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GULF WAR VETERANS' ILLNESSES: THE CURRENT RESEARCH AGENDA

HEARING

BEFORE THE

SUBCOMMITTEE ON NATIONAL SECURITY, VETERANS AFFAIRS, AND INTERNATIONAL RELATIONS

OF THE

COMMITTEE ON GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED SIXTH CONGRESS

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GULF WAR VETERANS' ILLNESSES: THE CURRENT RESEARCH AGENDA

WEDNESDAY, FEBRUARY 2, 2000

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON NATIONAL SECURITY, VETERANS AFFAIRS, AND INTERNATIONAL RELATIONS,
COMMITTEE ON GOVERNMENT REFORM,
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, Blagojevich, Tierney, Allen, Sanders, and Schakowsky.

Also present: Representative Metcalf.

Staff present: Lawrence Halloran, staff director and counsel; Robert Newman, professional staff member; Jason Chung, clerk; David Rapallo, minority counsel; Earley Green, minority assistant clerk; and Chris Traci, minority staff assistant.

Mr. SHAYS. I would like to call this hearing to order.

In November 1997, after extensive hearings on Gulf war veterans' illnesses, this committee found, quote, current approaches to research, diagnosis and treatment unlikely to yield answers to veterans' life-or-death questions in the foreseeable, or even far distant, future. We called for an aggressive, well-coordinated research effort, independent from constitutional inertia and bureaucratic self-interest, to support the goals of accurate diagnosis, effective treatment and fair compensation for all Gulf war veterans.

Since 1997, the Departments of Defense, Veterans Affairs, and Health and Human Services, have spent more than $121 million trying to meet basic research goals to better understand the extent, the causes and the cures of Gulf war veterans' illnesses. More than 150 studies have been funded. The Office of the Special Assistant for Gulf War Illnesses contracted for additional studies and surveys.

To assess the productivity of this substantial research program, we asked the General Accounting Office, GAO, to examine the extent to which the agenda is being managed effectively, efficiently and with an appropriate sense of urgency. Their findings validate our initial assessment and confirm our worst fears about the pace and prospects of the search for answers for sick Gulf war veterans.

The group charged to coordinate the research effort has not even assessed how well the current portfolio is meeting established objectives. More than half of DOD's total expenditures took place outside the multi-agency coordination framework designed to focus re-

search and avoid costly duplication. Nine years after the Persian Gulf war, basic questions remain unanswered. We still don't know how many veterans are suffering unexplained illnesses. We still don't know how their illnesses progress, and we still don't know if they're getting any better.

We are, of course, mindful of the incremental nature of scientific inquiry. Many Gulf war veterans' illnesses are difficult to diagnose, can only be treated symptomatically, and may be impossible to associate with a wartime exposure or event. But patience is no excuse for a lack of vigilance. We must be certain all Federal research into Gulf war illnesses is well designed, vigorously pursued, and keenly focused on the most promising hypotheses.

Our witnesses today represent the GAO, the Federal departments and agencies conducting Gulf war studies, and private researchers who have made some of the most significant findings in this area, often without Federal funding. We look forward to their testimony. And I might say, given the number of witnesses, it will be more testimony than questions.

Mr. SHAYS. My colleague, Mr. Sanders.

Mr. SANDERS. Thank you very much, Mr. Chairman, and thank you for all of your efforts over the last several years.

I will be brief. I think there's some good news, and I think there is some bad news out there. The good news is that when you and I and others began bringing this issue to the floor because we were responding to the pleas of thousands of Gulf war veterans all over this country who told us they were hurting, who told us when they walked into the VA hospital they were ignored or at best told they had a psychological problem, I think we can say fairly that, since that point, we have made some progress. That's the good news.

The bad news, as you've just indicated, that after all the large amounts of money that the government has spent on Gulf war research, the truth of the matter is that today we do not have a treatment for the close to 100,000 veterans who are hurting. We do not fully understand the cause of the problem.

What is the good news? The good news is that, over the last number of years, there have in fact been a number of studies which we hope are bringing us closer to the truth. And I will just point out a few.

Right now—and I see Dr. Jack Feussner here, and I'm glad he is here—there is an important study being conducted at the VA hospitals throughout this country testing a hypothesis. Microplasma infection may in fact be one of the causes of Gulf war illness, and a treatment protocol is being developed. That is a step forward.

Just the other day, we read in the papers that at Tulane University it appears that Gulf war veterans who are suffering from a variety of illnesses have antibodies to squalene in their blood. This may tell us something.

A couple of months ago, we heard from the Veterans' Administration. Despite, Mr. Chairman, all that we had heard in the past that pyridostigmine was ever so benevolent, it turns out that a study came out from them that says that may not be the case, and they're not going to rule that out as a cause of Gulf war illness. We have studies that suggest that veterans who are susceptible for

multiple chemical sensitivity may in fact have higher incidences of Gulf war illness than others. There are studies coming out of Texas that suggest that people who are suffering from Gulf war illness now have determinable brain damage that can be objectified and seen. There are a number of other studies out there as well.

Now, my conclusion is that some serious scientists in this country are making some serious progress. I am pleased to see that the VA is beginning, in terms of the microplasmic study, to begin to move forward, but clearly they are not doing it enough and fast enough.

My own hope, Mr. Chairman, is that we will be supportive of those people in academia who have begun to make some breakthroughs and give them the support that they need. The truth of the matter is that, from World War II to today, whether it is radiation illness, whether it is Agent Orange, whether it is Gulf war illness, the sad truth is that the U.S. Government has not treated veterans with the dignity and the care that they deserve. And I would hope that we support those men and women who put their lives on the line who are hurting today by supporting that research out there which is leading us closer to understanding the cause of this terrible problem and developing an effective treatment.

Mr. SHAYS. Thanks.

Before calling on the first panel, I would also like to welcome Mr. Metcalf, who has been very interested and active in this issue and welcome any statement you would like to make for the committee and also appreciate your participation in the hearing.

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

Thank you, Congressman Sanders, for signing my letter and for your testimony today.

I would like to thank the other members of the subcommittee for allowing me to participate in this hearing and express my concerns regarding the Federal Government's research efforts into the causes and treatment also of Gulf war illnesses. I am deeply grateful that you have remained steadfast in your efforts to try to find the truth and to require accountability.

This hearing is focused on the fact that the Federal Government has spent more than $133 million in research to determine the causes of Gulf war illnesses and to find treatments. I applaud this committee for asking what American taxpayers got for their money, $133 million. Sadly, however, I must state that, in my mind, far too little has been accomplished to actually help veterans suffering from Gulf war illnesses.

I would like to draw the subcommittee's attention to a new piece of research that could make a significant contribution in addressing the health issues of those suffering from Gulf war illnesses. The paper is "Antibodies to Squalene in Gulf War Syndrome," is an article that has just been published in the February 2000, issue of Experimental and Molecular Pathology. Today, I am providing copies of this important study for members of the subcommittee. Joined by several colleagues, yesterday I wrote to Secretary of Defense William Cohen asking for an objective analysis of this research.

This peer-reviewed article found anti-squalene antibodies in a very high percentage of sick Gulf war-era veterans. As a biomarker

for the disease process involved in Gulf war illnesses, the assay/blood test cited in the study could provide a vital diagnostic tool. I hope this will quickly lead to improved medical treatments for many who are suffering.

Many who have heard about this issue are anxious to understand the ramifications, especially those veterans and their families whose lives sadly have been directly affected. We certainly acknowledge the need for further research. However, that should not preclude a vigorous examination of the immediate benefits this study may provide medical practitioners treating those who suffer from Gulf war illnesses.

The House-passed version of the fiscal year 2000 defense appropriations bill included report language instructing the Department of Defense to develop and/or validate the assay to test for the presence of squalene antibodies. This action was taken in response to DOD unwillingness to cooperate with the March 1999, General Accounting Office recommendation. It is my firm belief that the integrity of the assay was the first step in finding answers.

Now that this study has been peer-reviewed and published, we need to take the next step and build on established science. An internal review by the same individuals within the DOD who were unwilling to cooperate for months does not constitute the kind of science that those who sacrificed for this Nation deserve. Given the published article, it seems prudent to use the assay if it could help sick Gulf war veterans. At this critical juncture, I fervently hope that Secretary Cohen agrees. All agencies charged with helping our Gulf war era veterans should closely review this now peer-reviewed study.

Mr. Chairman, I want to thank you again for your leadership and look forward to continuing to work with you to find answers and the best in medical treatment for our Gulf war era veterans. Thank you.

Mr. SHAYS. Thank you.

We've been joined by two other Members—Ms. Schakowsky from Illinois—and welcome any statement you would like to make.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman.

I just wanted to say that it was my honor to join Congressman Metcalf in that letter to Secretary Cohen asking for an objective analysis of the article, the study, the Antibodies to Squalene in Gulf War Syndrome, and certainly hope that we can do everything possible to quickly lead to improved medical treatments for the many, many who are suffering.

Mr. SHAYS. Thank you.

Mr. Allen, nice to have you here.

Mr. ALLEN. Mr. Chairman, I'm happy to be here. I want to thank you for holding these hearings. If I have other comments, I'll add them later. Thank you.

Mr. SHAYS. Thank you.

We have three panels. The first panel we have one speaker accompanied by someone else as well, and we have on the second panel five speakers and in the third panel four. The staff will pay for this later. But we will be very attentive; and it will, in fact, be helpful. There's really no way to get around it. We do need to hear

from each and every one of you, but we will have to give deference to the testimony more than to the questions.

Our first panel is Mr. Kwai Chan, Director of Special Studies and Evaluations Group, General Accounting Office, accompanied by Dr. Sushil Sharma, Assistant Director from the same group. And we are also going to have someone else as well, Dr. Betty Ward-Zukerman from the GAO National Security and International Affairs Division.

If you would all three stand and I'll swear you in.

[Witnesses sworn.]

Mr. SHAYS. The answer is yes on the part of all four.

Would you identify yourself for the record as well?

Mr. WOODS. My name is William Woods. I'm with the Office of the General Counsel of the General Accounting Office.

Mr. SHAYS. I appreciate your being sworn in in case we need to rely on you for an answer to a question. Thank you.

I ask unanimous consent that all members of the subcommittee be permitted to place an opening statement in the record and that the record remain open for 3 days for that purpose. Without objection, so ordered.

[The prepared statement of Hon. Helen Chenoweth-Hage follows:]

Statement of Congressman Helen Chenoweth-Hage
Subcommittee on National Security, Veterans Affairs and International Affairs
Committee on Government Reform
2154 Rayburn House Office Building
February 2, 1999

Thank you Chairman Shays. I would like to thank the Subcommittee for holding this hearing to examine the research agenda for Gulf War veterans' illnesses.

Mr. Chairman, since the end of the Gulf War 100,000 veterans have reported illnesses, rashes, and other ongoing health problems. Over the past four years, this Subcommittee has investigated Gulf War veterans' health problems and provided important oversight for federal research programs. Additionally, in examining the ongoing federal research efforts today, this Subcommittee will provide critical insight as to the progress federal agencies have made in coordinating their research activities and as to whether research objectives have been fulfilled.

However, the fact remains that many of our veterans are still sick today. These veterans risked their lives in service to this country to expel Sadaam Hussein from Kuwait. The least America can do is ensure that they receive the proper care and research into the illness that so many of them are experiencing. This subcommittee has provided important oversight in this respect, and I am sure that it will continue to do so in the future.

Just in the past few days, a peer-reviewed study was published in the most recent issue of *Experimental and Molecular Pathology.* This study revealed the presence of anti-squalene antibodies present in high percentages among Gulf War veterans. As this study demonstrates, much research into the cause of Gulf War veterans' health problems remains to be done. Solid results regarding these illnesses must be obtained.

The most recent GAO report regarding Gulf War veterans' illnesses indicates that, "Basic questions about the causes, course of development, and treatments of Gulf War veterans' illnesses remain unanswered" (*Gulf War Illnesses: Management Actions Needed to Answer Basic Research Questions,* GAO/NSIAD-00-32, January 2000, p.4) This is unacceptable. Better coordination of research is required for the veterans.

Mr. Chairman, thank you for scheduling this hearing today. I look forward to hearing from our witnesses and believe that they will be able to accurately answer the many questions and concerns that this subcommittee may have surrounding the coordination of federal research on Gulf War veterans' illnesses.

Thank you, Mr. Chairman.

Mr. SHAYS. I ask further unanimous consent that all witnesses be permitted to include their written statement in the record. Without objection, so ordered.

Mr. Chan, you have the floor.

STATEMENT OF KWAI CHAN, DIRECTOR, SPECIAL STUDIES AND EVALUATIONS GROUP, GENERAL ACCOUNTING OFFICE, ACCOMPANIED BY SUSHIL SHARMA, PH.D., ASSISTANT DIRECTOR, AND BETTY WARD-ZUKERMAN, NATIONAL SECURITY AND INTERNATIONAL AFFAIRS DIVISION

Mr. CHAN. Mr. Chairman and members of the subcommittee, it is my pleasure to be here today——

Mr. SHAYS. I'm going to remind you to put that mic down a little bit farther and turn it that way a little bit.

Great, thanks.

Mr. CHAN. It's my pleasure to be here today to discuss the results of our work evaluating the outcome of Federal investment on Gulf war illnesses research conducted by VA, DOD, and HHS.

Before I begin, Mr. Chairman, I would like to go back to our June 1997, report and repeat two of our major findings. First, we found that neither DOD nor VA knew whether ill Gulf war veterans had gotten better or worse since they were first examined. Second, we reported that the ongoing epidemiological research would not provide any meaningful information regarding the causes of veterans' illnesses.

Today I regret to report that little has changed. In spite of considerable additional expenditures, we still do not know whether our Gulf war veterans are any better or worse off since they were first examined. Basic questions about the causes and treatment of their illnesses still remain unanswered, and these agencies still have not adopted one or more case definitions that might focus Federal research efforts.

Let me discuss our results. I have four findings to report.

First, DOD, VA, and HHS spent over $121 million on research investigations in fiscal year 1997 and 1998. DOD efforts account for over 90 percent of that total. Over half was spent by DOD's Office of the Special Assistant for Gulf War Illnesses, which I will refer to as OSAGWI.

Our second finding concerned the results of these expenditures. In this regard, we have three observations.

No. 1, the Persian Gulf Veterans' Coordinating Board's Research Working Group has not published any assessment of the extent to which its specific research objectives have been satisfied. We recommended and the agency agreed that such an assessment should be published by the end of this year.

No. 2, most research is still ongoing. By mid 1999, of the 151 projects funded by the Federal Government, 30 percent had been completed. While OSAGWI has received 19 of the 20 reports due from its contractors, it has publicly released only 6 of them. Of these reports, 14 had remained in draft or in review status for a year or longer.

No. 3, even basic questions regarding the number of veterans with unexplained symptoms and the causes and progression of the illnesses remain unanswered. In addition, the Research Working

Group has not endorsed any case definitions that might focus Federal research efforts. Most of the federally funded epidemiologic studies have been descriptive and not designed to test specific hypotheses about causes of veterans' illnesses.

Our third finding pertains to the activity of OSAGWI. We found its research activities were not effectively coordinated with the Research Working Group. The rationale given to us was based on semantic distinctions. Both VA and DOD tell us OSAGWI's activities involve investigations rather than research and therefore are not subject to oversight or monitoring by the Research Working Group. This weak coordination resulted in some duplication of effort. For instance, OSAGWI, VA, and HHS commissioned separate reviews of the literature on the health effects of depleted uranium. In addition, OSAGWI and VA have funded RAND and the National Academy of Sciences respectively to perform literature reviews regarding potential Gulf war exposures.

Finally, with regard to the management of contracts supporting OSAGWI, we found that task orders worth over $20 million were awarded improperly, and the office discouraged competition for another task order by specifying a preferred vendor. Because OSAGWI is likely to continue to spend a significant part of its budget on support contracts, it needs to ensure that its contracts fully comply with applicable laws and regulations.

Mr. Chairman, this concludes my statement; and I would be happy to answer any questions you may have.

Mr. SHAYS. Thank you.

[The prepared statement of Mr. Chan follows:]

United States General Accounting Office

GAO

Testimony

Before the Subcommittee on National Security, Veterans' Affairs, and International Relations, Committee on Government Reform, House of Representatives

For Release on Delivery
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GULF WAR ILLNESSES

Basic Questions Unanswered

Statement of Kwai-Cheung Chan, Director, Special Studies and Evaluations, National Security and International Affairs Division

Mr. Chairman and Members of the Subcommittee:

We are pleased to be here today to discuss our recently completed report on the research and investigations conducted on Gulf War veterans' illnesses.[1] Many of the approximately 700,000 Gulf War veterans have complained of illnesses since the war's end in 1991, and over 10 percent have completed health examinations through the Department of Veterans' Affairs (VA) or Department of Defense (DOD). Some are concerned they are suffering from chronic disabling conditions because of exposures during the war to agents with known or suspected effects on health. In response to this concern, the government has funded research, investigation, and information activities through various agencies, including DOD, VA, and the Department of Health and Human Services (HHS). These agencies participate in an interagency group, the Persian Gulf Veterans' Coordinating Board, which was established in 1994 to coordinate these activities. The Coordinating Board's Research Working Group, currently chaired by the Department of Veterans' Affairs, focuses on research planning, review, and dissemination, but it is not authorized to manage or distribute the Departments' research funds. In 1996, DOD established the Office of the Special Assistant for Gulf War Illnesses to oversee DOD's efforts regarding illnesses being experienced by Gulf War veterans.

As requested, today we will discuss the expenditures on these efforts by the Departments of Defense, Veterans' Affairs, and Health and Human Services and our work to evaluate their results. Specifically, we determined

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[1] Gulf War Illnesses: Management Actions Needed to Answer Basic Research Questions (GAO/NSIAD-00-32, Jan. 6, 2000).

- the amount of money that these three departments spent in fiscal years 1997 and 1998 on research and investigation into Gulf War veterans' illnesses and health concerns,

- the results of the research and investigation spending,

- the extent of coordination between the Coordinating Board's Research Working Group and DOD's Office of the Special Assistant for Gulf War Illnesses, and

- the management of contracts supporting DOD's Office of the Special Assistant.

SUMMARY

I will briefly summarize our four principal findings before providing more detail.

- First, during fiscal 1997 and 1998, the Departments of Veterans' Affairs, Health and Human Services, and Defense spent more than $121 million for research and investigation into Gulf veterans' illnesses. The Defense Department spent $112 million of this total, mostly through its Office of the Special Assistant for Gulf War Illnesses.

- Second, results of the research and investigation activities are accruing slowly and basic questions about the causes, course of development, and treatments of Gulf War veterans' illnesses remain unanswered.

- Third, the activities of the Office of the Special Assistant are not effectively coordinated with those of the Research Working Group.

- Finally, work was improperly awarded to the Office's support contractors for tasks worth more than $20 million.

DOD SPENT MOST OF THE RESEARCH AND INVESTIGATION FUNDS

DOD spent most of the $121 million used for Gulf War research and investigation by the three agencies in fiscal 1997 and 1998. The Department of Health and Human Services reported it spent less than $2 million, the Department of Veterans' Affairs $7 million, and DOD $112 million. These amounts exclude expenses for examinations and clinical care of ill veterans. Within DOD, the Office of the Special Assistant spent the largest amount, $65 million, while other activities, such as the medical research efforts catalogued by the Research Working Group, accounted for $47 million.[2]

Representatives of the Office of the Special Assistant told us that the Office had projected spending $36 million in fiscal 1999 and $30 million in fiscal 2000. These officials told us in 1998 that they were seeking the guidance of the President's Special Oversight Board on DOD Investigations of Chemical and Biological Incidents to determine what portion of the Office's investigative work should continue and how it should reduce the role of the Office. However, funding for the Office is included in DOD's budget through fiscal 2005.

[2] The expenditures for VA's studies do not include overhead costs because indirect costs are included under VA's medical care appropriation. Similarly, the majority of HHS' expenditures represent direct costs only. DOD's spending does not include overhead costs for internal studies run by the Department but does for external ones financed by the Department. In addition, the numbers reported for the Office of the Special Assistant include overhead costs and some spending on veteran outreach.

BASIC QUESTIONS ABOUT VETERANS' ILLNESSES REMAIN UNANSWERED

Regarding the results to date of the three Departments' research and investigations, we have several observations. First, as of November 30, 1999, the Research Working Group of the Persian Gulf Veterans' Coordinating Board had not published an assessment of the extent to which the research agenda has satisfied the objectives it identified in 1995. These objectives include questions about the prevalence of specific health problems and exposures among the veteran population and the way the prevalence differs between Gulf War veterans and appropriate control populations. We recommended, and agency officials agreed, that a date should be established in 2000 for publication of this assessment.

Also, while findings from research are beginning to accumulate, most of the sponsored studies are ongoing or in review. By mid-1999, of the 151 research projects monitored by the Research Working Group, 70 percent were still ongoing, including 19, or about 30 percent of the 62 that were scheduled for completion by then. Group officials attributed the extended completion dates either to efforts to collect or incorporate additional data or to unanticipated delays, such as difficulties in securing approval to collect data or problems in locating and recruiting veteran participants.

In addition, DOD's Office of the Special Assistant for Gulf War Illnesses had received 19 of the 20 reports due from its major research contractors. However, only 6 had been publicly

released; the remainder was largely in various stages of interagency review. Fourteen of these reports had remained in draft or review status for a year or longer.[3]

While federally sponsored studies have resulted in some descriptive information concerning veterans' symptoms, many basic questions remain. Identification of the potential causes of veterans' unexplained symptoms has been difficult because researchers are faced by persistent problems in ascertaining veterans' specific exposures. In addition, the Research Working Group has not endorsed any case definition or set of such definitions that might focus federal research. These difficulties led us to conclude in our 1997 report that the many epidemiological studies being sponsored would not provide definitive information on the causes of veterans' illnesses.[4] In particular, difficulty in accurately classifying veterans by the levels of their exposure to specific agents makes it hard to detect associations between exposures and health outcomes.

Other basic questions remain unanswered 9 years after the veterans returned home. As early as 1994, a National Institutes of Health Work Group that met to consider research needs on Gulf War veterans' illnesses, observed that better estimates of the prevalence of symptoms were desirable. In 1997, we noted -- as did the Special Investigative Unit of the Senate Veterans' Affairs Committee -- that open questions included how many of the veterans who had been examined had unexplained illnesses or symptoms. However, a

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[3] For a review of the Office's investigatory activities, see Gulf War Illnesses: Improved Monitoring of Clinical Progress and Reexamination of Research Emphasis Are Needed (GAO/NSIAD-97-163, June 23, 1997).

[4] Epidemiology is the study of the distribution of illness. Epidemiological studies generally first describe patterns of illness, environmental factors, and exposures. Researchers then form hypotheses based on patterns seen in such descriptive data and conduct analytic epidemiological studies to test these hypotheses, often by comparing the exposures of persons who fit specific illness criteria to those who do not or by comparing rates of illness among persons with different levels of specific exposures.

September 1999 report of the Institute of Medicine noted that no systematic evaluation has been done to determine whether or how veterans' health status is changing.[5] Also, in its 1998 report to Congress, the Research Working Group acknowledged that no government research is specifically directed toward understanding the progress of Gulf War veterans' illnesses over time and that research should assess the long-term health of these veterans.[6]

Some data that might be helpful in answering such questions are being collected as part of a national health survey of Gulf War veterans being conducted by VA, but an analysis of these data was not available at the close of our review. In addition, an HHS-sponsored project, which began in 1997, is assessing the persistence and stability of veterans' symptoms over time. This study is planned to end in 2000.

