe it is not one silver bullet; we think it is a combination of many things.

But during the course of our hearings, there were parts that were very distressing. One was that we felt the VA and DOD were not listening to our veterans. That's a documented fact. They had incredible stories, and they weren't being listened to. So that's one reason we began every hearing with the VA—with the veterans speaking and encouraging Government officials to come to the hearing and listen before they have testified.

I am going to tell you some of the distressing elements of the hearings and ask you to comment. Dr. Joseph, when he was working in DOD, said that basically low-level chemical exposure does not lead to chronic illness and ultimate death. I want to know, Dr. Winegar, do you believe that's true?

Ms. WINEGAR. I think——

Mr. SHAYS. Not that he said it, but do you believe that low-level chemical exposure does not lead to chronic illness and ultimate death?

Ms. WINEGAR. I don't think that we have enough information at the time for me to make a definitive statement like that. But just for the record, I do want to clarify that I am not a physician and feel unqualified to comment on patient care issues.

Mr. SHAYS. OK. What is your Ph.D. in?

Ms. WINEGAR. Microbiology.

Mr. SHAYS. OK. Dr. Gerrity?

Dr. FEUSSNER. He is also not a physician.

Mr. SHAYS. I am still going to ask everyone this question, and if they want to discount their answer and if we have the wrong witnesses, I apologize that we invited them.

Mr. GERRITY. My original training was as a physicist. I did post doctoral training as a pulmonary physiologist.

Mr. SHAYS. Do you believe that low-level chemical exposure does not lead to chronic illness and ultimate death?

Mr. GERRITY. I think that there is not enough information in the scientific literature to——

Mr. SHAYS. Dr. Feussner?

Dr. FEUSSNER. I think it is possible that low-level chemical exposure could lead to chronic illness. I think, unfortunately, there is not enough information to say definitively whether it is probable or likely.

Mr. SHAYS. Dr. Barrett?

Mr. BARRETT. I would agree with Dr. Feussner's statement.

Mr. SHAYS. Dr. Newton?

Ms. NEWTON. I am sorry. Could you repeat the statement?

Mr. SHAYS. Do you believe that low-level chemical exposure does not lead to chronic illness and ultimate death?

Ms. NEWTON. I believe that that is—that there is insufficient information to answer that question.

Mr. SHAYS. The answer was insufficient information.

Well, tell me why I spent all of my time as a State legislator making sure that OSHA established rules and regulations to make sure that our workers were not exposed to low-level chemical exposure because they would ultimately get illness and die?

Why does the military look at this issue so differently than we do in the private sector? Why is there such a double standard on this issue? I would love an answer. Did I waste my time for 13 years in the State house trying to protect workers from low-level exposure to chemicals because we believed that it led to chronic illness and death?

Dr. FEUSSNER. I think—no. I think what you did is you tried—in the absence of evidence about low-level exposures, you assumed that there was danger until proven otherwise and so that you tried to protect workers against low-level chemical exposures.

Mr. SHAYS. We have lawsuits, we have workers who are getting financial assistance from businesses because the businesses were sued because of low-level exposure to chemicals; and they have chronic illnesses, and some have died. I mean, that's what is happening in the private sector, the world I know.

Ms. NEWTON. Clearly there are low levels of some chemicals that can cause illness and death.

Mr. SHAYS. The comment I heard from you is that there are some chemicals for which low-level exposure can cause illness and death. I mean, I think that's pretty basic. So then the question is that some chemicals may and some chemicals may not.

Dr. Feussner, your comment to me basically is that, in essence, you can't disprove that it doesn't; therefore, you make the assumption that it may until you know otherwise. Correct?

Dr. FEUSSNER. Yes, I think it is possible, yes.

Mr. SHAYS. Therefore, because it is possible, you don't use it to prove that it can't happen because you don't know. You make an assumption that it may and, therefore, respond accordingly. And that was one of the problems we had with the VA and the DOD.

For about 3 years they didn't even want to look at any potential chemical exposure, we didn't fund any chemical research; and it was not until the DOD basically had to acknowledge on a Friday night at 4 that maybe, perhaps some of our troops might have been exposed to chemicals at Khamisiyah. And we have already made an assumption that every place that we bombed that was a chemical plant or a biological plant, that the plumes went away from us, not toward the troops, which was another gigantic assumption.

So what you have said to me—basically, what the panelists have said to me, is that the answer is, "no, but." You have qualified your answer by saying, "some may." And I tell you that I am not a Ph.D., I am not a doctor, as you know, and I think it is insane that we have one standard in the private sector and a whole different standard in the public sector with the military.

That's one of the reasons why—your answer to that question is one of the reasons why some of us want to give this to somewhere else. Because I could have a number of doctors in the private sector who would say, of course, Congressman, that is the case, and then it just depends on what chemicals and it depends on what level. That would have been the answer I would have gotten from people in the private sector, not people from the public sector.

Your answer to that question is one of the reasons why we want someone else to do the research.

I would like to tell you another thing that distressed us. The other thing that distressed us was that when we asked the VA how many doctors they had who had any background in chemical exposure, they could only name one out of the thousands and thousands; and then when we said, please submit it in writing, they could give us a handful. And I gather that the schools don't teach it and we don't have it; and I want to know, on this panel, who has expertise in chemical exposure?

Dr. FEUSSNER. I do not.

Mr. GERRITY. For 10 years I conducted clinical research for the Environmental Protection Agency at their Health Effects Research Laboratory, Clinical Studies Division, in Chapel Hill, NC. Before I

came to Washington, I was the Chief of the Clinical Research branch where we investigated the health effects of ambient air pollutants on the lungs and on the nervous system.

Mr. SHAYS. Were you concerned about low-level exposure when you worked there?

Mr. GERRITY. Absolutely. You know, the ambient levels——

Mr. SHAYS. Why was there concern about low-level exposure in the private sector?

Mr. GERRITY. I was in the public sector, sir.

Mr. SHAYS. I am sorry. What were you in the public sector?

Mr. GERRITY. U.S. Environmental Protection Agency.

Mr. SHAYS. Working with the private sector, not—getting the private sector to abide by sensible rules and regulations about exposure to chemicals, correct?

Mr. GERRITY. Correct.

Mr. SHAYS. OK. Why were you concerned that in the private sector we don't want people exposed to chemicals?

Mr. GERRITY. I am sorry, sir, would you clarify that question for me?

Mr. SHAYS. It is a simple question. Why, when you worked for EPA, were you concerned about people in the private sector being exposed to low-level chemicals?

Mr. GERRITY. The charge of the EPA was broader than protection of the private sector. It actually went to protection of the entire population of the United States.

Mr. SHAYS. I just want to ask about the private sector. Why were you concerned about the private sector?

Mr. GERRITY. Because I think that the Government has an obligation to protect the health of the citizens of the United States.

Mr. SHAYS. OK. What would you have to protect them from? Chemicals aren't a harm. Spell it out to me. You have the expertise. Say what is the obvious.

What is the obvious? The obvious is that you wanted to make sure that people weren't exposed to chemicals.

Mr. GERRITY. What we wanted to make sure of was that the levels to which people would be exposed, because I think it has to be recognized that——

Mr. SHAYS. You didn't mind if they were exposed to low-level chemicals?

Mr. GERRITY. Well, our job was to determine what level would be considered safe.

Mr. SHAYS. OK. And low-level was safe?

Mr. GERRITY. It depends upon how you define low-level.

Mr. SHAYS. OK.

Mr. GERRITY. But what I wanted to say was that, as you pointed out yourself, for different chemicals, the—as——

Mr. SHAYS. I am talking about Dr. Newton. You didn't point that out to me and you have the expertise. The honest answer and the more precise answer would have been, there are some low-level chemicals that can lead to chronic illness and death. That's the honest answer. And it doesn't take a rocket scientist to know that. We already know it.

And instead, you——

Mr. SANDERS. Dr. Gerrity, do you know that?

Mr. GERRITY. Certainly.

Mr. SANDERS. OK. Thank you.

Mr. SHAYS. Why didn't you say that the first time? You have the expertise. It would have been very helpful to us. It would have made me feel like maybe we were wrong, that maybe there isn't any resistance to focusing on chemical exposure.

But there seems to be a resistance to just saying the truth: Low-level exposure to certain chemicals can lead to chronic illness and death, period, case closed. And because of that, we'd better study it. And that's what causes my frustration.

I didn't come to be frustrated. I can't get an answer that frustrates me.

Do you want to say something, Dr. Feussner?

Dr. FEUSSNER. Yes, sir. I was just going to followup to say that until recently, our Department did not have a focused research effort dealing with environmental hazards, and that research focus really wasn't created until 1993–1994, with the funding of environmental hazard centers in Boston, Portland, East Orange and most recently a fourth focusing on birth defects and exposures that might cause birth defects.

The second issue, I would say, is that with the creation of those environmental hazards, we also started funding research, looking at multiple chemical sensitivity as a condition, using working case definitions, since a more definite case definition for that problem is also somewhat illusive. And we have projects nested primarily within our environmental hazards program in Boston, and East Orange, NJ, but have also funded a project that came through the VA's intramural program, not part of the Persian Gulf research effort, in Tucson, dealing with chemical intolerance.

So I think that we have not had an extensive research capacity in this area in the past. We have worked since 1993 to try to rectify that. We have funded centers of excellence, environmental hazard centers, in trying to address those issues.

Mr. SHAYS. The challenge is, though, we still have a handful of doctors who have expertise within, and there are people outside.

Let me just ask two other questions quickly and they don't need long answers.

Excuse me. I will go to Mr. Allen and then we will come back.

Mr. ALLEN. Thank you.

Mr. SHAYS. Mr. Allen, you have the floor.

Mr. ALLEN. Thank you, Mr. Chairman. I will, I think, follow along in this vein.

As I listen to this discussion, a couple of things come to my mind. I had some background years ago representing some plaintiffs who were affected by an aerial spraying incident. A paper company up in Maine sprayed an herbicide in an area where it drifted and it affected their gardens. So this long story—I just say that by way of background; this is an area where I have some little amount of knowledge, and a little knowledge may be a dangerous thing. But it does seem to me that one of the things we have to get in line is what our expectations are for an outcome.

I do not expect that there is a cause to a Gulf war illness and that you—and that, at the end of the day, whether that is 5 years or 10 years or 20 years, there will be research which shows that,

yes, this particular chemical is the source of all of these particular incidents.

The difficulty—but having said that, there is a lot of anecdotal stuff out there. There has been testimony before these—before this committee that all of us, when we go home, hear some of the antidotes. So what I worry about is the methodology by which research is either conducted or approved.

By that I mean this: If you—it seems to me appropriate that you do at least some studies which measure the Gulf—those who were deployed to the Gulf and those who were not. Those are big, complicated studies, and they will show you perhaps—you know, they have to be done because you need to know is there a different death rate, is there a different illness rate? But I suspect that to really get quality research, to try to draw the connection between the scientific research and the antidotes, to figure out whether or not there is something there, you have got to look either at the folks sitting around in Burlington, VT—all of them say, yes, I have got the same kind of sensitivity to candles—or you have got to go back to the Gulf and try to figure out who was in a particular place at a particular time.

Now, I understand how difficult that is. But it seems to me that the attitude with which you look at the proposals that are coming is really important, very important, in trying to figure out what kinds of proposals will be funded. And it seems to me that it is critically important to look for those proposals which are trying to find a connection, trying to find a chemical or a certain mix of chemicals with a smaller group, so you are not just doing the global studies, those deployed and those not deployed.

And I guess what I would like is a reaction to that comment, and whether, when you are looking at proposals trying to figure out which ones to approve and which ones not to approve, how you are taking into consideration those—how you are taking those kinds of issues into consideration.

Dr. FEUSSNER. Well, I think that the external peer review groups are receptive to novel hypotheses that can be tested rigorously so that the hypothesis, as posed, can be answered. And basically that's the essence of the scientific method, that there is a hypothesis or a question that you are asking and that the measurements you are proposing to make will answer that question either in a definitive way or in an innovative way.

The difficulty in my mind with low-level exposures is that as the exposures are large and cause serious, acute problems, we are able to associate the exposure with the outcome. As the exposure becomes more subtle and the outcome less precise—for example, your blood pressure falls, which is something you can measure precisely, versus you have subtle cognitive memory defects which are harder to measure, no less pertinent, certainly, but harder to measure definitively, I think the research problem becomes more difficult.

My impression is that the review committees are open to virtually any testable hypothesis, and I have seen no evidence that that is not the case.

Mr. ALLEN. Well, my—I guess my concern is, is there—are there any guiding policies or anything to guide these—the independent—the peer review organizations to—I mean to say we are simply

going to do research on the Gulf war illness of whatever kind, whatever seems interesting, strikes me as not having enough of a focus on what exactly it is we are trying to look at.

I can envision, for as long as people who served in the Gulf are alive, there are research proposals that could be undertaken. And I am wondering whether there is enough policy guidance in terms of what—you know, what you are looking for, to be productive.

Dr. FEUSSNER. You would like the policy guidance to be specific enough so the research projects are focused within the area of interest, but not so specific enough that they exclude research projects that might be relevant.

And I think one of the reasons that we ask the several constituent members of the Research Working Group to have these documents reviewed before they are released is an effort to get enough input to try to walk the line between being sufficiently specific without being overly prescriptive. On the one hand, the danger being that you are not focused enough; on the other hand, the danger is that you are being overly exclusive. And we do try to walk that line to give sufficient guidance so that the investigators know what to submit or know that this is an area of high priority and their research fits into that area, without being prescriptive.

Mr. ALLEN. One last area of questions.

How much—you mentioned earlier, and I thought it was an interesting suggestion, that—you know, if you had treatments for multiple chemical sensitivity, you might not need to know the causation. Is that followed up in any of the research you are doing? I mean, are you working on research that was more focused on the treatment than on the causation?

Dr. FEUSSNER. Well, I think Mr. Sanders' criticism on that is fair criticism. At the moment. We have no active treatment trials ongoing in any of these areas. We are trying to stimulate treatment trials initially in chronic fatigue syndrome and fibromyalgia. We have had discussions about antibiotic treatment protocols, not with Dr. Nicholson but with the folks at Walter Reed, who also have expertise in mycoplasma problems.

And we specifically released a program announcement that is open-ended and solicits research on any treatment modality with three requirements: No. 1, that the patient population who would be the subject of the experiment are clearly defined; No. 2, that the treatment protocols are replicable so if we show this treatment works we can just disseminate it throughout the country; and No. 3, that the outcome measures, if not precise, at least use valid instruments to make the measures. Those were the only three caveats.

Now, it is an open-ended program announcement. There are no deadlines.

Mr. ALLEN. It seems to me a very important area to pursue.

With that, Mr. Chairman, I would yield back.

Mr. SHAYS. Thank you. The Chair recognizes Mr. Kucinich for 5 minutes and then another 5 minutes for 10.

Mr. KUCINICH. Thank you very much, Mr. Chairman. The question to Dr.——

Dr. FEUSSNER. Feussner.

Mr. KUCINICH [continuing]. Feussner?

Dr. FEUSSNER. Yes, sir.

Mr. KUCINICH. You know, in listening to your testimony, in reading it and also in reading some background material, something occurs to me. And maybe this question was asked before, but if it wasn't you could help elucidate this for all of us. If we don't even know what Gulf war syndrome is, then how can we protect the troops who are out in the Gulf region right now?

Dr. FEUSSNER. Do you want to do that?

Ms. WINEGAR. I will try to give you a partial answer to that. I think that one of the things that Dr. Feussner alluded to was the fact that we need a lot more information; and I think that we have taken some positive steps on being able to better track individuals as to their location, being able to keep better records for what types of medications they might be given, as far as their personal record, their personal histories, and I think that the Department of Defense has become attuned to the needs to be more exact in all the records that we keep.

And so I think that this kind of data will certainly help us to assess where these problem areas are and to make some positive correction, so that we don't do that again.

I mean, we will never be able to get to the point where we can test the hypothesis of every possible combination for every single individual who may have inherent genetic differences or who may have a history of exposures to some compound or the other. It is an infinite number of possibilities, and I don't think there is anything we can do about that at the moment.

Dr. FEUSSNER. I think the short answer to your question is—and there are some parallels here actually with Legionella and the pneumonia caused by that organism. One of the earlier epidemics there was the Pontiac fever in 1968, and not knowing what caused that syndrome made it impossible to prevent subsequent exposures and subsequent illnesses.

It is difficult to prevent something when you don't exactly know what the target is.

I think this committee and others have made recommendations about chemical exposures, biological exposures, et cetera; and my impression is that DOD is trying to deal with the ones they know about. Dealing with the ones we don't know about is——

Mr. KUCINICH. Well, but, Doctor, with all due respect, we have a national policy now where we are sending thousands upon thousands of troops to that region. And is your Department in contact with the—those elements of the Defense Department that are deploying these troops to immediately set into place certain analyses and data collection and monitoring and means by which the American people can be assured that their sons and daughters are not going to be exposed to harm from a syndrome which has not yet been clearly identified, let alone harm from the combat which we hope—which we hope never comes?

Dr. FEUSSNER. Well, again, the short answer to that question is yes. And I think that——

Mr. KUCINICH. Tell me how. You know, the—my short rejoinder is how? How?

Ms. WINEGAR. How are we in communication or how are we——

Mr. KUCINICH. You know, is there monitoring going on right now with the new troop deployment? Is that happening? How?

Ms. WINEGAR. We have not yet fully implemented all the plans.

Mr. KUCINICH. I am sorry. Wait a minute. Mr. Shays, you know I have always been very patient at these meetings, but you just gave me—the doctor gave me a very short answer to that long question, which was yes. Now I am getting an elaboration of it that doesn't seem to be quite yes.

Dr. FEUSSNER. My fault. I was saying yes to the question about us communicating and discussing these issues.

Mr. KUCINICH. What is being done right now to make sure that this doesn't keep happening, that we don't create thousands of more victims?

Ms. WINEGAR. Well, we in the Defense Department are currently in the process of developing and executing detailed plans, and as was indicated in a hearing a couple of weeks ago by Mr. Christopherson, who is the principal deputy in Health Affairs, when questioned about the specific issue of widespread use of the anthrax vaccine, he indicated that the Defense Department has not undertaken that initiative yet simply because we do not have all the detailed plans in place.

I think that we have made a full and honest commitment to the members of the military to have all of those plans in place for their individual medical records, for the records of their deployment positions, for all the types of information that we can gather. We certainly will try to do whatever we can for those things that are under our control.

Many of the things, I think, are beyond our control, and I think that we have admitted that and need to do as best we can to identify the things that we know about. That's our commitment at the moment. To make a guarantee that there won't be——

Mr. KUCINICH. Who is in touch with whom? Who from the health part of this is in touch with the people who are doing the deployment? What is the communication that is going on?

Dr. FEUSSNER. Well, the clinical arm in VA is headed up by Dr. Murphy, and she is in contact with her DOD counterparts on the predeployment planning issues.

Mr. KUCINICH. And are we going to—and are we—so who is in contact on the predeployment planning? Who did you say it was?

Dr. FEUSSNER. The person who represents VA is Dr. Murphy.

Mr. KUCINICH. And they are now working with whom?

Ms. WINEGAR. I am sorry. Would you repeat that?

Mr. KUCINICH. Who is Dr. Murphy working with?

Dr. FEUSSNER. Health Affairs?

Ms. WINEGAR. Well, there are, within the Department of Defense, the Assistant Secretary for Health Affairs working with the Joint Staff; and a number of other offices are making the plans and looking at how we are going to keep the detailed records.

The VA is used as a consultant and a wealth of knowledge on that, but it is not their direct responsibility for the deployment issues.

Mr. KUCINICH. I understand that.

Mr. Chairman, I think, with the Chair's permission, it would be very helpful for this committee to receive a report on a chain of

command here and on the communications between the relevant oversight responsibilities here, to make sure that we can fix the responsibility for any unforeseen consequences, shall we say, that might be experienced by those who are now in the Persian Gulf. Because I think the question that many Americans are going to be concerned about: Their sons and daughters who are there now, are they going to be returning with symptoms and will they be exposed to the same kinds of toxins, and can we be assured that they won't be given toxic drugs?

Mr. SHAYS. And the reason why that question is important is, we want someone to take ownership.

Mr. KUCINICH. Right.

[The information referred to follows:]

THE DEPARTMENT OF DEFENSE ORGANIZATIONAL STRUCTURE

Organizational Structure

Department of Defense
Secretary of Defense
Deputy Secretary of Defense
Office of the Secretary of Defense
Military Departments
The Joint Chiefs of Staff and Joint Staff
Unified Combatant Commands

The Department of Defense (DoD) (DoD Directive 5100.1) is responsible for providing the military forces needed to deter war and protect the security of the United States. The major elements of these forces are the Army, Navy, Air Force, and Marine Corps. Under the President, who is also Commander-in- Chief, the Secretary of Defense exercises authority, direction, and control over the Department which includes the Office of the Secretary of Defense, the Chairman of the Joint Chiefs of Staff and the Joint Staff, three Military Departments, nine Unified Combatant Commands, the DoD Inspector General, fifteen Defense Agencies, and nine DoD Field Activities.