We recommended that steps be completed to compile data on the number of Gulf War veterans with unexplained illnesses, the treatments they were receiving, and the success of these treatments. DOD partially concurred with this recommendation and VA did not concur. Neither agency opposed the collection of information on the number and health status of Gulf War veterans with unexplained illnesses. However, VA stated that it could not implement the recommendation as worded without specific case definitions (that is, criteria to identify distinct illnesses). DOD objected that veterans' illnesses were not amenable to a single, unifying case definition. Although consensus on a single definition

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[5] Institute of Medicine, Gulf War Veterans: Measuring Health (Washington, D.C.: National Academy Press, Sept. 1999), p. 3, 35.
[6] Persian Gulf Veterans' Coordinating Board – Research Working Group, Annual Report to Congress – 1998 (Washington, D.C.: PGVCB RWG, June 1999), p. 53.

would simplify this task, it is not essential. Nonetheless, we agree that some categorization scheme or set of working case definitions will be useful in counting the numbers of veterans that have unexplained illnesses of some type and we revised our recommendation to reflect this. In September 1999, the Institute of Medicine issued a report to VA which recommended a methodology for measuring veterans' health status. This approach is consistent with our recommendation that VA and DOD select a strategy for answering this question and compile the appropriate data.

ACTIVITIES ARE NOT EFFECTIVELY COORDINATED

The Office of the Special Assistant's activities have not been effectively coordinated with those of the Research Working Group to maximize the efficient use of resources. Group and Office representatives stated that the Office's activities involve investigations, not research, and were therefore not subject to coordination. However, in a 1997 letter to the Office of the Special Assistant, the Research Working Group clearly regarded some of the Office's activities as research. Regardless of whether the work of the Office is considered research or not, it describes the extent and nature of veterans' possible exposures to hazardous materials. Characterizing veterans' exposures is the focus of several of the research objectives the Group established in 1995, and the Office's investigations of potential exposures should be germane to researchers trying to identify the consequences of such exposure.

The lack of effective coordination between the Group and the Office also increases the potential to miss opportunities to take advantage of ongoing and completed work by other

agencies. For example, in January 1998, the Institute of Medicine presented a proposal to VA, which was funded under a congressional mandate, to pursue studies at a projected cost of $1.25 million to review, evaluate and summarize the available scientific and medical information regarding the association between Gulf War veterans' exposures and the adverse health effects they had experienced. However, in 1997, the Office of the Special Assistant contracted with RAND at a cost of more than $1.5 million to conduct a similar review.[7] In addition, the three Departments separately funded reviews of the health effects of depleted uranium. Better coordination of these efforts might have saved both time and money.

To prompt these offices to work more closely on behalf of all veterans, we have recommended that the three Department secretaries direct the Executive Director of the Research Working Group to effectively coordinate the efforts of the Office of the Special Assistant for Gulf War Illnesses with related activities of DOD, VA, and HHS to prevent duplication and improve the efficiency of resource use. We believe that greater cooperation, exchange of information, and coordination will help expedite the process and help find solutions the veterans need.

CONTRACTING FOR THE OFFICE'S SUPPORT SERVICES WAS FLAWED

With regard to the management of contracts supporting the Office, we reviewed four support agreements, which accounted for more than 91 percent of the $47 million the Office spent for support services. We found that two task orders worth over $20 million were awarded improperly, and the Office discouraged competition for another task order by

[7] The Office eventually authorized RAND work valued at $3.2 million.

specifying a preferred vendor. Because the Office is likely to continue to spend a significant part of its budget on support contracts, the Office needs to ensure that its contracts fully comply with applicable requirements.

We recommended that the Secretary of Defense direct the Office of the Special Assistant to replace an improperly awarded task order with a proper contracting arrangement as soon as practicable. Finally, we recommended that the Secretary direct the Office that all future support contracts should comply fully with applicable laws and regulations. DOD did not concur with these recommendations, stating that the Office of the Special Assistant does not have its own contracting officers and relied on the judgment of contracting professionals outside the office, who did not object to the Office's contract actions. We recognize that the Office of the Special Assistant relies on contracting professionals outside the office to execute its support contracts. Nevertheless, the office is, at a minimum, responsible for determining its requirements for support, a process that in one instance resulted in naming a preferred vendor and in another led to an overly broad statement of work. The effect of these practices is to discourage competition. It is important that both requiring agencies, such as the Office, as well as agencies that execute contracts, adhere to the statutes and regulations designed to maximize competition.

Mr. Chairman, this concludes my statement. I would be happy to answer any questions you may have.

Mr. SHAYS. The chair recognizes Mr. Sanders.

Mr. SANDERS. Thank you, Mr. Chairman.

Mr. SHAYS. I'm sorry. I do want to recognize Mr. Blagojevich.

Mr. SANDERS. Mr. Chan, thank you for your testimony.

Let me ask you a question. What concerns me is that a number of studies have been done, a lot of money has been spent. In your judgment does—do the people who are funding these studies now in the VA and the DOD and the relevant committees, can they come before us today and say, look, the good news is that we are making some progress here. We are looking at this. This theory has now been disregarded. We know this, we know that. Or are we going to continue to see a myriad of studies all over the place leading us nowhere?

The question is, 9 years later, where are we? Where are we going to go? I'll ask representatives of the VA and DOD this question in a little while.

But what have we learned? It doesn't do us any good to have a million studies if we don't have any conclusions. What have we learned? It sometimes sounds nice or it is a good press release. We are spending $5 million for another study. What have we learned? Where are we going? What are we trying to prove?

So what I'm asking you is, what hypotheses are out there based on all of these studies? Where do you recommend that we continue to go? What theories should we be pursuing?

It seems to me that in recent years, as I said a moment ago, there have been what appears to those of us who are laymen some breakthroughs. Are those being pursued?

Now, a couple of years ago, before this committee, we were told by many of the VA and the DOD people that the problem was "stress." Is that still a hypothesis that is being advanced or have we gone beyond that?

Bottom line is, after all of this money, where are we today? Where do you think we should be going?

Mr. CHAN. Should I answer question one or two?

Mr. SANDERS. Both.

Mr. CHAN. We said that there are over 151 of these projects and that Federal research began back in 1994, so if you look at it from that perspective, we are generating probably two projects a month over this period. So we have lots of work in progress.

And, initially, I think, we started very slowly. I'm talking about the agencies' acceptance that in fact the illnesses are out there. By the time they accepted it, I think they had attached to a specific hypothesis, which was stress, to the exclusion of any other kinds of hypotheses. When Khamisiyah came along, then it became another set of hypotheses about low-level exposure to chemicals and then suddenly have a whole set of different possible causes or agents. And so now what you see is really almost like fruit trees with lots of fruit hanging and we are picking one or the other.

I think you're right that, in a certain way, we reached a certain stage. Now there are, in fact, some scientific results that show promise; and we are beginning to find that—in fact, I think CDC had found that, through its Pennsylvania study—that there are potentially some broad case definitions to allow people to at least focus on where the efforts should be.

But generally, I think, a different way to answer your question, is that the impression from the outside is that the agencies are very slow in accepting that, in fact, they need to investigate in this area, that the pursuit of science is the end goal of this research, not treating the soldiers. So in 1997 when we testified before you, our comment was that in fact a lot of projects are focused on epidemiolog study and there are potential problems in gathering that information because of difficulty in recall and specifying locations and exposure and the problem of not having a case definition.

Mr. SANDERS. Let me just reiterate, Mr. Chan, and I'll end at that.

If we had before us today a panel of experts dealing with AIDS, for example, they could tell us over the last 10 years what has been discarded, what has been accepted, and where they are going and where they hope to be in the next 5 years. I have the unfortunate feeling, the unpleasant feeling that that is not the case with Gulf war illness, that we may well hear the same testimony, well, we're not quite sure. It may be stress. It may be not. Blah, blah, blah. And after $120 million there will not be somebody from the VA or DOD to say, well, we have discarded this theory. It is not stress, that is for sure, because of a, b, and c. We're narrowing in on this. We've made some progress on that. We're going to put more money into that, but that's no longer relevant.

Is my statement a fair statement?

Mr. CHAN. I believe so. I think initially DOD basically stated that there were no problems out there; and when we found there were some problems, they said, well, they are not unique. When we found there are unique things have been found then DOD says we need more research. That's the paradigm you have.

If I step back from it, my question would be not so much are these successful research projects but rather "now what?" Where do we go from here? At what point do we decide to emphasize moving on to diagnosis and treatment because the research really doesn't touch the soldiers in the way you intended.

Mr. SANDERS. I'm concluding by saying we hope the result—one clinical test that is out there is testing the mycoplasmic theory. The VA is doing that. We hope if that test turns out to be positive, we will in fact have a treatment. Other than that, I'm not quite sure I know what the VA and DOD are doing.

Mr. Chairman, thank you; and, Mr. Chan, thank you.

Mr. SHAYS. Ms. Schakowsky.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman.

Being new to this panel, I learn things every day that astonish me. That of the nearly 700,000 veterans of the Gulf war, I understand from our committee memo, 100,000 or more have been complaining of illnesses. And we hear about $121 million and all of these committees and 9 years. And so let me ask a couple of I think pretty obvious questions that come to mind.

In one part of your testimony, you said there is no government research specifically directed toward understanding the progress of these illnesses over time. What do you mean by that?

And in another part of this, the testimony, you mentioned an HHS project to assess the persistence and stability of veterans'

symptoms over time. What's the difference? On the one hand you say there isn't one and there's an HHS study.

Mr. SHARMA. I think what we said before in 1997, that since we cannot conclude what may have caused their illnesses because of the absence of precise and accurate information about how many agents they were exposed to for how long, et cetera, a different way of approaching this issue would be to understand the natural history of the disease by following these individuals over time and monitor the progression of the disease.

At the same time, you take a look at what kind of symptomatic treatment physicians are currently providing because they are being treated by a number of physicians all over the country. Some of those treatments may or may not be effective, and therefore you take a look at what works, what doesn't work, and then you share this information with the rest of the physician community.

That type of research was not being done and after a considerable amount of time, VA has now reluctantly agreed to do this type of work. The CDC report that we are referring to is a survey in which they looked at two points in time but this is the kind of work that should be systematically done.

Ms. SCHAKOWSKY. To followup on something that Mr. Sanders was saying, it seems like there's a lot of data and none of it fits together and none of it leads anywhere and none of it seems to make any sense in the end. You talk a good deal on the report about coordination. What can we do to get better coordination?

You have, for example, lack of coordination which could result in duplication as in the literature review contracts from the VA and DOD. The VA responded in comments to your draft report that these two projects used different methods, have different goals and are not duplicative. Do you agree?

Mr. CHAN. No. I think that example is symptomatic of the problem in the approach being taken toward research.

You know, literature review is great if the literature includes relevant cases, but basically they are not really there. The problems with pyridostigmine bromide have been known for a long time. I said, so what? What do we do from here?

I think there's a disconnect here basically between science and policy. And I really hate to bring it up at this stage like that, but, generally, the public wants answers to questions like who is sick, how many are sick, are they being treated, are they being taken care of, how well are they being treated, are they getting better, are they worse, is there something that is helpful, that can be shared with others? Those are the kind of questions people are asking.

The inside researchers are focused on testing specific hypotheses. Is it this agent, is it that agent, is it chemical, is it PB, is it Leishmaniasis, is it oil well fires, and so on. They focus on very specific agents and toxins that can affect the body. So the two types of questions are disconnected in a sense. Then when you find out that one agenct is an unlikely cause, the other one is also unlikely and so on, it doesn't satisfy the people who are left suffering.

I'm trying to look for an analogy. It's almost like if someone tells you we have reduced the sulfur level in the air by X percent, the

question that you want to ask is, can I breathe? We're not answering that. That's the disconnect I see.

So I agree that, in a way, we're advancing through hypotheses and find some interesting stuff. But in the end you find the people who are suffering just want treatment and attention.

Ms. SCHAKOWSKY. Thank you.

Mr. SHAYS. Mr. Allen.

Mr. ALLEN. Thank you, Mr. Chairman.

Forgive me for groping on this issue a little bit, because, obviously, there are those of you who spent a good deal more time trying to understand this than I have, but I am struck by a couple of your comments, Mr. Chan, and some other things that I have been through. I am just going to talk for a moment and then I would like your reaction to what I say. Because though I'm obviously in a field that is not my field, there are a couple of things that strike me about how this research might be going based on what you said and how it might be redirected.

It strikes me that to the extent—you just said that a lot of the research focuses on specific toxins as if the analogy were to find the particular virus that was causing a particular illness that basically acts the same way on all human beings and that, it strikes me, is a path of the research that may not be particularly productive because we may be dealing with something that is different.

And I'm going to mention now a woman in my district has just put together this collection called Casualties of Progress: Personal Histories from the Chemically Sensitive. Her name is Allison Johnson. And what she's done—she's published this at her own expense—is a series of stories. Six of them are stories of Gulf war veterans, but they are stories about people who are afflicted with multiple chemical sensitivity. And though I would not pretend to have read this, I only got this 2 days ago, what I would say is this.

It strikes me that you have very individual reactions of the multiple chemically sensitive to a wide variety of different kinds of—and I hesitate even to use the word toxins—chemicals of different kinds. But what's striking is the reaction. The symptoms may be different for different individuals; and, in fact, the causation, the chemicals, the agents that are causing a human being to react this way are different for different people. So to the extent we do research pursuing is it PB, is it the oil, whatever, that research is not as likely to lead anywhere productive.

What I am struck with from just glancing this moment at your report is appendix III and the failure and the effort to reach a working definition and, in particular, Mr. Haley's definition saying the three primary syndromes are impaired cognition, confusion-ataxia, this is page 31 of the report, and arthro-myo-neuropathy. I guess that's how you pronounce it. Isn't it the case that if we're going to get a grip on this problem that there needs to be sort of some consensus about how to go at it, what kind of problem we're dealing with?

To me, that's not so much a problem of research. It's a problem of conceptualizing what it is we're talking about.

And so what I guess what I'm asking is, is any of the research directed, first of all, specifically to the multiply chemically sensitive

to this sort of area and, second, is there in your opinion a focus of the research that is off track or needs to be changed or whatever?

That's a long, rambling statement, but I trust you can do something with it.

Mr. CHAN. Let me try.

I think the approach that's been taken over the past 9 years is the classic scientific approach one would take. That is, you look for possible agents and then determine potentially what's the exposure level, are there responses to it, are there potential causes and effects. If there is something, then what the diagnosis should be and then the treatment and measure outcome. That can be done if it's merely a single exposure, particularly if we're talking about a virus or other things of that kind.

I think that worked well in the past as a model that I've seen, and certainly there are lots of success stories from that. But I think—I tend to agree with you that this model may not work here, that a different model may be needed—not so much because scientists cannot arrive at conclusions but rather because you're talking about multifactorial effects.

The approach basically they have done is to take out the possible potential causes individually rather than accepting multifunctional causation as a possibility. That is, if you have one agent and find it can cause a 1 percent change and that's not significant, then you withdraw that and try another one. But putting them together may identify synergisms that occur. So I don't think the model used starts out looking at it that way.

Back in 1997, we felt that reliance on the traditional model of those responses and exposures which we didn't know much about for this particular war, then why not begin to diagnose the problem of the illness and then look for treatment that may turn out to be successful or even failure, to learn from that. That's how we ended up with our recommendations.

So I agree that you have to look at it differently.

Mr. SHAYS. Mr. Blagojevich.

Mr. BLAGOJEVICH. Thank you, Mr. Chairman.

First of all, Mr. Chan, let me just reiterate what Congressman Schakowsky said about 700,000 Gulf war veterans across the country. Of them, over 100,000 nationwide—in our State of Illinois, 3,500 of them are sick due to possible toxic exposure during the Gulf war, yet we have no diagnosis or a cure. My question to you, sir, is are we getting any closer to understanding the causes of the Gulf war illness? That's my first question.

Mr. SHARMA. I think there are several testable hypotheses that have been proposed in the published research that was done outside the Federal Government funded research.

One way to approach this issue is to test those hypotheses and see if indeed these individuals could get better.

The second approach is that if you're not going to do a hypotheses testing research, then you monitor these individuals over time because these individuals are experiencing symptoms which we may not be able to explain why, such as headaches or arthritis, but there are certainly some symptomatic treatments available. If those symptomatic treatments are effective and working and different people have different approaches for treating the

same thing, then that kind of information should be systematically collected, evaluated and then disseminated to others. This is currently not being done. Specifically, there are several testable hypotheses. They are not being proactively and vigorously pursued.

Mr. BLAGOJEVICH. You've mentioned that researchers face persistent problems in ascertaining veterans' specific exposures. What do you mean when you say that?

Mr. CHAN. Well, most of the data that's gathered through the registries and the studies, through telephone interviews, are based on recall. They ask questions not only on where you were. It's very difficult for a soldier to say I think I have been exposed to, let's say, chemical agents without knowing it's ever been used. That's the difficulty about it and that's what I meant by the need to know what you've been exposed to.

And even tracking who got what type of vaccine was difficult because the records weren't clear as well as how many PB pills that you would take and could you be affected by radiation because when we start bombing Iraq the radiation could leak out and so on.

The soldiers have no idea about what they were exposed to. All they know is they're feeling bad, and these are the kinds of symptoms that they have. So it's hard to reconstruct. And I think the example one would go back to is how difficult it was for us to track the use of dioxins such as Agent Orange back in Vietnam.

Mr. BLAGOJEVICH. Thank you.

Mr. SHAYS. Mr. Chan, we want our troops properly diagnosed. We want them effectively treated, and we want them fairly compensated. That's the bottom line. Do we know who is sick? Answering this way doesn't allow the recorder to respond. Do we know who is sick?

Mr. CHAN. We know some people who are sick. We don't know how many are sick and whether they are coming through the system or going to private physicians.

Mr. SHAYS. Do we know how sick they are?

Mr. CHAN. No.

Mr. SHAYS. Do we know if they are getting any better or any worse?

Mr. CHAN. We don't know.

Mr. SHAYS. Has there been any progress in GAO's 1997 recommendations to the research board?

Mr. CHAN. Well, there were a few more studies done, but generally I would say that concerning the progress to the end goal or treatment, no, there hasn't been any progress toward that.

Mr. SHAYS. To what extent does the Federal research effort on Gulf war illnesses include the development of a system to track, diagnose, and treatment outcomes of veterans?

Mr. SHARMA. I don't think there has been any systematic approach to following up these individuals over time. These agencies have not shared with us any such plan.

Mr. SHAYS. To what extent have the 21 major research questions set by the Research Working Group in 1995 been answered?

Ms. ZUKERMAN. The Research Working Group hasn't published an assessment of the extent to which those questions have been answered. They told us last year that some of them had been answered more completely than others.

Mr. SHAYS. So there have been—there's been none, correct?

Ms. ZUKERMAN. No assessment, that's right.

Mr. SHAYS. In what ways was OSAGWI's support contracts improperly awarded?

Mr. CHAN. I can answer in general. I think we looked at the contract and we found a problem with three of the contracts that were made. The problem with one was the statement of work was too broad. The second was that it was outside of the scope of the contract for what the contractor was doing. And, finally, OSAGWI made known up front that they have a preferred vendor so, as a result, they are the only one who actually compete for it. But the general principle we go by is that these contracts should be there to enhance competition, and by these actions we find that it did not enhance competition.

Mr. SHAYS. The President established a Research Working Group which was to get the DOD and the VA and HHS to work together. What are the consequences of OSAGWI's decision to avoid coordination of its activities with the Research Working Group?

Mr. CHAN. Well, the consequences that you end up having duplication. We have two examples of that, particularly with depleted uranium and PB.

Ms. ZUKERMAN. The review of literature.

Mr. CHAN. Right, the review of literature and so on. I think those were the examples. And I think the issue is really not so much of the costs involved but rather the lost opportunity to address other more important issues that need to be addressed.

Mr. SHAYS. In your four findings—obviously, we spent $121 million in 2 years. You said that the Persian Gulf War Coordinating Board's research group has not published any assessment to the extent of to which its specific research objectives has been satisfied. That's just a devastating finding. You said research is ongoing, and then you said OSAGWI has received 19 of the 20 reports due from its contractors. It has published only six. Of these reports, 14 remained in draft or review status for a year or longer. That to me is unbelievable. I'd like to know what the heck is going on as it relates to that point.

Mr. CHAN. Well, when we initiated our study at your request one of the purposes was to examine the contracts—particularly the ones with RAND—and at that time OSAGWI had six of the draft reports to review. And the review, that they're talking about, occurred when the contractor had delivered the product to DOD and then it was reviewed internally.

Mr. SHAYS. But it sounds like, one, you don't like the results or you're trying to change the results. But the bottom line is you paid for a study. Show us the study.

Mr. Metcalf, you have the floor.

Mr. METCALF. Thank you, Mr. Chairman.

Yes, Mr. Chan, I would like to ask you and your colleagues to comment on this new peer review study, if you will. Since it has now met the criteria that the Department of Defense had set forth, that is, peer review publication, and the antibodies to squalene and Gulf War Syndrome appears to me to meet that request, how should we best use what we now know to date?

Mr. CHAN. Well, at your request, we did a study and published it back in March of last year; and at that time I think we did not really evaluate the science of developing an assay to the squalene. We did find it's plausible that it could be done but certainly we did not examine the possible cause and effect in terms of the health of the veterans. But, nevertheless, I think the title of our report stated that questions about presence of squalene antibody in veterans, can be resolved.

I want to emphasize the words "can be resolved". At the time, the Department of Defense, particularly in the Office of Health Affairs, said we never gave them the squalene, and it's not our problem, and if indeed it's a case, it's important for the research to publish their results through a peer-reviewed journal.

At that time we also said that we disagreed with DOD in regard to that issue, because we felt that DOD should take the opportunity to begin addressing the potential and possibly resolving the question of whether or not the squalene antibody could be contributing to the illness of Gulf war veterans. And what we suggested was a very small step. The small step is, well, if it takes too much effort internally to develop such an assay and develop it, why don't we just go and ask the researchers at Tulane and try it out if in fact the researcher is willing to share their own assay. And DOD did not do that. And so, as a result, I think finally this article has been published; and I hope DOD would consider this thing seriously.

Mr. METCALF. Has there been a serious examination of the role that vaccinations may have played in Gulf war illnesses and should there be a serious examination in your view by the DOD?

Mr. CHAN. I think the answer is yes, but I would like to raise it in light of—unfortunately, I'm trying to recall.

I think it's important to understand—not just to focus on the Anthrax vaccine per se but also that the soldiers received over a dozen and a half different vaccines during that period because they are being deployed into areas where it's unclear how well they are prepared to meet the environmental conditions. So not only did they have the normal type of vaccines but also vaccines against biological agents and even countermeasures against chemical agents such as PB pills and so on. So there are a lot of things that the soldiers received. There's no study as to whether the combination of these things the soldiers received could have any effect on them in general.

Mr. METCALF. Thank you.

Mr. SHAYS. We will go back to other committee members and see if they have a followup question, but I want to just ask you how many peer review studies has Federal research spending produced in the last 2 years?

Ms. ZUKERMAN. We looked at those projects that had been completed by the end of 1998 to see what portion of the completed projects had resulted in one or more peer reviewed reports, and we found that about two-thirds of them had. I think Dr. Feussner can probably provide current information on the total number of publications.

Mr. SHAYS. Thank you.

Mr. Sanders.

Mr. SANDERS. Thank you, Mr. Chairman.

Let me get back to a point that I tried to raise before. During World War II, the U.S. Government wanted to build an atomic bomb, and they developed—that was the end goal. For better or worse, they wanted an atomic bomb.

The President then put together a project called the Manhattan Project. They assembled the best minds in the country. They went forward in a relatively short time. They got their goal. My thought had been from the very beginning that, to solve the problem of Gulf war illness, that is something that we had to do as well. What I am stunned and distressed about is the absolute lack of direction.

Now, the military knows something about winning wars. It doesn't matter if you win a battle over here or if you do something over there. The goal is to win the war.

Our goal is to understand the cause of Gulf war illness and to develop an effective treatment. That's clearly what we want to do. We don't want to scatter over a million different directions. We need a general, somebody who is ultimately saying this is good research. We're gaining on it. This is useless, forget it. Let's keep going. We're putting our money in here.

Clearly, it seems to me that has not been the case, at least from the U.S. Government. That's the bad news.

The good news, it seems to me, is that, as I think Dr. Sharma indicated, outside of Federal funded research, there appears to have been some breakthroughs. None of us to the best of my knowledge here are scientists. That's our problem. We have to rely on you and others to tell us the truth and the validity of some of the studies that we're seeing.

This is my question. Mr. Metcalf raised this a moment ago. Just the other day at Tulane a study comes out that says that it is, in layman's terms, if somebody has squalene antibodies in them, it is likely that they are suffering from Gulf war illness. If they do not, it is likely they are not suffering. From a layman's point of view, this seems to be a breakthrough done outside, I guess, of federally funded research. Simple question. After 9 years, has the U.S. Government itself, the VA, the DOD, been doing research on this issue?

Mr. CHAN. Not in terms of the effect of squalene on individuals, but they have done research using squalene in other vaccines.

Mr. SANDERS. Let me again, as a layman, if it turns out that he has squalene antibodies, he does not have squalene antibodies, he has Gulf war illness, he does not. Am I wrong in suggesting that is a significant breakthrough, that we have learned something?

Mr. CHAN. Potentially, yes.

Mr. SANDERS. Potentially, yes. It stuns me that we need Tulane to come up with this, and where was the VA?

Dr. James Fleckensteen from the Texas Southwestern Medical Center says, according to the AP, brain scans of soldiers who believe they suffer from Gulf war illness indicate evidence of brain damage. Now, again, I don't know whether it's true or not. That's what Dr. Fleckensteen says.

If I go to the VA or the DOD, what are they going to tell me about those studies? Have they tested that hypothesis? Has the VA or the DOD said, yeah, we've done a brain scan. There's brain dam-

age. He was in the Gulf war. We have learned something. He may have a treatment.

What has the U.S. Government done with that? Anything?

No, OK. Multiple chemical sensitivity, Tom Allen talked to that, and I talked to that particular woman on the phone. I have talked to hundreds of veterans in the State of Vermont who are suffering from Gulf war illness. Some of them tell me when they are around perfume, they get sick. If they walk through a grocery store and detergent smell comes up, they become sick. What studies have been done to say are these guys crazy or have they been exposed to chemicals and do more chemicals impact them?

If I am suffering from multiple chemical sensitivity, the last thing that I want is to be eating certain foods that make me ill. What does the U.S. Government have to say about the truth about that hypothesis? Does the Government say we are going to pursue that? Are there any studies to help me with whether these people are crazy or not?

No.

You remember years ago we heard shocking testimony about the potential of pyridostigmine bromide. I gather a number of months ago the VA said yeah, we cannot rule that out.

I mean, we cannot rule that out.

What studies have been done to tell us if in fact pyridostigmine is part of the problem? Have they told us after $120 million that we cannot rule it out?

Dr. Robert Haley said that a genetic trait can predispose people to Gulf War Syndrome. People can have the same exposure, but with a genetic trait, you are more likely to get sick. Is Haley right or wrong?

In other words, there is some important research taking place out there. We are not scientists. We can't judge the validity of that. Some people are making important statements which if they are correct sounds to me like we are going in the right direction. Who in the Government is making the judgment no, this is wrong, we have tested that. That is nonsense, this is right. Who is the general in charge of telling us what direction we should go?

There is some good news, Garth Nicolson out in California had a hypothesis that mycoplasma infection might be a cause. The VA is testing that hypothesis. The VA is doing the right thing.

But where else is the VA doing the right thing to validate or not these and other hypotheses. That is my question?

Mr. CHAN. Well, I think what you've said describes the basic frustration that we hear from the veterans about the process. They don't feel that the agencies are hearing them, representing them, responding to them to address those issues in a vigorous way. They raise all kinds of questions and those are pretty well known questions that you brought up. It requires an extraordinary effort to have the agency to initiate something that is coming from the outside.

So I think there is a natural distrust of the agency as a result. Therefore, even when vigorous research done by the Federal Government comes out as saying that there are really no problems out there with this particular exposure, it is difficult to make it believable because I don't think if you look at the structure that is made,

the veterans are not represented in terms of the voices within the VA, DOD and HHS.

So that is what I meant that there is a real disconnect here in terms of science and policy. I am not questioning the science and the research done, let me make sure that you understand that. But at the same time, veterans are saying, "That is not what is happening to me and who is listening to me?" First they say, you know, the diseases you mentioned are not in ICD–9 code; and, therefore, we don't consider those. Then we go to the next thing.

Yet then you come out and say even though there is a higher prevalence of this kind of disease, it is not unique. So then you begin to say, what do I have to do to prove to you—and I am speaking from the veterans' point of view—that I am sick?

You see what I am saying? We keep on raising the bar to a different level.

Mr. SANDERS. Let me jump in and conclude my remarks. Mr. Chairman, what I have concluded and what Mr. Chan has said, what we are dealing with is a new type of illness. If someone was wounded in battle with shrapnel or gunshot wounds, I suspect the VA and the DOD is best to treat those problems. But we are dealing with something which is new and different. There is not familiarity or an openness to understanding that new type of illness which may have been caused by environmental degradation and toxicity and so forth and so on.

It seems to me, Mr. Chairman, that we have got to conclude that while there is some important research going on around this country, the Federal Government is not taking advantage, it is not trying to grapple with that research and give us a direction where to go, and I think we have got to conclude that ultimately we should be taking the responsibility for going forward out of the Federal Government and giving it to those people who believe that there is an illness and who know how to manage the research so we finally will understand the cause of this problem and develop a treatment. I think you will agree, Mr. Chairman, 5 years from now we don't want to go through a similar hearing.

Mr. SHAYS. Thank you. Ms. Schakowsky.

Ms. SCHAKOWSKY. I have to say I was stunned once again when the chairman asked a series of obvious and very simple questions, the response to which was we don't know.

When I look at the research objectives identified by the Research Working Group of the Persian Gulf Coordinating Board, the 21 questions that were asked, 11 of those questions would indicate to me that you have to go to the veterans themselves.

The first question, what is the prevalence of symptoms, illnesses in the Persian Gulf veteran population? Questions like do Persian Gulf veterans have a greater prevalence of altered immune functions? There are 11 questions that deal specifically with the veterans themselves.

Then I look at the reports received and released, the research which has been done, the many studies which have been done, and what I, in looking through these, and again I am not a scientist, what I see is two which would address themselves specifically to the veterans. One that says birth defects among children of Gulf war veterans and potential nerve agent exposure, a report which

was completed in draft of 1998 and has not been released, and a comprehensive clinical evaluation, reports on findings from a telephone survey of Persian Gulf war veterans, a draft submitted in 1997 and not released, so when you talk about a disconnect, it seems like all of the money, and it is clearly considerable, $121 million, not all on research, but why is it that the studies which have been done seem not to connect with the research questions that have been asked? And why do so few of them actually focus on the veterans?

Mr. SHARMA. I think you have really hit on a very important issue. Questions have been raised about the credibility of the Federal research in this arena. When we went out and talked to the veterans, there was an overwhelming perception that the Federal Government is only interested in demonstrating that their illness is not unique or it is psychological. And if much of the findings of the federally funded research shows there is no difference. No difference does not imply that they are no illness. We still need to provide them some treatment, and we also must pay attention to what may have caused their illnesses.

Our in depth examination of that research showed that because there are some significant methodological problems with that research that would question the conclusions that have been reached.

One in particular that I will discuss with you is the birth defect studies. In that study they looked at——

Ms. SCHAKOWSKY. I'm sorry, which study?

Mr. SHARMA. The birth defects.

Ms. SCHAKOWSKY. Thank you.

Mr. SHARMA. First of all, they only looked at the military hospitals in that study, and we know that if you are going to have a complicated pregnancy, that you are more likely to be referred out.

Second, they only looked at those who were on active duty so it wasn't a very comprehensive, well-designed study which would allow you to conclude definitively on this issue, but the way that the study was presented, case closed. That brings some question into the minds of some of the veterans who are experiencing these illnesses.

Ms. SCHAKOWSKY. Why was that study not released? It says here no.

Ms. WARD-ZUKERMAN. The report that was done for us, we looked at the rates of release among products due from OSAGWI's research contracts just to see how productive their expenditures in that direction had been. We didn't draw any conclusions about why they were not released.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman.

Mr. SHAYS. Thank you, Ms. Schakowsky. Mr. Blagojevich.

Mr. BLAGOJEVICH. First of all, Congressman Sanders, the last time anyone suggested I had brain damage was the last election.

Let me followup on what Congressman Sanders and Congresswoman Schakowsky asked the panel. What exactly is the Research Working Group charged with coordinating?

Ms. WARD-ZUKERMAN. They are charged with coordinating research in general. There is nothing in the law to prevent them from coordinating other things. They are just to organize the Federal research effort.

Mr. BLAGOJEVICH. And that includes only medical research or other things as well? What would you say that their jurisdiction is, or where is it established?

Ms. WARD-ZUKERMAN. There is no reason that they could not coordinate with, for example, the Office of the Special Assistant and its work on exposures.

Mr. BLAGOJEVICH. Let me be more specific. Which agencies are currently operating projects that are coordinated through the Research Working Group?

Ms. WARD-ZUKERMAN. The Department of Defense, Health and Human Services, Veterans Affairs. At one point they had a representative from the Environmental Protection Agency.

Mr. BLAGOJEVICH. Is there anything that you can tell us about what we might need to go forward to make serious progress in these research efforts, something positive to suggest here about the future on this?

Mr. SHARMA. As Mr. Chan mentioned earlier, we need to be proactive. We have several testable hypotheses out there. They have been published in peer reviewed journals, and we must have an open mind and aggressively pursue those hypotheses.

When we look at the portfolio of the existing research, we still see that those researchers from the private sector that have come out with some testable hypotheses are still not being funded by the Federal Government. A couple of them initially did get funded through OSAGWI's efforts, but later on the funds were withdrawn so they still are not receiving any Federal support. It is very difficult to explain why or why not. When they come, you can ask them and they will be able to address this issue better.

Mr. CHAN. Let me answer the question a different way.

I believe what I said earlier about the mismatch between public policy and the science side, particularly in the questions that Mr. Allen had asked. When I mention things such as disconnect, to me it needs to be a totally different way to look at science and how to approach it.

To me it seems like science has a tendency to look at research as an end goal rather than treating people as an end goal, and I am not denigrating science in any sense, but each time you find some findings such as what was done in the RAND study, what is the bottom line. The bottom line is we need to do more research.

So you find from the general public's point of view there is a great finding, we got something after a long time of reviews and so on, but let's look some more. Let us be sure. I think we can never reach that stage where we are so certain about cause and effect even on a single agent.

So to keep on pursuing it to the nth degree I think it is fine from the science point of view in terms of research, but from the health side, I don't think that model is the best way. I am not taking a position and discussing this in terms of what one would question in terms of where does one go from here, but I think the kind of research that Mr. Sanders talked about are people with expertise out there who say hey, based on the description of these patients, I have similar kinds of experience with them. Let me try that out. It is more from that direction than to say I need to know exactly what they are exposed to and what the dose is and what kind of

response are they having. Are they common to a single person, is it only applied to women versus men and all of that stuff. They just say hey, this looks like something that I am aware of, and they talk a long time before the agency would accept putting money in, and it is usually through congressional pressure.

So in that sense I am talking about the process itself. It needs to be examined from that light because otherwise we can never solve the problem. Maybe we will never know what caused these illnesses, but at the very least, we try our very best to take care of the soldiers, and they are indeed sick; and meanwhile science can march on on its own.

Mr. SANDERS. Mr. Chan, isn't really what you are saying is that in one sense we are looking at theory, and in the other sense we have a soldier who is sick and after 9 years of research, what is the treatment? Is that what you are really saying?

Mr. CHAN. Yes.

Mr. SHAYS. Mr. Allen.

Mr. ALLEN. Mr. Chan, thank you. I think what you were saying just now is the heart of the matter. It comes back to what I was saying earlier about there needs to be a conceptual shift here in terms of the objectives. While the conversation has been going on, I looked back at the research objectives identified by the Research Working Group, and it is interesting. You add up the number of questions that are about specific exposures, and then you add up the number of questions about specific symptoms in this group as opposed to the control group, and you have pretty much exhausted the entire list.

If our focus were on the veterans, and you just said that certainty in determining cause and effect, you said in so many words, is not achievable perhaps in this area. Or at least if it is achievable in some measure, it will take us some period of time to get there. And the focus really should be dealing with the veterans' problems as they exist and figuring out how to help them. There needs to be I would say a new focus to the research.

I have to say while I am here looking through this report, I was struck by appendix 6, the comments from the Centers for Disease Control and Prevention because they refer to two studies, one a health assessment of Gulf war veterans from Iowa and a CDC-Air Force study, and I want to mention that CDC-Air Force study. On page 54 they defined a case as having one or more chronic symptoms from at least two of three categories, fatigue, mood cognition and musculoskeletal. So they are not requiring that each case be exactly the same, but are saying two of these three categories you would have to have a symptom. And it is categorized as mild to moderate or severe. The prevalence of mild to moderate and severe cases were 39 percent and 6 percent respectively among 1,155 Gulf war veterans. Versus 14 percent compared to 39 percent and 0.7 percent compared to 6 percent among 29 nondeployed veterans.

The interesting thing about this is that they found no association between the chronic multi-symptom illness and a variety of factors involving service in the Gulf war. They also found these symptoms were prevalent in 15 percent of the control group. Think about that.

That means that the Gulf War Syndrome is a subset of a larger problem. And so to the extent we are focused on specific chemicals in the Gulf war, we are going to miss the point in part, that if it is something like multiple chemical sensitivity, it is prevalent in the rest of the population, too, and we would advance our research about Gulf war if we looked at the rest of the population that has these symptoms and if we refocused the research on trying to deal with the symptoms and with the veterans and not the particular chemical that may or may not have been present in the Gulf war.

I guess there is not a question buried in there, but is that a direction that we ought to move in?

Mr. CHAN. I think, you know, I would agree with you that we should look at it in a different way and see if we can really resolve some of these issues. I agree with you, yes.

Mr. SANDERS. Tom, if I can interject, and I agree with everything that you have said, after years of discussion about multiple chemical sensitivity, to the best of my knowledge the U.S. Government does not own one what we call environmental chamber by which you can begin to treat and better understand multiple chemical sensitivity. A few million dollars, and we still don't own that.

Mr. SHAYS. I would share with you the observation that Henry Kissinger made of Jimmy Carter's foreign policy and say that I think it applies to the Research Working Group. He said when you don't know where you are going, any road will get you there.

We will go to our next panel. It is comprised of five people: Dr. John Feussner, Chief Research & Development Officer, Department of Veterans Affairs; Dr. John Mazzuchi, Deputy Assistant Secretary for Health Affairs, Department of Defense; Dr. Robert Foster, Director of BioSystems, Department of Defense; General Dale Vesser, U.S. Army (Ret.), Deputy to Special Assistant for Gulf War Illnesses, Department of Defense; and Dr. Drue Barrett, Chief Veterans Health Activity Working Group, Centers for Disease Control & Prevention, DHHS. I invite all our witnesses to stand, and I will swear them in.

[Witnesses sworn.]

Mr. SHAYS. I note for the record that all five witnesses have responded in the affirmative.

We will do it in the order that I called you. Let me just say that any comments that you want to make about observations about the first panel are welcome. This is your opportunity to make your points.

Dr. Feussner.

STATEMENTS OF JOHN FEUSSNER, M.D., CHIEF RESEARCH & DEVELOPMENT OFFICER, DEPARTMENT OF VETERANS AFFAIRS; JOHN MAZZUCHI, PH.D., DEPUTY ASSISTANT SECRETARY FOR HEALTH AFFAIRS, DEPARTMENT OF DEFENSE; ROBERT FOSTER, PH.D., DIRECTOR, BIOSYSTEMS, DEPARTMENT OF DEFENSE; LT. GEN. DALE VESSER, USA (RET.), DEPUTY TO THE SPECIAL ASSISTANT FOR GULF WAR ILLNESSES, DEPARTMENT OF DEFENSE; AND DRUE BARRETT, PH.D., CHIEF, VETERANS' HEALTH ACTIVITY WORKING GROUP, CENTERS FOR DISEASE CONTROL & PREVENTION

Dr. FEUSSNER. Thank you, sir. Mr. Chairman and members of the subcommittee, thank you for the opportunity to discuss research in Gulf war veterans' illnesses today. I do request that my formal statement be entered into the record as if read.

Mr. Chairman, at the outset let me say that as a physician and scientist with over 25 years experience I believe that the research challenge posed by Gulf war illnesses represents one of the greatest recently faced by the medical research community. These veterans' illnesses, their fears about their current and future health, their frustrations with a paucity of hard answers and ready treatments motivate all of us to persist in our efforts to understand the nature of their illnesses, to explore new treatment strategies, and to be responsive when new concerns or potential illnesses arise. In my opinion these veterans earned and in fact deserve every consideration and every effort that we can muster on their behalf.

Mr. Chairman, by year's end the Federal Government will have expended approximately $159 million for health research in the Gulf war. Right now there are over 150 projects in a research portfolio. To date 47 projects have been completed, resulting in 98 peer reviewed publications in the scientific literature. There are currently 116 principal investigators from DOD, VA, HHS, universities and other nongovernment organizations engaged in this effort.

Because of the obvious importance of our ensuring appropriate effective treatment of Gulf war veterans' illnesses, my office invited proposals for multi-center trials for candidate treatments of medical syndromes or illnesses among Gulf war veterans. The VA Cooperative Studies Program is conducting two treatment trials known as the ABT, for antibiotic treatment, and EBT, for exercise and behavioral treatment. Patient characteristics for entry into both of these trials are similar. All Gulf war veterans who served in the Gulf between August 1990 and 1991 may participate. Patients are considered eligible for enrollment into the trial if they have at least two of three symptoms: Fatiguing illness, musculoskeletal pain and neurocognitive dysfunction.

The ABT trial, the antibiotic trial, seeks to study 450 Gulf war veterans at 28 sites throughout the United States. The hypothesis of this study is antibiotic treatment directed against mycoplasma species would improve functional status of patients with Gulf war veterans illness who are tested as mycoplasma positive at baseline. Early demographic information from the study shows that 15 percent of the participants are women, nearly 20 percent are minority groups, and about 70 percent are currently employed. Nearly 85

percent currently enrolled in this study have all three symptoms that I mentioned earlier.

The EBT trial seeks to study about 1,350 Gulf war veterans at 20 sites throughout the United States. The primary hypothesis is that aerobic exercise and cognitive behavioral therapy will significantly improve physical function in veterans with Gulf war illnesses and that the combination of CBT and exercise will be more beneficial than either treatment alone. So far nearly 500 veterans have joined this study.

Mr. Chairman, I now want to update you on a national survey of Gulf war veterans authorized by public law. The survey has been conducted in three phases. My office awarded funds for Phase III of the National Health Survey in November 1998. Currently 16 sites are participating in this nationwide study, which involves special examinations, including neurologic, rheumatologic, psychologic and pulmonary or lung evaluations. To date over 1,000 veterans have participated in this study and 1,230 spouses and children of these veterans have been examined.

Our broad research partnership has yielded important new information about our veterans and their health problems. Mr. Chairman, I would like to share some of these with you today.

The Iowa study of Gulf war veterans indicates that nearly 90 percent of veterans rated their health status as good to excellent while the remainder rated their health status as fair to poor. Of Gulf war veterans, 14 percent said they experienced a significant decline in their health status. Based on VA and DOD mortality studies it appears that there are not more deaths from disease-related causes among Gulf war veterans, but we continue with this study.

From a DOD study, infants of Gulf war veterans have not experienced a greater prevalence of birth defects but studies here also continue.

The Baltimore VA is following 33 United States soldiers wounded by DU during the Gulf war. The team recently demonstrated elevated urine uranium excretion by these soldiers who have retained DU shrapnel. Importantly, there is no evidence of a relationship yet between the uranium excretion and kidney function. While we have no evidence of adverse outcomes from the uranium exposure, these veterans remain under close surveillance.

One chemical study in mice indicated, for example, that swimming stress increased penetration of pyridostigmine bromide across the blood-brain barrier. We had discussed that study in our February 1998 hearing. However, other studies in Guinea pigs exposed to extreme heat stress suggested that PB does not cross the blood-brain barrier. Yet another research project recently reported that the effects of low-dose PB on the neuromuscular junction were fully reversible following cessation of PB treatment.

The Research Working Group will continue its research on the toxicology of such chemicals. Veterans of the Gulf war have voiced concerns about possible association between ALS, amyotrophic lateral sclerosis, and service in the war. Although there is no indication of an excess rate of ALS, available data may underestimate the true rate. The VA is leading an effort to identify all cases of ALS among Gulf war veterans. This case finding effort will take

about 1 year and will provide definitive information about the rate of ALS among Gulf war veterans.

Mr. Chairman, thank you for giving me the opportunity to appear before your subcommittee. My written testimony covers in more detail these and other matters of concern to the subcommittee. I conclude my remarks now and will await your questions.

[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 National Security, Veterans Affairs, and
International Relations Subcommittee
House Committee on Government Reform

Research on Gulf War Veterans' Illnesses

February 2, 2000

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 (PGVCB).

In your invitation to this hearing, you indicated that the purpose of the hearing was to examine the pending report of the General Accounting Office (GAO): ***Gulf War Illnesses: Management Actions Needed to Answer Basic Questions.*** Indeed, VA commented on the draft report last summer; until today we have not seen the final report. Nevertheless, as I update your Subcommittee on our research concerning Gulf War veterans' illnesses, I have attempted to incorporate appropriate references and sensitivity to the GAO's work. While we did not agree with everything the draft report contained six months ago, we do agree that we should continue reviewing these matters as we develop future plans and studies.

Mr. Chairman, 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.

An important function of the RWG is programmatic review of, and recommendation to, funding agencies on research proposals that have been competitively and scientifically reviewed. The RWG continues to work diligently to foster the highest standards of competition and scientific review for all research on Gulf War veterans' illnesses.

As an operational policy, the RWG works through the line management authority each department maintains over its intramural scientists, extramural research program managers, and budgets.

By drawing together the three Departments (Defense, Health and Human Services, Veterans Affairs), the RWG has been able to develop an overall research strategy, serve as a common forum for researchers to present ideas and findings, and collectively respond to emerging research issues and problems.

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 (IOM), the National Institutes of Health (NIH); the Senate Veterans' Affairs Committee Special Investigations Unit; several Congressional committees including this Subcommittee; the Presidential Advisory Committee on Gulf War Veterans' Illnesses; independent scientists; and Gulf War veterans themselves. The RWG has used advice and information from these sources in developing and implementing a research strategy embodied in ***A Working Plan for Research on Persian Gulf Veterans Illnesses***. This strategy was first released in August 1995 and revised in November 1996. These documents resulted in twenty-one research objectives. The RWG is currently developing summary updates of these research objectives, work, which should be finalized prior to the end of this fiscal year. This plan is responsive to the draft recommendation of GAO that we publish an assessment of progress on the 1995-96 research objectives stated in the working plan.

Mr. Chairman, 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 RWG;
- Organization of annual meetings for 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; and
- Development of treatment trials for Gulf War veterans.

To date, the federal government is projecting cumulative expenditures of $159 million for Gulf War research from FY 1994 through FY 2000. There are over 150 projects at various stages of completion in the research portfolio on these veterans' illnesses. In the past two years alone, 30 projects have been added to this portfolio. Research projects have been funded in the categories of basic research and applied research such as clinical epidemiology and population-based epidemiologic research. Thus far, the overall emphasis of research has been in the areas of the brain and nervous system and in symptoms and general health of Gulf War veterans. After these, the greatest research emphasis is in diagnosis. To date, 47 federally funded projects have been completed resulting in a total of 98 peer-reviewed publications in the scientific literature. Government and non-government researchers conduct research on Gulf War veterans' illnesses. There are currently a total of 116 principal investigators, including 25 from DoD, 38 from VA, 4 from HHS, 32 who are university-affiliated, 5 non-U. S. counterparts, and 12 from non-government organizations other than universities. All projects and their categories are described in complete detail in the ***Annual Report to Congress*** for 1998. The next annual report will include research updates through calendar year 1999. We believe that this kind of collaboration within the federal medical and research communities is consistent with that which was recommended in the GAO's draft report.