The Secretary of Defense is the principal defense policy advisor to the President and is responsible for the formulation of general defense policy and policy related to all matters of direct and primary concern to the DoD, and for the execution of approved policy. Under the direction of the President, the Secretary exercises authority, direction, and control over the Department of Defense.

The Deputy Secretary of Defense is delegated full power and authority to act for the Secretary of Defense and to exercise the powers of the Secretary on any and all matters for which the Secretary is authorized to act pursuant to law.

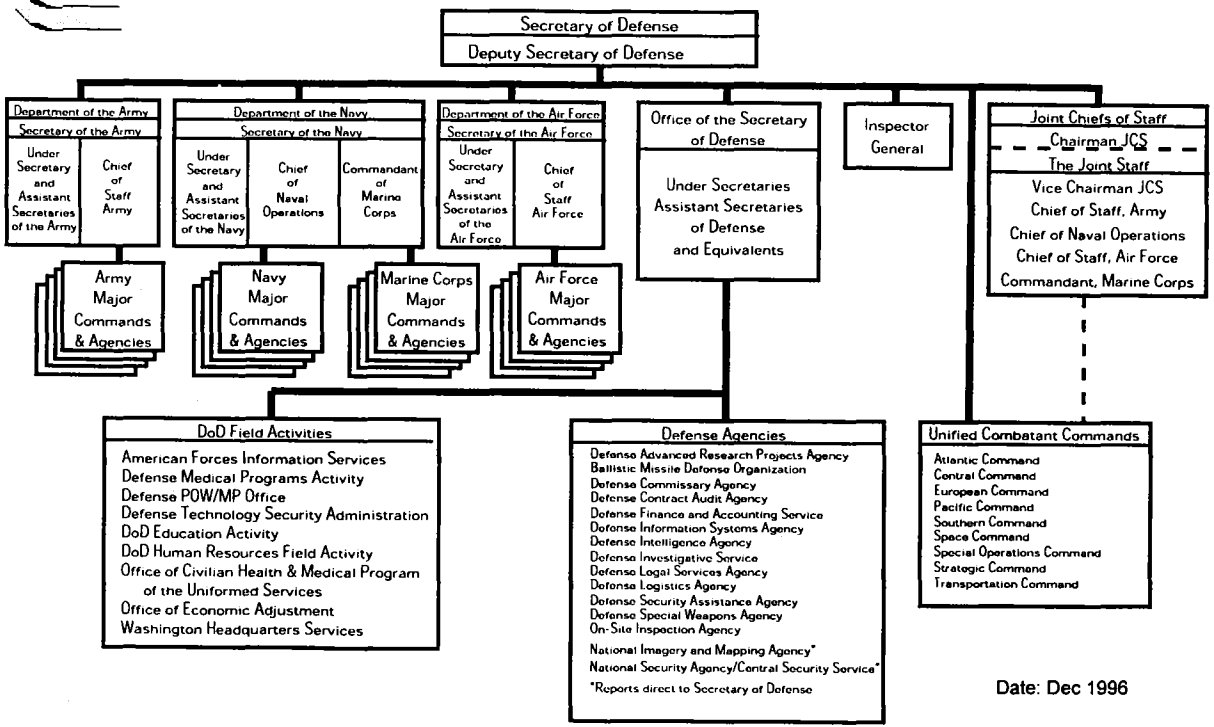
The Office of the Secretary of Defense (OSD) is the principal staff element of the Secretary in the exercise of policy development, planning, resource management, fiscal, and program evaluation responsibilities. OSD includes the immediate offices of the Secretary and Deputy Secretary of Defense, Under Secretary of Defense for Acquisition and Technology, Under Secretary of Defense for Policy, Under Secretary of Defense for Personnel and Readiness, Under Secretary of Defense (Comptroller), Director of Defense Research and Engineering, Assistant Secretaries of Defense, General Counsel, Director of Operational Test and Evaluation, Assistants to the Secretary of Defense, Director of Administration and Management, and such other staff offices as the Secretary establishes to assist in carrying out assigned responsibilities.

The Military Departments (DoD Directive 5100.1) are the Departments of the Army, Navy, and Air Force (the Marine Corps is a part of the Department of the Navy). Each Military Department is separately organized under its own Secretary and functions under the authority, direction, and control of the Secretary of Defense. The Military Departments are responsible for organizing, training, supplying, and equipping forces for assignment to Unified Combatant Commands. (See Chart.)

The Unified Combatant Commands (DoD Directive 5100.1) are responsible to the President and the Secretary of Defense for accomplishing the military missions assigned to them. Commanders of the Unified Combatant Commands exercise command authority over forces assigned to them as directed by the Secretary of Defense. The operational chain of command runs from the President to the Secretary of Defense to the Commanders of the Unified Combatant Commands. The Chairman of the Joint Chiefs of Staff functions within the chain of command by transmitting to the Commanders of the Unified Combatant Commands the orders of the President or the Secretary of Defense. Unified Combatant Commands include the European Command, Pacific Command, Atlantic Command, Southern Command, Special Operations Command, Strategic Command, Central Command, Transportation Command, and Space Command. (See Chart.)

The Joint Chiefs of Staff (JCS) and Joint Staff (DoD Directive 5100.1). The Joint Chiefs of Staff, headed by the Chairman of the Joint Chiefs of Staff, consists of the Chairman, the Vice Chairman, JCS, the Chief of Staff, U.S. Army, the Chief of Naval Operations, the Chief of Staff, U.S. Air Force; and the Commandant of the Marine Corps, and supported, subject to the authority, direction, and control of the Chairman, by the Joint Staff, constitute the immediate military staff of the Secretary of Defense. The Chairman of the JCS is the principal military advisor to the President, the National Security Council, and the Secretary of Defense. The Chiefs of Service are the senior military officers of their respective Services and are responsible for keeping the Secretaries of the Military Departments fully informed on matters considered or acted upon by the JCS, and are military advisers to the President, the National Security Council, and the Secretary of Defense. The Vice Chairman of the JCS performs such duties as may be prescribed by the Chairman with the approval of the Secretary of Defense. When there is a vacancy in the Office of the Chairman or in the absence or disability of the Chairman, the Vice Chairman acts as Chairman and performs the duties of the Chairman until a successor is appointed or the absence or disability ceases. (See Chart.)

Department of Defense



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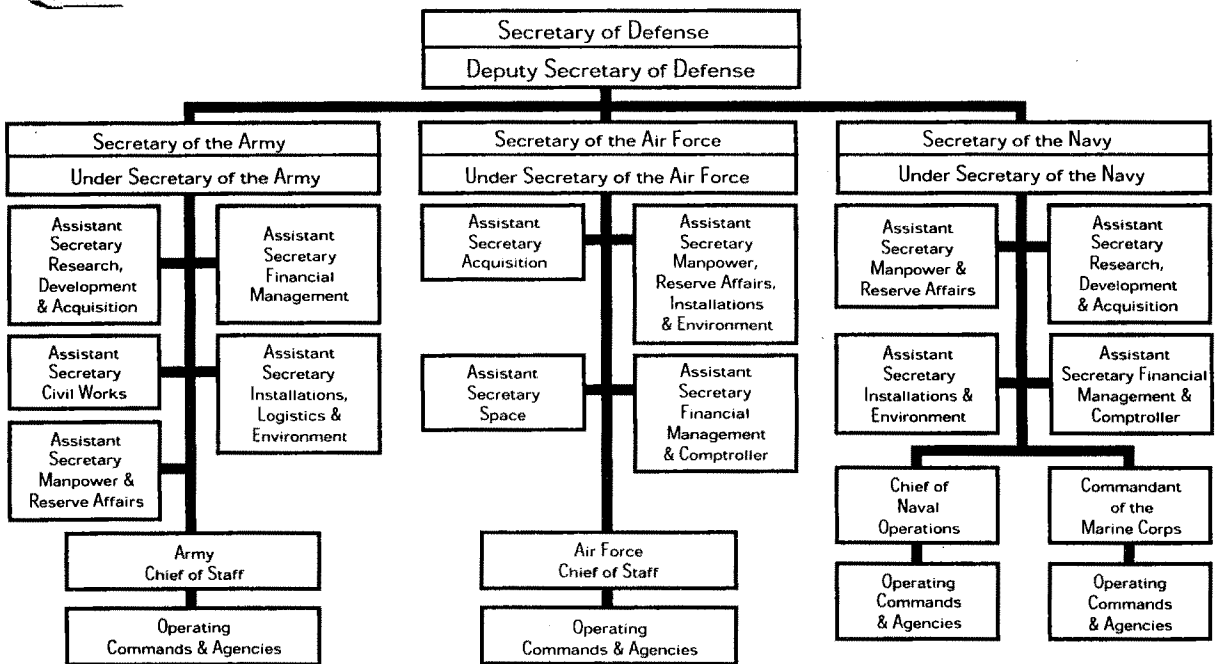
Military Departments



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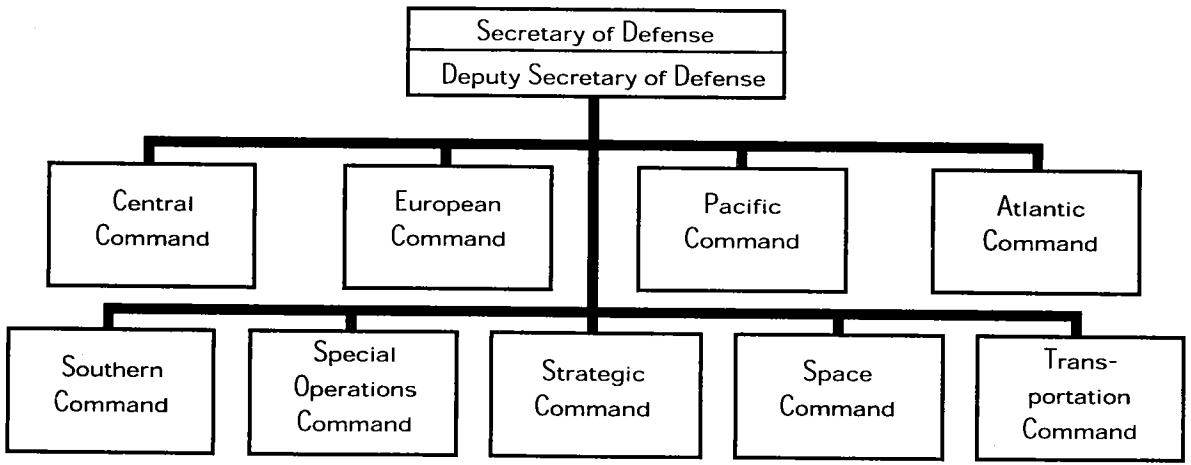
Unified Combatant Commands



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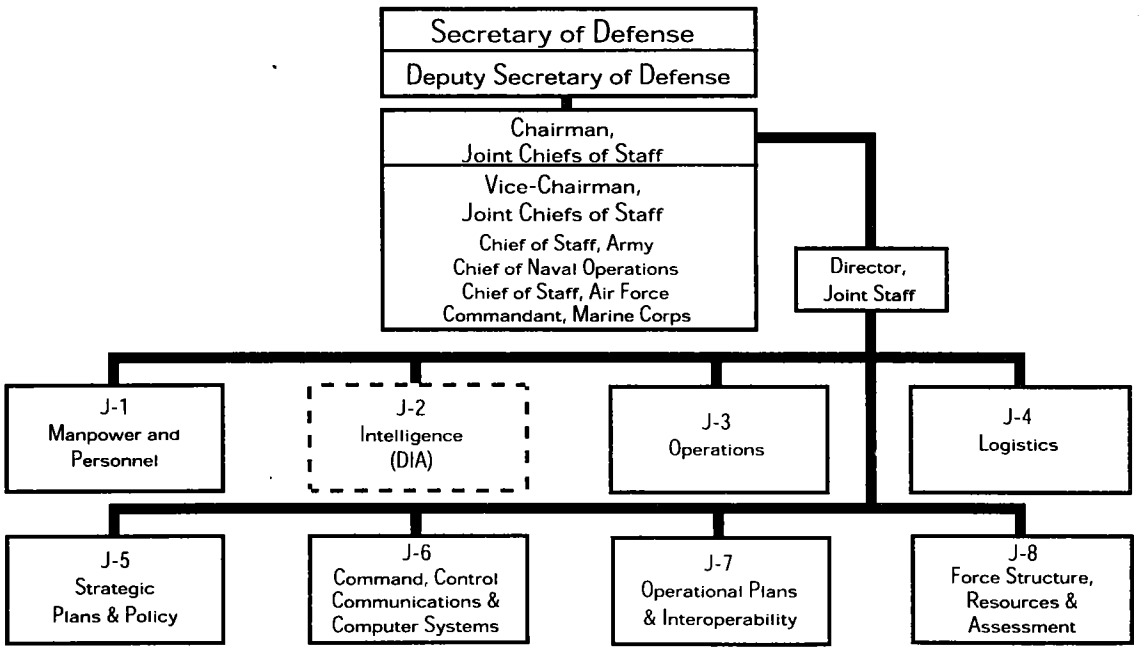
Joint Chiefs of Staff



Date: May 1996

Mr. SHAYS. When the FDA allowed the Department of Defense to use pyridostigmine bromide, PB, two requirements, one, they tell the soldiers, and two, they keep records. They didn't tell all the soldiers and they didn't keep any records.

Ms. WINEGAR. Right.

Mr. SHAYS. Nobody wants to take ownership.

Mr. KUCINICH. Thank you very much, Mr. Chairman, because that's a very important point; that is that, you know, the Department of Defense had a so-called honest commitment to the FDA not to give experimental drugs to soldiers without their consent and then we found——

Mr. SHAYS. They couldn't consent. They were ordered to.

Mr. KUCINICH. They were ordered to, right.

Mr. SHAYS. They were just to be told that they were taking an experimental drug.

Mr. KUCINICH. Thank you.

Thank you, Mr. Chairman. Thank you.

Mr. SHAYS. Thank you. At this time, the Chair would call on Mr. Sanders.

Mr. SANDERS. Thank you very much, Mr. Chairman.

What I would like to do, I am going to go back to the report that the committee published, because I was very impressed by it, and I would like to ask Dr. Feussner to comment on some of the statements that I am going to read you.

This is a statement that was made by Dr. Harold—Dr. Howard Ernovitz. This is what he says, he testified before this committee and he said, quote,

> Recent studies have shown that prolonged and aggressive antibiotic therapy appears to abate many of the symptoms associated with Gulf War syndrome. Usually the therapy takes longer than ordinary treatments, i.e., 6 to 9 weeks instead of less than 3 weeks. In many cases, the symptoms return when the therapy is discontinued . . .

et cetera.

He has a thought about a therapy. My understanding is that you have said there is no active treatments; trials are now being undertaken. What do you think about Dr. Ernovitz' theory? Are we working on that?

Dr. FEUSSNER. Yes, sir. I think that an antibiotic treatment with our preliminary information, an antibiotic treatment trial may be warranted. The difficulty with an antibiotic treatment trial is to target the antibiotic treatment to eradicate the offending organism. From my perspective of the literature, the best bet at the moment, the clearest hypothesis for testing may be the issue of mycoplasma that Dr. Nicholson has raised.

Mr. SANDERS. We have been talking about this for years. Now, in the State of Vermont, I specifically asked the guys who were hurting, and I said, listen, no one can guarantee any cures. But if there were an experimental treatment that we are pretty sure was not going to make you worse than you are today, would you be prepared to undertake that? Every hand in the room went up.

Now, this guy is doing work. Are you prepared to come to the State of Vermont and start this antibiotic therapy?

Dr. FEUSSNER. The antibiotics that are typically suggested are not investigational agents and are FDA-approved agents.

Mr. SANDERS. Right, exactly.

Dr. FEUSSNER. And so that a physician, for example, who might believe that this antibiotic could alleviate these symptoms or cure this disease is in a position to prescribe those antibiotics.

Mr. SANDERS. And how many doctors in the VA system are doing that right now?

Dr. FEUSSNER. I don't know the answer to that.

Mr. SANDERS. I believe none. And it is not as easy as you think, because there is no presumption that is not yet VA approved.

I mean, if this were stress, for example, you were operating under the assumption of stress, you would not use antibiotics in that sense, would you?

Dr. FEUSSNER. Well, the antibiotic treatment is a potential therapeutic avenue. The antibiotics are not harmless, and difficulties with chronic antibiotic therapy such as modification of the gut flora, precipitation of persistent diarrhea, adverse drug effects, superinfection with other fungal infections, et cetera, are credible risks.

Mr. SANDERS. But don't you think that if veterans understood the risk and you explained it, as you just did right now and said, look, we are not guaranteeing anything; there is a chance, in fact, that you may have a problem——

Dr. FEUSSNER. I think the veterans could make an informed decision about whether to participate in a study or not.

Mr. SANDERS. Now the question is, so we don't discuss this 5 years from now again and go through all of this stuff again, when are you going to allow veterans that choice?

In my State of Vermont, I am here to tell you, many of these guys would like that.

Will you come to the State of Vermont and start a controlled experiment so we can learn something? Yes?

Dr. FEUSSNER. I will try to start an experimental trial of antibiotic therapies, yes.

Mr. SANDERS. OK. We will be in touch with you, and Dr. Victor Gordon, whom you may know, who is one of the better physicians in the VA system, valiantly trying to do this, will be delighted to work with you. He is from Manchester, NH. I think I can speak for Dr. Gordon in that respect.

That's No. 1. I am glad to hear that and I will be in touch with you.

The No. 2 question I would like to raise to you, in our report we heard—and again, we are not scientists here, so I am not saying the people are right or whether they are wrong, but I want you to comment. OK?

We heard from a gentleman named Dr. Thomas Tiedt, T-I-E-D-T, a neuroscientist and former pharmaceutical industry researcher, and this is what he told us. He told us some scary stuff. This was his opinion.

He said—he worked at the University of Maryland on pyridostigmine bromide. He is an expert, and this is what he said. He said, "Our work was followed by an explosion of research by DOD during the 1980's, the most relevant of which was produced by my co-authors," et cetera, and this is what they concluded. "DOD research established by the early 1980's that PB would be

harmful in healthy individuals; two, PB was worthless, even counterproductive as a protectant against chemical warfare; and three, PB was more toxic than sublethal doses of chemical warfare agents."

That was his opinion. I am not saying he is right or wrong. You tell me. Is he right or wrong? Should we be scared?

Dr. FEUSSNER. I think that decisions that were made regarding that drug suggested that the risks were worth the benefit.

Mr. SANDERS. You disagree with Dr. Tiedt then?

Dr. FEUSSNER. I can't agree—I think you said that he said that this drug was worse than toxic warfare agents, and I don't believe I can agree with that.

Mr. SANDERS. He said it was worthless, even counterproductive, as a protectant against chemical warfare; and three, PB was more toxic than sublethal doses of chemical warfare agents.

I am not saying whether he is right or wrong.

Dr. FEUSSNER. I can't agree with that.

Mr. SANDERS. OK. Are you doing—I mean, he makes serious charges. Are we doing work now to say—so that you can come before this committee to say, he is dead wrong and we know that he is dead wrong?

Dr. FEUSSNER. Well——

Mr. SHAYS. How do define "wrong"?

Mr. SANDERS. Picking up on Mr. Kucinich's point, if he is right, or half right, we should be very cautious about what happens in the future.

Yes, Dr. Newton.

Ms. NEWTON. The National Toxicology Program has conducted studies on pyridostigmine bromide. I do not have the results, but I can get them.

Mr. SHAYS. I need a translation. You need to speak a little more slowly.

Mr. SANDERS. They have done research. They can get——

Ms. NEWTON. The National Toxicology Program, which NIEHS is the lead agency for, has done toxicity studies of pyridostigmine bromide.

Mr. SHAYS. Did they do those studies?

Ms. NEWTON. I don't know.

Mr. SANDERS. Then how do they respond to those—to Dr. Tiedt's charges?

Ms. NEWTON. Like I say, all I know is that the studies were done. I can get you the results.

Mr. SANDERS. I am not saying that Dr. Tiedt is right. I am not saying that. But he made extraordinarily—he has experience. He claims that the DOD itself did research which backs up his assertions.

I can't say if it is right or wrong, but I would hope that you would be able to tell the soldiers in the United States today that he is wrong and very clearly wrong.

Now, the last point that I want to make, Mr. Chairman, gets back to a point that I made earlier that deals with multiple chemical sensitivity. The chairman was talking about that when he was in the Connecticut Legislature he was very concerned about the impact of low-level exposure on human health.

There is research being done by a number of people, including Dr. Claudia Miller of the University of Texas, Southwest Medical Center, who testified before this committee; and basically what she said, relevant to the chairman's discussion a little while ago, is that many of the symptoms that she is seeing in Gulf war patients are precisely the same symptoms that she saw among workers who were exposed to heavy doses of pesticides or other organophosphates, and she believes there is a connection between the two. But she believes in the issue of multiple chemical sensitivity.

And she says, she—let me read from the report. She testified that common symptoms reported by these patients at the time they were exposed were often flu-like illnesses—fatigue, concentration difficulties, headaches, shortness of death, musculoskeletal pain and gastrointestinal symptoms. She saw the same problems between people in the civilian sector and Gulf war veterans.

What conclusion do you reach? Do you agree with that?