Other highlights of the ongoing research efforts on Gulf War veterans' illnesses include the following:

In early 1997, VA and DoD tasked the Medical Follow-up Agency (MFUA) of the Institute of Medicine to undertake a feasibility study on the potential to do follow-up of individuals at Aberdeen Proving Ground to examine for potential 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 as a part of their research on the health effects of low-level exposure to nerve agents dating back to the 1950s. The MFUA completed the pilot study in 1998 and determined that the full study could be completed. DoD funded the MFUA (#DoD-93) to proceed with the full-scale study, which is currently underway.

Shortly after the June 1996 announcement of the events at Khamisiyah, Iraq, the RWG recommended that DoD fund three scientifically-meritorious projects in the areas of (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 is described in more detail in the ***Annual Report to Congress on Federally Sponsored Research on Gulf War Veterans' Illnesses*** (Projects DoD-49 through 51). We expect that these studies will be completed this year.

The 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 and heat stress, alone and in various combinations.

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 from the scientific community to this request. The DoD subsequently asked MFUA 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 proposal was deemed meritorious by an independent scientific peer-review panel and the RWG recommended to DoD that this project be funded. This project (#DoD-69) is anticipated to be completed this year.

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, musculoskeletal conditions among Gulf War veterans are clearly evident based on the frequency of these conditions among veterans reporting to the VA and DoD registries, and on results of a number of research studies, including CDC's study of Iowa Gulf War veterans. The federal government sponsors a significant amount of research to better clarify the pathophysiology and clinical significance of musculoskeletal conditions in Gulf War veterans.

Because of the importance of ensuring appropriate and effective treatment for Gulf War veterans' illnesses, my office formed a planning group and charged it with developing a Program Announcement (a type of invitation for applications) requesting 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. This Program Announcement was issued in January 1998.

As a result of epidemiological findings to date, subgroups of ill Gulf War veterans have been identified for whom trials of potential treatment are appropriate. In the spring of 1998, the VA Cooperative Studies Program initiated planning for two treatment trials, subsequently known as the "ABT" (antibiotic treatment) and "EBT" (exercise-behavioral therapy) trials. Both trials underwent thorough scientific review and were approved for funding only after rigorous external review provided by the Cooperative Studies Evaluation Committee. Patient characteristics for entry into both trials are similar. All veterans who served in the Gulf between August 1990 and August 1991 are eligible for the studies. Patients are considered to have Gulf War Veterans' Illnesses (GWVI) if they have at least two of three symptoms (fatigue, musculoskeletal pain, neurocognitive

dysfunction) that began after August 1990 and that have lasted for more than six months up to the present.

The ABT trial seeks to study 450 Gulf War veterans at 28 sites throughout the U.S. The study initiated patient accession in May of 1999. The primary hypothesis of the study is that antibiotic treatment directed against mycoplasma species will improve functional status of patients with GWVI who are tested as mycoplasma positive at baseline. The total cost of this treatment trial is approximately $13 million. The trial will be completed about one year from now. Preliminary demographic information indicates that 15% of the study participants are women, nearly 20% represent minority groups, 37% have attained an educational level of college or higher, and about 70% are employed. Nearly 85% of patients currently enrolled in the study exhibit all three symptoms of fatigue, pain, and neurocognitive difficulties. Recruitment of Gulf War veterans into the antibiotic trial is proceeding ahead of schedule.

The EBT trial seeks to study 1,356 Gulf War veterans at 20 sites throughout the U.S. The study initiated patient accessions in April of 1999. The primary hypotheses of the study is that both aerobic exercise and cognitive behavioral therapy (CBT) will significantly improve physical function in veterans with GWVI, and that the combination of CBT and exercise will be more beneficial than either treatment would be alone. The cost of this treatment trial is approximately $9.3 million. The trial will be completed on or about December 2001. Thus far, nearly 500 veterans have joined the study.

Both VA and DoD have undertaken new initiatives that are focused on the neurobiology of stress and stress-related disorders. In addition, other new research efforts include:

- A total of 14 new projects were initiated in FY 1998/99 as part of the 1997 DoD BAA request for proposals for studies of post conflict illnesses that extend beyond the Persian Gulf War. These studies will 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.
- A total of nine new projects were funded in July 1998 as a result of VA and DoD's request for intramural proposals valued at $5 million for research on the neurobiology

of stress. Expected completion dates for these studies range from the year 2000 through 2002.

Mr. Chairman, I will now provide you with an update of the VA National Survey of Persian Gulf Veterans authorized by Public Law 103-446.

As you may recall, the National Survey is designed to determine the prevalence of symptoms and illnesses among a national random sampling of Gulf War veterans. 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 Gulf War era (15,000 Gulf War veterans and 15,000 non-Gulf War 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. Phase II is complete. In Phase III, 2,000 of the 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 are being conducted at 16 VA medical centers and involve specialized examinations including neurological, rheumatological, psychological, and pulmonological evaluations. 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 VA's Office of Research and Development awarded funds for Phase III of the National Health Survey of Persian Gulf Veterans in November 1998. Currently, 16 sites are participating in these physical examinations. A subcommittee of the Cooperative Studies Evaluation Committee (CSEC, a federally chartered advisory committee) scientifically reviewed the protocol for Phase III and recommended funding. This study is scheduled to examine approximately 2,000 veterans, plus 3,000 of their spouses and children. To date, over 1,000 veterans have joined this observational study, and another 1,230 spouses and children have been examined. The study will cost approximately $12 million and will complete patient recruitment in May of 2001.

The medical evaluations in Phase III are designed to determine:

- Whether 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.

- Whether 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.
- Whether the prevalence of any of these conditions is greater among the spouses of Gulf War veterans than among spouses of non-deployed veterans.
- Whether 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.

Mr. Chairman, one of the GAO draft report's recommendations addressed the need to compile data on Gulf War veterans, track their health problems and map the care they receive. We believe that our work in implementing the survey required under Pub. L. 103-446 is responsive to the intent of GAO's draft recommendation.

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:

- Ongoing analysis from the Iowa epidemiologic study of Gulf War veterans using standard measures of health status indicate that nearly 90% of Gulf War veterans reported their health status as "good" to "excellent," while the remainder rate their health status as "poor" to "fair." Interim analysis of this population-based cohort of Gulf veterans also indicates that a minority of them (14%) experienced a significant decline in their health status. Declines were noted in physical functioning and social functioning, while mental health scales showed improvement.
- Population-based epidemiological studies are showing that Gulf War veterans self-report more symptoms and exposures than non-deployed veterans of the same era. Ongoing and newly-funded projects are directed toward determining whether a causal connection may exist.
- Based on VA and DoD mortality studies there does not appear to be more deaths from disease-related causes among Gulf veterans when compared to non-deployed

veterans of the same era. VA plans to continue following the mortality trends of these veterans.

- 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, who remain on active duty, are not experiencing more illnesses of an acuity or 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 sub-study of the hospitalization study shows that infants of Gulf War veterans have not experienced 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 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.
- The Baltimore VAMC Depleted Uranium Program team recently published results showing elevated urine uranium excretion by soldiers who had been wounded by uranium shrapnel. The Baltimore VAMC has an ongoing medical surveillance program that is following a cohort of 33 U.S. soldiers wounded while on or in vehicles struck by depleted uranium penetrators during the Gulf War. The presence of retained shrapnel was identified by x-ray. Urine uranium concentrations were measured. The presence of uranium in the urine can be used to determine the rate at which embedded depleted uranium fragments are releasing biologically active uranium ions. Importantly, there is no evidence of a relationship between urine uranium excretion and kidney function. While we have seen no definitive evidence of adverse clinical outcomes associated with uranium exposure, these veterans will remain under continuing medical surveillance.
- Recent research studies have provided important information on the interactions of neurotoxins and other exposures. One study indicates that exercise stress can increase the penetration of pyridostigmine (PB) across the blood-brain barrier in mice suggesting the possibility that PB could cause a central nervous system effect.

Another published study, however, suggests that PB does not cross the blood-brain barrier in guinea pigs exposed to extreme heat stress. These inconsistent results with different stressors, in different rodent species, suggest that any extrapolation of such results to humans would be premature. Still another research project has reported on the effects of two weeks' exposure to low doses of PB on the neuromuscular junction. Although ultra-structural examination of the nerve terminal showed degeneration after two weeks of exposure, the effects were reversed following cessation of exposure. The RWG will continue its research on the toxicology of such interactions.

- Neurobehavioral studies of Gulf War veterans and control populations suggest that some Gulf War veterans have brain function abnormalities in such areas as memory, cognition, and motor control. The current RWG research portfolio includes seven studies using methods of sophisticated brain imaging such as conventional and functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy, and "SPECT" imaging. In addition, four studies are currently under contract review.
- 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 (PAH) (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.
- Recently, Gulf War veterans have voiced concerns about a possible association between amyotrophic lateral sclerosis (ALS) and service in the war. Although there is no clear indication of an excess rate of ALS among Gulf veterans, the available data could represent an underestimate of the actual rate. Furthermore, preliminary data suggested that the age distribution of cases of ALS in Gulf veterans appeared to be younger than the age distribution of cases of ALS in the general U.S. population. Accordingly, VA is leading a research effort to identify all cases of ALS, or other motor-neuron diseases, occurring among Gulf War veterans. VA is collaborating with DoD, CDC, and various university disease experts to determine the veterans' health status and to describe their exposures to potential causal and risk factors for ALS, based on clinical examinations at VA or non-VA centers of excellence in

neurologic diseases. This initial case-finding effort will take approximately one year and will provide the most definitive information about the rate of ALS among Gulf veterans, and the age distribution of the diagnosed patients.

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

Mr. Chairman, thank you again for permitting me this opportunity to summarize our work to date so that, using science, we may better understand the health problems of Gulf War veterans. You have my assurance that we will continue this effort to resolve or ameliorate health problems in this population to the greatest extent possible.

Mr. Chairman, I will conclude my testimony here and am happy to answer any questions you or other Committee members may have.

Mr. SHAYS. Thank you. Mr. Mazzuchi.

Dr. MAZZUCHI. Thank you, Mr. Chairman, and members of the subcommittee, I am pleased to be here today to provide testimony on our current clinical and research efforts to understand and treat illnesses among Gulf war veterans. I too would ask that my formal statement be entered for the record. This is a summation of it in the interest of time.

The Office of the Assistant Secretary of Defense for Health Affairs has a primary interface in the Department's biomedical research program and that derives primarily from our role as cochair along with the Director of the Department of Defense Research and Engineering of the Armed Services Biomedical Research Evaluation and Management Committee, which facilitates consideration of DOD biomedical research. The Assistant Secretary of Defense for Health Affairs also serves as the primary alternate member and primary DOD liaison official with the Military and Veterans Health Coordinating Board and is a voting member of the board's research working group which Dr. Feussner chairs.

Through many years of research and progress in military medicine, tremendous strides have been made in medical protection and care provided to our soldiers, sailors, airmen and marines. The medical consequences of the Gulf war made it clear, however, that threats remain—some threats remain poorly understood and inadequately addressed. Despite few combat casualties and low rates of disease in nonbattle injuries in both the buildup to the war and the war itself, many veterans have since reported health problems, including medically unexplained symptoms which followed their service in the Gulf war. These unexplained illnesses have proven to be both frustrating to diagnose and frustrating to treat. Efforts within the Department of Defense to care for Gulf war veterans have reinforced our appreciation of the seriousness of their health problems, and military physicians fully recognize that these veterans require compassionate evaluation and care.

The lack of predeployment health and deployment exposure data is recognized as a chief limitation in the evaluation of Gulf war veterans illnesses. Numerous improvements are being made to gain and analyze such data regarding future U.S. military deployments. These efforts include capturing better service entry health data, pre and post-deployment health data, environmental and morbidity data during deployment, improved communication with troops regarding deployment health risks, and focused clinical evaluation and epidemiologic research programs of our deployed populations.

In the 1998 report to Congress, Effectiveness of Medical Research Initiatives Regarding Gulf War Illnesses, the Department of Defense identified the need for a coordinated capability to apply epidemiologic research to determine whether deployment related exposures are associated with post-deployment health problems. Subsequent to this report, Congress authorized the Secretary of Defense to establish a center devoted to "longitudinal study to evaluate data on the health conditions of members of the armed forces upon their return from deployment."

On September 30, 1999 Dr. Sue Bailey, the Assistant Secretary of Defense for Health Affairs, directed the establishment of DOD Centers for Deployment Health, creating a research center at the

Naval Health Research Center, San Diego, CA with the mission of longitudinal study to evaluate data on the health conditions of members of the armed forces upon their return from deployment. A clinical center was also established at the Walter Reed Army Medical Center to oversee the Department's clinical evaluation program for deployed service personnel.

One of the many lessons learned of the Gulf war is that the lack of ongoing population based longitudinal health studies has limited our capability to identify deployment-related health outcomes. Additionally, the only way to determine health status change is through a prospective monitoring of health. Recognizing the challenges of conducting such studies, DOD and VA asked the National Academy of Sciences Institute of Medicine to suggest appropriate scientific and practical methodologies to do this. In response the Institute of Medicine recommended in its report, Gulf War Veterans Measuring Health, that DOD and VA institute longitudinal cohort studies of both Gulf war and other deployed veterans. DOD and VA have initiated planning to develop a research program of ongoing longitudinal studies with a specific aim of determining how the health of U.S. military veterans changes over time. This study, entitled the Millennium Cohort Study, will focus on U.S. military cohorts of the future yet be constructed so as to enable comparison to military cohorts of the recent past. A concurrent program will use similar data collection methods to study a comparable Gulf war veteran population. The goal for these two comprehensive studies is to determine how the health of several veterans' cohorts changes over time. The specific goal of the Millennium Cohort Study is to identify and prospectively follow health outcomes of future U.S. military cohorts beginning in the year 2001. In this study we intend to guide the development of DOD medical information programs so that future investigators will not have to rely so much on special investigative studies to determine the effects on health of military deployments.

We appreciate the interest this committee has shown in the health of our men and women who have served their Nation in the armed forces. The military health system wants to achieve its goal to care for those men and women and their families and to protect their health. We also recognize that our commitment to veterans' health cannot end when they leave active service. We will maintain a strong post-deployment evaluation and care program in coordination with the VA and move forward to strengthen our force health protection program.

Again we appreciated the opportunity to testify before the subcommittee, and look forward to receiving your questions. Thank you, Mr. Chairman.

[The prepared statement of Mr. Mazzuchi follows:]

DEPARTMENT OF DEFENSE

WRITTEN STATEMENT OF

JOHN F. MAZZUCHI, Ph.D.
DEPUTY ASSISTANT SECRETARY
OF DEFENSE
(CLINICAL AND PROGRAM POLICY)

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM
SUBCOMMITTEE ON NATIONAL SECURITY, VETERANS AFFAIRS
AND INTERNATIONAL RELATIONS

FEBRUARY 2, 2000

NOT FOR PUBLICATION
UNTIL RELEASED BY THE
COMMITTEE ON GOVERNMENT REFORM
SUBCOMMITTEE ON NATIONAL SECURITY, VETERANS AFFAIRS
AND INTERNATIONAL RELATIONS
UNITED STATES HOUSE OF REPRESENTATIVES

Mr. Chairman and members of the Committee, I am pleased to be here today to provide testimony before this subcommittee on our current clinical and research efforts to understand and treat illnesses among Gulf War veterans.

I am Dr. John F. Mazzuchi, Deputy Assistant Secretary of Defense, Clinical and Program Policy, Office of the Assistant Secretary of Defense for Health Affairs. Within the Department of Defense, the primary role of Health Affairs is to ensure medical services and support to members of the Armed Forces during military operations, and to provide medical services and support to members of the Armed Forces, their dependents, and others entitled to DoD medical care. Our interface with the Departments biomedical research programs derives primarily from our role as Co-chair, along with the Director, Defense Research and Engineering, of the Armed Services Biomedical Research Evaluation and Management Committee, which facilitates consideration of DoD biomedical research.

The Assistant Secretary of Defense for Health Affairs also serves as the principal alternate member and primary DoD liaison official to the Military and Veterans Health Coordinating Board and is a voting member of the Research Working Group, along with the Director, Defense Research and Engineering.

The Gulf War in 1991 was the last critical test of military medicine during full-scale ground and air combat operations. By nearly all measures, this war was a victory not only for United States combat troops and its allies but also for the military health care system. The Department of Defense (DoD) was able to deploy an extensive clinical care and preventive medicine infrastructure rapidly to a distant, desert environment. As a result of these efforts and prevention programs established before the war, the disease and non-battle injury rate among deployed U.S. forces was lower in this war than in previous major conflicts.

Despite the success of military medicine in the Arabian Gulf, the general perception almost ten years later is considerably different because of unresolved questions about the health of Gulf War veterans. In particular, veterans have experienced fatigue, joint pains, sleep problems and other diverse symptoms that have not been definitively explained. Gulf War health questions have resulted in substantial controversy over potentially hazardous exposures during the deployment, the possibility of adverse affects from preventive health measures, and the role of stress in causing chronic illness.

Deployments present unique and difficult challenges. Through many years of research and progress in military medicine, tremendous strides have been made in the medical protection and care provided to soldiers, sailors, airmen, and marines. The medical consequences of the Gulf War made it clear, however, that some threats remain poorly understood and inadequately addressed. Despite few combat causalities and low rates of disease and non-battle injuries

during both the build-up to the war and the war itself, many veterans have since reported health problems, including medically unexplained symptoms, that followed their service in the Gulf War. These unexplained illnesses have proved to be frustrating to diagnose and treat.

Although further research is in progress, much information on veterans' health already has been provided by an extensive research effort. Systematic clinical examinations have not identified a unique syndrome or a characteristic organic abnormality among over 100,000 U.S., British, and Canadian Gulf War veterans. Additionally, the overall mortality rate of Gulf War veterans has been less than half that of the civilian population (adjusted standardized mortality ratio of 0.44), and deaths due to medical causes have not increased. Only deaths due to accidents have been higher, as similarly observed after previous wars. Moreover, there has been no overall increase in hospitalizations among Gulf War veterans or birth defects among their children.

Efforts within the Department to care for Gulf War veterans have reinforced our appreciation of the seriousness of their health complaints, and military physicians fully recognize that these veterans require careful evaluations and appropriate therapeutic programs.

The Comprehensive Clinical Evaluation Program (CCEP) has provided an in-depth medical evaluation to Department of Defense beneficiaries who are experiencing illnesses which may be related to their service during the Gulf War. The clinical protocol of the CCEP currently involves a three-phase evaluation process developed in close coordination with the Department of Veterans Affairs (VA). The initial phase of the protocol consists of a physical examination, supplemental baseline laboratory tests, and clinically directed specialty consultations available at the local MTF. Patients with unexplained symptoms who lack definitive diagnoses are referred to one of fourteen TRICARE Regional Medical Centers (TRMCs) where they progress to the second phase for further evaluation according to an established clinical protocol. Patients with unexplained symptoms or symptoms not completely explained by the second phase diagnoses, can be referred to the Specialized Care Center at Walter Reed Army Medical Center. The CCEP protocol provides a framework for diagnostic evaluation and is not all-inclusive or restrictive.

The Specialized Care Center at Walter Reed Army Medical Center is available to members of the armed services and family members with persistent symptoms who have completed the first and second phases of the CCEP. This program is a three-week intensive outpatient program that emphasizes treatment over evaluation. The Specialized Care Center at the Walter Reed Army Medical Center continues to offer a more intensive therapeutic program for those veterans on active duty or in the reserves with more disabling health problems related to their Gulf War service.

The CCEP has highlighted the need to develop a comprehensive medical surveillance system that is capable of monitoring the health outcome of individuals upon return from deployments. On January 14, 1995 the ASD(HA) announced a medical surveillance plan for the deployment to Bosnia which reflects many of the "lessons learned" from the Department's experiences in the aftermath of the Gulf War. Guidelines for implementation of a medical surveillance system which features pre-deployment education, enhanced capability to assess health hazards in theater, standardized pre- and post-deployment health screening, and monitoring of health consequences were promulgated in August 1997, in DoD Directive 6490.2 and DoD Instruction 6490.3. A Joint Preventive Medicine Policy Group has been established to work implementation of these guidelines.

Health problems among Gulf War veterans, however, persist. Therefore the Department remains engaged in a comprehensive, coordinated effort to respond to the health concerns of Gulf War veterans; our veterans and their families deserve no less. The Departments of Defense (DoD), Veterans Affairs (VA), and Health and Human Services (HHS) are committed to finding answers to Gulf War veterans' questions. To address these complicated issues, we will continue to solicit advice from independent scientists and experts.

In response to health questions following the Gulf War and the increasing demands of a series of hazardous deployments, the military health system has undergone a fundamental reorientation. A new strategy has been developed and is being implemented to protect U.S. forces against foreseeable physical and psychological threats. DoD's "Force Health Protection" strategy balances the military's key responsibilities to: 1) promote and sustain health and wellness throughout each person's military service; 2) prevent acute and chronic casualties; 3) rapidly stabilize, treat, and evacuate casualties; and, 4) perform medical surveillance, longitudinal health studies, and ensure adequate medical records documentation and clinical follow-up for deployed forces. The Force Health Protection strategy has played a key role in further reductions in illness and injury rates since the Gulf War.

The development of sound health policy for Force Health Protection has to rely on a rigorous standard of scientific proof to improve clinical care and preventive medicine practices. Preferably, such proof should be based on peer-reviewed science published in leading medical journals; because of the limitations of individual studies, research findings require expert review and confirmation before conclusions are adopted. Multiple and sometimes conflicting hypotheses and suggested changes are continually being advanced by clinicians, scientists, advocates, and concerned citizens, both in and out of the military and federal government. These diverse ideas have to be evaluated by rigorous scientific methods to provide the best possible health care for military service members and veterans.

The Department of Defense is committed to an aggressive program of Force Health Protection. A comprehensive approach to health care and prevention has been implemented that will coordinate the activities within DoD and among multiple federal agencies. New DoD and VA deployment health clinical and research centers are being established that will actively investigate potential health risks and medical, psychological, and reproductive outcomes. DoD has recognized the need for proactive health risk communication as an essential part of the force health protection strategy. Specific Force Health Protection initiatives include:

- Documentation of health status, including mental health assessments, blood sample collections, and health threat briefings before deployment.
- Improvement in medical record keeping, including tracking of immunizations and other preventive countermeasures, during deployment.
- Assessment of health status -- individual and force - after deployment.
- Improvement of health risk communication efforts.
- Prospective cohort studies of deployed military personnel.

The Department and our Federal partners are committed to resolving Gulf War veterans' health concerns and preventing similar occurrences 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.

The lack of predeployment health and deployment exposure data is recognized as a chief limitation in evaluation of Gulf War veterans' illnesses. Numerous improvements have or are being made to document and analyze health data regarding future US military deployments. These efforts include capturing better service-entry health data, pre- and post-deployment health data, environmental and morbidity data during deployments, improved communications to troops regarding deployment risks, and focused clinical evaluation and epidemiological research programs of deployed populations.