Dr. FEUSSNER. Well, I think that there are several possible explanations for these exposures. I think you mentioned organophosphate pesticides. Earlier in these hearings we have talked about chronic fatigue syndrome, we talked about fibromyalgia, and we have talked about exposure to multiple chemicals, and I think those are all potential exposures that are causing symptoms in our patients.

Mr. SANDERS. OK. Dr. Feussner, before we leave today, I will get your card, I will call you up, and I will work with you to develop a treatment protocol.

Dr. FEUSSNER. The antibiotic arm.

Mr. SANDERS. OK?

Dr. FEUSSNER. Yes, sir.

Mr. SHAYS. I wouldn't wish that on my worst enemy.

Dr. FEUSSNER. Well, he is not suggesting that he is going to plan the trial, just to facilitate.

Mr. SHAYS. That's for sure.

Mr. SANDERS. Thank you. Thank you, Mr. Chairman.

Mr. SHAYS. I would like to ask each of you, to the extent that you would be able to answer this question, whether we have any known way of detecting chemical exposure. I will start with you, Dr. Winegar, and just go right down the list. Thank you.

Ms. WINEGAR. Yes, we do have ways of detecting chemical exposure, but before I go further, I do want to clarify the interchanging of the word "chemicals" and the DOD's perhaps limited context of chemical warfare agents, and those are not necessarily the same. And I think that in some of the questions and answers, we may have misconstrued what the context of the question was.

When you were referring earlier to Dr. Joseph's quotation and asking me whether I believe that low-level exposure to chemicals could lead to serious illness or death, I believe that his statement was made in the context of the known chemical warfare agents——

Mr. SHAYS. No, no, no, no, no. Just a basic question about chemicals.

Ms. WINEGAR. Well, then my answer—that was how I interpreted the question.

Mr. SHAYS. So how would you have answered the question?

Ms. WINEGAR. If the question were open-ended for any chemical, then I would agree with Dr. Feussner that yes, that definitely is a possibility.

Mr. SHAYS. Well, he didn't really say——

Ms. WINEGAR. Maybe I am going a little bit further.

Mr. SHAYS. Dr. Newton came to the rescue of all of you, I think, by saying that some chemicals could lead to chronic illness and death, which is a basic statement that you don't need to be a Ph.D. to know.

Ms. WINEGAR. Right. But that leads me back to the answer that I wanted to give to your current question on——

Mr. SHAYS. Well, before we do that, I want to know under what context would you have answered differently? I don't understand why you gave your first answer, regardless of——

Ms. WINEGAR. Oh, my answer was limited to chemical warfare agents, and I don't think we have enough data on low-level exposure to such things as sarin, et cetera, to indicate whether that could lead to serious illness or death.

Mr. SHAYS. Well, we made an assumption in DOD that because people didn't die on the spot, therefore our troops weren't exposed to chemicals. That was one of the things that set our hearings off. There was an assumption on the part of DOD that because there was no chronic illness and death, therefore our troops were not exposed to chemicals. Case closed.

Ms. WINEGAR. I think you mean acute.

Mr. SHAYS. What?

Ms. WINEGAR. There was no acute illness or death; therefore, the assumption was that there was no exposure.

Mr. SHAYS. Yes, that's exactly what I mean.

Ms. WINEGAR. And I think that we have insufficient data to make that conclusion at the moment.

Mr. SHAYS. And I think it is an outrage that that statement guided our research for 3 years into not looking at low-level chemical exposure.

Ms. WINEGAR. I would like to indicate that we do currently have a number of studies ongoing, looking at exactly that point.

Mr. SHAYS. Right. It is amazing to me that we haven't been looking at this for years; I mean after World War I, I would think. See, we had troops who had acute illness and became sick and died. Either they died on the spot or they died quickly after coming home from World War I. We also had troops who had low-level exposures to these and died later on. They didn't die right away, but they died later on. And for me, in my wildest imaginations, I can't comprehend that DOD wouldn't have been researching this for years.

Then what really bothered me was that we had Dr. Joseph and others say we hadn't done any research on chemical exposure, and then we find out that you have a long list of studies that were done on chemical exposure in past years, you just didn't bring them out. And you didn't bring them out, in my judgment, because our troops weren't exposed to chemicals. And then at 12 o'clock, DOD announces that at 4 o'clock they are going to have a press conference, before a Monday story by Jack Anderson and our hearings on Tuesday, that our troops were exposed to chemicals in Khamisiyah, and then all of a sudden we have a different attitude.

That is why I have concerns about the whole way we approach this, because there is still this reluctance on the part of all of you to just accept the fact that our troops may have been exposed to chemicals and we need to go overtime to deal with this. And it is still there. It still came out in that first question. You wanted to accept the most narrow way to respond to the question.

How do we determine chemical exposure? You answered yes, we can detect chemical exposure. How do we detect chemical exposure?

Ms. WINEGAR. We have a number of different methods for detecting the known chemical warfare agents. Again, I am sorry if my answer is limiting to you, but that is the priority and the mission of the DOD. It is not within our purview or our mission to measure for every possible chemical that occurs in the environment. We don't have the capability to do that.

Mr. SHAYS. Well, one of the reasons we didn't detect is we didn't think there was offensive or defensive use of chemicals. We made an assumption that our chemical fumes were going in one direction. Is it your testimony that the known chemical agents that we have don't lead to chronic illness and death?

Ms. WINEGAR. I don't think that we have any data one way or the other on very low levels of exposure to those chemical warfare agents.

Mr. SHAYS. When did you learn that our troops were exposed to low level chemicals? When did you learn it?

Ms. WINEGAR. I learned it at the same time everyone else did: when the announcement was made.

Mr. SHAYS. Were you outraged that you didn't know sooner?

Ms. WINEGAR. It is not within my jurisdiction. As I indicated earlier, my responsibility is in the research——

Mr. SHAYS. I am just asking you as an American who was—were you working at DOD at that time?

Ms. WINEGAR. Yes.

Mr. SHAYS. Were you outraged?

Ms. WINEGAR. I was surprised.

Mr. SHAYS. Not outraged?

Ms. WINEGAR. No, I don't think so.

Mr. SHAYS. You weren't outraged that CIA had this information and DOD had this information for years and didn't come forward until we were going to have a hearing to expose it? That didn't outrage you?

Ms. WINEGAR. No, I don't think so.

Mr. SHAYS. Why not?

Ms. WINEGAR. It takes an awful lot to outrage me.

Mr. SHAYS. See, that's the other reason why I think we need to move it away from this panel, because I want people, and I think others do, who get outraged a little sooner. They are not outraged when soldiers come to them that are sick and describe their illnesses and say an alarm went off.

See, I asked you about detection because I want to know how we detect it on the body. But we had detections. We had equipment that a lot of soldiers were given. They didn't go on before the war, they went on during the war. Then we were told the hundreds of alarms that went off during the war were all false, because they weren't calibrated right, and then we had testimony from two sepa-

rate incidents from people with FOX equipment who said that we detect it with our FOX equipment, well-calibrated equipment. And then their superiors say, "well, they were mistaken." They were trained to do this, and they said that they were mistaken. So we just become very suspicious.

I wondered, Mr. Gerrity, how do we detect—Dr. Gerrity, I am sorry—how do we detect chemical exposure on the body?

Mr. GERRITY. There are a number of ways to do it depending upon what the chemical is, and so it is highly chemical specific. And some chemicals are very, very difficult to detect on the body.

Mr. SHAYS. Very difficult to detect?

Mr. GERRITY. Are very difficult to detect, especially after the exposure has occurred, because they may disappear rapidly from the body. For example, volatile organic compounds, because of their nature, tend to be expired through the breath and leave the body, so that hours, days later, you won't be able to detect them in the blood. However, there is a lot of research that is going on at EPA, and at the Centers for Disease Control and Prevention, trying to develop ways to relate the chemicals that we can measure in human bodies to atrial exposures that may have occurred but left to those body burdens.

Mr. SHAYS. So your testimony would be if you don't detect it right away, it is unlikely you are going to detect it?

Mr. GERRITY. Oh, no. It is highly chemical dependent. There are some chemicals, for example, that are highly fat soluble, that you can detect years after.

Mr. SHAYS. So some you can detect years after, but some you can't. How about the chemicals that Saddam had?

Mr. GERRITY. For example, sarin?

Mr. SHAYS. I am curious to know what you know he had.

Mr. GERRITY. Sarin is an anticholesterase agent. It binds up with acetylcholine and in a matter of days after an exposure, your levels of acetylcholine approach normal. The marker there is—actually, your level of acetylcholine is the marker of exposure. Now, there are research efforts that are going on——

Mr. SHAYS. So in sarin, if you don't detect it fairly quickly, it is very difficult to detect?

Mr. GERRITY. Sarin is very difficult to detect. Research funded by the Department of Defense, that was just recently published, from working on other ones where they have been able to look at the amount of sarin in Japanese victims of both Matsumoto and——

Mr. SHAYS. But the bottom line is if you don't detect them quickly, then you are likely not to be able to know?

Mr. GERRITY. Again, it is chemical dependent. But for sarin, that is true. I think one of the things, though, is that what we would like to know is whether—and we have asked for continued development on this—there are surrogate markers that might last longer.

Mr. SHAYS. Right. Just memory loss and other things that relate to—but what I am interested to first establish is that DOD didn't test our soldiers right after the war, did they, or during the war? They didn't test them. They came in and said the alarms are false, the FOX equipment is false and they didn't test. That is a fact, isn't it?

Mr. GERRITY. You would have to ask that of DOD.

Mr. SHAYS. DOD? I am really asking for the record.

Ms. WINEGAR. To the best of my knowledge, they did not test.

Mr. SHAYS. There was no testing. We had soldiers who described pretty horrific experiences. Soldiers telling us what they described to their doctors: alarms went off, SCUD missiles came in; alarms went off, we went undercover, into the bunker; alarms went off, going on, rather, and then the signal that the coast was clear. They came up, they tasted, they smelled, they spit up blood, threw up and had rashes, and ran down. They testified to that under oath. They testified that they told the VA doctors that.

What—why—I don't need to ask that question. I don't want to go over the past in that sense. What I want to go over is just the fact that it is established that the VA didn't respond and make any assumptions that it might be chemical exposure, in spite of the fact that Saddam Hussein had chemicals and used them on civilians and Iranians.

My question is this: What test did the VA do to see if our troops were exposed to chemicals? Dr. Gerrity. The DOD didn't test.

Mr. GERRITY. Certainly by the time soldiers were coming back to the United States, there would be no tests that could adequately measure levels of exposure to sarin. However, the Department of Veterans Affairs did establish a clinical program focusing on neurological outcomes at the Birmingham VA, looking specifically at the question of whether or not veterans may have been exposed to chemical warfare.

Mr. SHAYS. I thought they were. The problem was that we didn't really do—we didn't have in the protocol early on to even ask them about chemical exposure. Specifically, we had it in places like New Haven—excuse me, West Haven—because one of the doctors at the VA was an environmental scientist from Yale who had some expertise, so he introduced some questioning.

The point I am trying to get to is this: We didn't—it is my understanding that—so correct me if I'm wrong—that if we don't—that some chemicals you can't detect even early on for chemical exposure; others you can early on. But in many cases, the longer time that passes, the more difficult it is to detect chemical exposure. Now they may have the effects of chemical exposure, but you can't detect the chemical, is that correct?

Mr. GERRITY. That is correct.

Mr. SHAYS. So the challenge, it seems to me in our protocol now, is to—and it is even more so with biological agents—is this right, Dr. Barrett and Dr. Newton, or Dr. Fuessner? Biological exposure. You wouldn't know that there was a biological agent out there providing exposure, would you, at low level?

Ms. WINEGAR. I think the converse is true. Quite often, exposure to a biological agent leads to a specific antibody response that may last for quite some time, whereas that is not true for exposure to chemical agents, simply because of the amount of material required.

Mr. SHAYS. So it is easier to detect biological exposure, low level?

Ms. WINEGAR. In people that have been exposed, I believe so, yes.

Mr. SHAYS. Would that be the testimony of all of you? Dr. Newton.

Ms. NEWTON. It is outside the purview of my institute. I would have to get the——

Mr. SHAYS. Do you have any background?

Ms. NEWTON. My degree is in biochemistry, but in my institute we work on chemical exposures, not biological.

Ms. BARRETT. I have no background on that. I would like to add some information regarding——

Mr. SHAYS. Sure. I am sorry, I should have asked both of you. Let me ask both of you in terms of detection of chemical exposure. I apologize.

Ms. BARRETT. There was CDC involvement early on. At the time, the exposure of concern was oil well-fire smoke, and there was very early involvement of sending a group of scientists over and doing measurements of volatile organic compounds, both in the theater of operations and from the base camp. I think CDC also has quite a bit of expertise in doing measurement of chemical exposures and looking at biomeasurement, biomarkers.

Mr. SHAYS. So do you concur with the answer, though, that some chemicals cannot be easily detected even after acute exposure and that some can, and that over time it is very difficult to get any detection?

Ms. BARRETT. Yes, I agree with that. I think it also points to the importance of trying to develop better biomarkers. I know our lab is very involved in this issue and is very interested in trying to develop a rapid assessment battery that could be used for future deployments, where you could have immediate assessment of whether troops were exposed to chemicals and get a very rapid turnaround on, you know, up to 150 different types of chemicals.

Mr. SHAYS. You all are under oath, and I only say this because I am going to ask a question that I want you to really think about before you answer.

There have been studies of the viability of our masks. Are any of you aware—I don't want you to go into them, because they are classified. But have any of you heard or read any reports on the viability of our masks? I would ask each of you.

Dr. FEUSSNER. No, sir.

Mr. SHAYS. OK.

Mr. GERRITY. No.

Ms. WINEGAR. Yes.

Mr. SHAYS. OK.

Ms. BARRETT. No.

Ms. NEWTON. No.

Mr. SHAYS. Doctor, don't you think it is important that—excuse me. Dr. Winegar, don't you think it is important that others that have to deal with this issue should know about these studies? Do you think that these studies should be made available to the VA?

Ms. WINEGAR. I certainly think that the relevant information that is needed regarding possible failures of masks which would lead to subsequent exposure is something that is generally known. It is not only the intactness——

Mr. SHAYS. What is generally known?

Ms. WINEGAR. That sometimes the masks don't fit perfectly, and that therefore they could leak.

Mr. SHAYS. Well, we can't get into the issue of the studies, but I have a feeling that you are aware that the studies go into more than whether they fit properly.

Ms. WINEGAR. Yes, that is correct.

Mr. SHAYS. And the question I am asking is should someone like Dr. Feussner and Dr. Barrett and Dr. Newton and Dr. Gerrity, shouldn't they be aware of these studies? Do you all have a security clearance?

Ms. BARRETT. No.

Dr. FEUSSNER. No, sir.

Mr. GERRITY. No, sir.

Mr. SHAYS. You don't have security clearances?

Dr. FEUSSNER. No, sir.

Mr. SHAYS. You see, my problem is there are studies out there that I think people should get and see and evaluate, and you are not even allowed to see them. I find that incomprehensible.

Let me take one more line of questioning and then we will get to you again, Mr. Sanders.

There is a question on whether our studies have not been focused too much on trying to find the smoking gun, even if it is chemical, and that it should be more focused on treatment and treatment outcomes. Dr. Feussner, why don't you respond to that.

Dr. FEUSSNER. Well, I've indicated before that we have program announcements that are open-ended to solicit research for treatment trials. We have convened a planning group to plan a trial in the area of chronic fatigue syndrome and fibromyalgia. We are quite receptive to trying to plan an antibiotic trial, and Mr. Sanders has volunteered to help me with that. And we have treatment trials under way, at least one treatment trial under way for posttraumatic stress disorder that we began in, I believe, June or September 1996. The reason we released the program announcement was to make it clear that there is essentially an open-ended solicitation for treatment trials. We made the criteria for those trials, I think explicit.

The way that VA would typically go about planning these trials is we would convene a planning committee that would bring in whatever expertise is required to plan the study; we would assign it to one of our coordinating centers. We have four such centers around the country who would facilitate the methodological, statistical, and data management issues. The completed proposals then are submitted for peer review by our Cooperative Studies Evaluation Committee. If they are approved, then we would initiate them.

So that is the process that exists. The program announcement opens the door, in my view, to trials, at least on subsets of patients who can be defined. As I said earlier, they require that the patients be definable, that the treatment protocols be replicable and explicit, and that the outcome measures be credible. Other than that, I think it is an open opportunity.

Mr. SHAYS. But do you think that most of our research is more toward trying to find the cause and less—or more on trying to find treatment and focusing on treatment outcomes?

Dr. FEUSSNER. I think that we have not had research efforts to systematically approach treatment issues.

Mr. SHAYS. So we need to do more on that?

Dr. FEUSSNER. Yes, sir.

Mr. SHAYS. Let me just—one last point. I am sorry, but I want to get on the record—the VA officials, and I should have gotten the name of the individual in the report—Dr. Murphy, described, characterized the registry as "a very crude health surveillance tool," and a primary source of primary hypotheses for subsequent research.

I want to know what role the registry plays, the Gulf War Health Registry plays in our research?

Dr. FEUSSNER. Specifically regarding treatment?

Mr. SHAYS. Just in terms of guiding any research.

Dr. FEUSSNER. Well, I think that it is—it collects information on patients, it identifies symptoms; issues of fatigue, issues of myalgias and muscle problems, issues relating to cognitive impairment have been detected on the registry. I think that those problems are potential treatment targets. As I say, my impression is that patients have been getting treatments that are symptom-based, but there have not been systematic clinical research treatment protocols that we have embarked on as yet.

Mr. SHAYS. I will just conclude by making a statement. I had Dr. Rosker who told me he was not aware of the two studies I made reference to in regards to the viability of the masks. He told me that he would work hard to have them released and put on the Internet, and it still hasn't been done. And when people like yourself don't have access to those studies, I find it beyond my patience.

I am going to personally write the President of the United States to ask him to intervene. I am going to ask you, Dr. Winegar, because you are aware of those studies, to make sure that we find a way that people in the VA get to see these studies, and I am going to pursue this. This is classified information that I can't disclose publicly, other than to say it exists, which I am allowed to do. And I am determined, after 5 or 6 years, that these reports be made public, unless someone can tell me why there is a national interest reason why it can't be, and why someone like Dr. Feussner can't get access to that report. Reports, two. Excuse me, two.

You are on.

Mr. SANDERS. I will be very brief, because I look forward to hearing the next panel.

No. 1, I look forward to working with you, Dr. Feussner. We can maybe just chat for a few minutes and then decide how we will proceed.

My question, my brief question to Dr. Winegar, maybe you answered that in terms of what Mr. Kucinich was asking, but I am still not quite clear. I hope very much for a dozen different reasons that there is not a war in the Gulf, but what is the position of the DOD regarding pyridostigmine bromide and the administration of that drug to the men and women who are over there right now? Are you asking a waiver from FDA? What is going on with that?

Ms. WINEGAR. No. We have no plans at this time to use pyridostigmine, nor have we made any request to the FDA for any waivers.

Mr. SANDERS. OK. So you are pretty definitive on that. At this point there are no plans?

Ms. WINEGAR. That is correct.

Mr. SANDERS. What about your response to the FDA filing in September? Does that mean anything to you?

Ms. WINEGAR. Our response to the interim rule, or our response——

Mr. SANDERS. Yes.

Ms. WINEGAR. Yes. I indicated that we would make that available to you.

Mr. SANDERS. You would make that available to us?

Ms. WINEGAR. Yes.

Mr. SANDERS. But what I am hearing you saying is that in terms of the present military situation, you have no—you are not intending to go to the FDA for the waiver of the use of pyridostigmine bromide?

Ms. WINEGAR. That is correct.

Mr. SANDERS. Thank you. That's all I have,

Mr. Chairman.

Mr. SHAYS. I do want to say to you that I know that there is enough blame to go around on this issue. Congress was asleep, I was asleep, we all were asleep on this issue. My big concern is the eagerness in which we try to undo the past and move forward. With that, I thank all of you for your participation.

We will now call on our second panel. We appreciate the patience of our second panel, as well as the patience of our first panel.

Dr. FEUSSNER. Thank you, sir.

Mr. SHAYS. Our panel consists of testimony from five people and six will sit on the panel. Excuse me, four testimonies: Dr. Heivilin, Director of Planning and Reporting, General Accounting Office, accompanied by Kwai Chan, Director of Special Studies Evaluation, General Accounting Office, and Sushil Sharma, Assistant Director of Special Studies and Evaluation, General Accounting Office; Dr. Robert Haley, director, Epidemiology and Scientific Graphics Laboratory, University of Texas Southwestern Medical Center; Dr. Daniel Clauw, chief of rheumatology, Georgetown University School of Medicine; and Dr. William Reeves, Branch Chief, Viral Exanthems, Center for Disease Control and Prevention.

[Witnesses sworn.]

Mr. SHAYS. For the record, all witnesses have responded in the affirmative.

We will start, I think, by the way I called you. Do you remember how we started? We will start with Dr. Heivilin.