In the 1998 report to Congress, *Effectiveness of Medical Research Initiatives Regarding Gulf War Illnesses,* DoD identified the need for a coordinated capability to apply epidemiological research to determine whether deployment-related exposures are associated with post-deployment health outcomes. Subsequent to this report, Congress authorized the Secretary of Defense to establish a center devoted to "...longitudinal study to evaluate data on the health conditions of members of the Armed Forces upon their return from deployment..." On 30 September 1999, Dr. Sue Bailey, the Assistant Secretary of Defense for Health Affairs directed establishment of DoD Centers for Deployment Health, creating a research center at the Naval Health Research Center, San Diego, with the mission of "...longitudinal study to evaluate data on the health conditions of members of the Armed Forces upon their return from

deployment..." A clinical center was established at the Walter Reed Army Medical Center, to oversee the Departments clinical evaluation programs for deployed service personnel.

One of the many lessons of the Gulf War is that the lack of ongoing population-based longitudinal health studies has limited our capabilities to identify deployment-related health outcomes. Additionally, the only way to determine health status change is through prospective monitoring of health and health outcomes. Recognizing the challenges of conducting such studies, DoD and VA asked the National Academy of Sciences, Institute of Medicine, to establish a committee to consider these questions and suggest appropriate scientific and practical methodologies. In response, the Institute of Medicine recommended in the report *Gulf War Veterans: Measuring Health,* that DoD and VA initiate longitudinal cohort studies of both Gulf War and deployed veterans.

DoD and VA have initiated planning to develop a research program of ongoing longitudinal studies with the specific aim of determining how the health of US military veterans changes over time. This study - the Millennium Cohort Study - will focus upon US military cohorts of the future, yet be constructed so as to enable comparisons to military cohorts of the recent past. A concurrent program will use similar data collection methods to study a comparable Gulf War veteran population.

Our goal for the two studies is to determine how the health of several veteran cohorts changes over time. The specific goal of the Millennium Cohort Study is to identify and prospectively follow health outcomes in future US military cohorts beginning in the year 2001. In this study we intend to adapt and coordinate the numerous dynamic medical information systems that are currently being developed such that future investigators will not have to rely as much on special investigative studies to determine the effects on health of military deployments.

We appreciate the interest this Committee and others have shown in the health of the men and women who serve and have served this nation in our armed forces. The health and fitness of military personnel have long been concerns of those responsible for ensuring troop readiness and effectiveness. The Military Health System wants to achieve its goal to take care of those men and women and their families, and protect their health. We recognize that our commitment to keeping our veterans healthy does not end when they leave active service. We will maintain a strong post deployment evaluation and care program in coordination with the VA and continue to move forward to strengthen our Force Health Protection Program as well as the total Military Health System.

Again, we appreciate the opportunity to testify before this Committee, and look forward to answering your questions.

Mr. SHAYS. Thank you, Dr. Mazzuchi. Dr. Foster.

Dr. FOSTER. Thank you, Mr. Chairman, and members of the subcommittee. Thank you for the opportunity to briefly discuss the Department's science and technology program addressing Gulf war veterans' illnesses and general deployment health concerns. I too request that my formal testimony be entered for the record, and I will be abstracting some of the information from that formal testimony.

In my remarks today, I will focus on a research program that was initiated with the fiscal year 1999 defense appropriation in the research development test and evaluation account. With that appropriation, the Department established the dedicated program element to support basic research into Gulf war illnesses and related deployment health concerns.

The Department's research program has three overarching research objectives in mind. We want to further the understanding of illnesses relevant to service during conflict, including the Gulf war deployments, we want to provide enhanced diagnostic capabilities and effective treatments for these illnesses, and we want to support the establishment of policies and preventive measures that minimize the risk for such illnesses during future military operations. This research program will be of the highest quality.

In this enterprise we are pleased to have the Army's Medical Research and Materiel Command at Fort Detrick as the program management agency. They have an exemplary record of achievement in managing medical research. The Army's program manager for this effort, Lieutenant Colonel Karl Friedl, is seated just behind me. We should all thank him for his untiring efforts on behalf of our veterans.

Turning to the funding associated with research in this area, from 1994 to 1998 there were "special appropriations" for Gulf war illnesses issues and research, and we have gained numerous insights from research projects initiated with that funding.

We have now transitioned to a formal defense research program. This occurred with the fiscal year 1999 defense appropriation. The funding is in the basic research account. This provides more stable funding for systematically tackling research gaps in our understanding of Gulf war veterans' illnesses and in force protection issues. The program will be addressing issues in five research thrust areas, and will support any continuation of promising leads from the previous program.

Our program management approach includes periodic evaluation of progress resulting in an annual tailored solicitation for research proposals from anyone anywhere who is willing to propose to do research. This annual investment plan is carefully developed in coordination with the interagency Research Working Group. An important characteristic of this new dedicated program is the ability to plan and implement a long term strategy of deployment health research in support of the Department's force health protection initiative. Indeed, establishment of a dedicated research program is a key enabler for this initiative. The 1999 program, the first year of our program, had four solicitations. We received 81 proposals and we will probably make about 17 awards from those proposals. I

have provided the current statistics and examples of the research covered in the written testimony.

With fiscal year 2000 funding, new research solicitations will be developed and issued. We are also initiating an investment in the longitudinal cohort study that Dr. Mazzuchi mentioned that addresses the recommendations of the IOM's assessment entitled, "Gulf War Veterans Measuring Health."

I think that the program is proving highly effective in providing new information on the impact of Gulf war service on health-related problems and identifying new areas to explore with research, and in prompting new force protection initiatives that provide for medical surveillance during future operations.

Although the investment in Gulf war veterans' illness research has already provided meaningful results, we must be cautious in anticipating the true impact of this research. That impact may not be fully assessed and realized for years after this early stage of the program and the awards have been made.

In conclusion, I believe that the organizations testifying before you today that are engaged in research share a genuine concern for and a recognition of the magnitude and consequences of the medical and scientific challenges before us. While there may be no quick solutions to the health problems experienced with Gulf war veterans, the participants in our interagency Research Working Group and our research program are genuinely committed to a responsible and aggressive pursuit of reasonable hypotheses and to the prevention of similar illnesses following future deployments.

This concludes my remarks, Mr. Chairman, and I am pleased to answer your questions.

[The prepared statement of Mr. Foster follows:]

DEPARTMENT OF DEFENSE

STATEMENT OF

DR. ROBERT FOSTER
DIRECTOR, BIOSYSTEMS
OFFICE OF THE DEPUTY UNDER SECRETARY OF DEFENSE
(SCIENCE AND TECHNOLOGY)

BEFORE THE
COMMITTEE ON GOVERNMENT REFORM
SUBCOMMITTEE ON NATIONAL SECURITY, VETERANS AFFAIRS
AND INTERNATIONAL RELATIONS

FEBRUARY 2, 2000

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UNITED STATES HOUSE OF REPRESENTATIVES

Mr. Chairman, thank you for the opportunity to review with you and the members of this subcommittee the Department of Defense's (DoD's) science and technology program addressing multiple aspects of Gulf War Veterans' Illnesses (GWVI) and general deployment health concerns.

I am Dr. Robert Foster, Director for BioSystems, Office of the Deputy Undersecretary of Defense (Science and Technology) (ODUSD(S&T)). My office is a component in the organization managed by the Director of Defense Research and Engineering (DDR&E). As the Director for BioSystems, I oversee the Defense biomedical science and technology program.

Today I will focus my testimony on a research program that was initiated with the Fiscal Year 1999 Defense appropriation for Research Development Test and Evaluation (RDT&E). At that time the Department established a dedicated program element to support basic research into Gulf War Illnesses and related deployment health concerns. I also will address research activities funded with special Defense RDT&E appropriations over the period of Fiscal Years 1994 to 1998 and focused on GWVI. I will begin by briefly reviewing our processes for initiation and oversight of these research efforts.

Department of Defense Oversight of Research

In February 1998, my predecessor, Dr. Anna Johnson-Winegar, provided a detailed overview of the processes that the Department uses for establishing research priorities and for selecting proposals for contract and grant awards. The processes have not materially changed since that testimony. Hallmarks of the process include independent scientific review for technical merit and programmatic review for relevance. This process is further augmented through assistance with defining research scope from the interagency Research Working Group (RWG) of the Persian Gulf Veterans Coordinating Board (PGVCB). The assistance of this interagency RWG is essential in order for this program to focus on the most vexing health care issues in GWVI and deployment health. Dr. Feussner and Dr. Mazzuchi have already provided more detailed information on the role of the DoD and Veterans Administration's clinical systems in defining research needs. In many ways the success of our research program depends on insights from medical practitioners, from the results of clinical epidemiological studies, and from the process of defining the clinical characteristics of disease.

The RWG plays the essential role of providing the linkage between medical practitioners both inside and outside the Department and the scientists doing the basic research and allows each individual Department's scientific strengths to be unified into a productive, responsive and fully integrated national research effort.

The Department is committed to a coordinated and scientifically meritorious research program that accomplishes the following:

- Furthers the fundamental understanding of illnesses relevant to service during conflict including the Gulf War deployments;
- Provides enhanced diagnostic capabilities and effective treatments for these illnesses; and
- Supports the establishment of policies and preventive measures that minimize the risk of such illnesses during future military operations.

The Department and our Federal partners are committed to answering basic science questions related to Gulf War Veterans' health concerns and any emerging health concerns associated in general with military deployments. The challenges to the scientists supported by this program are great and, while there may be no quick solutions, all concerned have devoted their energy to responsible, aggressive pursuit and resolution of the problems. Dedication to partnership is an essential element of the scientific community that is engaged in this effort. The clinical and research components of the Veterans Administration, the military health care community led by the Office of the Assistant Secretary of Defense for Health Affairs, and the basic scientists of our in-house laboratories and from the independent science community all intersect. I believe that this research program can address the breadth of issues related to GWI and deployment health. A broad spectrum of hypotheses concerning illnesses in Gulf War veterans have been or are being pursued through this program of basic science research. I will highlight some specific examples later in this testimony.

We are steadfast in ensuring that our research program is of the highest quality. We use competition and independent review for scientific merit to secure the 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 this research appropriation. It also reflects our desire to quickly transfer knowledge derived

from the research into a form that can assist Gulf War veterans to secure diagnoses and treatments for their disabilities and illnesses, and to prevent such disabilities and illnesses as a consequence of future deployments.

Research Solicitations and Awards

The majority of all appropriations to date (1994-1999) for GWVI research have been executed as part of a technically meritorious, competitive research program. The U.S. Army Medical Research and Materiel Command (USAMRMC) is the program management agency for this DoD research program. The processes and procedures of USAMRMC are utilized to solicit, review, award, monitor, and close out all research projects. The majority of the contract and grant awards have resulted from DoD solicitations using "specific purpose announcements" issued under a USAMRMC Broad Agency Announcement (BAA).

Seven GWVI special-topic BAAs were issued for RDT&E appropriations from 1994-1998. To date, these seven announcements have resulted in 43 contract or grant awards. A summary of this activity is provided in the following Table.

GWVI BAA SUMMARY (FY94 – FY98)

Date of Announcement	Special Solicitation Subject Area	Proposals Received	Awards/ Completed	Funding*	Reports
29 Apr 94	Low-level chemical sensitivities	5	1/1	375,000	GL:1 OL:6
29 Apr 94	Depleted uranium	2	2/1	1,916,214	GL:3 OL:5
24 May 95	Gulf War Illness, 3 subtopics	117	14/3	8,922,100	GL:3 OL:17
10 Dec 96	Low-level chemical exposures (includes open BAA submissions)	22	8/1	6,722,000	GL:1 OL:16
29 Jan 97	Gulf War Illnesses (non-Federal) (includes addition of DoD $3M)	36	9/2	12,198,516	GL:3 OL:23
29 Jan 97	Historical War Syndromes	14	3/0	1,915,687	GL:0 OL:1
20 Nov 97	Gulf War Illnesses (non-Federal, U.S. universities)	41	5/0	7,432,791	GL:0 OL:0

Key: Funding* – amount provided to contractors/grantees and does not include other Defense RDT&E program costs
GL: - government technical literature publication
OL: - open source technical literature publication

Numerous insights have resulted from the research projects initiated with the RDT&E funding from 1994-1998, and work on some efforts has been extended. Following are five examples:

1. Development of an effective skin test for Leishmania was expanded to include New World antigens as well as a diagnostic capability for the type of Leishmania encountered in the Persian Gulf. This product provides important new diagnostic capabilities for future deployment, and it is expected to enter Food and Drug Administration approved Phase I clinical trials this year. Further Leishmania research supported with Fiscal Year 2000 GWVI funding is expected to improve prevention and treatment capabilities.

2. Results from a study with Dr. Garth Nicolson that evaluates his mycoplasma assay in Gulf War veterans who have health problems compared to a group in good health will be forthcoming. At our last briefing to this committee, it was noted that we had provided funding to Dr. Nicolson to provide the training in his assay technique for other investigators involved in this validation study. After delays associated with selection of an appropriate test population, an additional contract for more than a half million dollars was awarded to collect and manage blood samples and to fund the participation of Dr. Nicolson and other independent mycoplasma investigators. Collection of the needed blood samples will be completed this calendar year. In addition, we have initiated an antibiotic treatment trial that will test if treatment of mycoplasma infection results in improvement of symptoms.

3. Our cooperative research agreement with Dr. Robert Haley was extended to permit analysis of the large amount of data that he has collected in tests of a Seabee veteran population. He recently reported finding a significant neurochemical difference between symptomatic veterans and his healthy group. Although this was only one test from a large battery of tests applied in the study and, of course, needs to be confirmed in further studies, this may contribute to objective measures which can be linked to specific subjective symptom reports. Dr. Haley's work has already advanced our

knowledge of disease variables in GWVI that should be examined with basic research in neurobiology.

4. At the last hearing, Dr. Dan Clauw presented research on hard-to-diagnose conditions such as chronic fatigue syndrome (CFS), fibromyalgia (FM), and chemical sensitivities, conditions with symptom complexes very similar to those of undiagnosed problems in Gulf War veterans. Since then, he has shown that Gulf War veterans have many similarities to patients in the general population with these diagnoses, such as changes in pain sensitivity and other changes in nervous system activity. Dr. Clauw has demonstrated the importance of health habits as simple as exercise frequency, following up on the finding that modest exercise is an effective treatment for some patients with CFS and FM. Subjects who experimentally ceased their regular exercise routines developed symptoms common to these conditions and with similarities to those of undiagnosed Gulf War veterans. In addition, Dr. Clauw will be participating with colleagues from the DoD and DoVA in a treatment trial investigating the potential benefits of exercise and cognitive behavior therapy. We expect that Dr. Clauw's work will substantially advance understanding and treatment of these illnesses.

5. Finally, Dr. Simon Wessely at King's College in London has explored hypotheses similar to those of Dr. Haley and Dr. Clauw using a population of British veterans of the Gulf War. His findings of undiagnosed symptoms are similar to ours. Although physical symptom measures were reported more frequently in their Gulf War veterans, the pattern of symptoms was also present in Bosnia and non-deployed groups of soldiers. His project was extended to permit completion of objective clinical tests of symptomatic and healthy veterans.

I now will turn to the research program established in Fiscal Year 1999 in the basic research account of the Defense-wide RDT&E appropriation.

<u>New Gulf War Illnesses and Force Health Protection Research Funding</u>

In 1999, DoD established a new program element within the basic research budget to provide stable funding for systematically tackling research gaps in our understanding of GWVI and Force Health Protection issues. The appropriated amounts for this Program Element were $22.588 million in FY 1999 and $24.543 million in FY 2000. The overall strategy is to deal with relevant research issues in five thrust areas, with periodic evaluation of progress resulting in an annual, tailored solicitation for research proposals. The five thrust areas are, as follows:

- Health-hazard assessment methods for toxic industrial and agricultural chemicals and mixtures;
- Force Health Protection – epidemiological studies and deployment health monitoring methods;
- Safety of medical materiel in operational environments;
- Prevention and treatment of undiagnosed persistent stress symptoms; and
- Leishmania diagnosis methods, treatments, and vaccine.

Funding also will be available to continue research in the original portfolio to permit follow up on emerging findings. This plan has been carefully developed in coordination with the RWG. As mentioned before, the role of the RWG is to provide an essential linkage and communications path to the interagency research effort, to health care communities, and to Veterans.

In comparison to the 1994-1998 program, the most important distinction of this new, dedicated program funding is the ability to plan and implement a long-term strategy of deployment health research. In response to health questions following the Gulf War and the increasing demands of a series of hazardous deployments, the Department has undergone a fundamental reorientation. A new strategy has been developed and is being implemented to protect U.S. forces against all foreseeable physical and psychological threats. DoD's "Force Health Protection" strategy balances the military's key responsibilities to: 1) promote and sustain health and wellness throughout each person's military service; 2) prevent acute and chronic casualties; 3) rapidly stabilize, treat, and evacuate casualties; and, 4) perform medical surveillance, longitudinal health studies, and ensure adequate medical records documentation and clinical follow-up for deployed forces. The establishment of a dedicated research program is a key enabler for this new strategy on deployment health.

New Research in FY99

In 1999, tailored research solicitations were advertised to pursue significant areas of research under most of the GWVI and force health protection thrusts. The topics of the four solicitations were, as follows:

- Force health protection and deployment health;
- Innovative biologically-based toxicology methods and models for assessing mixed chemical exposures with potential neurotoxicological and other health effects;
- Interactions of drug, biologics and chemicals in service members in deployment environments; and
- Integrated psychosocial and neuroscience research on stress and somatic consequences.

In addition, the Leishmania thrust area is being addressed by in-house research at the Walter Reed Army Institute of Research and the Naval Medical Research Center.

The solicitations elicited 81 proposals. From this group of proposals, there have been or will be approximately 17 awards for research work. A summary of this solicitation will be included in the Annual Report to Congress. I will briefly highlight four of the awards as representative of the breadth and quality of the research we are pursuing, and will describe some anticipated benefits of this work to past, current, or future military members:

1. Motor-vehicle crashes are the leading cause of death among active-duty Army personnel, and are the only cause of death significantly higher for GW veterans compared to non-deployed veterans. Potential risk factors for fatal motor vehicle accidents will be studied in a large population of current and former military personnel.

2. The role that deployment experiences play in Army National Guard soldiers' health will be examined. This establishes baseline health parameters and follows changes when soldiers are deployed and after they leave the military, considering also the effect of job strain associated with National Guard service as a "second job."

3. The metabolism of chemicals important in military deployments and that were also important in the Gulf War will be studied. Using animal studies, effects of these chemicals on activation of the enzyme systems important in humans for disposal of toxic chemicals will be investigated. This will lead to identification of populations at special risk for health consequences from exposure to these toxic chemicals and may provide methods to determine exposures after the fact.

4. We will reexamine the question of whether or not physical and biochemical stressors can modify access to the brain of chemicals that would normally be prevented from reaching the brain. This study will help determine whether normal assumptions about the safety of drugs need to be reconsidered in the context of use in military settings.

New Research Solicitations in FY00

With the Fiscal Year 2000 Defense RDT&E appropriation, a new round of research solicitations will be developed and issued. In fact, the USAMRMC proposal for the Fiscal Year 2000 topics has been reviewed and approved by the RWG. The topics are in the following key areas:

- Biochemical and physiological markers to assess toxic chemical exposures and health effects in deployed military personnel;
- Epidemiological investigations of deployment health monitoring methods;
- Toxicity of militarily-relevant heavy metals; and
- Deployment stress health and performance consequences.

It should be apparent that these topics carry forward some concerns identified in previous years. Projects that result from successful proposals, together with additional funding for Fiscal Year 1999 research projects on health behavior interventions and improved monitoring of the health of deployed soldiers, will contribute to our goal of ensuring that many health problems encountered in the Gulf War will not be repeated in future deployments.

Additionally, the DoD and VA are acting on the recommendations from the recent Institute of Medicine (IOM) report, *Gulf War Veterans: Measuring Health.* In response to questions from Congress and the GAO, the DoD and VA asked the IOM to recommend strategies and methodologies to answer the following questions: 1) how many Gulf War veterans are suffering from health problems that affect their ability to function; 2) whether the prevalence of such problems among gulf War veterans is consistent with their prevalence among the general public or among other veterans groups; and 3) whether the health of veterans is getting better, staying the same, or deteriorating with time. The IOM noted in this report that many veterans, active-duty personnel, governmental agencies, and non-governmental scientists and physicians have a strong interest in finding answers to the numerous and complex questions regarding the health of Gulf War veterans, and that various types of research and health measurement are needed to address these diverse issues.

To address these questions, the IOM stated that it will be necessary to measure not only the health status of those who served in the Gulf War, but also to compare Gulf War veterans with other groups through time to determine whether the groups differ in the way their health status is changing. The IOM committee quickly realized that such a study could have important implications for understanding not only the health of Gulf War veterans, but also the health of veterans of other conflicts.

The IOM Committee recognized that the recommended study will be challenging and that it will require a sustained commitment of resources by Congress, VA and DoD, and of time and cooperation by study participants. Nevertheless, the Committee felt that these commitments are important and worthwhile if the nation is to adequately understand and respond to the health needs of not only Gulf War veterans, but veterans of any conflict in which significant U.S. military forces are committed. The IOM recognized that if study began immediately upon return from participation in a conflict, many of the problems we face in attempting to resolve Gulf War veterans health issues, several years removed from the end of that conflict, could be mitigated. The IOM, DoD and VA agreed that such efforts would contribute greatly to our understanding of the impact of military conflict on the health of the men and women who serve in those conflicts.

The DoD and VA are currently working on a research strategy to implement the recommendations of the IOM and conduct longitudinal cohort studies on military forces including follow-up of Gulf War veterans. These studies will be national in scope, based on probability sampling, and used to collect a broad range of morbidity data related to health outcomes among deployed military forces. The study design will permit estimation of the distribution within the population of a broad variety of health-related measurements, including psychological measurements. The study design will capitalize on existing and planned DoD and VA infrastructure and resources to track and measure health of military forces and veterans. The stable nature of the new program funding will provide for consistency in the research component of this study approach.

Summary of Oversight Initiatives and the Research Investment

In the presentation to this committee in 1998, you heard about several actions to be taken by the DDR&E to increase visibility and oversight of Defense research efforts on GWVI. Those initiatives have paid significant dividends in terms of program quality, and it is appropriate to provide an update at this time:

1. The first action was the establishment of a single Defense Program Element for dedicated research into GWVI and deployment health. As you have heard, this has been completed. In fact, program accomplishments, plans and resource information will appear as a single program on the RDT&E Budget Item Justification Sheet (R-2 Exhibit) in the future submissions for the Defense-wide Science and Technology program.

2. For the second, we chartered a Working Integrated Process Team (WIPT) on Deployment Toxicology in November 1997 and their work has been completed successfully. This team was established to review current toxicology research initiatives and to develop appropriate recommendations for the Defense biomedical research oversight body, the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee. The issues addressed by the WIPT originated from a concern that DoD research on long-term health consequences,

such as from low level chemical exposures, may have less visibility and priority in comparison to more immediate health and performance issues facing deployed soldiers. Indeed, greater attention to these types of issues is one of the positive changes produced by the public dialogue on GWVI. The WIPT has identified a timely, proactive process for bringing operational, occupational, and environmental health issues to the research community. The process has been implemented with productive interactions between the Joint Environmental Safety Working Group (JESWG) (health-care requirements) and the Military Operational Medicine (MOM) Joint Technology Coordinating Group (medical research).

3. The third and last initiative concerned outside review of research. We have incorporated review of DoD-sponsored GWVI science and technology in the Technology Area Review and Assessment (TARA) process. This subjects the program to scrutiny by recognized experts in biomedical science and technology who assess its objectives, scientific rigor, resources, and output. The Biomedical TARA Panel reviewed the program in March 1999, rating it positively and looked forward to a report of continuing success when the review is held again in 2001.

These initiatives are indicative of the Department's determination to invest in an aggressive, coordinated program of basic research into Gulf War Illnesses. In doing so, we are following the general procedures for conducting a quality program as mandated by the Deputy Under Secretary of Defense (Science and Technology). It is important to recognize that each specific RDT&E program has its own detailed, tailored approach under the Department's broader policy guidance for science and technology programs. In the case of the GWVI and Force Deployment Health program, USAMRMC serves as program manager. A unique aspect of this program is that USAMRMC utilizes the members of the RWG in developing the investment strategy and in assessing proposals. This interagency coordination mechanism is essential and has been successful.

One indicator of that success is that the investment in GWVI has been highly effective in providing new information on the impact of military service in the Gulf War on health-related problems, in providing new areas of research

exploration, and in 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 research has already provided meaningful results, the true impact of this research cannot be fully assessed for years after awards are made. Once initiated, 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. Over time, these individual studies eventually merge into a body of knowledge that may be used for definitive prevention and treatment of an illness, as well as for advancing related scientific hypotheses for subsequent work. Nonetheless, progress in this research area will be evident in the summaries provided in the annual interagency report. Indeed, the details of the RWG-coordinated and -integrated research efforts of DoD, VA, and DHHS will be provided in the Annual Report to Congress that the Secretary of Veterans Affairs will submit this calendar year. When you review that report, I believe you will see ample evidence of a high-quality, carefully planned research program.

Conclusion

The organizations testifying before you today share a genuine concern for and recognition of the magnitude and consequences of the medical and scientific challenges before us. Our sense of shared responsibility is reflected in our commitment to work in a productive and cooperative manner that exploits our respective Departments' scientific strengths and unifies them into a productive, responsive and fully integrated research effort. As you are aware, 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 current medical science offers little in the way of long-lasting relief or a cure.

While there may be no quick solutions to the health problems experienced by Gulf War veterans, we are committed to responsible and aggressive pursuit and resolution of those problems and to the prevention of similar illnesses following future deployments. We appreciate the continuing interest in this important topic shown by members of the committee.

Mr. Chairman, I am prepared to answer your questions.

Mr. SHAYS. Thank you, Dr. Foster. General Vesser.

General VESSER. Mr. Chairman, I appreciate the opportunity to appear before your subcommittee to review with you and its members the support the Office of the Special Assistant for Gulf War Illnesses, referred to earlier as OSAGWI, provides to the ongoing research into the potential causes of Gulf war illnesses.

As you know, the Office of the Special Assistant for Gulf War Illnesses does not directly undertake medical research and, with a few exceptions, does not directly sponsor medical research. Our primary tasking when established was to find out what happened on the battlefield. Dr. Rostker was specifically tasked to find out what the problems are and to fix them. When the office was established the then Deputy Secretary of Defense, Dr. John White, reconfirmed the Department's policy that the Assistant Secretary of Defense for Health Affairs was responsible for the Department's medical programs. In that regard, the Assistant Secretary of Defense for Health Affairs and the Deputy Under Secretary of Defense for Science and Technology represented the Department on the Research Working Group of the Persian Gulf Veterans Coordinating Board, which coordinates pertinent medical research for DOD, Veterans Affairs, and Health and Human Services. We do have an observer who also sits with that group.

Over the last 3 years, the Office of the Special Assistant has been instrumental, however, in funding or impacting the funds of several medical research programs that, for one reason or another, were not being supported by the traditional medical research funding process. Generally speaking, these did not receive sufficiently high evaluation scores in the competitive medical review process, but had become a great concern with a significant number of Gulf war veterans. Our work in OSAGWI begins and ends with the veterans. We recognize, therefore, that sometimes exceptions need to be made to the competitive medical review process. Specifically, we believe that in the case of Gulf war illnesses, it is important to listen to our veterans and provide any assistance we can by researching claims to the potential cause and cures for unexplained illnesses that are affecting many of them.

Frankly, we have a credibility problem with some veterans who believe that we are not funding promising research because we either don't care about their health or that we have something to hide. In such cases, we can demonstrate that neither is the case. We owe it to our veterans to apply accepted medical research standards to determine if the theory being proposed can help either explain why veterans are ill or help in their treatment.

Let me highlight for you the projects that we have either directly funded or have been instrumental in making sure that funds were provided. This is in addition to the general work of our office.

Specifically, we have funded or impacted the funding of the work of Dr. Garth Nicolson, tests for mycoplasma fermentans incognitus strain in human blood, and Dr. Robert Haley, multi-disciplinary pathophysiologic studies of neurotoxic Gulf war-related syndromes. We have also funded a review of the medical records of the Saudi Arabian National Guard by the Uniformed Services University of the Health Sciences and the Naval Health Research Center.

As you know, we have commissioned a number of medical literature review papers prepared by the RAND Corp. These papers are not medical research in the traditional sense, but were important to inform and direct the work of our office. These papers, case narratives, information papers, and our environmental exposure reports are available on the Internet at GulfLINK, and have been reviewed by the Presidential Special Oversight Board headed by former Senator Warren Rudman.

We also helped to coordinate for DOD funds to be provided to the Department of Veterans Affairs program in Baltimore to monitor the health of veterans exposed to depleted uranium. I am pleased to say that the last published results for this program, "show no evidence of adverse clinical outcomes associated with uranium exposures at this time in these individuals."

Again, thank you, Mr. Chairman, for giving me the opportunity to put the work of the Office of the Special Assistant into the proper context. I stand ready to answer any questions you or the subcommittee may have, and I ask that my remarks be made part of the record.

[The prepared statement of General Vesser follows:]

Statement
of
LTG (Ret) Dale A. Vesser
Deputy Special Assistant to the
Deputy Secretary of Defense for Gulf War Illnesses

House Committee on Government Reform
Subcommittee on National Security, Veterans Affairs,
and International Relations
February 2, 2000

Mr. Chairman, I appreciate the opportunity to appear before the Subcommittee on National Security, Veterans Affairs, and International Relations to review with you and the members of the subcommittee the support the Office of the Special Assistant for Gulf War Illnesses provides to the ongoing research into the potential causes of Gulf War illnesses.

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Disciplinary Pathophysiologic Studies of Neurotoxic Gulf War Related Syndromes). We have also funded a review of the medical records of the Saudi Arabian National Guard by the Uniformed Services University of the Health Sciences and the Naval Health Research Center.

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Again, thank you Mr. Chairman for giving me the opportunity to put the work of the Office of the Special Assistant into the proper context, I stand ready to answer any question you or the Subcommittee may have.

Mr. SHAYS. Thank you, General Vesser. Dr. Barrett.

Dr. BARRETT. Thank you, Mr. Chairman. Thank you for the opportunity to update the subcommittee on the Centers for Disease Control and Prevention's research programs pertaining to Gulf war veterans' illnesses, and to discuss the General Accounting Office's report.

I am Dr. Drue Barrett of the National Center for Environmental Health. I serve as CDC's liaison to the Department of Health and Human Services on Gulf war issues, and I am a member of the Research Working Group of the Persian Gulf Veterans Coordinating Board.

Our research efforts on Gulf war veterans' health concerns date back to 1991, with the larger epidemiologic studies beginning in 1994. I would like to briefly mention our most recent Gulf war activities and refer you to my written testimony for further details. Two completed CDC-funded studies directly pertain to questions raised by the GAO regarding the success of the Federal Government in documenting the symptoms of Gulf war veterans.

The Iowa study conducted in collaboration with the Iowa Department of Public Health and the University of Iowa 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. In fact, the study was recently described by the Institute of Medicine as perhaps "the strongest study on Gulf veterans' experience of symptoms related to deployment in the Gulf."

The Iowa study found that the Gulf war military personnel were more likely than those who did not serve in the Gulf war to report symptoms suggestive of cognitive dysfunction, depression, chronic fatigue, post-traumatic stress disorder and respiratory illness. The conditions identified in the study appeared to have had a measurable impact on the functional activity and daily lives of these Gulf war veterans.

Likewise, the CDC-Air Force study has significantly contributed to our understanding of the health consequences of the Gulf war. This study organized symptoms into a case definition, characterized clinical features, and evaluated risk factors. The key observation of the study was that Air Force Gulf war veterans were significantly more likely to meet our case definition of illness than were nondeployed personnel. However, there was no association between this chronic multisymptom illness and risk factors specific to combat in the Gulf war, such as month or season of deployment, duration of deployment, duties in the Gulf war, direct participation in combat, or locality of Gulf war service.

We found that nondeployed veterans also met our case definition, suggesting that the illness observed in this population is not unique to Gulf war service. The clinical evaluation component found that ill Gulf war veterans did not have clinically significant abnormalities on physical examination or routine laboratory tests. However, they did report a significant decrease in functioning and well-being.

The results from both the Iowa study and the Air Force study were published in the Journal of the American Medical Association. In addition, both of these studies have resulted in a number of

other articles which have been published or about to be published. CDC is currently funding a followup to the Iowa study focusing on evaluating self-reported symptoms of asthma. We are also funding the Boston University School of Public Health to conduct a study examining the relationship between cognitive function and symptom patterns among Gulf war veterans, and we are funding the University of Medicine and Dentistry of New Jersey to conduct a study examining case definition issues.

In addition to these current research projects, in 1999 CDC sponsored a conference to develop future Gulf war research recommendations. We brought together scientists, clinicians, veterans, veteran service organizations, congressional staff and other interested parties to discuss and make recommendations regarding the direction of future research of undiagnosed illnesses among Gulf war veterans and their links with multiple chemical and environmental exposures.

The conference highlighted the importance of including veterans in the process of planning and implementing research. A report is soon to be released that summarizes the outcome of the conference.

Finally, I would like to briefly address the issue of 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, the National Institutes of Health, and the Agency for Toxic Substances and Disease Registry are represented. Through its membership, HHS has been involved in providing guidance and coordination for DOD, VA and the HHS research activities relating to Gulf war veterans.

In conclusion, an intensive research effort to address Gulf war veterans' health concerns has been mounted by Federal agencies. The research projects funded to date represent a broad spectrum of efforts ranging from small pilot studies to large scale epidemiology studies. In addition, numerous review panels and expert committees have evaluated the available data on Gulf war veterans' illnesses.

As noted in the GAO report, despite these extensive research and review efforts, many questions remain regarding the health impact of the Gulf war. These remaining questions reflect the complexity of assessing and predicting the health impact of military deployments.

Mr. Chairman, this concludes my oral remarks, and I would be happy to answer any questions the subcommittee may have.

[The prepared statement of Dr. Barrett follows:]

TESTIMONY OF

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

BEFORE THE

SUBCOMMITTEE ON NATIONAL SECURITY, VETERANS AFFAIRS AND

INTERNATIONAL AFFAIRS

COMMITTEE ON GOVERNMENT REFORM

U.S. HOUSE OF REPRESENTATIVES

FEBRUARY 2, 2000

Mr. Chairman, thank you for the opportunity to update the Subcommittee on the Centers for Disease Control and Prevention's (CDC) research programs pertaining to Gulf War veterans' illnesses and to discuss the General Accounting Office's (GAO) report, "Gulf War Illnesses: Management Actions Needed to Answer Basic Research Questions." I am Dr. Drue Barrett, Chief of the Veterans' Health Activity Working Group in the Division of Environmental Hazards and Health Effects of the National Center for Environmental Health (NCEH). I serve as CDC's liaison to the Department of Health and Human Services (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, most notably, the National Center for Infectious Diseases.

The purpose of my testimony is to update the Committee on the extent of CDC's Gulf War research activities, the productivity of our research efforts, and how our research has been coordinated with the research being conducted by other Federal agencies.

Completed CDC-funded Gulf War Studies:

Before describing our current studies, I would like to review the results from two completed CDC-funded studies because these studies are pertinent to questions raised by the GAO regarding the success of the federal government in documenting the symptoms of Gulf War veterans. The Iowa study, conducted in collaboration with the Iowa Department of Public Health and the University of Iowa, was one of the first population-based epidemiologic studies to document that Gulf War veterans are reporting more medical and psychiatric conditions than their non-deployed military peers. In fact, this study was recently described by the Institute of

Medicine as "perhaps the strongest study on Gulf War veterans' experience of symptoms related to deployment in the Gulf." The 3,695 subjects who completed this study were selected from a larger population of almost 29,000 military personnel who listed Iowa as their home of record. Furthermore, the subjects in this study were specifically selected to represent individuals from all four branches of the military, and include both regular military personnel and National Guard and reservists. Seventy-six percent of the eligible study subjects completed the detailed telephone interviews. This study is also one of the first controlled epidemiological studies to evaluate the health consequences of the Gulf War. The study included a carefully selected comparison group of military personnel who were not deployed to the Persian Gulf but who served during the time of the Gulf War. The Iowa study found that the Gulf War military personnel were more likely than those who did not serve in the Gulf War to report symptoms suggestive of 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. Among Gulf War veterans, minimal differences were observed between the National Guard or reserve troops and the regular military personnel.

The results of the Iowa study were published in the *Journal of the American Medical Association* in 1997. In addition, a number of other manuscripts from the Iowa study have been published, are in press, or are currently in the process of peer review. These include an article on quality of life and health service utilization among military personnel reporting multiple chemical sensitivities, published in 1999 in the *Journal of Occupational and Environmental Medicine*, and an article on symptom prevalence and risk factors of multiple chemical

sensitivities, in press in the *Archives of Internal Medicine*. Manuscripts are currently being considered at peer-reviewed journals on the topics of defining a Gulf War syndrome, the relationship between post-traumatic stress disorder and physical health status, and self-reported injuries among Gulf War veterans.

Likewise, the CDC Air Force study has significantly contributed to our understanding of the health consequences of the Gulf War. This study organized symptoms reported by Air Force Gulf War veterans into a case definition, characterized clinical features, and evaluated risk factors. The cross-sectional questionnaire was sent to 3723 currently active volunteers from four Air Force populations. Clinical evaluations were performed on 158 Gulf War veterans from one unit, irrespective of health status. A case was defined based on reporting one or more chronic symptoms from at least 2 of 3 categories (fatigue, mood-cognition and musculoskeletal) and was further characterized as mild-to-moderate or severe depending on the severity of the reported symptoms. The prevalence of mild-to-moderate and severe cases were 39% and 6%, respectively, among 1155 Gulf War veterans versus 14% and 0.7% among 2520 non-deployed veterans. Fifty-nine (37%) clinically evaluated Gulf War veterans were non-cases, 86 (54%) were mild-to-moderate cases and 13 (8%) were severe cases. The key observation of the study was that Air Force Gulf War veterans were significantly more likely to meet criteria for severe and mild-to-moderate illness than were non-deployed personnel. There was no association between the chronic multisymptom illness and risk factors specific to combat in the Gulf War (month of season of deployment, duration of deployment, duties in the Gulf War, direct participation in combat, or locality of Gulf War service). The finding that 15% of non-deployed veterans also met illness criteria was equally important and suggests that the multisymptom

illness observed in this population is not unique to Gulf War service. The clinical evaluation component of the study found that neither mild-to-moderate nor severe cases were associated with clinically significant abnormalities on physical examination or routine laboratory tests. However, Gulf War veterans classified as having mild-to-moderate and severe illness had a significant decrease in functioning and well-being compared with non-cases.

The results from this study were published in CDC's *Morbidity and Mortality Weekly Report* in 1995 and in the *Journal of the American Medical Association* in 1998. In addition, an article from the Air Force study examining the relationship between deployment stressors and chronic multisymptom illness is currently in press in the *Journal of Nervous and Mental Disorders*.

Current CDC-funded Gulf War Studies:

CDC is currently funding a follow-up to the Iowa study focusing on evaluating self-reported symptoms of asthma. This study involves a detailed clinical evaluation of a sample of subjects who completed the initial telephone survey. This evaluation includes a physical examination; tests of lung functioning; questions regarding medical, occupational, and exposure history; assessment of functional status and quality of life; and assessment of psychiatric history and personality functioning. The examinations are being conducted at the University of Iowa Hospitals and Clinics in Iowa City, Iowa. This study is in its final phases of data collection and we anticipate that results should be available later this year.

The University of Iowa has also been funded by the Department of Defense (DoD) to conduct validation studies of additional health outcomes among participants of the telephone survey. These include validation of depression, cognitive dysfunction, and fibromyalgia. CDC is

providing technical assistance to DoD and the University of Iowa for this study.

We are also funding the Boston University School of Public Health to conduct a study examining the relationship between cognitive function and symptom patterns among Gulf War veterans. In one component of this study, functional magnetic resonance imaging (fMRI) is being used to examine possible differences in brain activation patterns between Gulf War veterans and era controls with different levels of symptoms. A second component of the study is using a new data-driven mathematical technique, Logical Analysis of Data, to examine how Gulf War veterans' symptoms cluster together. This may provide useful information for determining etiology or for developing a case definition. Finally, this study also includes a component examining the neuropsychological functioning of a sample of Danish Gulf War troops. Investigators are currently in the data collection phase for the fMRI component of this study and in the data analysis phase for the other two components. We anticipate that this study will be complete by the end of this year.

Finally, CDC is funding the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School to conduct a study examining case definition issues. The study will assess the persistence and stability of Gulf War veterans symptoms over time, compare the performance of data-driven case definitions to existing definitions for medically unexplained symptoms, and examine the role of psychiatric conditions in Gulf War veterans' unexplained illnesses. We originally expected that this study would be completed in late 2000, however the process of protocol development and clearance took somewhat longer than we anticipated. Thus, we expect that this study will require an additional year to complete.

Research Collaborations:

CDC is collaborating with DoD and the Department of Veterans Affairs (VA) on a number of projects including a study of health outcomes among Saudi Arabia National Guard members and a study of Amyotrophic Lateral Sclerosis (ALS) among Gulf War veterans. This collaboration has included providing input on study protocols, reviewing human subjects issues, and assisting in laboratory assessments.

Future Gulf War Research Planning:

In addition to these current research projects, CDC, in collaboration with other HHS agencies, recently sponsored a conference to develop future Gulf War research recommendations. On February 28 through March 2, 1999, CDC brought together scientists, clinicians, veterans, veterans' service organizations, Congressional staff, and other interested parties to discuss and make recommendations regarding the direction of future research on undiagnosed illnesses among Gulf War veterans and their links with multiple chemical and environmental exposures.

Concurrent workgroups were convened in order to develop research recommendations in four areas: pathophysiology, etiology, and mechanisms of action; assessment and diagnosis of illnesses; treatment; and prevention of illnesses in future deployments. This conference highlighted the importance of including veterans in the process of planning and implementing research. Veterans and scientists alike expressed that they found the process useful and that future similar efforts should be encouraged. A report is soon to be released that summarizes the outcome of each of the four workgroup sessions. It is anticipated that this report will be of interest to a broad range of individuals and organizations and may provide the basis for development of new research collaborations and exchanges. Recommendations for new research

will need to be considered in light of the existing research portfolio of the Research Working Group in order to avoid unnecessary duplication of efforts.

Coordination of Federal Research Efforts:

Finally, I would like to address the issue of coordination of federal research efforts. There has been HHS representation on the Persian Gulf Veterans Coordinating Board Research Working Group since its inception. In addition to CDC, the Office of the Secretary, the National Institutes of Health, and the Agency for Toxic Substances and Disease Registry are represented. Through its membership, 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.

The Research Working Group also serves as a forum for research data exchange among the three departments and among federally funded investigators. CDC's role in this area has included providing information on the status of projects for a research database of all VA, DoD, and HHS research activities, input on the Annual Report to Congress on federally sponsored Gulf War Veterans' Illnesses research, and participation on the planning committee for the federal investigators meeting where new research results are shared.

Conclusions:

An intensive research effort to address Gulf War veterans' health concerns has been mounted by federal agencies and non-governmental scientists. As of 1999, there have been 145 federally-funded research projects on Gulf War veterans' illnesses with a cumulative expenditure

of $133.5 million for research from FY94 through FY99. These projects represent a broad spectrum of research efforts, ranging from small pilot studies to large-scale epidemiology studies addressing mechanistic, clinical, and epidemiological issues. Similar efforts have been initiated in other coalition countries, most notably in the United Kingdom and Canada. In addition, numerous review panels and expert committees have evaluated the available data on Gulf War veterans' illnesses. As noted in the GAO report, despite these extensive research and review efforts, many questions remain regarding the health impact of the Gulf War. However, these remaining questions do not reflect scientific indifference; instead they reflect the complexity of assessing and predicting the health impact of military deployments. Despite this complexity, the federal research effort continues in an effort to uncover the causes of illnesses among Gulf War veterans so that effective treatment approaches can be developed and similar illnesses in future deployments can be prevented.

Mr. Chairman, this concludes my testimony. I would be happy to answer any questions the Subcommittee may have.

Mr. SHAYS. I would just make the observation it is almost like we have two separate hearings. We had the GAO who was basically commenting on your work and had some extraordinarily significant statements, and you didn't address any of them. You just had your statements.

Mr. Sanders.

Mr. SANDERS. Thank you, Mr. Chairman.

Let me start off with General. Thank you very much for being with us. Let me call on your military background, General, to ask you a question. If the U.S. military were engaged in a major military operation with unlimited resources befitting the wealthiest Nation on Earth, and we were fighting that war for 9 years and at the end of those 9 years the military objectives were not one step closer to being obtained in the sense of winning the war, would it be fair to say that it would be in the country's best interests to remove the generals who are in charge of that military operation?

General VESSER. Of course it would be appropriate, but one has to ask what the objectives are.

Mr. SANDERS. If the objectives here are quite clear, they are not complicated, the objectives that we have close to 100,000 men and women who are ill, and the objective is we want an understanding of their illness and we want an effective treatment, and it seems to me 9 years later we have zero in that regard from the U.S. Government, tell me why given that rather sad track record the chairman and I and Members of Congress should not say thank you very much for your well-meaning efforts, you have failed, we need other people to take up the battle?

General VESSER. I would say to you what have we done. I can speak only for my office. My office was charged to discover what happened on the battlefield. I am not a medical person. I was a line officer, and I am both a Vietnam vet and also served as a civilian during Desert Storm in the desert.

I would say to you that we have developed models to estimate who was exposed to the low levels of chemical warfare agent. We have target notified over 157,000 veterans by letter of their potential exposure to that and to other hazards that we have looked at.

Mr. SANDERS. General, we don't have unlimited time, and I don't mean to be rude in interrupting you. I am aware of that. I am not saying that is insignificant, but using the analogy of a military conflict, we are not winning this battle. We are losing it. We have tens and tens of thousands of people who are ill. Let us see our eyes on the prize. What are we talking about. We are talking about treating sick veterans. We are zero step closer today it seems to me. And I think the record on the part of the VA and the DOD has not been a good one.

Let me speak to Dr. Foster, if I might.

I notice on page 5 and on you comment on some of the research. Let's deal with that.

It seems to me that in fact there have been some breakthroughs. What concerns me in terms of the last panel, the words that we keep hearing is lack of focus, disconnect, a lack of sense of urgency. In other words, it appears that there have been some studies which are making some breakthroughs and it seems to me that we have got to put our resources into those studies. I am not happy to hear

from Dr. Barrett that after 9 years we have concluded that some people are ill or are not ill. We are starting with the assumption that there are tens of thousands of people who are ill. That was a 9-year-old discussion.

What we want to know now is what are you doing to discover the cause of illness and what treatments have you developed.

Now on page 5 you mention Dr. Garth Nicolson's study, and I will be talking to Dr. Feussner about this. We have put a significant amount of money into Nicolson's hypothesis. Is Nicolson right or wrong. If he is wrong, we have learned something. If he is right we may have a treatment model. Thank God we have something, good.

Haley has come before this committee on several occasions. He has impressed some of us as being a vigorous and intelligent researcher. He has suggested, among other things, that a genetic trait can predispose people to Gulf War Syndrome. In other words, what he has suggested is two people with the same exposure will react differently. What are we doing? That is an important step forward.

He and his researchers have suggested that we can now objectively look at a brain scan and maybe tell us who has Gulf war illness and who does not. As a layman, that seems to me to be a breakthrough. It objectifies. It ends the discussion whether somebody is ill or not ill. If we can see changes in the brain, we know something. What are we doing to go forward on that particular study?

Dr. FOSTER. I believe Dr. Feussner would like to speak to that rather than me.