STATEMENTS OF DONNA HEIVILIN, PH.D., DIRECTOR, PLANNING AND REPORTING, GENERAL ACCOUNTING OFFICE, ACCOMPANIED BY KWAI-CHEUNG CHAN, DIRECTOR, SPECIAL STUDIES AND EVALUATION, GENERAL ACCOUNTING OFFICE, AND SUSHIL SHARMA, PH.D., ASSISTANT DIRECTOR, SPECIAL STUDIES AND EVALUATION, GENERAL ACCOUNTING OFFICE; ROBERT HALEY, M.D., DIRECTOR, EPIDEMIOLOGY AND SCIENTIFIC GRAPHICS LABORATORY, UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER; DANIEL CLAUW, M.D., CHIEF OF RHEUMATOLOGY, GEORGETOWN UNIVERSITY SCHOOL OF MEDICINE; AND WILLIAM REEVES, M.D., BRANCH CHIEF, VIRAL EXANTHEMS, CENTER FOR DISEASE CONTROL AND PREVENTION

Ms. HEIVILIN. Mr. Chairman, members of the subcommittee, I am pleased to be here to discuss GAO's evaluation of the Federal strategy to research Gulf war illnesses. We reported our findings on this strategy in June 1997 as part of our response to a congressional mandate. However, before I discuss our findings, I would like to provide a little background information.

The United States troops were reportedly exposed before, during, and after the Gulf war to a variety of risk factors. The Federal Government, primarily through DOD and VA, has sponsored a variety of research on the Gulf war veterans' illnesses.

Most of the research sponsored by the Federal Government is characterized as epidemiological. The objectives of epidemiologic research are to determine the extent of the disease and illnesses in the populations and subpopulations, the causes of the disease and its modes of transmission, the natural history of the disease, and the basis for developing preventive strategies or interventions.

I would like to point out that epidemiological research is a useful tool for determining the cause of illness and effective treatment. However, to conduct such research, investigators must follow three principles: first, they must specify diagnostic criteria which can be used to reliably determine who has the disease or condition being studied and who does not, and select appropriate controls; that is, people who do not have the disease or condition, for comparative purposes.

Second, the investigators must have valid and reliable methods of collecting data on the past exposures of those in the study, and possible factors that may have caused the symptoms. It is particularly critical when studying low-level or intermittent exposure to drugs or chemicals to be able to obtain dose-specific exposure information as well as data on the intensity and duration of the exposure, and it is difficult to detect any effects of the exposure when the type, amount, and extent of the exposure of individuals is reported incorrectly.

Third, it is important that a sufficient number of persons be studied to have a reasonable likelihood of detecting any relationship between exposures and disease.

I would like to turn to our findings at this point, and I have five that I want to report. First, the Government was not proactive in researching Gulf war illnesses. Although the veterans' health problems began to surface in the early 1990's, the vast majority of the research was not initiated until 1994 or later, and much of it re-

sponded to legislative requirements. For example, the three studies on low-level chemical exposure which were funded by the coordinating board were funded in direct response to congressional mandate.

By the time the research was accelerated and broadened, opportunities had been missed to collect critical data that cannot be accurately reconstructed.

Second, the Government's early research emphasized stress as a cause and gave other hypotheses such as multiple chemical sensitivity short shrift. Although veterans raised concerns about potential chemical exposure soon after the war, the Federal research plan was not modified to include these concerns until 1996, when DOD acknowledged that potential exposures to chemical agents at Khamisiyah Iraq.

Third, in contrast, the private sector pursued research on low-level exposures to certain chemical warfare agents or industrial chemical compounds. Although the government argued that there was no evidence that low-level exposure can have adverse health effects, we found a substantial body of research which suggests otherwise.

For example, abundant evidence from animal experiments, studies of accidental human exposures, and epidemiological studies of humans shows that low-level exposures to certain organophosphorous compounds, including sarin nerve agents to which our troops were exposed, can caused delayed chronic neurotoxic effects. In addition, research that we reviewed also indicates that agents like pyridostigmine bromide, also called PB, which the Gulf war veterans took to protect themselves against the immediate life-threatening effects of nerve agents, may alter the metabolism of organophosphates in ways that activate their delayed chronic effects on the brain.

Fourth, the Government funded little research on treatment.

Finally, while the Federal Government research strategy heavily emphasized epidemiological research, we believe that the ongoing epidemiological research cannot provide precise, accurate, and conclusive answers regarding the causes of the veterans' illnesses because of methodological problems. To date, most of the studies completed are epidemiologic studies and at this point there has been no light shed on causes or possible treatments.

There are a number of reasons for this. First, researchers have found it extremely difficult to gather information about many key exposures. For example, medical records on the use of PB tablets and vaccinations to protect against chemical-biological warfare exposures are inadequate. Second, Gulf war veterans were typically exposed to a wide array of agents, making it difficult to isolate and characterize the effects of individual agents or to study their combined effects. Third, most of the epidemiological studies on Gulf war veterans' illnesses have relied only on self reports for measuring most of the agents to which veterans might have been exposed. Fourth, the information gathered from Gulf war veterans years after the war may be inaccurate or biased. There is often no straightforward way to test the validity of self-reported exposure information, making it impossible to separate bias and recalled in-

formation from actual differences in the frequency of exposures. As a result, findings from these studies may be spurious or equivocal.

Fifth and last, classifying the veterans' symptoms and identifying the illnesses have been difficult. From the outset, the symptoms reported have been varied and difficult to classify into one or more distinct groups. Moreover, several different diagnoses might provide plausible explanations for some of the specific health complaints. It has thus been difficult to develop one or more working case definitions to describe veterans' undiagnosed complaints.

Given these methodological limitations which are faced in the epidemiological studies and because of the numbers of veterans who experienced illnesses that might be related to their Gulf war service, we recommended in our report that the Secretary of Defense, with the Secretary of the VA, give greater priority to research on effective treatment for ill veterans and on low-level exposures to chemicals and other agents, as well as their interactive effects, and less priority to further epidemiological studies.

Mr. Chairman, that concludes my prepared remarks. I will be happy to answer any questions you may have.

[The prepared statement of Ms. Heivilin follows:]

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here today to discuss our evaluation of the federal strategy to research Gulf War illnesses. We reported our findings on this strategy in June 1997 as part of our response to a congressional mandate regarding the government's clinical care and medical research programs relating to illnesses suffered by Gulf War veterans.[1] I will first summarize our findings and provide some background information on the government's research program before giving you the details on our findings.

RESULTS IN BRIEF

In short, we found that

(1) the government was not proactive in researching Gulf War illnesses;

(2) the government's early research emphasized stress as a cause for Gulf War veterans' illnesses and gave other hypotheses, such as multiple chemical sensitivity, little attention;

[1]Gulf War Illnesses: Improved Monitoring of Clinical Progress and Reexamination of Research Emphasis Are Needed (GAO/NSIAD-97-163, June 23, 1997).

(3) in contrast, the private sector pursued research on the health effects of low-level exposures to certain chemical warfare agents or industrial chemical compounds;

(4) government research used an epidemiological approach, but little research on treatment was funded; and

(5) most of the ongoing epidemiological research focusing on the prevalence or causes of Gulf War-related illnesses will not provide conclusive answers, particularly in identifying risk factors or potential causes due to formidable methodological and data problems.

BACKGROUND

U.S. troops were reportedly exposed before, during, and after the Gulf War to a variety of potentially hazardous substances. These substances include decontaminating and protective compounds used without proper safeguards (particularly decontaminating solution 2, or DS2, and chemical agent resistant coating); diesel fuel used as a sand suppressant in and around encampments, fuel oil used to burn human waste; fuel in shower water; and leaded vehicle exhaust used to dry sleeping bags. Other potential hazards included infectious diseases (most prominently leishmaniasis, a parasitic infection); pyridostigmine bromide and vaccines (to protect against chemical and biological weapons); depleted uranium (contained in certain

ammunition and in residues from the use of this ammunition); pesticides and insect repellents, chemical and biological warfare agents; and compounds and particulate matter contained in the extensive smoke from the oil-well fires at the end of the war. Over 100,000 of the approximately 700,000 Gulf War veterans have participated in health examination programs that the Department of Defense (DOD) and the Department of Veterans Affairs (VA) established between 1992 and 1994. Of those veterans examined by DOD and VA, nearly 90 percent have reported a wide array of health complaints and disabling conditions, including fatigue, muscle and joint pain, gastrointestinal complaints, headaches, depression, neurologic and neurocognitive impairments, memory loss, shortness of breath, and sleep disturbances. Some of the veterans fear that they are suffering from chronic disabling conditions because of exposure during the war to substances with known or suspected health effects.

The federal government, primarily through DOD and VA, has sponsored a variety of research on Gulf War veterans' illnesses. DOD's research is one component of a broader agenda coordinated under the aegis of the Persian Gulf Veterans' Coordinating Board (PGVCB), which comprises the Secretaries of the Department of Health and Human Services, VA, and DOD. The details of this agenda are described in the PGVCB publication entitled A Working Plan for

Research on Persian Gulf Veterans' Illnesses.[2] This agenda was developed in response to an Institute of Medicine conclusion that the DOD and VA should determine specific research questions that need to be answered and design epidemiologic research to these questions. Accordingly, most of the research sponsored under this agenda is characterized by PGVCB as epidemiological.

The objectives of epidemiologic research are to determine the extent of diseases and illness in the population or subpopulations, the causes of disease and its modes of transmission, the natural history of disease, and the basis for developing preventive strategies or interventions.[3] To conduct such research, investigators must follow a few basic generally accepted principles.

First, they must specify diagnostic criteria to (1) reliably determine who has the disease or condition being studied and who does not and (2) select appropriate controls (people who do not have the disease or condition).

Second, the investigators must have valid and reliable methods of collecting data on the past exposure(s) of those in the study and possible factors that may have caused the symptoms. The need for

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[2]A Working Plan for Research on Persian Gulf Veterans' Illnesses, (First Revision), Department of Veterans Affairs, November 1996.

[3]A. M. Lilienfeld and D. E. Lilienfeld, Foundations of Epidemiology (New York: Oxford University Press, 1980).

accurate, dose-specific exposure information is particularly critical when low-level or intermittent exposure to drugs, chemicals, or air pollutants is possible. It is important not only to assess the presence or absence of exposure but also to characterize the intensity and duration of exposure. To the extent that the actual exposure of individuals is misclassified, it is difficult to detect any effects of the exposure. Another means of linking environmental factors to disease is to determine whether or not evidence shows that as the exposure increases, the risk of disease also increases. However, this dose-response pattern can be detected only if the degree of exposure among different groups can be determined.

Finally, in addition to specific case definition and dose-specific exposure information with known accuracy, it is important that a sufficient number of persons be studied to have a reasonable likelihood of detecting any relationship between exposures and disease. To the extent that this relationship is subtle or obscured in particular investigations by "loose" case definition (that is, a case definition that is too broad and encompasses different types of illnesses) or problems in measuring exposure, larger samples would be required. For example, the Institute of Medicine noted that "very large groups must be studied in order to identify the small risks associated with low levels of exposure, whereas a relatively small study may be able to detect the effect of heavy or sustained exposure to a toxic substance. In this way,

a study's precision or statistical power is also linked to the extent of the exposure and the accuracy of its measurement. Inaccurate assessment of exposure can obscure the existence of such a trend and thus make it less likely that a true risk will be identified."[4] Similarly, if an exposure had an effect only on a particular birth defect for example, this effect might be missed by studying all birth defects as a group.

GOVERNMENT WAS NOT PROACTIVE IN RESEARCHING CAUSES OF GULF WAR VETERANS' ILLNESSES

Although Gulf War veterans' health problems began surfacing in the early 1990s, the vast majority of research was not initiated until 1994 or later. And much of that research responded to legislative requirements or external reviewers' recommendations. As noted by external reviewers, since federal research goals and objectives were not identified until 1995, after most research activities had been initiated, the research reflects a rationalization of ongoing activity rather than a research management strategy.

The government's 3-year delay complicated the researchers' tasks and limited the amount of completed research available. Of the 91 studies receiving federal funding, over 70 had not been completed

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[4]Veterans and Agent Orange: Update 1996 (Washington, D.C.: Institute of Medicine, 1996), pp. 99-100.

at the time of our review. The results of some studies will not be available until after 2000.

By the time research was accelerated and broadened, opportunities had been missed to collect critical data that researchers cannot accurately reconstruct. Even efforts to measure the chemical content of the oil-fire smoke, begun only 2 months after the fires began burning, were initiated after most troops had left the affected areas and the climatological dynamics were different. Consequently, researchers had to use statistical models of the behavior of smoke plumes in order to infer the ground-level exposures experienced by the large numbers of troops who had departed by the time they began collecting data. Even if such models could accurately explain the behavior of the smoke plumes, they had not been validated as measures of individual exposure, and their accuracy for this purpose could not be presumed. Similar and even more serious problems were caused in the measurement of other exposures by the failure to collect data promptly and maintain adequate records.[5]

The delay in starting research has also hindered accurate reporting of exposures by Gulf War veterans. At the time of our review, 6

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[5]See Defense Health Care: Medical Surveillance Has Improved Since the Gulf War, but Results in Bosnia Are Mixed (GAO/NSIAD-97-136, May 13, 1997) and Institute of Medicine, Health Consequences of Service During the Persian Gulf War: Recommendations for Research and Information Systems, p. 5 (Washington, D.C.: National Academy Press), 1996.

years after the war ended, questionnaires were being distributed requesting information from veterans on their exposures to certain agents during the war.

INITIAL GOVERNMENT RESEARCH EMPHASIZED STRESS; OTHER HYPOTHESES WERE NOT PURSUED UNTIL LATER

Early federal research appeared to emphasize risks associated with psychological factors such as stress. To support this emphasis, DOD pointed out that the psychological state of mind can influence physical well-being. DOD also pointed to a recent argument that from the American Civil War onward (and perhaps even earlier), a small number of veterans have reacted to the stress of war by suffering symptoms similar to those reported by some Gulf War veterans.[6]

Of the 19 studies initiated before 1994, roughly half focused on exposures to stress or the potential for posttraumatic stress disorder (PTSD) among returning troops.[7] As late as December 1996, the Presidential Advisory Committee noted that "stress is the risk

[6]K.C. Hyams et al., "War Syndromes and Their Evaluation: From Civil War to the Persian Gulf War," Annals of Internal Medicine, vol. 125 (1996), pp. 398-405.

[7]An additional 3 of the 19 studies did not provide information about veterans' illnesses but were instead building databases or methods to be used in later studies. Notably, according to PGVCB, none of these 3 studies had been completed as of June 1997.

factor funded for the greatest fraction of total - 32 studies (30 percent)."[8]

While research on exposures to stress received early emphasis, other hypotheses have received scant support. In its Final Report, the Institute of Medicine discusses the evidence for a number of disease hypotheses, including multiple chemical sensitivity, fibromyalgia, and organophosphate-induced delayed neuropathy. However, the federal research program has supported only one study of the relationship between symptoms reported by veterans and fibromyalgia. In addition, prior to October 1996, only one of the studies initiated in response to Gulf War veterans' illnesses focused on the health effects of potential exposures to chemical warfare agents.[9] While multiple studies of the role of stress in the veterans' illnesses have been supported with federal research dollars, other hypotheses have been pursued largely outside the federal research program.

Although veterans raised concerns about potential chemical exposures soon after the war, the federal research plan was not modified to include an investigation of these concerns until 1996,

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[8]Presidential Advisory Committee on Gulf War Veterans' Illnesses, Final Report, p. 34 (Washington D.C.:GPO), December 1996.

[9]This study of the impacts of sulfur mustard agent is a collaborative effort between the Portland VA Medical Center and the Oregon Health Sciences University. The principal investigator for the study pointed out that the possibility of chemical warfare exposure seemed plausible even in 1994 when he sought initial funding for this research.

when DOD acknowledged potential exposures to chemical agents at Khamisiyah, Iraq. The failure to fund such research cannot be traced to an absence of investigator-initiated submissions. According to DOD officials, three recently funded proposals on low-level chemical exposure had previously been rejected.[10]

PRIVATE SECTOR PURSUED VARIETY OF HYPOTHESES

A substantial body of research suggests that low-level exposures to chemical warfare agents or chemically related compounds, such as certain pesticides, are associated with delayed or long-term health effects. For example, abundant evidence from animal experiments, studies of accidental human exposures, and epidemiologic studies of humans shows that low-level exposures to certain organophosphorus compounds, including sarin nerve agents to which our troops may have been exposed, can cause delayed, chronic neurotoxic effects. This syndrome is characterized by clinical signs and symptoms manifested 4 to 21 days after exposure to organophosphate compounds. The symptoms of delayed neurotoxicity can take at least two forms: (1) a single large dose may cause nerve damage with paralysis and later spastic movement, and (2) repetitive low doses may damage the brain, causing impaired concentration and memory,

[10]The three previously unfunded proposals address central nervous system targets for organophosphates, development of a DNA-based method for assessing exposures to mustard agent, and work on the pharmacokinetics of the nerve agent VX.

depression, fatigue, and irritability. These delayed symptoms may be permanent.

As early as the 1950s, studies demonstrated that repeated oral and subcutaneous exposures to neurotoxic organophosphates produced delayed neurotoxic effects in rats and mice. In addition, German personnel who were exposed to nerve agents during World War II displayed signs and symptoms of neurological problems even 5 to 10 years after their last exposure. Long-term abnormal neurological and psychiatric symptoms as well as disturbed brain wave patterns have also been seen in workers exposed to sarin in sarin manufacturing plants.[11] The same abnormal brain wave disturbances were produced experimentally in primates by exposing them to low doses of sarin.[12]

Delayed, chronic neurotoxic effects were also seen in animal experiments after the administration of organophosphates.[13] These

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[11]F. H. Duffy et al., "Long-Term Effects of an Organophosphate Upon the Human Electroencephalogram," Toxicology and Applied Pharmacology, vol. 47 (1979), pp. 161-175, and F.R. Sidell, "Soman and Sarin: Clinical Manifestations and Treatment of Accidental Poisoning by Organophosphates," Clinical Toxicology, vol. 7 (1979), pp. 1-17.

[12]J. L. Burchfield et al., "Persistent Effect of Sarin and Diodrin Upon the Primate Electroencephalogram," Toxicology and Applied Pharmacology, vol. 35 (1976), pp. 365-379.

[13]M. B. Abou-Donia, "Organophosphorus Ester-induced Delayed Neurotoxicity," Annual Review of Pharmacology Toxicology, vol. 21 (1981), pp. 511-548, and M. K. Johnson, "The Target for Initiation of Delayed Neurotoxicity by Organophosphorus Esters: Biochemical Studies and Neurotoxicological Applications," Review of Biochemistry and Toxicology, vol. 4 (1982), pp. 141-212.

effects include difficulty in walking and paralysis. In recent experiments, animals given a low dosage of the nerve agent sarin for 10 days showed no signs of immediate illness but developed delayed chronic neurotoxicity after 2 weeks.[14]

It has been suggested that the ill-defined symptoms experienced by Gulf War veterans may be due in part to Organophosphate-induced Delayed neuropathy.[15] This hypothesis was tested in a privately supported epidemiological study of Gulf War veterans.[16] In addition to clarifying the patterns among veterans' symptoms by use of statistical factor analysis, this study concluded that vague symptoms of the ill veterans are associated with objective brain and nerve damage compatible with the known chronic effects of

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[14]K. Husain et al., "Assessing Delayed Neurotoxicity in Rodents after Nerve Gas Exposure," Defense Science Journal, vol. 44 (1994), pp. 161-164; K. Husain et al., "Delayed Neurotoxic Effects of Sarin in Mice After Repeated Inhalation Exposure," Journal of Applied Toxicology, vol. 13 (1993), pp. 143-145; and K. Husain et al., "A Comparative Study of Delayed Neurotoxicity in Hens Following Repeated Administration of Organophosphorus Compounds," Indian Journal of Physiology and Pharmacology, vol. 39 (1995), pp. 47-50.

[15]R. W. Haley et al., "Preliminary Findings of Studies on the Gulf War Syndrome," Presentations to the Intergovernmental Coordinating Board for the Gulf War Illnesses and the Staff of the Presidential Advisory Committee on Gulf War Veterans' Illnesses," September 16, 1995, and R. W. Haley, "Organophosphate-Induced Delayed Neurotoxicity," Internal Medicine Grand Rounds, University of Texas Southwestern Medical Center, Dallas, Texas, October 10, 1996.

[16]This research, conducted at the University of Texas Southwestern Medical Center, has been supported in part by funding from the Perot Foundation.

exposures to low levels of organophosphates.[17] It further linked the veterans' illnesses to exposure to combinations of chemicals, including nerve agents, pesticides in flea collars; DEET and highly concentrated insect repellents; and pyridostigmine bromide tablets.

Finally, research that we reviewed also indicates that agents like pyridostigmine bromide, which some Gulf War veterans took to protect themselves against the immediate, life-threatening effects of nerve agents, may alter the metabolism of organophosphates in ways that activate their delayed, chronic effects on the brain.[18] Moreover, exposure to combinations of organophosphates and related chemicals like pyridostigmine or DEET has been shown in animal studies to be far more likely to cause morbidity and mortality than any of the chemicals acting alone.[19]

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[17]R. W. Haley et al., "Is There a Gulf War Syndrome? Searching for Syndromes by Factor Analysis of Symptoms," Journal of American Medical Association, vol. 277 (1997), pp. 215-222; R. W. Haley et al., "Evaluation of Neurologic Function in Gulf War Veterans: A Blinded Case-Control Study," Journal of American Medical Association, vol. 277 (1997), pp. 223-230; and R. W. Haley et al., "Self-reported Exposure to Neurotoxic Chemical Combinations in the Gulf War: A Cross-sectional Epidemiologic Study," Journal of American Medical Association, vol. 277 (1997), pp. 231-237.