Dr. FEUSSNER. Yes, I would like to speak to that, Congressman.

Before I do, we have had numerous discussions in the past that I would characterize as straightforward.

Mr. SANDERS. Yes.

And I would say that, as you know, I agree with you that we have tens of thousands of veterans who are sick. We are treating hundreds of thousands of veterans in VA hospitals. I believe last year almost 300,000 Gulf war veterans received care in VA making in excess of 3½ million outpatient visits to VA.

I think there's no question that Gulf war veterans are being treated. I think the difficulty that we have is that they're not being fixed; that is, they are not being cured. And you are quite correct that we have no cure for Gulf war veterans' illness. That is absolutely, unequivocally correct. It's also absolutely, unequivocally correct that we have no cure for AIDS.

Mr. SANDERS. John, let me interrupt you. We have no cure for AIDS?

Dr. FEUSSNER. But we have treatments.

Mr. SANDERS. Here is an important distinction if you want to make an analogy between Gulf war illness and AIDS. Researchers today have made significant progress. If you or I had AIDS, we'd be better treated today, have a longer life-span than was the case 10 years ago. Research has resulted in improved treatment.

What I asked General Vesser and Dr. Foster is, has research in Gulf war illness resulted in better treatment in terms of curing people who are sick? I think the answer is no.

Dr. FEUSSNER. I concur.

The issue about the brain—the brain issue, I think, is quite a pertinent one, and in my lengthier testimony—I apologize in my effort to beat the red light—I omitted my comments about our brain imaging studies. But what I would like to say is, yes, these imaging studies are highly important. The research portfolio at the moment includes seven studies using sophisticated brain imaging technologies ranging from the typical one that you would encounter in a hospital—traditional, conventional magnetic resonance imaging, which looks at issues of anatomy; functional magnetic imaging, that tends to look at issues of function; magnetic resonance spectroscopy and SPECT scanning, which can actually look at chemical reactions in the brain without invading the skull.

Mr. SANDERS. Let me interrupt you and ask you this question. Again, I'm a layman.

What seemed to me important about Haley's work is we are beginning—I don't know what the scientific word is, but looking at—in an objective way, if you're looking—you can show me on a piece of paper the brain damage of somebody and say, this person has Gulf war illness, it seems to me to be a significant breakthrough.

Are your studies confirming what Haley has shown or are you not?

Dr. FEUSSNER. The studies haven't been completed yet, unfortunately. What—but I can tell you what the studies are focused on. The studies are somewhat different than Dr. Haley's. Dr. Haley focused on a general chemical in the brain that's dispersed throughout the brain and is a potentially general marker for nerve cell damage.

The studies that we have looked at focus on parts of the brain that are known to be associated with memory processing called a hippocampus and others, since many of the patients complain of having memory dysfunction, et cetera.

The other major focus of the research is looking at chemical neurotransmitters; that is, chemicals in the brain that allow cells within the brain to communicate among themselves and with other parts of the brain.

But there is research in the pipeline, yes, sir, that will confirm, advance, et cetera, the results of Haley's work.

Mr. SANDERS. I want to say something that while I have been very critical, and I think quite rightly, of the DOD and VA, I think Dr. Feussner is a bright light and probably will get you fired. But nonetheless I think he is at least one person trying to get forward.

Here is the point; let's get back to the treatment aspect. Presumably, if Haley is right, maybe—I don't know this, but if he is right—there might be a treatment that can be built around that understanding. I mean, don't we want to develop a treatment? How close are we developing a treatment based on the brain research that you're doing?

Dr. FEUSSNER. We're not close to developing treatment based on brain research that anyone has done to date. But I think your assertion is fundamentally correct; that is, you don't want to give a patient with hypertension insulin, because you'll do much more harm than good. And one of the conundrums of the research process is, fundamental understanding about some of the mechanisms

might allow you to make better judgments about treatments that are likely to provide more benefit than treatments that are likely to do more harm. And that's the pathway we have taken, as you asserted earlier, with the mycoplasma idea. Those are the pathways we are taking as a matter of fact with the EBT trial.

Congressman Allen commented on the fact that the working case definitions could actually be useful, and I would like to point out that that is, in fact, correct; and in both our treatment trials those working-case definitions are being used to select subgroup of patients for treatment, and what we have observed is that those patients are quite sick, based on the measures we're making of their health status.

Mr. SANDERS. Let me ask you this. Let me shift gears a little bit and go to the issue which Mr. Allen, among others, has raised; that is the issue of multiple chemical sensitivity. Again, you're talking to a Member of Congress for whom this is not an abstract issue. I have talked to hundreds of veterans in the State of Vermont. As you know, I think Vermont probably ranks the highest in the country in terms of participation in the mycoplasmic study. We have worked very hard to involve people in that study and to work with veterans.

A veteran in Springfield, VT, tells me if he is exposed to his wife's perfume or walks into a grocery store, he becomes ill. It sounds to me like this is a reasonably conventional symptom of what we call "multichemical sensitivity." What are you doing to treat, to acknowledge that problem and to treat that problem?

I have a nightmarish feeling that there are thousands of veterans who are walking around today who probably have a lot of toxicity within their systems or damage in their systems as a result of exposure to toxicity, who continue to get exposed to the food they eat, the air they breath, the work that they do, to toxic elements that perhaps make them iller than they otherwise should be if they avoid that type of environment and yet they are not told about that.

What are we doing to understand and treat multiple chemical sensitivity? There are a number of studies—perhaps we'll hear from Dr. Miller in a little while—that suggest that what we're seeing in some of our Gulf war veterans are not dissimilar from what doctors are seeing from civilians who have been exposed to excessive amounts of chemicals. Now, this is an issue not just for Gulf war veterans but for the population at large. What are we, in fact, doing on that issue?

Dr. FEUSSNER. The research that's ongoing in low-level chemical exposures and low-level chemical toxicity is small. I think probably fewer than a dozen projects that look at efforts to understand how exposures to various chemicals, low doses of chemicals might affect various body systems. We have no treatment trials at the moment.

Mr. SANDERS. It seems to me, Dr. Feussner, that is a great lack. That is one of the important hypotheses out there.

Why is the VA not going forward on it?

Dr. FEUSSNER. Well, in part, I think you already know the answer to this question, but let me try to answer it nonetheless. I think there are two issues. One of the issues is that some of the treatment strategies that are proposed require unique environ-

mental chambers, and the Department has no or virtually no such facilities at the moment. So it doesn't permit any research that one would want to do——

Mr. SANDERS. Let me interrupt. I don't mean to be rude. I'm a fan of yours. I'm not being rude here, but let's stop for a moment.

You've spent, gentlemen, how much, $130 million? Almost everybody is of the opinion that one of the causes of Gulf war illness may be the fact that our veterans were exposed to a very toxic environment. There's no doubt about it. We, generally speaking, call that type of process multiple chemical sensitivity. How could it be that when an environmental chamber costs a few million dollars and you need that environmental chamber to do the work that needs to be done to fully understand multiple chemical sensitivity, that after spending $120 million-plus, we still do not have that chamber.

Doctor.

Dr. FEUSSNER. Well, I don't know the answer to that question, Congressman. What I would say is that in—with regards to our Environmental Hazard Research Center in East Orange, in East Orange, that the low-level exposure research that's going on there avails itself of the collaboration with the Robert Wood Johnson Medical School, which does have access to such chambers, and MCS research is going on there using the university-based chamber.

Mr. SANDERS. Let me interrupt you again.

Dr. FEUSSNER. Now, the other issue, however——

Mr. SANDERS. Sorry. Let me interrupt you again. I open it up to any of the five people up there.

Tell me why if exposure to chemicals is considered to be one of the important causes, what might be one of the important causes of Gulf war illness. If an environmental chamber is absolutely needed to better understand this problem, tell me why for a few million dollars the U.S. Government does not own one environmental chamber? Can anybody answer me that question?

Mr. Chairman, I must tell you I put in the last——

Dr. FEUSSNER. Congressman, if I may say, I believe the Federal Government does own such chambers. I'm not specifically aware of DOD, but I'm quite aware that the EPA site at the University of North Carolina in the Research Triangle has, I believe, such facilities.

Mr. SANDERS. I am not aware of that. I may be wrong on this. I will——

Dr. FEUSSNER. But I think in terms of——

Mr. SANDERS. Even if they do, where is the collaboration? Why are you not availing yourself of that chamber if, in fact, it does exist? How many years do we have to go through the routine of talking about multiple chemical sensitivity and understanding it? Now, I do understand it.

Here's the root of the problem, I think—I know I'm taking up much too much time—multiple chemical sensitivity or multiple chemical illness is a controversial definition, right? There are some people in the medical world who simply do not agree with it, I understand that, but it seems to me in fairness to Gulf war veterans who are ill, we have got to pursue every avenue that is out there.

Dr. Feussner, what you are telling me is, you think there may be a chamber, but certainly it is not a chamber that I gather any of the research here has worked with.

I would mention, Mr. Chairman, in the last military appropriations bill, I put in some language—I guess, calls for the need for a chamber, but I would hope very much that with all of the money we are spending, we will build a chamber so we can better understand multiple chemical sensitivity. I think it's an outrage that we don't have one.

Dr. Feussner, let me give it back to you. Do you agree?

Dr. FEUSSNER. Well, I think there's no question that having a facility available certainly would facilitate use of that and subsequent research. You also are aware that that problem confounding us, we are receptive to research in this area that specifically focuses on treatment trials, I think, all of us that are receptive to that research—NIH, DOD, and VA.

Mr. SANDERS. Tell me about the research—all right. He gets sick—I keep pointing to my colleagues here—if his wife has perfume. I don't know if you talked to them, but in Vermont we have veterans. Dr. Vesser, he is nodding his head. That is a symptom that you picked up, right?

General VESSER. I have talked to over 3,000 veterans in our town halls that come to tell us what their problem is, and probably another—my teams have probably talked to another 20,000. And this is one of the symptoms that we hear, sir.

Mr. SANDERS. Good. So we're in agreement. What are we doing to better understand that and treat that so a man can be with his wife who wears perfume? What have we learned from that all of these years?

Dr. Vesser, you want to help me with what we've learned? I've heard it; you've heard it; what have we learned? If a guy gets sick exposed to detergent or perfume, what have we learned?

Who wants to tell me what we have learned? What are we doing to treat that?

Dr. FEUSSNER. I don't know that we've learned very much, but what I would say on the other hand is that this issue suffers from some of the same problems that Gulf war veterans' illnesses have, vis-a-vis sharply defining the patient population, defining interventions that are testable and that can be given homogeneously across populations and then having explicit outcome measures.

Mr. SANDERS. John, will you promise me this—and you've been a man of your word: It sounds to me like we're really lacking going forward, and I understand that it's controversial, and I understand that some of the researchers in this area get criticized and they don't have all the peer reviews and everybody else—millions of Americans.

Dr. Vesser, you have heard the same thing that I have heard, right?

General VESSER. That's correct, but it's General Vesser, sir, not doctor, with all due respect.

Mr. SANDERS. I'm sorry. You've heard the same thing and you have just told me by your silence that we're not doing very much in responding to those concerns that the veterans have?

General VESSER. Well, my own office is trying to do some environmental reports. One of them will deal with pesticides, because we know that all soldiers who served in the Gulf war were exposed to pesticides, one chemical that we are concerned about, so we're trying to get some information about potential dosage.

Mr. SANDERS. Dr. Feussner, can you make a promise to this committee today that you will make multiple chemical sensitivity a top priority, that you will work with us for an environmental chamber so that we can begin to treat and understand that problem better? Can you make that promise or commitment to us?

Dr. FEUSSNER. Yes, I think that I will—I think, sir, I have tried to work with you on this effort in the past and, yes, I will continue to work with you on this effort.

Mr. SANDERS. You have worked with us, and I applaud you for that. But we have not worked effectively—you have worked very well on the mycoplasmic theory. I applaud you.

We have not worked effectively on MCS.

Dr. FEUSSNER. Which we have not gotten to, yes, yet.

Mr. SANDERS. You will make that commitment to us?

Dr. FEUSSNER. Yes, sir, I will certainly continue to work with you.

Mr. SANDERS. Will you support our effort to fund an environmental chamber?

Dr. FEUSSNER. I believe I've made that commitment to you in the past, that if there was a way to find the money, I would be with you.

Mr. SANDERS. But this is what is a little bit crazy. We're talking about spending $130 million. The Congress has not been cheap. We've allocated a lot of money. There is money out there; you can make that happen if you want.

Mr. Chairman, you've been very gracious here. I've gone three times over my limit here. I thank you.

Mr. SHAYS. I will try to get you all out before we have to vote, so you don't have to wait for us.

You are all parts of various departments who are part of the coordinating working group, and not only do I feel like the GAO's report before yours was ignored by your statements; but I also don't have a sense of comfort that you are part of one group.

Who is in charge right now of the working group? Dr. Feussner.

Dr. FEUSSNER. I am sir.

Mr. SHAYS. How does the system work? It rotates every 3 months or what?

Dr. FEUSSNER. No, sir. I became chairman of the Research Working Group in 1996, and I have been chair of the Research Working Group through the entire subsequent time.

Mr. SHAYS. I get the feeling that OSAGWI is basically the 10,000-pound gorilla in this group though. Hearing from you, General Vesser, it's like you're just getting an assessment of where our soldiers are coming from and that's the extent of it. Isn't your agency basically doing most of the funding?

General VESSER. We have spent a lot of money on our investigations and all that work hasn't gone solely on investigations. The Research Working Group, as we understand it, is concerned primarily with medical research and research, scientific research.

Mr. SHAYS. Is it your testimony that you don't do 90 percent of the research projects?

General VESSER. Ninety percent of the research projects?

Mr. SHAYS. Of the $121 million, how much are you spending?

General VESSER. OSAGWI isn't spending any of that, sir. That money is in a separate account.

Mr. SHAYS. You're in charge of coordinating DOD's effort, correct?

General VESSER. Dr. Rostker is in charge of coordinating DOD's efforts, but they do not extend, as I said in my prepared statement, to the conduct of medical research, the research that the Research Working Group is responsible for.

Mr. SHAYS. I just want to pursue that. You work as the Deputy to the Special Assistant for Gulf War Illnesses; your office does this?

General VESSER. That's my office, yes, sir.

Mr. SHAYS. Are you telling me that your office makes no determination on who gets funded and who doesn't get funded?

General VESSER. That's correct. We're not voting members of the Research Working Group in terms of funding these $121 million of projects you've heard about. We're concerned with modeling to find out what soldiers who served in the Gulf might have been exposed to in terms of low levels of chemicals, funding the experiments at Dugway, funding the chemical rocket warheads that had to be made, trying to define the hazards that people——

Mr. SHAYS. How much money do you spend on research and studies?

General VESSER. Research per se? I don't have the figure right in front of me, but I'll provide an answer for the record, sir.

Mr. SHAYS. Give me an idea.

General VESSER. I'd say all together, thus far, on the subjects we're talking about, we've probably spent something on the order of $10 to $13 million, including the travel for people to come in and help us determine where our soldiers were, on declassification of——

Mr. SHAYS. Let me say this to you. I'm going to say this to each and every one of you.

Every accusation that the GAO made about the working group or your participation in the working group stands as fact unless you refute it—stands as fact. Now, one of the statements they said was, first, DOD, VA, and HHS spent over $121 million in research investigation in fiscal 1997 and 1998. DOD's efforts account for 90 percent of the total.

Now, you are my representative of DOD. Dr. Foster and Dr. Vesser, do you guys coordinate? I mean, who is in charge here?

Dr. FOSTER. The research account that I have oversight for is the investments coordinated through the Research Working Group, and we actively solicit as part of the research strategy the input from the VA and Health and Human Services and from OSAGWI, and the actual investment is tailored to their advice.

Mr. SHAYS. Does that constitute 90 percent of the funding?

Dr. FOSTER. No.

Mr. SHAYS. You were here. You heard this statement. If this statement is inaccurate, tell me it's inaccurate.

General VESSER. I believe that statement is inaccurate, Mr. Chairman, because it includes all the money that we spent on investigations, on other types of scientific efforts that are not medical research that comes under the Research Working Group.

Mr. SHAYS. I'm sorry, I'm going to have to hold you over. I'll go vote and I'll come back. I thought I could get us done.

I'm sorry. We'll stand in recess.

Why don't we do this? Why don't you—I'll be back here in 20 minutes.

[Recess.]

Mr. SHAYS. I'd like to call the hearing to order. When I was gone, I was just trying to think what my frustration is, and I don't like to use that word often. One of the things I realize is that I can be up here in the chair, and I can yell at witnesses and I have tried not to do that. I have tried not to do that for the many years I've been chairman. I've tried to realize that I have a special advantage up here, and I can just throw stones and I don't have to answer.

But it does strike me as not unreasonable that if you had the GAO that basically tore apart the working group and each of you had your own statements that somehow are self-contained, that there would be some recognition that it deserves to be responded to. And so I do think it's fair to say that GAO tore apart the working group, and now I think the working group needs to respond. And I began to realize that I think for instance, Dr. Feussner, you're speaking from the perspective of the VA; and you're speaking, Dr. Mazzuchi, from the DOD's perspective; and Dr. Foster from DOD's perspective; and General Vesser's from DOD's perspective; and Dr. Barrett from HHS's perspective. But you're part of a working team that just got clobbered this morning, and I want, before we end, to know where you agree or disagree. And, for instance, in the document that they provided, they share with us the fact that you had certain objectives and you haven't responded to any of them that told us where you are on them.

So I want to know, Dr. Feussner—I'm going to go right down the list—I want to know where you agree and disagree with GAO.

Dr. FEUSSNER. Sir, I haven't seen the final GAO report, but I have seen the GAO report that they shared with our group 6 months ago, and VA did respond to the criticisms of the GAO.

One of the criticisms——

Mr. SHAYS. Let me back up a second, Doctor. You were here this morning. You did hear what they said today.

Dr. FEUSSNER. That is correct.

Mr. SHAYS. OK.

Dr. FEUSSNER. My full statement does refer to comments that the GAO made earlier.

Let me say we did concur with the GAO criticism that we have not summarized perhaps optimally the status of the research that has been going on in the Research Working Group on the one hand. On the other hand, GAO has noticed correctly that most of the research is ongoing and not complete. And it's really been only recently that a series of research products have become available.

One of the reasons for not synthesizing comments about the original working plan is that the research results are just now becoming available. We have given updates in the annual report to

Congress, that says what has gone on recently; and we have concurred with the GAO recommendation that we develop this synthesis during the course of this fiscal year, and we will do that.

Now, several of the activities that are going on in the research arena have had, I think, important results, and several of those important results I alluded to in my testimony. Unlike the GAO, I think that the epidemiological research has been quite important and quite beneficial. It sets the context for Gulf war veterans' illnesses. It shows preliminary information about mortality, birth defects. It shows preliminary information about health status, and that's very valuable information.

When the GAO criticizes us for saying that the research work needs—that we need to continue the work, they don't seem to appreciate that many of these exposures have long latencies, so that while I can say today that the mortality study has shown no increase in disease-specific mortality, that's not a completed statement. That's—that mortality observation needs to be made for 5, 10, 15 more years.

Similarly, with depleted uranium, we can say that for patients known to have embedded DU shrapnel, that they are mobilizing radioactive urine—excuse me, sir, radioactive uranium. They are excreting it in their urine. At this point in time, it has caused no ill effects on the kidneys and it has caused no other ill health effects, but it's too early to say that the depleted uranium is harmless. We need to keep those patients under surveillance.

The situation with the oil well fires and the measures of the hydrocarbon, potential hydrocarbon toxicity is very helpful. The National Cancer Institute study, a small study of soldiers from Germany to the Gulf, immediately after the war back to Germany, showing more toxicity while in Germany than in theater—a very useful observation.

The pyridostigmine bromide, we were concerned 2 years ago about penetration of the blood brain barrier. GAO might say that we are duplicating this research. We are not duplicating this research; we are replicating the research.

I can't tell Congressman Sanders if the result from Dr. Haley is a breakthrough. It could be. But if two, three other investigators make the same observation, if this looks like it's a reproducible observation, then it could be a breakthrough. So I feel like, in many areas we've made substantial progress.

In the infectious disease area, this research plan that we put together is organized by exposures, yes, but it's also organized by research strategies; and it provides guidance, but it also provides flexibility. We, in essence, have diminished the research commitment to infectious disease research because it seemed to be going nowhere beyond the issue of leishmaniasis. Well, we have changed that with the business being raised about mycoplasma, with a question that chronic antibiotic therapy might be able to affect that. We revisited that issue.

So in my sense, we have difficulty because the research portfolio is complex. It's not just one virus causing one illness. There's a long latency with many of these exposures and the spectrum of research goes from animal research, basic research, to population-based epidemiology to patient-based treatment trials.

Now, we've talked with GAO about that and we are working now. I think the criticism about the synthesis is fair with the caveat that much of the work is just now being finished, so we actually now have some things to synthesize. We will produce that this fiscal year, no later than September 30.

The other responses with regards to the coordination, I do disagree with and we disagreed for the record. All of these groups are represented on the Research Working Group. We discuss the research products; we discuss new research directions.

Mr. SHAYS. In DOD, we have three people from DOD. Who on DOD is on that board? So both of you serve?

General VESSER. We have an observer.

Dr. FEUSSNER. Dr. Kilpatrick was on the board as an observer.

Mr. SHAYS. How does it work? Is it one from VA, one from HHS and four or five from DOD? How does it work?

Dr. FEUSSNER. No. There are several from DOD. There are three from VA. There are representation from EPA and ATSD, the toxic substances and disease registry. There is NIH, the Secretary's office, CDC. So there are multiple representatives on the Research Working Group from each of the departments.

Mr. SHAYS. Before I'm concluded, I have to have a better comfort level of the coordination between OSAGWI and the working group, because I really feel that OSAGWI is basically kind of outside in a tremendous capacity to dominate and just do some on their own. But that's my feeling and your response is helpful. Thank you.

Dr. Barrett, I would like to know where you agree and disagree with the GAO findings.

Dr. BARRETT. I think the criticism that we haven't provided any information that addresses the objectives is unfair criticism. I think there is—there's been numerous publications that have addressed many of the objectives. It may not—like Dr. Feussner has said, it's not synthesized in such a way that it's—specifically states objective one and "this is what we found," but certainly an example is the objective regarding prevalence of symptoms and understanding the conditions.

Now, there is a criticism that we should be beyond that. Well, we do have current projects that are trying to move us beyond that. The New Jersey study is looking at the issue of stability of symptoms over time, how have the veterans' health conditions changed over time? The Boston study is trying to look at the issue of brain functioning and how brain function relates to this complex of symptoms.

Mr. SANDERS. May I interrupt for 1 brief second, Mr. Chairman.

What I'm hearing from both Dr. Feussner and Dr. Barrett is interesting, but it is missing one point and that is one word called "treatment." What you're working for is to help close to 100,000 people who are ill. It is interesting and it is important to know prevalence, et cetera, but if there is somebody over there who tells you that they have short-term memory loss or blinding headaches, what are we doing?

Now, I know—I would hope that Dr. Feussner would say that if the clinical trial with doxycycline goes well, you may in fact have a treatment for some of the symptoms. That is good news.

Tell me one other example where you're ready to have a treatment, based on $121 million of research. Do I hear any other?

Dr. FEUSSNER. The EBT trial.

Mr. SANDERS. But that's more disease management in fairness.

General VESSER. I think, sir, that it's useful to talk about outreach, which is one of our activities. The nearly 30 town halls we have conducted, we bring together representatives of the VA, of the military hospital or treatment facility in the area so that they can answer veterans' questions directly in terms of referring veterans who have had difficulty getting treatment. Now, that's not funded, as I said earlier, through research funding, but rather through O&M funding.

Mr. SANDERS. General, we can refer people all we want, but if there is no treatment, there are rather limits in terms of what we're referring.