[18]C. N. Pope and S. Padilla, "Potentiation of Organophosphorus Delayed Neurotoxicity," Journal of Toxicology and Environmental Health, vol. 31 (1990), pp. 261-273.

[19]M. B. Abou-Donia et al., "Increased Neurotoxicity Following Concurrent Exposure to Pyridostigmine Bromide, DEET, and Chlorpyrifos," Fundamental of Applied Toxicology, vol. 34 (1996), pp. 201-222. and M. B. Abou-Donia et al., "Neurotoxicity Resulting From Coexposure to Pyridostigmine Bromide, Deet, and Permethrin," Journal of Toxicology and Environmental Health, vol. 48 (1996), pp. 35-56.

Despite the fact that in 1994, Congress directed DOD and VA to research treatments for ailing Gulf War veterans, such research has largely not taken place. While 61 of the 91 federally sponsored studies (67 percent) were classified as epidemiological by the Persian Gulf Veterans Coordinating Board, only three of the studies had focused primarily on identification and improvement of treatments for these illnesses.

FORMIDABLE METHODOLOGICAL PROBLEMS HAVE HAMPERED RESEARCH

Our review indicated that most of the epidemiological studies have been hampered by data problems and methodological limitations and consequently may not provide conclusive answers in response to their stated objectives, particularly in identifying risk factors or potential causes.

Measurement of Exposures Is Problematic

The research program to answer basic questions about the illnesses that afflict Gulf War veterans has at least three major problems in linking exposures to observed illness or symptoms. First, it is extremely difficult to gather information about unplanned exposures (for example, oil-fire smoke and insects) that may have occurred in the Gulf. And DOD has acknowledged that records of planned or intentional exposures (for example, the use of vaccines and pyridostigmine bromide to protect against chemical/biological

warfare agents) were inadequate. Second, the veterans were typically exposed to a wide array of agents with commonly accepted health effects, making it difficult to isolate and characterize the effects of individual factors or to study their combined effects. Third, the passage of time following these exposures has made it increasingly difficult to have confidence in any information gathered through retrospective questioning of veterans.[20]

In part, the latter difficulty was created by the delayed release of information about detection of chemical warfare agents during the war as well as the delayed collection of exposure data. Five years passed before DOD acknowledged that American soldiers may have been exposed to chemical warfare agents shortly after the war ended in 1991 (at the Khamisiyah site). Moreover, although chemical detections by Czech forces are regarded as valid by DOD, the origin of the detected chemical agents has not been identified by either DOD or CIA. In the face of denials by DOD officials,

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[20]Large numbers of veterans questioned during their participation in the VA's health registry examination program reported they did not know whether they were exposed to certain agents. "Don't know" responses were greatest for nerve gas (64.9 percent), mustard gas (60.2 percent), depleted uranium (52.5 percent), chemical-agent resistant coating (47.8 percent), microwaves (32.8 percent), paints or solvents (24.9 percent), and pyridostigmine (21.1 percent). To the extent that a response of some kind reflects greater certainty, veterans were more confident in their reports regarding smoke from tent heaters, passive smoking, diesel or other petrochemical fumes, skin exposure to fuel, pesticides in cream or spray form, and burning trash or feces, each of which resulted in fewer than 11 percent of respondents reporting "don't know." While such confidence does not necessarily mean that the reports are accurate, the lack of confidence in responding to questions about some exposures raises questions about studies relying on self-reports to assess these exposures.

several researchers told us that they had considered it pointless to pursue hypotheses that the symptoms may have been associated with exposures to chemical weapons.

When we asked investigators responsible for federally funded epidemiological research how they were collecting data on the various elements to which Gulf veterans may have been exposed, they indicated that they had no means other than self-reports for measuring most of these elements. This reliance on self-reports was not much less for elements such as vaccines, for which the opportunity for record keeping clearly existed.[21]

Two problems are associated with reliance on self-reports for exposure assessments. First, recalled information may be inaccurate or biased after such a long time period; that is, some veterans may not remember that they were exposed to particular factors, while others may not have been exposed but nonetheless inaccurately report that they were. Information also may be biased if, for example, veterans who became sick following the war recalled their exposures earlier, more often, or differently from veterans who had not become sick. Second, there is often no straightforward way to test the validity of self-reported exposure information, making it impossible to separate bias from actual differences in exposure frequency.

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[21]Defense Health Care: Medical Surveillance Improved Since Gulf War, but Mixed Results in Bosnia (GAO/NSIAD-97-136).

Several investigators were also relying on a model developed by the U.S. Army Environmental Hygiene Agency for assessing exposures to components of oil-fire smoke through the combination of unit location data with information from models of the distribution of oil-fire smoke. However, this model requires the use of unit location as a proxy for exposure, and the validity of this approach is unknown. The Presidential Advisory Committee has noted, "DOD's Persian Gulf Registry of Unit Locations lacks the precision and detail necessary to be an effective tool for the investigation of exposure incidents."

Case Definition Is Complicated by Presence of Nonspecific Symptoms

Another major hurdle to the development of a successful research agenda has been the difficulty in classifying symptoms into one or more distinct illnesses. Some veterans complain of gastrointestinal pain, others report musculoskeletal pain or weakness, and still others report emotional or neurological symptoms. As explained previously, development of one or more specific case definition is essential to conducting certain types of epidemiological studies.

The VA collected some data on symptoms beginning in 1992 with the initiation of its registry. However, these efforts to collect information about symptoms and exposures from registry participants were limited and nonspecific. This constrained VA's potential use

of the information for improving understanding of the patterns of veterans' complaints. These data limitations were unfortunate, as detailed information about symptoms and exposures might have yielded earlier, more reliable analyses of the nature and causes of veterans' complaints and could have also assisted in developing working case definitions.

We also found that both the federally supported projects and the federal registry programs have generally failed to study the conjunction of multiple symptoms in individual veterans. Articles and briefing documents that we obtained from DoD and VA reported findings that addressed only the incidence of single symptoms and diagnoses. There were two exceptions. First, for an Air National Guard unit in Pennsylvania, the Center for Disease Control and Prevention developed an operational case definition, which was quite similar to the case definition of chronic fatigue syndrome. Second, the studies conducted by Haley et al. also focused on identifying symptom clusters.

For those ongoing, epidemiological studies that were built on case-control designs, we asked about how a case was defined. The specificity of this definition is important because a vague case definition can lead to considering multiple kinds of illnesses together. When this is done, it is not surprising to find no commonality of experience among the cases. Moreover, the use of specific case definition is particularly critical to achieving

meaningful results within this type of research design. At the same time, for the case definition to be relevant, it must fit the symptoms described by an important portion of the group being studied.

Sample Size

Most of the investigators we interviewed took steps to estimate the size of the sample they would require to have a reasonable expectation of detecting the effects of exposures to hazardous substances. However, many other variables were involved in such calculations, for example, the prevalence of exposures, some of which were unknown at the time the studies were planned. Thus, they had to make estimates within somewhat broad parameters.

Although steps were clearly taken to plan for an adequate sample size, some investigators reported difficulty in locating subjects due to factors beyond their control, such as the rate of referrals from VA examination centers or the rate of identification of subjects that fit highly specific case definitions. Moreover, other studies, such as those on specific birth defects, required extremely large samples.

CONCLUSIONS

The ongoing epidemiological research cannot provide precise, accurate, and conclusive answers regarding the causes of veterans' illnesses because of researchers' methodological problems as well as the following:

-- Researchers have found it extremely difficult to gather information about many key exposures. For example, medical records of the use of pyridostigmine bromide tablets and vaccinations to protect against chemical/biological warfare exposures were inadequate.

-- Gulf War veterans were typically exposed to a wide array of agents, making it difficult to isolate and characterize the effects of individual agents or to study their combined effects.

-- Most of the epidemiological studies on Gulf War veterans' illnesses have relied only on self-reports for measuring most of the agents to which veterans might have been exposed.

-- The information gathered from Gulf War veterans years after the war may be inaccurate or biased. There is often no straightforward way to test the validity of self-reported exposure information, making it impossible to separate bias in

recalled information from actual differences in the frequency of exposures. As a result, findings from these studies may be spurious or equivocal.

-- Classifying Gulf War veterans' symptoms and identifying their illnesses have been difficult. From the outset, the symptoms reported have been varied and difficult to classify into one or more distinct groups. Moreover, several different diagnoses might provide plausible explanations for some of the specific health complaints. It has thus been difficult to develop one or more working case definitions to describe veterans undiagnosed complaints.

RECOMMENDATIONS

Because of the numbers of veterans who have experienced illnesses that might be related to their service during the Gulf War, we recommended in our report that the Secretary of Defense, with the Secretary of Veterans Affairs, give greater priority to research on effective treatment for ill veterans and on low-level exposures to chemicals and other agents as well as their interactive effects and less priority to further epidemiological studies.

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Mr. Chairman, that concludes my prepared remarks. I will be happy to answer any questions you may have.

(713019)

Mr. SHAYS. Thank you very much. I think we are now going to Dr. Haley.

Dr. HALEY. I am going to talk today as a private researcher out in the private world who has been working on this full-time for 4 years, but pretty much outside the Government realm, outside of the decisionmaking process, which gives me the advantage of not having been involved in the decisionmaking and influenced by it. On the other hand, I don't know how the decisions were made.

My overall impression of the Government's research effort, though I think well meant, particularly recently, and painstakingly thought out more recently, has really misfired and is showing little sign of getting back on track in a way that is really going to solve the problem, which I think is your concern. Here is why.

First of all, a little history. I think as our troops returned from the Gulf, it appears now in retrospect that about 10 to 20 percent of the 700,000 may have been affected by an epidemic disease. That is, there really may be a real disease. In anybody's book, that should have triggered an epidemic investigation. Now, that is not an epidemiologic study, in a broad sense, the types of studies that we have been seeing. There is a very carefully worked out "fire drill," you might say, that the CDC has been using for 30 years to investigate epidemics, and that has not been applied, except in one instance. Now, what is that?

Actually, it almost happened. Back in 1991, late 1991 and early 1992, the Navy epidemiology group in San Diego sent out teams and started looking at some of the affected units and performed initial descriptive epidemiology, and they came up with symptoms that might be a syndrome. What they didn't do, though, is write down a case definition, as my GAO colleagues have emphasized. That should have been the first step, and then we should have done a case-control study dividing people, possible exposed groups, into the cases meeting the case definition and controls, not meeting the case definition and we should have identified risk factors. This sounds theoretical, but this is the way it has been done for 30 years: Identify risk factors by doing careful questionnaires of self-reported exposures in the war, like being in the area where chemical alarms went off and so forth. Then, do analyses to see which of those risk factors are associated with being a case and not with being a control. In other words, they are significantly related with the cases.

Now, that is not definitive, but then you go a step further, and any risk factors that are positively associated like that, you then introduce those into animals in experiments, and if you get a positive—you reproduce the disease that you see in the people—then that is very strong evidence. That is the model that was used to solve hundreds and hundreds of epidemics over the last 30 years, such as Legionnaire's disease, toxic shock syndrome, AIDS, and on and on and on. This was not done for the Gulf war syndrome. This is the standard technique and it was not applied.

It almost was, though. Back in 1993, Dr. Ronald Blanck who was at Walter Reed, who is now the Army Surgeon General, was on that track and he commissioned Dr. Jay Sanford, who is one of the greatest military medical experts of this half of the century, also a good epidemiologist, had him formulate a case definition which

has been known as "the Sanford definition." It was written down, it was disseminated, and then something happened; we don't know what happened, but at that point, just as it was about to be used, the CCEP was inaugurated and we went off in the other direction of examining tens of thousands of Gulf war veterans with standard medical examinations that had no chance of finding neurotoxicity, OK? That, I think, took all of the interest and strength and money away from epidemic investigations.

At about that time, I think a far-reaching policy was established. I think that policy was that there is no single epidemic disease. That was based on no data, but that was decided. Second, that soldiers' symptoms are due to posttraumatic stress disorder. Third, that large epidemiologic studies, big statistical studies, should be done to show that this is really not hurting anybody; and fourth a public relations campaign should be waged to convince the American people and the scientific community that this is not really a problem. In other words, I believe it was decided in early 1994, that this is not a problem and we are going to make sure that it doesn't get mistaken to be one.

Accordingly—now this is very important. Accordingly, orders went down through the DOD and the VA medical authorities that a doctor may not write down the diagnosis of "Gulf war syndrome"; that may not be recorded in a medical record. If you look in the medical records, it is never recorded. I have talked to many medical people in the DOD and the VA who say, "Oh, well, you know, we cannot write that down. That is not allowed."

So this became the policy. I believe that what happened after that was a pervasive exercise in what I call "conservation of belief." That is, all incoming information that would challenge this belief, this policy, was unconsciously filtered out, and I think by well-meaning people. All studies were designed to confirm the lack of physical effects, again, by well-meaning people who probably didn't realize that that is what was happening, and research delving directly into hypotheses of environmental causes was discouraged subtly by lack of funding, and by excessive criticism that would never have been leveled at epidemiologic studies of epidemics from CDC back in the past.

Now, this had a number of systemic effects. Let me list some of them in whatever time that we want to go over this. First, since no case definition of Gulf war syndrome was sanctioned and, in fact, doctors were forbidden to write it down in an individual patient's records, the CCEP and the VA registries found only all of those other things that veterans might have in addition to their Gulf war syndrome—you know, their stomach ulcer, their lung disease, whatever, and they found no Gulf war syndrome. Why? Because they were forbidden to write it down. This led to the ubiquitous expression that we hear all the time: "There is no single disease, only a variety of symptoms." That is a self-fulfilling prophecy, and a reaffirmation of the policy.

Second, 16 different studies were done to look for posttraumatic stress disorder. Most of them used a psychometric screening device called the Mississippi PTSD scale or other similar instruments. These are not diagnostic. When they are positive, there is a very high probability that they are false positive, OK?

Now any psychiatrist will tell you that you cannot make the diagnosis of PTSD with one of these scales, one of these instruments. It takes a psychiatrist's examination.

Well, in these studies they found that 10 to 15 to 20 percent of veterans had a slightly elevated score on the PTSD scale. People jumped at that, because it substantiated the policy, and they said well, that confirms the policy. This must be stress. It must be mild PTSD, and therein verified the policy. However, I recently published an article in the American Journal of Epidemiology which has been absolutely ignored, but which shows definitively that those studies did not show that there is anything wrong with these veterans having to do with stress, and that's all the evidence that's used to back up the stress argument. In fact, this is the "Emperor's New Clothes." Any doctor in the military who is worth their job must believe this is stress, when, in fact, there is absolutely not one shred of evidence that stress has anything to do with this problem.

All the time, however, VA psychiatrists were examining these veterans, finding no PTSD, finding no stress-related illness, and yet they couldn't speak up. Why? Because that would have been to speak out against the policy and I think they would not have been in their jobs long.

Third: Now, instead of getting busy on an epidemic investigation with a case definition, case control studies which probably would have solved the problem, instead we undertook large statistical studies with computers and comparing the 700,000 deployed with the ones who were not deployed. You recall the results published in the New England Journal of Medicine: No excess mortality, hospitalization or birth defect rates in the deployed group compared with those not deployed. The Iowa study was a similar study showing very little difference in symptoms.

Now, although this strategy seems scientifically sound and has been widely touted, published in the New England Journal of Medicine, presumably refereed by some good people, it was actually a terrible mistake. The problem was very subtle, but very malignant. Let me explain.

By comparing the prevalence of individual symptoms or mortality or whatever in the deployed versus the nondeployed groups, you are unable to measure the impact of a Gulf war syndrome; if there is a real disease or an injury, a brain injury or whatever, you cannot see it in that kind of a study, and the reason is because the real disease only affects about 10 to 20 percent of the deployed, right? And therefore, its impact, its symptoms or mortality or whatever are too small. They get washed out by being combined with this large group, all of the rest of the deployed who are not sick. So you don't see a difference in these big studies. The difference, the disease can only really be seen by a case control study in which you first find out who has the disease and compare them to controls. Then you see big differences. We did that in our study and we found big differences. However, our study was shunned because it went against the policy.

Now, in these studies another interesting thing happened. I had also written an article, which will come out in the next couple of months in the American Journal of Epidemiology, which showed

that these three studies in the New England Journal of Medicine are seriously affected by three biases which, in effect, based on data that is actually in those studies, turned evidence, the real effects, real differences between the two populations into conclusions that there were no differences.

There are the three biases. First, the researchers calculated statistical significance levels incorrectly so as to make it harder to find significant differences between the two groups. They handicapped it by using the wrong statistical significance formula. I am not saying they did this on purpose. I think it was totally unconscious.

Second, they failed to correct for the fact that the deployed troops are all well. They had to be well to go to the war. So therefore, all the people who were sick before the war, who have been going to the hospital and maybe the possibility of dying, they had to stay home because you can't go to the war if you are about to die or if you are going to the hospital. This we call the "healthy warrior effect," because you have to be healthy to be a warrior. Well, by comparing just the deployed and all the nondeployed, you see you have stacked it against finding a difference related to illness from the deployed. So the two groups come out equal after the war. Well, that doesn't mean that there is not an illness in the deployed.

Third, they failed to measure hospitalization and birth defects in the sickest Gulf war veterans who were discharged soon after they got home from the war because they were too sick to be a soldier and they didn't follow those up, so all that was lost.

Now, these biases are still present in studies that are comparing deployed and nondeployed, such as the big VA followup study. That is influenced by these three kinds of biases and is very likely to show nothing. Also, without a case definition, treatment studies are not going to show anything, because you are lumping together large numbers of people. Some of them have the illness and many others don't.

Two other points.

Mr. SHAYS. Just to be clear, on those two points we will conclude, because have you gone 10 minutes now so you need to conclude.

Dr. HALEY. Two other points. Isn't it interesting that all of this time we have been debating that maybe low-level chemicals may have caused brain damage and yet the CCEP and the VA's Gulf war diagnostic protocol exam do not include tests that could show the type of brain damage that would result from neurotoxic exposure? Also, the peer review groups; this is not only related to military and VA people.

Scientists out there in the world also do not believe this is a real disease. They believe that it is stress, that it is complaining veterans who are trying to get benefits. That is the strong, ingrained belief that has been embedded by a big PR campaign from the government.

In that circumstance, I have sat in a peer review panel that was looking and evaluating Gulf war research studies. In that panel, the other side is sitting around and saying well, of course, this is due to stress; and I brought up, well, maybe could it be due to chemical exposures? Oh, are you kidding? That's just crazy. And then the decisions they made about peer review I felt were highly biased by that view that they brought in. So I am not sure we are

protected by the honored peer review process, although I am not sure what to do instead of that.

Finally, now, with all the talk about a case definition, there are people coming forth that are going to talk the case definition talk, but they are going to talk, instead of a case definition of the Gulf war illness which includes symptoms that are very unique to Gulf war veterans, they are going to tell you about the case definition of chronic fatigue syndrome, multiple chemical sensitivity, and fibromyalgia. These are things that occur in the civilian population that have similarities to Gulf war syndrome, but are not the same. If we use those case definitions not developed in Gulf war syndrome, what you are going to find is yes, you are going to have some sick Gulf war veterans in there, but you are going to have a lot of Gulf war veterans that are going to have other things. You will water down the studies and not find anything.

My conclusion is that I think what has happened is there was a strong belief early throughout the government, throughout the population, that this was not real. I think that is a self-fulfilling prophecy, and through conservation of belief we have filtered out any evidence to the contrary, and I am very pessimistic that that can be fixed.

[The prepared statement of Dr. Haley follows:]

I am speaking today as a physician and epidemiologist who has been investigating the Gulf War syndrome full time for over four years as an outsider to the government research process. I will offer my impression of how the government research process is going, from the viewpoint of an outsider, with the advantage of not having been caught up in the government thought process but with the disadvantage of not knowing all the reasons why things have been done.

My overall impression is that the government's research effort, though well meant and painstakingly thought out, has misfired entirely and is showing little sign of getting back on track in the near future. Here is what I think the problem is.

As our troops returned from the Gulf War, tens of thousands began complaining of hard-to-express symptoms within a few months of their return. We now know that it may have affected 10 to 20 percent. In anybody's book, this was an epidemic and needed to be approached with the standard method for an **epidemic investigation**. This investigatory approach was developed into an standard "fire drill" by CDC over the past 30 years.

Sure enough, in late 1991 and 1992 epidemiologists from the Naval epidemiology unit in San Diego and others immediately went out to affected units and performed initial descriptive epidemiology that gave a good picture of the problem. At that point, someone should have taken "step 1" of the standard epidemic investigation fire drill by writing down a **case definition** of the Gulf War syndrome and then following through by performing a **case-control study** in one of the affected units, identifying **risk factors** reported by the cases but not by the controls, performing **animal studies** to test the biological plausibility of the risk factors, and so on. In other words, they should have performed a **standard epidemic investigation**.

In fact, this almost happened. In late 1993, Dr. Ronald Blanck, who is now Surgeon General of the Army, commissioned Dr. Jay Sanford, one of the greatest experts of military medicine of the past half century and a competent epidemiologist, to formulate a case definition of the Gulf War syndrome. He did it and proposed a case-control study to test it. However, in early 1994 the process got derailed. The Sanford case definition was shelved, and no case-control study was done.

Simultaneously, the CCEP was inaugurated, and the decision was made to put tens of millions of dollars into performing medical examinations on individual active duty soldiers who were encouraged to step forward. This clinical approach, performed on tens of thousands of troops, provided no useful insight over and above what was already known. But it also drained away the energy and resources that might have gone into case-control studies, which could have discovered the nature of the Gulf War syndrome and the cause of the epidemic.

At the same time, a far reaching policy decision was made to the effect that 1) there is no single epidemic disease, 2) the soldiers' symptoms are due to post-traumatic stress disorder (PTSD), 3) large epidemiologic studies need to be done to prove it, and 4) a public relations campaign should be waged to convince the American people of this explanation. Accordingly, orders came down to doctors throughout the military and VA systems that they must not write down a diagnosis of "Gulf War syndrome," and new protocols were developed to treat "stress." It became The Policy.

I believe that what happened after that was a pervasive exercise in, what is called, "conservation of belief." That is, all incoming information that would challenge the belief was unconsciously filtered out, all studies were designed to confirm the lack of physical effects,

and research delving too directly into hypotheses of environmental causes were discouraged by lack of funding. Here are some of the systemic effects:

1. Since no case definition of Gulf War syndrome was sanctioned and doctors were forbidden to record it as a diagnosis, the CCEP and the VA registries found only the other conditions that active duty troops might have in addition to their Gulf War syndrome, but they "found" no Gulf War syndrome. This led to the ubiquitous expression, "There is no single disease, only a variety of symptoms," as a self-fulfilling prophecy–a reaffirmation of The Policy. When confronted by soldiers with severe, disabling physical and cognitive symptoms, they recorded diagnoses like "somatization disorder" and "adult attention deficit disorder." (Somatization disorder (formerly hysterical neurosis) is exceedingly rare in men, rarely, if ever, begins after puberty, and is characterized by changing symptoms. "Adult ADD" is always preceded by childhood ADHD. These are not the problem, but they fit The Policy.)
2. Sixteen surveys of returning veterans using the Mississippi PTSD Scale found slightly elevated scores, and even though they were not high enough to qualify as PTSD, they were widely quoted as proof that the veterans' symptoms were psychological problems caused by "stress." I recently published an article in The American Journal of Epidemiology (November 1, 1997) showing that the stress argument was based entirely on a misinterpretation of the Mississippi PTSD scores. It is "The Emperor's New Clothes." Now, all that time, VA psychiatrists were examining the Gulf War veterans and finding no PTSD or anything that could be called a "stress-related illness." And yet, none of them spoke out against the stress theory (The Policy). Since I published my paper in November, you don't hear anyone mentioning the "S word" anymore, but millions of dollars more are about to go into stress research--more reaffirmation of The Policy.
3. Instead of getting busy on epidemic investigations with a case definition, government epidemiologists undertook large computer analyses comparing the veterans deployed to the Gulf War and those who were not deployed to the war. You recall the results published in The New England Journal of Medicine in late 1996 and early 1997 showing no excess mortality, hospitalization or birth defects in the deployed group compared to the nondeployed. The Iowa study published in JAMA in January 1997 was another example. Although this strategy seemed scientifically sound and has been widely touted, it was in actuality a terrible mistake. The problem is very subtle but malignant. *By comparing the prevalence of individual symptoms in the deployed and nondeployed populations, you are unable to measure the impact of the Gulf War syndrome. This is because it affects only 10 to 20 percent of the deployed and its impact is washed out by the far larger numbers of well veterans in the deployed group.* This problem can only be overcome by employing a case definition derived directly from ill Gulf War veterans. And yet, a case definition is against The Policy.
4. In these studies, the researchers inexplicably overlooked severe biases in the study design that masked real and important increases in mortality, hospitalization and birth defects. I recently authored a paper documenting the errors in those studies, which has been accepted for publication in The American Journal of Epidemiology.

In it, I showed three pervading biases that were overlooked and that caused the results to be 180 degrees wrong. These are: 1) the researchers calculated the statistical significance levels incorrectly so as to make it harder to find significant differences between the two groups; 2) they failed to correct for the fact that deployed troops are all well and the soldiers who are sick with chronic diseases remain at home with the nondeployed group (the "healthy-warrior effect"); and 3) they failed to measure hospitalization and birth defects in the sickest Gulf War veterans who were discharged from the service soon after the war. All of these biases obscured real increases in mortality, hospitalization and birth defects in the deployed population. These biases are still present in the newly announced VA studies comparing samples of deployed and nondeployed veterans and are likely to obscure the illness in the future.

5. The scientific review committees who periodically commented on the government's progress and who reviewed the studies for scientific journals, themselves convinced of the Stress Theory, also overlooked these biases and were satisfied not to go directly at the problem with an epidemic investigation to test a case definition.
6. Despite the nationwide furor over whether troops sustained neurotoxic injuries from chemical nerve agents and other organophosphate chemicals, the standard CCEP examination and the VA Gulf War diagnostic protocol examination did not include tests that could detect neurotoxic brain damage. These include audiovestibular tests of brainstem function, brainstem evoked potentials, neuropsychological tests like the Halstead-Reitan battery but not others commonly used, et cetera. When we performed these on ill veterans meeting our case definition of Gulf War syndrome and carefully matched controls, they showed evidence of neurotoxic brain damage. Our results, however, have been shunned because they run counter to The Policy.
7. Recently, as calls for a case definition and an explanation have continued to intensify, enterprising researchers are pulling out the case definitions of **chronic fatigue syndrome**, **fibromyalgia**, and **multiple chemical sensitivity**--never mind that these are medical terms for civilian conditions that are not understood.
8. I served on a study section peer reviewing grant proposals for government funding about a year ago. My fellow peer reviewers were mostly prominent scientists with the best of intentions, but their reviews and the conversations around the table throughout the day revealed that most believed the stress theory and felt uncomfortable discussing the possibility that veterans might have been exposed to chemical weapons, or that the veterans' symptoms might have a neurotoxic etiology. Consequently, the grant decisions came out pretty consistent with The Policy.
9. I have spoken to VA researchers who felt that their careers might be jeopardized if they proposed research projects to study neurotoxic hypotheses rather than stress and others who say they were let go from the VA system for doing so.

What explains all of these puzzling phenomena? First, I don't see a conspiracy to avoid the costs of caring for injured veterans, or covering up culpability for not protecting our troops in the war. I think if the medical community were convinced of a treatable etiology for the Gulf War syndrome, the costs of caring for veterans would be born readily, and from my

review of the scientific literature prior to 1990, all of the decisions to protect troops in the war were based on the best science of the day.

I think the explanation, as I said at the start, is that a policy formed early, and all subsequent activity subtly, though inexorably, conformed to the policy. The present inertia is sustained by "Conservation of Belief."

I am afraid that this force is still so strong throughout the research hierarchy of the VA, the DoD, CDC and other branches of government that it will not be overcome soon. No case definition will be formulated. No epidemic investigation will be undertaken. Resources will be spent on basic research into "stress" and on statistical and clinical comparisons of samples of the deployed and nondeployed heedless of such biases as the "healthy-warrior effect," and they will show nothing. Some productive research in experimental animals will demonstrate the mechanisms of neurotoxic damage from chemical nerve agents and other chemical combinations, and this will translate into protecting troops in future deployments–though without directly challenging The Policy. But intramural government research and government-funded extramural research will not come to bear on the Gulf War syndrome.

Moreover, I am pessimistic that any help will come from the elite scientific community who will sit on government oversight committees and study sections for grant peer review. I think they are by and large equally convinced of the stress theory, and unconsciously conforming to The Policy, will not press hard enough to slow the current inertia.

What I am saying is that the problem is not with the structure of government research or funding mechanism, or with the ill intentions of the government people and the outside scientists. It is that there is a thoroughly ingrained Policy that is driving every person, every study design, and every grant decision. The problem is not structure, but inertia. And that will not be fixed easily or soon.

Mr. SHAYS. One of the things, Doctor, we tried to do early on is to say, "let's put the blame everywhere to see if we could have that bureaucratic hold kind of loosened." In other words, we will start fresh and not cast aspersions anywhere. But we still see it is very difficult to let go.

Dr. HALEY. There is a very strong belief that this isn't real. We are not going to do studies that could show it.

Mr. SHAYS. I hear you.

Dr. Clauw. Dr. Clauw, you came before us as well, is that correct?

Mr. CLAUW. Yes, I did.

Mr. SHAYS. What was the hearing that you came before us? Do you remember the hearing, how long ago it was?

Mr. CLAUW. About a year ago.

Mr. SHAYS. March of last year?

Mr. CLAUW. Yes.

Mr. SHAYS. Thank you.

Dr. CLAUW. Mr. Chairman, members of the subcommittee, I appreciate the opportunity to give my opinions on adequacy of the Government efforts to research causes and treatments of Gulf war related illnesses. I would first like to briefly state my views on the unique problems faced in researching these illnesses and then comment on the strengths and weaknesses in the Government research programs. I will conclude by making a few suggestions for how these efforts might be improved.

As you all know, most of the research on Gulf war illnesses has focused on the "unexplained" symptoms and conditions that have afflicted tens of thousands of veterans who were deployed to the Persian Gulf. These illnesses are unexplained because we are not certain in many cases of the precise physiologic cause for the symptoms such as fatigue, memory problems and/or pain in various areas of the body. In medicine when we don't know the cause of symptoms, then we likewise struggle with appropriate and effective treatments.

Although much remains unknown about these symptoms and conditions, I think that there are several irrefutable facts that have emerged. The first is that there is not one unique or discrete illness that occurred in veterans deployed to the Gulf war. Instead, these individuals suffer from the same patterns of symptoms that afflict millions of Americans and go by numerous overlapping semantic terms such as fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity, et cetera. Also, some individuals with these symptom complexes are inappropriately labeled as having a psychiatric or psychological problem.

I would encourage anyone who is truly interested in Gulf war illnesses to go to a meeting of patients that have fibromyalgia, chronic fatigue syndrome, or multiple chemical sensitivity. It is easy to find such meetings because these illnesses are so common in the general population that such support groups exist in nearly every city in the United States.

What you will find if you do this is that there is a room full of people who will have the same exact symptoms that Mr. Sanders described earlier, but who were never in the military or who never have been anywhere near the Persian Gulf. You will also find prob-

lems with these unexplained symptoms and syndromes, and the inappropriate psychiatric attribution of symptoms occurs whether these individuals are seen in the VA or military facilities or in the private sector. The important issue in this regard that I think needs emphasis is that the lack of a single definition for these illnesses or of any laboratory or diagnostic test that can definitively establish a diagnosis causes considerable problems in researching these conditions.

The second important point is that these conditions historically have received very little research attention. In contrast to illnesses such as cancer and infectious diseases which have been well funded, well researched, and thus are well understood, our baseline state of knowledge regarding the physiologic mechanisms and treatments for these types of conditions is primitive.

The final important aspect that I would like to highlight is that it appears as though the same exact symptom complex can be triggered by many different factors. Most are aware of the debate that has transpired with Gulf war illnesses with respect to the cause of these conditions. There appears to be a wide chiasm between two seemingly disparate views; those on one hand who feel that these illnesses are triggered by "stress" and those on the other hand who feel that toxins or infectious agents are involved. The scientific reality is that toxins and infectious agents can act in much the same way as biologic stressors, as does physical trauma, drugs and emotional stress. Just as there are clearly many different types of such stressors which are capable of triggering or worsening fibromyalgia, chronic fatigue syndrome, and multiple chemical sensitivity, there are likely to be a plethora of exposures which contribute to the Gulf war illnesses.

I give this background because the governmental effort to research the causes and treatment of Gulf war illnesses must be judged in the context of the complexity of the problem. These illnesses are difficult to define and diagnose, have been poorly studied to date, and are likely to be caused by complex interactions between an individual and numerous types of stressors they may have encountered in their environment.

With this in mind, my opinion is that the Government agencies in general, and the Research Working Group in particular, have performed very credibly. My sense is that each Government agency has examined the strengths and weaknesses in these areas and has promoted internal research in areas of strength, and looked for outside expertise and external funding in areas of weakness. This is a logical approach.

For example, it would be foolish for the CDC, arguably the world's finest epidemiologic research organization, to extensively outsource this type of work. In contrast, the Defense Department does not have as much internal expertise with these types of illnesses and has been aggressive in funding outside Government, as well as in stimulating its own researchers in new directions. The VA has likewise decided to capitalize on its strengths, including one of the world's best organizations for performing multicenter treatment trials. They have asked me and others outside the VA who have expertise in these illnesses to help work with them and their internal experts in these illnesses, to design a large treatment

trial for persons with these conditions. This project is undoubtedly the largest single clinical trial that has ever been performed in this type of illness and, in fact, the amount of money that has been set aside for this effort by the VA probably exceeds the amount spent on all treatment trials ever performed on these types of illnesses.

I was also asked to specifically comment on the procedures to review and fund research proposals. Although I do not know the precise mechanisms which have been used, the peer reviews of my two grants were every bit as critical and stringent as for NIH grants which I have submitted. In fact, the DOD even took the unusual step of asking the internal principal investigators to modify their proposals in response to the peer review comments, an extra step which is more stringent than the post-review process for funded NIH or National Science Foundation grants.

Although I feel that the Federal research effort to date has been appropriate, I have several comments suggesting future direction of these endeavors. First, we must acknowledge that it is likely that we will never know precisely what caused Gulf war illness. It has become clear, and numerous people have pointed out today, that there was inadequate information collected on veterans' predeployment health and on their potential exposures and stressors to learn precisely what made certain people ill. But we still have ample opportunities to learn about the cause of these conditions. Nearly all of the environmental exposures suspected to cause Gulf war illnesses also occur in the general population. And we know that some individuals exposed to physical trauma, emotional stress, infections, drugs, toxins and other types of stressors develop these chronic nonspecific symptom complexes, whereas many others do not. These individuals and the illnesses they develop need to be more extensively studied.

But even if we don't know exactly what caused the illnesses, again it has been stated that we need to get on with treatment of these conditions. Most who have studied these syndromes have agreed that although there may be many different types of triggers of these illnesses, once someone develops these conditions, the treatments are very similar. My opinion is that we have all been collectively paralyzed by this need to know what caused Gulf war illnesses and that we must aggressively move forward in pursuing treatment programs.

Last, I feel that research into the causes and treatments of these conditions may require some additional strategies to augment those employed to date. Much of the currently funded research has been on individual projects proposed by individual investigators who are pursuing their scientific hypotheses. These investigator-initiated projects have the advantage of promoting innovative ideas, but there are also significant disadvantages to this approach, including the fact that there is concurrent funding of duplicative efforts and there is very little coordination between projects. In most complex medical conditions such as cancer and AIDS, we have realized that there is a need for a more integrated approach which can link population-based epidemiologic studies, physiologic studies and treatment protocols. I feel that a similar strategy, modeled after the "institutes" that have been formed to comprehensively study other illnesses such as cancer, would be helpful in studying post-deploy-

ment illnesses such as Gulf war illness. These institutes should consist of the best and brightest scientists from a number of different disciplines who will work toward a common goal of determining the causes and treatments of these conditions. It would seem preferable to have such institutes housed outside of government agencies, or else pressure from patient advocacy groups, competing agencies, or even well-meaning politicians, may hinder the important scientific effort that is necessary for these endeavors. Thank you.

Mr. SHAYS. Thank you, Dr. Clauw.

[The prepared statement of Dr. Clauw follows:]

My name is Daniel Clauw, and I am an Associate Professor of Medicine and the Chief of the Division of Rheumatology, Immunology, and Allergy at Georgetown University Medical Center. I serve as the Principal Investigator of two Department of Defense grants on Gulf War Illnesses, and also have funding from the National Institutes of Health on related matters.

I appreciate the opportunity to give my opinions on the adequacy of the government efforts to research causes and treatments of Gulf War related illnesses. I would first like to briefly state my views on the unique problems faced in researching these illnesses, and then comment on the strengths and weaknesses in the government research programs. I will conclude by making a few suggestions for how these efforts might be improved.

As you know, most of the research on Gulf War Illness has focused on the "unexplained" symptoms and conditions that have affected tens of thousands of veterans who were deployed to the Persian Gulf during Operations Desert Shield and Desert Storm. These illnesses are "unexplained" because in these instances we are not certain of the precise physiologic cause for symptoms such as fatigue, memory problems, and/or pain in various areas of the body. And in medicine when we do not know the cause of symptoms, then we likewise struggle with appropriate and effective treatments.

Although much remains unknown about these symptoms and conditions, several irrefutable facts that have emerged. The first is that there is not one unique or discrete illness that occurred in veterans deployed to the Persian Gulf. Instead, these individuals suffer from the same patterns of symptoms that afflict millions of Americans, and go by numerous semantic terms such as Fibromyalgia, Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, etc. Also, some individuals with these symptom complexes are inappropriately labeled as having a psychological problem. These problems with overlapping symptoms and syndromes, and the inappropriate psychiatric attribution of symptoms, occur whether these individuals are seen in VA or military facilities, or in the private sector. The important issue in this regard is that the lack of a single definition for these illnesses, or of any laboratory or diagnostic tests that can definitively establish the diagnosis, causes considerable problems in researching these conditions.

The second important point is that these conditions historically have received very little research attention. In contrast to illnesses such as cancer and infectious diseases, which have been well-funded, well-researched, and are well-understood, our baseline state of knowledge regarding the physiologic mechanisms and treatments for these types of conditions is primitive.

The final important aspect about these illnesses is that the same exact symptom complex can be triggered by many different factors. Most are aware of the debate that

has transpired with respect to the cause(s) of Gulf War illnesses. There appears to be a wide chiasm between two seemingly disparate views: those on one hand who feel that these illnesses were triggered by "stress," and others who feel that toxins or infectious agents were involved. The scientific reality is that toxins and infectious agents can act as biological "stressors," in much the same way as physical trauma, drugs, *and* emotional stress. Just as there are many different types of "stressors" which appear to be capable of triggering or worsening Fibromyalgia, Chronic Fatigue Syndrome, and Multiple Chemical Sensitivity, there are likely to be a plethora of exposures which may have contributed to the development of Gulf War illnesses.

I give this background because the governmental effort to research the causes and treatment of Gulf War illnesses must be judged in the context of the complexity of the problem. These illnesses are difficult to define and diagnose, have been poorly studied to date, and are likely to be caused by complex interactions between an individual and numerous types of stressors.

With this in mind, my opinion is that the government research agencies in general, and the Research Working Group of the Persian Gulf Veterans Coordinating Board in particular, have performed very credibly. My sense is that each government agency has examined their strengths and weaknesses in these areas, and has promoted internal research in areas of strength, and looked toward outside expertise and external funding in areas of weakness. This is a logical approach. For example, it

would be foolish for the CDC, arguably the world's finest epidemiologic research organization, to extensively out source this type of work. In contrast, the Department of Defense does not have as much internal expertise with these types of illnesses, and has been aggressive in funding investigators outside the government, as well as in stimulating and directing its own researchers in new directions. The VA has likewise decided to capitalize on its strengths, including one of the world's best organizations for performing multi-center treatment trials. They have asked me and others outside the VA who have expertise in these illnesses to help design a large treatment trial for persons with these illnesses. This project is undoubtably the largest single clinical trial in this type of illness, and in fact the amount of money set aside for this effort by the VA probably exceeds the total amount spent on *all* treatment trials *ever* performed on these illnesses.

I was also asked to specifically comment on the procedures used to evaluate, review, and fund research proposals. Although I do not know the precise mechanisms which have been used, the peer reviews of my two grants were every bit as critical and stringent as for NIH grants I have submitted. In fact, the DOD even took the unusual step of asking the principal investigators of Gulf War projects to modify their protocols in response to the peer review comments. This extra step further strengthens the scientific integrity of the protocols, and is more stringent than the post-review process for funded NIH or NSF grants.

Although I feel that the federal research effort to date has been appropriate, I have several comments and suggestions regarding the future direction of these endeavors. First, we must acknowledge that we will likely never know precisely what caused Gulf War illnesses. It has become clear that there was inadequate information collected on Gulf War veterans' pre-deployment health, and on their potential environmental exposures and stressors, to learn precisely what made certain individuals ill. But we still have ample opportunities to learn about the causes of these symptom complexes. Nearly all of the environmental exposures suspected to cause Gulf War illnesses also occur in the general population. Some individuals exposed to physical trauma, emotional stress, infections, drugs, toxins, and other types of stressors develop these chronic nonspecific symptom complexes, whereas many others do not. These individuals and the illnesses they develop need to be more extensively studied.

But even if we do not know precisely what caused Gulf War illnesses, we must proceed with aggressively pursuing research focused on the treatment of these entities. Most who have studied these syndromes agree that although there may be many different types of triggers of these conditions, once someone develops one of these illnesses, the treatments are very similar. My opinion is that we have all been somewhat paralyzed by this need to know what caused Gulf War illnesses, and that we must aggressively move forward in pursuing treatment programs.

Lastly, I feel that further research into the causes and treatments of these

conditions may require a different organizational strategy than those employed to date. Much of the currently funded research has been of individual projects proposed by investigators who are pursuing their scientific hypotheses. These investigator-initiated research projects have the advantage of promoting innovative ideas. But there are also significant disadvantages to this approach, including the fact that there is concurrent funding of duplicative efforts, and there is very little coordination between projects. In most complex medical conditions such as cancer and AIDS we have realized that there is a need for more integrated approach which can link population-based epidemiologic studies, physiologic studies, and treatment protocols. I feel that a similar strategy, modeled after the "institutes" that have been formed to comprehensively study other complex illnesses, is necessary to study post-deployment illnesses such as Gulf War illness. These institutes should consist of the best and the brightest scientists from a number of different disciplines who would work toward a common goal of determining the causes and treatments of these conditions. It would also seem preferable to have such institutes housed outside of government agencies, or else pressure from patient advocacy groups, competing agencies, or politicians will hinder the scientific effort which is necessary.

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Mr. SHAYS. Dr. Reeves.

Dr. REEVES. I am Dr. William C. Reeves, Chief of the Viral Exanthems and Herpesvirus Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention.

In November 1994, the Department of Veterans' Affairs, the Department of Defense, and the Pennsylvania Department of Health requested that CDC conduct an independent investigation of a report of unexplained illness among Gulf war veterans in the 193rd Pennsylvania Air National Guard Special Operations Group. Between December 1994 and May 1995, we studied veterans and nondeployed personnel to document symptoms, develop a case definition, compare illness rates, clinically characterize the illness, and identify risk factors.

Initially, 3,927 volunteers from four Air Force bases in Pennsylvania and Florida, including the 193rd Air National Guard Special Operations Group, were interviewed without restrictions as to health or participation in the Gulf war. The veterans were interviewed anonymously for symptoms, demographic and military characteristics, and deployment history. Gulf war veterans, of whom there were 1,164, reported all symptoms more frequently than nondeployed personnel, of whom there were 2,763. We identified an illness defined by chronic fatigue, mood and cognition symptoms and musculoskeletal pain. Forty-five percent of Air Force Gulf war veterans were studied and 15 percent of nondeployed personnel met the case definition for illness.

Next, 158 volunteer Gulf war veterans from the 193rd Air National Guard Special Operations Group, which included 13 severe cases, 86 mild to moderate cases, and 59 noncases, as defined by the initial 4-base survey, completed a detailed clinical epidemiology questionnaire, had standardized physical and psychometric exams and submitted blood, urine and stool specimens for laboratory studies.

Case subjects had significant decrease in function and well-being, but illness was not associated with physical exam or laboratory abnormalities, or with exposure to any of the infectious agents that we measured. Specifics of deployment or military characteristics were not associated with illness.

In conclusion, we analyzed symptom data collected from all participants and identified or defined an illness that closely resembles chronic fatigue syndrome. Illness was 4 to 16 times more common among Gulf war veterans. Illness rates for nondeployed were similar to those in civilian populations, and other than deployment to the Gulf war, there were no unique risk factors.

Thank you for the opportunity to discuss this study of illness in Air Force Gulf war veterans. I will be pleased to answer questions you or other members of the subcommittee may have.

Mr. SHAYS. Thank you very much, Dr. Reeves. Let me ask you, before we start, I am going to defer—I am going to tell you what my question is and then I am going to call on Mr. Sanders before you answer. I want to know where you agree and disagree with each other and where you agree and disagree with the earlier panel. That is what I am going to want to know, and I would love you to think about that. I will yield to Mr. Sanders.

Mr. SANDERS. Thank you very much, Mr. Chairman. I want to thank all of you for coming and thank you very much for all the work that you have done. This has been an enormously difficult and frustrating process, and some of you have been enormously helpful in directing us.

Maybe let me start off with Dr. Haley, and I really appreciate the work that you have done, and others may want to jump in. I want to be very specific here.

Dr. Haley, if somebody walks into your office, they are suffering from short-term memory loss, otherwise a healthy person, they have mood swings, serious fatigue, gastrointestinal problems, perhaps diarrhea, and they tell you that they can't tolerate perfume that their wife may wear, they are an automobile mechanic but they can't work around cars anymore because oil makes them sick, cleaning agents make them sick, pesticides trigger off a reaction, if that patient walks into your office, what conclusion do you reach?

Dr. HALEY. Let me say if that person walked into my office 5 years ago, I would have said this is a person with some psychological problem, and I think they are either faking or trying to get money or something. Now that I have seen that in literally hundreds of Gulf war veterans, some of whom I believe have subcortical, mild subcortical dementia that I think we have been able to prove, I think these people, if they are Gulf war veterans and have an exposure that is reasonable, I would suspect that they have subcortical or brain stem injury, probably from exposures to chemicals in the war. I would want to, if it was feasible from a financial standpoint and so forth, I would want to do the right tests that would show or rule out subcortical brain damage.

Mr. SANDERS. You have led me almost to the next question.

Mr. SHAYS. If I could interrupt, is there a test to do that?

Dr. HALEY. Oh, yeah. We published a whole paper showing that audiovestibular tests—these are tests that test the reflexes of the brain stem the answer is yes, there are.

Mr. SHAYS. And you also testified at our last hearing on this issue?

Dr. HALEY. Yes.

Mr. SANDERS. Dr. Clauw, do you want to respond to that?

Dr. CLAUW. I would just like to respond by saying those individuals do walk into my office. In fact, at 2 o'clock I have 10 or 15 such individuals who never went to the Gulf war, who aren't exposed to some of the different things that we are talking about, and again, we call these illnesses multiple chemical sensitivity, chronic fatigue syndrome, fibromyalgia, in the general population.

I would be very careful about saying that these individuals have dementia or have damage to their central nervous system. My view is that they have dysfunction of their central nervous system, but I don't think this is clear that this is damage; that is, damage being something that is irreversible and can't be treated or can't be fixed.

Mr. SANDERS. Thank you for both of your responses. Let me go back to Dr. Haley, because I think the chairman asked the question that I was about to ask.

If I walk into your office because I am concerned about AIDS, you are going to give me a test, it is easily demonstrable whether

I have AIDS or not, whether I am HIV positive. What I think the chairman and I were trying to get at, what kind of physiological tests are available, or might you use, which suggest that in the broad sense, look, I can show you, young man, that you have Gulf war illness? Can you talk about that point for a moment?

Dr. HALEY. As I mentioned, we published a study comparing carefully selected cases and controls, we used audiovestibular tests, evoked potentials——

Mr. SANDERS. You have to talk in English.

Dr. HALEY. Well, the problem is these don't really have English names.

Mr. SANDERS. What are these tests?

Dr. HALEY. For example, an audiovestibular test, one that we are using now which we think is very sensitive, and potentially the test is a test of what is called eye saccade, S-A-C-C-A-D-E. A saccade is that little flicking eye movement. Let's say something moves and your eye just darts around, those little darting movements, the velocity of that movement always is the same in every person. We see that very regularly, Gulf war veterans who have the symptoms, particularly what we call our syndromes 2 and 3, have slowed eye movements or have a jerky eye movement or they have trouble initiating the eye movement.

There are similar other reflexes of the brain stem and the eyes that can be tested by other very standard tests that have been used for decades. The other set of tests, though, may be more sensitive and we are experimenting with that right now, and that is tests where you do clicks in the ear and then you measure with electrodes on the side of the head and the brain, you measure different spikes. As the sound or the stimulant goes into the brain stem, up the brain stem, you get three major spikes. You measure how long it takes the nerve impulse to get up the brain stem, and if this is not the same on both sides, it indicates dysfunction of the nervous system. These are the types of tests.

The grant that we are working with now is applying about 30 different tests to our cases and controls to try to work out which ones would be most sensitive and specific to make the diagnosis.

Mr. SANDERS. All right. This is very important stuff, because you are trying to give us some objective measurement for something that we can demonstrably show. Let me just ask Dr. Clauw.

Dr. CLAUW. I agree with what Dr. Haley says. I think there are a number of tests that in many of these individuals with illnesses will be abnormal, and I am glad Dr. Haley used the term dysfunction of the central nervous system rather than dementia, which implies damage.

My only concern is that again, if he looks at the same types of tests—we have done visual evoked responses and auditory evoked responses in people with fibromyalgia and chronic fatigue syndrome—we find that a significant number of these individuals are abnormal and they didn't have these exposures.

Mr. SANDERS. OK. Let me go on to my next question, and I think that that's important information.

I am happy to be hearing today from the previous panel and from the VA that there seems to be an increased focus and understanding that we need to move forward more vigorously on treat-

ment protocols, because after all is said and done, ultimately what we are dealing with is 70,000 to 100,000 people who are hurting, and we want to make them well.

I know the last time you were here, Dr. Haley, you were pessimistic that some of this damage may be irreparable, as unpleasant as that may be. Others may disagree with you. Why don't we start with you again and tell me, at this point are you comfortable with any treatment protocol that could improve these symptoms? What do you think?

Dr. HALEY. If it is neurological, neuronal damage, chances are you can't cure it. However, that damage in the brain stem and subcortical areas typically produces demonstrable changes in nerve function in the body. For example, the sympathetic nervous system may become hyperactive and so forth. These systemic manifestations, if we understand what they are, probably can be interrupted and made better.

For example, one of the things we are now noticing, now that I really know how to take a history in a Gulf war veteran, which I didn't know up until a year or two ago, often they describe two different components to their symptoms. There is a sustained component which is the cognitive problem. Those tend to be the same all the time. But the muscle aches, the systemic symptoms, those tend to come and go. You hear veterans say, I have good days and bad days. Things that come and go probably can be interrupted, and if we could interrupt those, most of these Gulf war veterans would really be happy. So I think there probably are medications. It is a matter of identifying them in good studies.

The key is, though, there must be a Gulf war specific case definition, and if you don't do that, you are going to be lumping people with this Gulf war related neurological problem with a whole bunch of other people and people who don't even have anything, and then the treatments, you are not going to show whether they work.

Mr. SANDERS. The bottom line of what you are saying is that the better we understand the cause of the problem, we can in your judgment make progress treating, significant progress, perhaps, in alleviating the symptoms?

Dr. HALEY. Right. I go back to my colleagues at GAO here. Read my lips. Case definition. There must be a case definition of the Gulf war syndrome. Otherwise, all the treatment trials are going to be like the three New England Journal studies; we are going to see no difference, because we are lumping things together that don't belong together.

Mr. SANDERS. Dr. Clauw, could you respond to that also?

Dr. CLAUW. I generally agree. Maybe I am even more optimistic that many of these conditions can be treated, and again, that is an area that needs intensive study.

Mr. SANDERS. Do you, Dr. Clauw, want to comment at this point on any treatments that you have seen out there, perhaps using antibiotics and so forth, as perhaps promising immediate hope?

Dr. CLAUW. I think there may very well be a subset of people with this whole spectrum of illness, again, not necessarily just Gulf war illness, but chronic fatigue, fibromyalgia, multiple chemical

sensitivity, where there is an infectious agent that we have yet to identify.

Going back to what some of the people on the earlier panel said, I think the problem with these types of treatment trials are to try to identify the subset of people who have the infectious illness and put them in the trial of antibiotics, rather than looking at the entire group of people, because I think you would have a very difficult time showing efficacy of antibiotics if you just looked at all comers with Gulf war illness. I think that would be unlikely to be successful.

Mr. SANDERS. Last question, and anybody can jump in. Dr. Chan, did you want to say something?

Mr. CHAN. Yes. I think what I would like to say is that from the previous panel and even the discussion currently, it is closer to what Nujaia was thinking about. What the previous panel interpreted, when we discuss the issue of treatment, was that they were really thinking about clinical trials and looking for treatment and having control groups and so on, which is extraordinarily lengthy in time and cost, and I wrote down on my paper why this was being discussed. I said, "haven for researchers for years to come."

I think the answer that is given here is more to what we were thinking about. Because you have a consolidation of illnesses and symptoms, and there are specific symptoms that may be treatable in the short term, possibly the long term, and some that may not be, and what we are hoping for is that the physicians and those researchers who are looking into these patients can come out with positive treatments with which they can actually show progress and share them among the other physicians.

Mr. SANDERS. Right.

Mr. CHAN. You can't just announce and say "let's have a clinical trial and treatments" and expect physicians to come through with a proposal, which is not the work that they are doing. I would like to clarify that point.

Mr. SANDERS. OK. Let me ask Dr. Chan or anybody else. Isn't it funny, or isn't it strange that after 7 years, there are not a dozen different treatment protocols out there; some may work, some may not work, but we can learn by failures as well as partial success. Am I missing something?

Dr. HALEY. We actually have a treatment trial going now, in the Seabees group. As we bring our cases and controls in, the controls just go home at the end, but the cases we enroll into a treatment trial. Our research group, based on the study of the symptoms, we have enumerated five different medications that we think will attack one of the symptoms, one of these variable symptoms that they have. So as they go on, we are going to enroll them so that they take one of these medicines for a month, and then they go off everything for 2 weeks and then they take the next one for a month. They are randomized and double blinded, and then at the end at 6 or 8 months we will then know whether these five drugs attack these symptoms. Let me just say we proposed this to the Persian Gulf Veterans Coordinating Board and it was rejected. We are doing this on private money.

Mr. SANDERS. I am not a scientist, but Mr. Chairman, what Dr. Haley is expressing, and it seems to me, please others jump in, to

be eminently sensible. Maybe you will fail and maybe we will learn something that doesn't work.

Dr. HALEY. Five drugs that don't work; that's great.

Mr. SANDERS. What I cannot understand from the very beginning is why we have not done this in 100 instances.

Dr. CLAUW. I would just like to say again, I think you need to be real careful about blaming the people who were sitting on this front panel. If the exact same treatment trial for chronic fatigue syndrome or for fibromyalgia were proposed; it likely would get panned. It has been, it will get. So be careful about saying this is a problem specific to the Gulf war. The problem is that these illnesses are so nebulous, so hard to define and so little about them is known that they don't do well in the peer review process. So again, this is not something that——

Mr. SANDERS. I am very upset at what has happened in the last 7 years. I don't agree with that assertion. I understand that it is difficult, but we have not done a good job.

Dr. CLAUW. I don't disagree with that either. You're right.

Dr. HALEY. The system doesn't want this done. That's the problem. The peer review groups would not go for any of this research.

Mr. SANDERS. Are we all in agreement, though, this seems pretty "common sensible"? I am delighted to hear that Dr. Haley is doing work, you will publish your results, they will be partially successful or fail, and we will learn from them. Is there any disagreement that we should be doing this all over the place?

Ms. HEIVILIN. One of the recommendations that we have made, that we have discussed quite extensively, is that we think that both the VA and the DOD should be following the treatment of the veterans, because they are all being treated for the symptoms that they have, and we should find out what is working that certain doctors are using, and share that information, because there might be some possible treatments out there that are working quite well that no one knows about, or very few people know about.

Mr. SANDERS. My last question, Mr. Chairman.

I believe, based on what little I may know in the concept of multiple chemical sensitivity, and I think we should be able to learn something, that if somebody walks into a room for Gulf war veteran or nonGulf war veteran, walks into a room where there is perfume or different types of chemicals, and that person reacts, we should be learning something from that process, I should think. That should teach us something.

Now, what has concerned me all along, and I would like somebody to comment on this, as to whether or not we have 70,000 or 100,000 time bombs out there, are we being fair to the veterans by saying to them, stay away from perhaps this type of food or chemicals in our food? Stay away from this type of pollution to the degree that you can.

Stay away from, you know—maybe people are getting ill and they haven't even seen the cause and the effect. Do you follow what I am saying? Is what I am saying making any sense?

Mr. CHAN. That's one solution, yes. And I think that hopefully with those people we can find out what could possibly be a cause, what is common. Were they located in the same area, were they doing something, were they getting vaccines? I mean instead of

looking at cause up front, we can look at subsequent symptoms and go back and look at causes.

Mr. SANDERS. But might we be able to prevent some suffering today if we are able to tell me, stay away from this? Most of these people, they didn't even know that they have Gulf war illnesses, they are just getting sick and they work in a certain climate every day.

Dr. Haley, is that correct?

Dr. HALEY. Yes. One of the notable veterans that we are following, every time he gets in an environment with automobile exhaust or whatever, he takes a turn—this is his feeling, he takes a turn for the worse. The problem is, he can't avoid all of those things, so we are really looking for that person for a medication that would make them more resistant to these because in our modern society it is just really hard. Now, they should be avoiding, to the extent they can, but you just can't avoid everything.

Mr. SANDERS. I understand. For some folks, some may not, they may not even understand why they are getting ill.

Mr. SHARMA. One of the purposes of the epidemiological studies is to develop the natural history of the disease. And the one that Dr. Haley mentioned earlier, that CDC could have done an epidemic investigation; and what we do is to redevelop the course of the illness as part of the investigation. Seven years our veterans have been suffering but we really don't know the natural progression of the disease, which way it goes, what is the order of the symptoms as they are appearing in subsets or among all of them; and at minimum, I think that is something that we could have done. And I don't see any studies, despite the fact that a large number of them are epidemiological studies, that are trying to understand what is going on with the veterans.

Mr. SANDERS. I am going to give the mic over to the chairman, but I would like you to think about my next question which will be, if you had a blank check, what would you do? Where would you go from here? Mr. Chairman.

Mr. SHAYS. That is a very provocative question. Dr. Haley, I saw you light up like a light bulb.

Dr. HALEY. Is that an offer?

Mr. SHAYS. Where would you disagree with each other and where would you disagree with the earlier panel? This isn't petty debate here, I just want to know—I need some definition to see where the differences are, where we do have honest disagreements. I will start again.

The previous panel, and I think most of you were here, you heard what they said. What would you like to amplify or disagree with the previous panel and what would you amplify or disagree with the present participants here?

Ms. HEIVILIN. We absolutely think that looking at low-level chemicals, the synergistic effects of low-level chemicals is a hypothesis, that definitely needs to be studied. We have said that. I would disagree with some of the members of that panel who didn't seem to think that that was a reasonable thing to do.

Mr. SHAYS. Dr. Haley.

Dr. HALEY. I would like to take real serious issue with the assumption, almost the mantra, that stress has anything to do with

anything here. I don't—I would really like to challenge the proponents of that to show me the evidence that stress causes any—does stress cause brain stem dysfunction? Does stress cause subcortical dementia? Does stress cause fibromyalgia? The evidence on that is highly equivocal. There is no agreement to that. Does stress cause peptic ulcer disease? What was the disease that was most caused by stress that everyone would agree with? Peptic ulcer disease. Now we know that is an infection and stress probably has nothing to do with it. Ulcerative colitis was one that was caused by stress. Good studies show stress levels are equal in people who will later develop ulcerative colitis. This is the emperor's new clothes. It is distracting us. It is taking millions of dollars to study an idea that had no basis to begin with, still has no basis, but it is taken for granted by the groups who are handing out the money.

Mr. SHAYS. Thank you. Anyone else before I ask the next question?

Dr. Sharma, you were here last time and I remember you were very outspoken. Do you have any comments you want to make?

Mr. SHARMA. Well, I think I would repeat earlier what the chairman said, that I strongly disagree with the method the previous panel had proposed of studying treatments. Certainly a clinical trial is not the way. The numbers that you are going to see are going to be very small, they are going to be very costly, their time—the information will not be available for a year while they are still ill. There are some other less costly ways of studying the effectiveness of treatment.

Mr. SHAYS. You want more research on treatment and outcomes?

Mr. SHARMA. Correct.

Mr. SHAYS. And you are nodding your head?

Ms. HEIVILIN. Yes.

Dr. CLAUW. I would ditto the need for more research on treatment and outcomes. I think that a part of that should be large clinical trials because there are some fundamental issues with these illnesses that we need to resolve as far as certain types of therapies that we all think are probably effective but never have been well tested. But it shouldn't be all in large clinical trials. I would agree with that.

The only thing I would really like to take issue with is the notion that Dr. Haley is raising about stress. I think all of us—I am a "stress researcher,"—I think that how you define stress to a large extent dictates what you really think are causing these illnesses, and what kinds of things are capable of triggering these illnesses.

Most people who study stress feel that there are stereotypical responses that the body has to physical trauma, certain types of drugs and toxins, emotional stress and a whole lot of different kinds of exposures that we come across in our environment. That is certainly my point of view and that is the way I use the term "stress." Not in a pejorative sense, not in an emotional sense, but rather the issue is that is the only word we have, and I would love for someone to come up with a better word, because I am stuck with it. I would rather not be pigeonholed into thinking this is an emotional or psychological disease because I think anything but that. So I think we should be careful.

Mr. SHAYS. You could say scared to——

Dr. CLAUW. But it's the body's response to—the body can only respond in a certain number of ways to different types of things. The nervous system, the hypothalamus, pituitary gland, there are different things that effect a stereotypical response, that will be the same to sarin as it will be to emotional stress, as it will be to an infection. It appears as though these types of illnesses are capable of being triggered by a whole host of different things again that I would view as "stressors."

Mr. SANDERS. If I may, I agree with everything you are saying, but doesn't that make the word "stress" a meaningless word?

Dr. CLAUW. It is a terrible word.

Mr. SANDERS. You go to 899 people and you say, what is stress? There's—you know, there is an emotional reaction, we are nervous, afraid. You are suggesting oh, sarin, bring forth a reaction. No one normally would think that sarin's effect on the body is the same as an emotional.

Dr. CLAUW. I guess I would say, though, that biologists and physicians and scientists view stress in the latter way rather than the former. You are talking about 99 lay people. I wish we had a different word that we could use for it, because it really causes a great deal of problem. It is as huge an emotional issue with fibromyalgia and chronic fatigue syndrome, multiple chemical sensitivity, as it is with Gulf war illness, and I think we need to get past this. I think it is too divisive.

Mr. CHAN. Can I add a little to this?

Mr. SHAYS. You may. I just want to—Dr. Reeves, I just want to make sure that I am getting your attention here in terms of whether you agree, or want to choose to point out any area where you would amplify or disagree with the earlier panel or the present discussion with this panel.

Dr. REEVES. I think there is a couple of caveats that I would make. I think one is that there is a very clear—and it is almost impossible to prevent—a level of misunderstanding between technical issues and nontechnical issues, the concept of stress being when one gets dengue fever, the virus is gone in 3 days and you are on your back for a half a year, and it is because of the stress of that infection.

When you are a prisoner of war, you have a chronic stress which may be an emotional stress, a physical stress, and there are problems in probably the public opinion understanding of these and the scientific. It is the same problem that came up with the wording of a hypothesis that serious scientists approach things in a very set, scientific fashion and this is often misunderstood by the general public.

I think the major problems in the area, I think for me, from a public health point of view, we have a large number of veterans who are currently not well, who need treatment. They need carefully considered treatment trials, not willy nilly treatment trials in which we can do more harm than we do good. I think that is very important. I think anything we treat with is not necessarily—not causing separate illnesses. We do not want to get into the same problems using antibiotics, et cetera, that we did using the PB. The argument goes both ways.

I think the major problem from a public health point of view, and the one that should be focused on, is the problem of prevention. There is evidence that this sort of illness has occurred after every major war. The major issues that we have is how to prevent this from happening in the next deployment, or in the next large deployment. I think the issues are, at least as far as issue research, are issues of case definition; what in fact are we dealing with? We are dealing with an illness that is very hard to characterize by physical findings or laboratory markers.

I would disagree very strenuously with Dr. Haley that we have any markers that will diagnose this illness. So I think a case definition, I think a search for markers of which there is a variety of serious research, including Dr. Haley's, and I think a search for risk factors that can be intervened are what need to be done, and I think that looking at the natural history, what is in fact getting better. We have that problem with chronic fatigue syndrome, where people are ill for many years and there is fluctuation in symptoms. We need an end point against which to gauge our interventions. But I think the primary questions are questions of prevention and questions of treatment, probably prevention being the most important for the future.

Mr. SHAYS. We all want to properly diagnose and we all want to effectively treat and I would think properly compensate our veterans who are sick. But you would all agree or disagree with the following: that some of our Gulf war veterans have come home sick due to their experience in the Gulf war. Would you agree with that or disagree?

Dr. REEVES. I would agree with that. I think the difficulty that I have with that personally is it is very clear in our studies and those of others that Gulf war illness or Gulf war experience has precipitated an illness or a variety of illnesses of veterans. But if I could enlarge, I think the interesting thing in our study is that 15 percent, if one uses the overall case definition that we derive, of people who did not go to the Gulf war and are in the military, have a similar illness. Chronic fatigue syndrome is a similar illness which is experienced by a proportion of the civilian population. So I don't think we have seen an illness unique to the Gulf war. I think we are seeing something——

Mr. SHAYS. I would like to pursue that, because I am not aware of a lot of our military men who have described throwing up and rashes and other things similar to that. They have described certain other parallels.

Let me just pursue this one question. You can come back and comment, but not at this moment.

Doctor Clauw, do you believe that our soldiers have come back sick due to their experience in the Gulf war?

Dr. CLAUW. Yes.

Dr. HALEY. Oh, definitely.

Ms. HEIVILIN. Yes. Can I add, since we have soldiers and sailors over there right now, and airmen, I think it is very, very important that we pursue the causes so that those that go over there in the future or stay over there now and into the future, will have some sense of security that they are not going to have to suffer the same

way, or at least that we are very actively trying to figure out what to do to prevent it and what to do to treat it.

Mr. SHAYS. OK.

Mr. CHAN. Yes.

Mr. SHARMA. I agree.

Mr. SHAYS. Did you want to make a comment on an earlier question?

Mr. CHAN. Well, the comment I would like to make is that there were a number of studies they planned to do, particularly on low-level chemical agents and other effects and so on. If indeed the hypothesis that stress is one of the so-called important factors is true, I really would like to suggest then, that the research being done should include stress as one of the dependent variables and consider, that stress could be tiring or whatever. Certainly other countries have examined stress as a factor, including the PB people and all the other agents that may cause the problem.

Mr. SHAYS. You were pretty firm in your attack about stress being a factor, and—not being a factor, excuse me, not being a factor—and it would seem to me that I would agree with your criticism that the presumption that it is a cause is an outrage, but not the effort to determine its role.

Dr. HALEY. Here is my problem with it. It was never—it never went through the stage of being a hypothesis. That is, we had 16 studies misapplying the Mississippi PDSD scale in which they looked at some minor elevations and said, oh, stress. That became accepted—it was a given then. It is no longer a hypothesis. That is where it came from and that was totally fallacious.

Mr. SHAYS. But to the extent you mean that, I think you find sympathy——

Dr. HALEY. You see, I don't know why we are treating this even as an important contributing factor. There is no evidence. The only study that has any merit, that is of any interest in my view, is the Israeli study showing that physical—that is fear, I believe that is what they studied—rats being thrown in water produces fear, and that is what the model measures, that fear, fright that you are imminently dying, that you are on the way out, that mortal fear, that may make the blood-brain barrier more permeable. That is a very interesting idea. Now, to translate that into the sorts of outlandish things that we are funding right now to look into stress and psychological issues and all of this is, to my mind, bizarre.

Mr. SHAYS. I do know this. If I were a veteran and I came back sick and I was told I had posttraumatic stress disorder, I would want to punch someone in the face, and then I would probably be—I would feel sicker. I mean it would make me sicker. Somehow just having those who are trying to help me recognize that I am sick and that I have a problem and I need their help and I want a little sensitivity on the part of the people examining me would make me feel a little better.

Let me just say, I am just interested in this one other area. You wrote, in response to—not this committee, though we have put you to work on many occasions—to Senator Thurman and Floyd Spence—well, actually, at the time they were the ranking minority members on the Armed Services Committee—excuse me. Were they? Excuse me. The chairman, and then to the ranking members,

you made recommendations in terms of the issue of improving and monitoring clinical process, emphasis is needed.

Based on your statement, I was trying to get a sense of it and it didn't hit me the way I wanted. I wanted you to be more direct.

Do you feel that some of the recommendations you reported are being implemented? Do you feel that it is being ignored? I want you to be very specific.

Ms. HEIVILIN. I think the one on monitoring the treatments and the effects of the treatments is being ignored.

Mr. SHAYS. Is what?

Ms. HEIVILIN. Being ignored.

Mr. SHAYS. And the other one?

Ms. HEIVILIN. The one to fund more low-level chemical research? That is happening. There are three studies that have been funded, but of course there was a congressional mandate that that was a response to.

Mr. SHAYS. OK. Dr. Haley, I just also want to comment that you—I have found myself trying to be responsible by saying there is no one Gulf war illness, there are many, and there is no silver bullet. So you kind of went after something that I need to think about. You went after something that my colleague Mr. Sanders also wrestles with, and that is multiple chemical sensitivity. I gather you feel that the focus—that my saying that there are many illnesses, is almost like what I say in my office that everybody is responsible, so no one is responsible.

Is that your concern, that by saying that there is multi-, that in essence we don't get an answer? I want you to kind of focus on why you——

Dr. HALEY. Right. Here is the reason. We sent 700,000 people over there, and when they come back 10 to 20 percent of them are complaining with very similar symptoms. Granted, the symptoms fit a spectrum. Not one guy has all of them. Now, maybe that is just 50 different things, but why would we assume that? They all went to the same place, they were exposed to the alarms going off, which may be chemical exposures, the litany of things, chemical exposures. I think it is very reasonable to entertain the idea that this is one injury, a subcortical brain stem injury that produces symptoms. It may be that that is what is involved with chronic fatigue syndrome and multiple chemical sensitivity and fibromyalgia. In fact, the most recent review on fibromyalgia says there is nothing wrong with muscles, it is probably a neurological problem.

Mr. SHAYS. I hear where you are coming from, and I would say that it is good for you to do that, but I wouldn't think it would be good for all of us to make an assumption that there is just one. I mean——

Dr. HALEY. Let me say, in saying that, then I also have to point out that in addition to the people that I think have this one illness that has maybe some subcomponents or variants, one illness with several variants, in addition, there are another 200,000 veterans who have all kinds of things that you and I have that are normal, and that is what the CCEP has focused on.

Mr. SHAYS. But I think it would be a shame if your view was ignored, because you may be right. But conversely, I wouldn't reverse it to say that only your view should be looked at.

Dr. HALEY. Yes. It would be the worst thing I could imagine for that to be taken as a dogma the way the opposite view, that there is not one illness, has been taken as a dogma and has determined the research.

Mr. SHAYS. Fair enough. And I don't know if I am going to change my ways, but at least you have me thinking.

Do you have any more questions? I am happy to wait. I am done.

Mr. SANDERS. Two more questions, Mr. Chairman.

Mr. SHAYS. I wanted to make a point. You have as much time as you want.

Mr. SANDERS. Thank you.

Dr. Heivilin, it goes without saying, Dr. Haley is now working on a treatment protocol and he will be finished in 6 or 8 months. Those results will be published. Common sense would suggest that if he has success, that we would immediately amplify that and we would go on from that; is that correct?

Ms. HEIVILIN. We would want to replicate it, yes.

Mr. SANDERS. Try to replicate and hopefully we would have something in it, et cetera.

Right now, do we have a list of those physicians who are doing different treatments and seeing how well or how not well they are succeeding?

Ms. HEIVILIN. No, we do not. And that is what one of our recommendations was leading to; we have a register of the first exams that were given to the Gulf war veterans who signed up for the register, but we don't have anything on the followup. The followup is being done individually by individual physicians. In some cases there might be a case monitor, but that isn't necessarily a physician, and that isn't necessarily someone who is looking at what is working and what isn't.

Mr. SANDERS. I can think of at least three physicians now who claim—who have done work with Gulf war veterans who claim to have had some success, but I gather we have—there is no protocol right now which says, OK, let's double check, let's—what is the expression you use—expand this or whatever we may do. Isn't that fairly absurd?

Ms. HEIVILIN. What we have heard from the VA is that this is very expensive, very expensive to do, and they claim that their data system, which has information on, all their patients on it, would just be too expensive to extend to do this. There are other ways, there are other cheaper ways to do this. We don't necessarily have to wait for automated data systems.

Mr. SANDERS. There are hundreds of treatment protocols out there, aren't there? How many—please help me, Dr. Heivilin. How many folks out there are even saying we are treating——

Ms. HEIVILIN. I haven't the slightest idea.

Dr. HALEY. Oh, yes. Every doctor who is seeing these people in a VA or private office is trying different treatments, experimenting, and that is what ought to be done. It is just what is lacking is coordination and recording, measuring the results to see if what the doctors think is a result really is a result. Some objective measurement.

Mr. SANDERS. But it is not really true that within the VA system—for example, I mean Prozac is still being given, I mean you

are working in a way presumably that no one else in the country is working; is that correct?

Dr. HALEY. I don't know.

Mr. SANDERS. That is one of the problems we have now, isn't it? You develop your own approach.

Dr. HALEY. Let me comment, because I think—see, I don't think you want to start right now, as I think maybe the VA is being pressured to do, and do a huge clinical trial with, you know, 500 or 1,000 sick Gulf war veterans and randomize them into treatment and placebo groups. The chances of that getting anywhere is zero. What you want to do is stimulate, and maybe this is what they are doing, I don't know the details of that trial yet, but maybe what we need to do is stimulate a number of researchers who have access to these people who really care for them on a daily basis and can understand what these symptoms are, to come up with a whole bunch of little trials and what I call phase 2 trials, not definitive trials. What we are doing is not something that, no matter what we find, is going to be definitive. What we are doing is, you might call it, an N of one trial or an individual patient trial. Each patient is his or her own control. This is a very preliminary type of trial to get some idea is there a medication that just looks like it is dazzling; but that doesn't mean that some of the things that don't show up are going to be given up. But we may be lucky and identify something. Chances are we probably won't, but if 100 other people were doing that, pretty soon somebody would come up with something that really looks good.

Mr. SANDERS. All that I was suggesting is that we should all know that there are 100 people doing it and we should know the results: this one failed, partial success or really great, and amplify that.

Dr. HALEY. It is crucial, though, and this was mentioned by the other panel; in doing a trial like that, though, you must have ways of measuring the end points: How did people respond? You can't just ask them. Many of the doctors out there who feel like they are getting really good results have not measured, so they don't know. They just are very enthusiastic that their patients like what they are doing, but they haven't measured really an effect.

Mr. SANDERS. I agree, but you agree that we should have definitive information about what is going on?

Dr. HALEY. Yes. To do all of the things that I just mentioned, even this little informal preliminary trial that we are doing is very complex. It has taken us 6 months to get it off the ground, the funding has been denied twice.

Mr. SANDERS. We have 750,000 people who are hurting and we spend $1.5 billion for the B–2 bomber, so I think we have the resources to do it.

Dr. HALEY. Just don't feel that this is something similar to do. I know Dr. Clauw is struggling with this. It is very complex to do it right, so that you don't injure people with medication and so forth, and that you measure accurately.

Mr. SANDERS. Mr. Chairman, I just wanted to ask Dr. Sharma.

Mr. SHARMA. I just wanted to mention that we have done studies called cross-syntheses to measure exactly the kinds of problem you are facing with Gulf war veterans. This is an alternative to doing

clinical trials and we would be very happy to provide you a copy of this report which articulates this methodology.

Mr. SANDERS. One last question, Mr. Chairman, a brief one, and it was thought of with Dr. Haley and we can go elsewhere, Dr. Reeves, Dr. Clauw—if we gave you the blank check and we said—and picking up the point that the chairman made an hour ago that there does not seem to be that sense of urgency, he and I believe that there is a sense of urgency. We want to see this problem resolved as quickly as possible, not discussed 20 years from now. If we gave you the resources and appreciated your sense of urgency, what would you do?

Dr. HALEY. Well, last March I submitted a grant proposal which was developed by about 30 members of our faculty, which is not an inconsequential medical school. We developed a plan that in 3 years would develop—granted, there is no test right now that anybody would consider definitive, including myself, but we proposed to develop such by testing all known methodologies that would look at subcortical brain function and brain stem function and so forth, which we think is the problem. It would also come up with a treatment by doing several sequential trials in very careful groups of studies. We would combine it in parallel with animal studies, testing the same thing in animals so we could correlate this and so forth. It was a very complicated thing and the price tag on it was $16 million; $16 million, including indirect costs.

Mr. SANDERS. $16 million.

Dr. HALEY. $12 million direct cost and the rest overhead. We proposed that. It went through the peer review process. The peer reviewers raved, thought the comments—and I will show you the comments privately if you want, I don't want to show them to the media who wants them—but the peer review comments of our work to find a test and to do the treatment component were very, very positive. They really didn't like the animal and the basic chemistry studies on PB that we are doing. I think they misunderstood them. They don't like them. As a result, we got only a moderately good summary score. The Persian Gulf Veterans Coordinating Board looked at it, and no funding. The Defense Department then realized what had happened, came back to us and decided to give partial funding for the human studies. The leadership of the Presidential Advisory Committee went ballistic, along with some of the members of the Persian Gulf Veterans Coordinating Board, went to the Washington Post and smeared us, and some of the Defense Department authors of scientific studies are putting similar comments in the medical press.

You see, the problem is, if you step out and you really want to go against the policy, which I mentioned a while ago, you are going to get fried, and that is why nobody in the Defense Department or the VA or the CDC is going to do it, because they all realize they are going to get fried if they do it. Everybody will deny that, but look what happened to us. We ended up getting $3 million from the Defense Department with the invitation to come back and put our protocol, the second part that is going to cover 6 months worth of work, and we are about halfway into that now. We just put in another—two more grant proposals to cover the second 6 months and to cover a big survey. We are proposing to do a survey with Re-

search Triangle Institute actually doing the work, so it is independent from us, to see whether the syndromes we described can really be found in other groups.

I fully expect, Congressman, that this will not be rated highly by the peer review groups because it is flying in the face of stress and the accepted view, and it is also too much money. I think they will turn us down, in which case we will seek funding in the private sector as we have done before. But I know what to do with that blank check. It is all on paper already.

Mr. SANDERS. Do you have any thoughts, Dr. Clauw, or Dr. Reeves?

Dr. REEVES. Not talking about exact amounts of blank checks, I think that again, the type of work that is needed does not necessarily cost as much as everybody thinks. My own plan, or our plans at CDC that have been looking at this illness within the context of Gulf war, are that we are looking very carefully, with the people at the Center for Environmental Health, Dr. Barrett, who has the—we are trying to work with as many groups of investigators as possible to come to grips with a definition of illness. There are a variety of people looking at ways to analyze this, and in working with groups who are working independently, one can come up with case definitions and a case definition, as has been mentioned, is critical.

Mr. SANDERS. What about treatment?

Dr. REEVES. Before I would go to treatment, because that is not really in my purview, I am more interested, as I mentioned earlier, in preventing this, in looking for markers. In other words, I need to define an illness that I can treat. Again, in chronic fatigue syndrome and in collaboration with funding for people doing Gulf war research, we are looking at markers in an open-ended fashion, looking at molecular epidemiologic markers, again by pulling things together and using things from existing studies. One does not necessarily need a huge amount of extra resources. I think the treatment issues and again the prevention issues are dependent on a case definition and on some knowledge of the etiology.

Mr. SANDERS. Thank you. Anyone else want to comment on that?

Dr. CLAUW. I would just agree with what both people just said. I think that we are all talking about the same type of thing, and that in addition to what the Government is already doing, these types of institutes that would be able to do cross-cutting, multidisciplinary research will be helpful to look at these kinds of problems. I think that is what Dr. Haley was describing. That is certainly what I was describing earlier.

Again, I would say that it needs to be in addition to, not instead of, what the Government is doing. I looked at the list of projects that have been funded and I had a hard time finding any of them that I didn't think would lead to useful information or helping us really understand this problem. It is a huge problem, and it seems like there is a lot of money being spent on it, but given the magnitude of the problem, it is not that much.

Ms. HEIVILIN. Can I respond?

Mr. SANDERS. Yes.

Ms. HEIVILIN. I would add, I think that we should spend some time and money monitoring and documenting the health—the progression of the disease, the health of the veterans.

Mr. CHAN. I like to look at this whole thing very differently. I think if you can imagine any contingency in the future where our soldiers are going and that we have to sort of anticipate what might happen to those soldiers and to look at it that way, you know, find that a single person will not only be exposed to the potential threat that is there, but also the environmental side that is there, from malaria to infectious disease, and also what we impose on the body of the soldiers, maybe a dozen or more different vaccines in his body or her body, to put that under stressful conditions, not knowing what the future is going to be like, and only to realize that afterwards; the government may not even know where he or she was, did not track, did not know where they were taken, cannot accept the responsibility of taking care of them, did not track their medical records and so on. I think it is doable if we do it up front, because a lot of research and all of this kind of discussion I have heard from PB to anthrax vaccine is that that a single agent is safe, but no one ever tells me whether the measles or the plague, the vaccine A, the B, and the mumps and rabies and all of those things that they are given, you know—I mean I could see antibody running through their body all the time, and yet we don't know if that is OK.

So I think I would address it from that perspective, other than what new research needs to be done. I think we have to look at it. We know these things. We know ahead of time how the sand flies may cause harm to people and all these things that we give shots to those soldiers for, and I think it is time to do it right now, rather than wait until another potential Bosnia or someplace else.

Mr. SHAYS. You make a good point, Mr. Chan, and it is very well taken and I think others would agree.

We will conclude this hearing, but I first off want to thank Dr. Feussner for staying and listening to the second panel. That is very—I think it is important that you did it and I thank you. Dr. Gerrity, you are here as well. And also Dr. Winegar, I appreciate you being here. That is very nice and helpful. I would welcome—I would just thank our panel, probably put in a pitch I think about our working group, HHS, DOD and VA and one person from VA, it would be nice to get a few veterans in there, maybe a veteran who could just provide a reality to all of the researchers. Not a doctor; just somebody who would say, "yes, but."

I would ask any of our previous panel if they would like to just come to put something on the record, I would be happy to have you do that, just to make a statement. Do you, Dr. Feussner, just want to make a comment for the record? Dr. Winegar? I just want you to know you were invited to do that.

So thank you again. This hearing is adjourned. It was a very interesting hearing, and I appreciate all our participants and thank our reporters.

[Whereupon, at 2 p.m., the subcommittee was adjourned.]

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