Now, it's not complicated. If Dr. Feussner's clinical trial is successful, as I understand it, we will have a treatment for some veterans. That is good influences. What I'm asking you is, what other treatments are you developing right now? All the research you're doing is important, it's good, but it's not going to help make one veteran better tomorrow; and that's what they want and that's what our job is.

Mr. SHAYS. We're going on two tracks here, so I'm going to suspend that. I'm going to suspend the answer to that question and you'll have time to think about how you further want to answer it but I just want to be clear as to, in your mind, where you agree with GAO and where you disagree. And I'm getting a better sense of it.

Dr. Barrett, had you concluded your response?

Dr. BARRETT. I think regarding the question about whether we have information of how veterans are currently faring, I think again there is research going on in that area. Again, the projects are starting to get to the end of their funding period, so hopefully some results will be coming out soon on that regard; but again, this research takes time.

Mr. SHAYS. Now, among DOD, first let me be clear as to your office, General Vesser. My view is that you are basically—your office was established to coordinate DOD's effort in dealing with Gulf war illnesses. If I'm incorrect, which I could be, I want it explained to me.

Is that accurate or not?

General VESSER. We are the single point of contact for the Department for Gulf war issues, sir, but in effect, as I said in my opening statement, the tasking order that came from the then-Deputy Secretary of Defense John White gave us that authority in all areas except medical programs, and that was seen at the time to include programs for medical research which lies specifically with health affairs and with the, as I indicated in my opening statement, with Mr. Foster's office or Dr. Foster's office.

I would go on to note that our person on their board who coordinates has made available the results of all our investigations as they became available and kept the Research Working Group apprised of the areas that we were working in, but we are not voting

members on the Research Working Group, so consequently we have no direct say in the award of the contracts for medical research.

Mr. SHAYS. But DOD has votes in there?

General VESSER. Dr. Foster and Dr. Mazzuchi.

Mr. SHAYS. But you basically oversee their activities. Is that not true?

General VESSER. We do not oversee that activity because that activity is overseen by the Assistant Secretary of Defense for Health Affairs, according to the tasking division that was made by the Deputy Secretary of Defense.

Mr. SHAYS. I have no vested interest one way or the other on whether what the GAO says is accurate or inaccurate. I'm not trying to prove they're accurate. I just want to know whether they are accurate or not. I want to know if this statement is accurate.

First, DOD, VA, and HHS spent over $121 million in research and investigation in fiscal year 1997 and 1998. DOD's efforts account for 90 percent of the total. That's the statement that Mr. Chan made. Over half was spent by DOD's Office of the Special Assistant for Gulf War Illnesses, which I will refer to as OSAGWI, which is your office.

Now, is that accurate?

General VESSER. That statement is accurate, but it overlooks the fact that there are two different kinds of money. One is R&D money and second is operations and maintenance money.

When OSAGWI was established, initially we received $4 million from Health Affairs in O&M money. Subsequently all our funding has been from Defense-wide O&M. We pointed this out to the GAO in additional Department of Defense comments when we commented on their draft report. This is a distinction that they do not recognize evidently.

Mr. SHAYS. Now, in that report, on page 15, it says OSAGWI's activities have not been effectively coordinated with those of the Research Working Group in order to maximize the efficient use of resources. We found conflicting information about the nature of OSAGWI's work and whether it should be coordinated; specifically, the Research Working Group and OSAGWI's officials told us that OSAGWI's activities involve investigation, not research, and therefore are not subject to coordination. Is that something that basically I should leave on the table? Is that what you're telling me?

General VESSER. I'm telling you, sir, that we have done very little medical research other than the people we have responded to veterans thinking they had things that might provide some insight into what was making them ill, that our work has primarily been investigations.

Mr. SHAYS. How much money have you spent on investigations?

General VESSER. Investigations and scientific work done associated with that, the creation of meteorological models, the use of diffusion models, bringing people together for conferences to find out where our troops were located. Those are the kinds of things we've been doing, sir.

Mr. SHAYS. Those are very important things to do, General. I am just trying to assess if that is part of the $121 million or not.

General VESSER. That is part of the $121 million that they're reporting to you, yes.

Mr. SHAYS. And it is your view that all of that effort does not have to go before the Research Working Group?

General VESSER. That is correct, because it is a different science. It is focused on trying to understand and make sense of what happened on the battlefield.

Mr. SHAYS. I'm going to release the floor in just a second, but Mr. Chan's No. 2 point that he wanted to make was, most research is ongoing in mid-1999. Of the 151 research projects funded by the Federal Government, 30 percent have been completed while OSAGWI had received 19 of the 21 reports due from its contractors. It had publicly released only six of them. Of these reports, 14 had remained in draft or review status for a year or longer.

Now I want to know, are those investigative reports or research reports?

General VESSER. I believe that some of them are investigative reports and some are research reports. The Presidential Advisory Committee told us to use risk communication in communicating with veterans. This is how one communicates bad news essentially without frightening the individual who is receiving that news.

All of the work we do goes through a risk communication specialist to make certain that it has been looked at from that perspective. In addition, we often receive reports from contractors which are currently undergoing thorough scientific review, and we get a draft; and until the thorough scientific review by other like experts is complete, there's no way that those reports can be released.

In addition, we——

Mr. SHAYS. Why not?

General VESSER. Because they may lack credibility, take our first report on the Khamisiyah plume. We were told by the Congress we had to have that work peer reviewed by the Senate investigation unit, because they felt that it was not properly peer reviewed. We're refining that work now and when the work is refined, it will have been peer reviewed and those things take time, sir.

Mr. SHAYS. General, you just touched a real sensitive chord. We had a witness years ago who was going to come in on a Tuesday to point out that the DOD had not been telling the truth that our troops had been exposed to defensive chemicals in Khamisiyah. We had this individual with his video and at 12 noon on Friday before our Tuesday hearing, DOD announces at 4 p.m. they will have a press conference in which they announce that our troops were exposed. And that's why you just touched a real sensitive chord.

So when you talk about how you want to deal with Khamisiyah and everything else, you lost me.

General VESSER. I'm sorry I wasn't in the business then, sir, but I wouldn't have done that. I think that's not the way to behave.

Mr. SHAYS. Thank you for saying that.

I will just conclude by asking you this. Of these 14 reports that are in draft or review status for over a year, how many of them relate to your investigative and how many relate to the medical research side?

Dr. Foster, can you answer that?

Dr. FOSTER. If the 14 reports were commissioned by OSAGWI, then none of them would be medical research.

Mr. SHAYS. So these are all relating to the investigative side?

General VESSER. We'd have to get you an answer for the record by identifying the reports that the GAO has identified and giving you their exact status, sir.

Mr. SHAYS. Thank you, General. Dr. Foster, I'm going to give you an opportunity to then clarify the issue of these reports. Are all the medical research investigations, all medical research, that goes through your office?

Dr. FOSTER. Medical research funded by the Defense research appropriation go through my office, yes. If there are clinical studies done in the health care side of the House, that is managed and monitored by the Assistant Secretary for Health Affairs.

Mr. SHAYS. Which is not OSAGWI?

Dr. FOSTER. Not OSAGWI, no. So the medical community is together through the ASBREM Committee but they would fund clinical type investigations with operations and maintenance money. I fund primary research science from the research appropriation, and the appropriations that we received specific to Gulf war illness are summarized on page 4 and those are the—those, up through 1998, are——

Mr. SHAYS. Four of——

Dr. FOSTER. Of my written testimony. Those are research and development test evaluation funds that we oversee.

Now, all those were special appropriations. They weren't part of the President's budget request. So they were added to the research account in those fiscal years.

Mr. SHAYS. If I were you, Dr. Mazzuchi, or even General Vesser, I think my response to—if I'm hearing you correctly, and I want you to correct me if I'm stating it incorrectly, I would say that GAO is crazy if they are implying that these 14 studies referred to anything dealing with the working effort of this Research Working Group; that all the medical research we have disclosed, we are not waiting for draft review status, that is, something dealing with investigations of OSAGWI which are not being or should be—I won't say "should be," but are not coordinated.

Is that—are not part of the research effort. Is that accurate or not accurate?

Dr. FOSTER. That is correct, and I would say if you ask the question coming down the line, that I feel that the GAO has just basically confused the issue in the title of the report having to do with research because we have mixed together research and what is normally termed "general medical operations" into one lump, and it's very difficult for you all to separate the two in your minds.

Mr. SHAYS. What stands is all of your comments that their recommendation that we need a better assessment of where we're at, and that will be done this year, will be done?

Dr. FEUSSNER. Yes, sir, this fiscal year.

Mr. SHAYS. Fiscal year by the end of September?

Dr. FEUSSNER. Yes, sir.

Mr. SHAYS. Thank you.

Dr. FOSTER. If I could leap in for one other thing, I would say the other area that I have a disagreement with the GAO is their assertion that the epidemiology studies are not useful. They're absolutely essential to the scientific community.

We have to understand what the medical conditions are out there so we can formulate hypotheses to be tested. And they were going down an argument line that the investment by the VA and by the health care part of DOD was not very helpful to us, and I fundamentally disagree; and that's why the Research Working Group is so important because you have the medical practitioners, basic scientists and other folks, including the studies folks from OSAGWI, working together to try to define the set of problems so that we can bring to bear research clinical studies, and health care type of approaches to helping the veterans, in order to understand the fundamental phenomynology.

And it's a good team. I've only been together with this 1½ years, and coming from the outside of into it, I thought, great, this is really going to help me in overseeing the medical research account and the investment strategies that will develop. I can't imagine another venue since these folks see the patients that I could imagine that would allow me the insight to help focus the research.

Dr. MAZZUCHI. If I might followup on that, one of the pieces I mentioned in my oral testimony, as well as my written testimony, was the Millennium Cohort Study. I think that is a very pivotal piece for the Department.

One of the issues that has occurred over and over—and we agree with the committee—is, it's very difficult to assess someone's health status or to understand what happened to a person in a deployment if you don't have good baseline data and if you don't follow them. What we do not know and what we are—this cohort study which we believe will give us the information—going to do is to follow a cohort of both deployed and nondeployed military personnel and then to follow people who come into the military in 2001 and follow their health status noting their different deployments because one of the issues that epidemiologic research has shown us is that while there seems to be no new disease entity, clearly people who have gone to the Persian Gulf have suffered conditions and symptoms and diseases at different rates. What we need to know is, is it deployment itself or a combination of deployments or multiple deployments that adds to that? We don't have the answer to that.

The epidemiologic research that is being funded and very well coordinated with the Research Working Group, I think it seems will be able to give us those answers.

In addition, I think one of the major lessons learned from the health community from the Persian Gulf experience is that we need not only to get baseline data, but we need to follow groups over time and then we need to find if there are interventions that work. As Mr. Sanders has said, we need to apply them.

We are working very hard with the VA to develop a practice guideline which will help our primary care providers both diagnose and recognize early symptoms of—I'll lump them into chronic fatigue syndrome-type symptoms so that treatments can be effected earlier, which ought to mitigate against chronicity of chronic disease symptoms. All of these things flow from the epidemiologic research.

The other thing I want to say is, I agree with Dr. Foster. I believe that the General Accounting Office confused—because they

used the word "research" in a broad sense, confused the effort I believe, and I've been with the Department for almost 30 years, that the research effort under Dr. Feussner's guidance has been unbelievably well coordinated and well thought through.

There are other efforts that are complementary, not contradictory to these that are being led by the OSAGWI group to look at veterans' complaints to find out what actually did happen on the battlefield. You could certainly call that research, but when we speak of research, we're talking about R&D dollars, research and development dollars, that are used in the scientific process for medical research. I think that's where some of the confusion has come in. That's why you have two very different stories from our group versus the GAO group, because we're talking more narrowly.

Mr. SHAYS. Can I—just for the record, I am getting a little uneasy. Some of the RAND studies were medical studies; they weren't investigative studies.

General VESSER. All of our studies were reviews of medical literature in the sense that although—in some sense they could be characterized as medical. They were an effort to inform the veterans. The Presidential Advisory Committee had about one paragraph on a number of topics.

Mr. SHAYS. But the problem is that some of these are not even out. So if the effort is to inform the veterans, they are not even out.

General VESSER. Five of the eight that we have commissioned from RAND are out. And the others are slow. The reason some of these are slow—and I didn't go into that—is that some of the authors are very elderly and one is fighting cancer. This has slowed down release of some of the reports.

In addition, some of the authors are doing more than a single report. So they are switching from one report to another, but essentially what they are doing is compiling medical literature so that veterans have an idea what it is that the medical community says about stress or PB or oil well fires or depleted uranium; so there are facts that are available.

Mr. SHAYS. Let me just say that just introduces a whole new level of discomfort that I have because you have responded that some of these are medical. Their purposes are to inform our soldiers, but it would strike me that they would be coordinated with this working group. I am just going to share with you I have some real discomfort.

In other words, in my judgment there is enough truth to the GAO's concern, and maybe technically I can agree with you that one is medical research and one is slightly different. They do come perilously close and do seem to invite that there would be some coordination.

We could go on longer. I am going to suspend my time with you to get to the third panel. I will concur with you and recognize you, Mr. Sanders. You may have as much time as you want.

General VESSER. May I make one comment.

You asked what we disagreed with in the GAO report.

We in OSAGWI do not feel that the GAO has demonstrated that our contract awards were in fact improper. We have made every effort to comply with the law, to use the system that is established, and contracting officers award contracts, not the sponsoring office.

On the other hand, the GAO points out we have the responsibility in their comments on the material we submitted to them for determining its requirements for support, a process that in one instance resulted in naming a preferred contractor and in another led to an overly broad statement of work. I would say that the guidance on this systemic process says that the contracting officer will review your requirements package for scope, accuracy, and completeness. Corrections and/or clarifications may be required.

So we did everything we could at the time. I would also note that with respect to the preferred contractor, we had a little bit of difficulty figuring that out because the contractor that they cited had four task orders, tasks to be performed. We believe that they are referring to the requirement that we get a risk communication service provided. That contract was posted. We had one inquiry. Others couldn't provide the expertise. There was only one contractor who could provide the expertise.

Last, I would say that we are sensitive to the GAO recommendations that we use a different contract vehicle for the BDM-TRW task. Consequently, we are currently working with Defense Supply Services and BDM-TRW on the creation of a blanket purchase agreement that will combine several GAO schedules to provide the services that we currently obtained through the MOBIS vehicle which they are critical of.

By creating this blanket purchase agreement, we are attempting to comply with the provisions of the audit while still continuing to fulfill our mandate to seek out potential sources of the illnesses being experienced by our veterans without interruption. We have also met with OSD space management personnel to discuss bringing our current lease space under a GSA lease to better meet the concerns of the GSA contract managers.

Mr. SHAYS. The bottom line is that the contract method is wrong, but you are going to change it in the future?

General VESSER. We have tried to work within the system. We have tried to point the GAO when they raised the issue with us toward those parts of the system. We are not contract specialists. We don't know the philosophy of differences in contracting approach, but we are for competition and for getting the best price on the work that is done.

Mr. SHAYS. Let me tell you where I think we are at, and then I am going to recognize Mr. Sanders.

I am going to leave with the confidence that you all are going to be making a heroic effort to assess where we are at and do it before the end of the budget year, and we can have another hearing and know where you are at.

I am going to share with you that I am uneasy with the outside investigative effort of OSAGWI's efforts and say to you that as we got more into it, I felt that there could be better coordination and sharing even though it is outside your technical definition of medical research; and I would also say to you that I think after 9 years we have got to get to some kind of treatment and that has ultimately got to be our goal, that we want to properly diagnose and effectively treat and fairly compensate. And so Mr. Sanders' ultimate goal to treatment, I think, stares us in the face. With that, Mr. Sanders, you have the floor.

Mr. SANDERS. Thank you. I will be brief. You have been very generous in allocating time.

I think it is very important as General Vesser said that we adequately inform veterans and keep them abreast what is happening. I think understanding what happened on the battlefield is absolutely important. I happen to believe very strongly in epidemiologic research and the National Cancer Registry Act, which is one of the important epidemiological tools being used by cancer researchers. No argument.

But after all is said and done, as the chairman just indicated, what 100,000 veterans want to know is how are they going to get better? That is what they want to know.

And in that respect, in all honesty I must say that given the fact that we have spent $120 million so far, we have done a rather poor job.

It seems to me, and let me—and Dr. Feussner, jump in if you think I am wrong. Where we are right now, I hope within a year we will know whether or not the use of doxycycline can treat some symptoms. We will know that and if it turns out positive, we will have a treatment; is that correct?

Dr. FEUSSNER. Approximately a year, yes, sir.

Mr. SANDERS. What I think—and I don't think that the U.S. Congress should be micromanaging, but I think we should be saying right now within another year we want five different treatments from you. We want treatments. That is what the veterans want.

Now, you have breakthroughs that are going on. I don't know what this squalene means, I don't know what you can learn from it, but I want you to translate that research into a treatment.

I don't know what Haley's brain scan implications are, but if it can be translated into a treatment, do it.

Multiple chemical sensitivity, we know that there are treatments out there. Start testing it. It is beyond comprehension that after 9 years we have not developed one treatment through the VA to treat those people who may have been made ill as a result of exposure to chemicals.

I don't know the possibility. You are studying pyridostigmine bromide. That is very important, and I know that relates to a treatment. Why don't we start. I think that I speak for veterans who say look, we recognize you don't have the magic bullet. But try to do something. If it fails, I will support you in saying we tried it. It failed; do something.

So I would hope, and we will be working together, Dr. Feussner, you will be hearing from me. I want treatments. That is what I want. I think I speak for the veterans' community in stating that.

Mr. SHAYS. We are going to get to our next panel, but I am very willing to have any of you make a closing statement.

Dr. FEUSSNER. If I may, sir, I would just like to agree with Congressman Sanders. As I think he knows, we are quite interested in identifying treatments that are likely to benefit patients.

The only caveat, the squalene story is not associated with a treatment option at this point, but we will keep an eye on it.

The observation of the brain is not associated with a treatment option yet; but again we will be attentive to that, just like there are efforts to treat other brain diseases, Alzheimer's, et cetera. We

will be very attentive to that. I think that the only caveat that the Congressman agrees with, the treatment trials involve human studies and the human studies are justly due the dual protections under the common rule of scientific review and informed consent. That is the only caveat. I know that Congressman Sanders concurs with that.

Mr. SHAYS. Thank you all very much. We appreciate your patience.

We will conclude with our third panel comprised of Dr. Iris Bell, associate professor, Program in Integrative Medicine, University of Arizona College of Medicine; Dr. Claudia Miller, assistant professor, Environmental & Occupational Medicine, University of Texas Health Science Center; and Dr. Mohamed Abou-Donia, professor, Department of Pharmacology and Cancer Biology, Duke University Medical Center; and Howard Urnovitz, scientific director, Chronic Illness Foundation. If you will remain standing, I will swear you in.

[Witnesses sworn.]

Mr. SHAYS. We have three witnesses, Dr. Bell, Dr. Miller and Dr. Urnovitz. I really appreciate your patience. It is toward the end of the day rather than the beginning of the day; but your testimony is very important, and we are grateful that you are here.

Dr. Bell, we will start with you.

STATEMENT OF IRIS BELL, M.D., PH.D., ASSOCIATE PROFESSOR, PROGRAM IN INTEGRATIVE MEDICINE, UNIVERSITY OF ARIZONA COLLEGE OF MEDICINE; CLAUDIA MILLER, M.D., M.S., ASSISTANT PROFESSOR, ENVIRONMENTAL AND OCCUPATIONAL MEDICINE, UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER; HOWARD URNOVITZ, PH.D., SCIENTIFIC DIRECTOR, CHRONIC ILLNESS RESEARCH FOUNDATION

Dr. BELL. Thank you, Mr. Chairman. I am speaking today as both a VA-funded researcher and as an independent researcher in the sense that I have funding from the VA; but at this point I am speaking primarily as an individual researcher who has been involved in multiple chemical sensitivity research for many, many years.

As the GAO report noted, the data from several studies in Gulf veterans with unexplained illness really converges on the likelihood that a large number of these individuals may have conditions that fall in the broad spectrum of chronic fatigue syndrome, fibromyalgia and chemical sensitivity.

However, in addition to that, from the data available, there appear to be a number of Gulf veterans who are suffering from something that falls along a continuum that may not reach a level of case definition criteria from an epidemiologic point of view. This creates methologic issues in terms of identifying people who are sick versus not sick but certainly does not eliminate the high likelihood that a number of people have this problem to a degree.

The trouble is that when a problem is so clinical in nature or is polysymptomatic, as in these conditions, generally conventional medicine has very little to offer for these difficulties. Most of these in fact are not specifically associated in a clear linked way with the toxicity with specific toxins in the environment, which again has

made it difficult in terms of prior research to identify specific causes.

Unfortunately, assuming even if the medical profession were to accept the validity of these polysymptomatic conditions, which they at this point frequently do not, conventional psychiatry in medicine has very few tools to treat them. Typically, medicine labels these individuals as having some form of, "somatoform disorder," which is basically a nonetiological label for having multiple symptoms in multiple systems with no known treatment and no other known diagnosis that can be identified.

This has led, I believe, to the unusual emphasis on stress research specifically within the Gulf war work, but this has indicated also that there may be more things to examine. Many Gulf veterans with these problems, such as chronic fatigue and chemical sensitivity, do have psychiatric issues as comorbidities. A definitely large number of them have no psychiatric problems; and yet in this area, the area of psychiatry has been emphasized to the exclusion of other possible mechanisms.

In the civilian population, a large proportion of affected individuals have given up on what conventional medicine may have to offer and have chosen to resort to various forms of what is called complementary and alternative medicine. The field of environmental medicine within which multiple chemical sensitivity does fall within the definition of the National Center for Complementary and Alternative Medicine at NIH is an area that could be researched but in general has not been at this point. However, because of the controversy around both the illnesses and the treatments, there are significant difficulties in people having addressed these issues up to this point.

My recommendation is that we take a patient-centered rather than a disease-centered approach to treatment research. That involves, as Congressman Sanders indicated, focusing on what the veterans are telling us they have tried and what they think helps them. That is a very pragmatic approach, but it appears to be time to do so; and it is quite possible that at this point this would be quite an appropriate time to pursue aggressive research on chemical sensitivity and related syndromes.

In my own research I have been looking at patient-centered mechanisms that have not been as specifically focused on specific toxins as on vulnerable individuals. In our own work in a very small but random sample at the Tucson VA, we found that 86 percent of ill Gulf veterans versus 30 percent of healthy Gulf veterans and 30 percent of healthy area veterans were reporting that they considered themselves especially sensitive to certain chemicals.

We have used this screening question in literally thousands of civilians, and we get a rate in answer to this particular screening question of about 30 percent in the general population. And so indeed we see it in veterans who were not in the Gulf, but we see it in a much higher rate by self-report in the ill Gulf war veterans.

At this point from the standpoint of looking at this issue, the Gulf veterans also reported without attributing particular cause that they had multiple chemical exposures, including oil well spills, pesticides, diesel fuel, et cetera, that they had these exposures at higher rates than the people who were healthy.

They particularly focused in this situation on insect repellants and pesticides. Conventional toxicology has no easy explanation for a diversity of eliciting factors, or for this enhanced low dose reactivity at this point. They are pursuing certain avenues, but this has not been overly fruitful to date. The field of pharmacology does offer a phenomenon which has been studied extensively for other purposes and can accommodate this diversity and enhanced reactivity. It is called neurosensitization.

Sensitization is a progressive amplification of response in the host to repeated intermittent exposures to an initiating stimulus. It is not seen when the exposure is continuous, which is a model frequently used in toxicology research. Once the sensitization is initiated, reexposures to the same or other cross-sensitizing stimuli can elicit a heightened response.

This amplification process probably reflects changes in cell functioning rather than structure and does not necessarily require the immune system, although it can be affected by a similar process. Our own research in this area in civilians has shown that, even though these people are psychologically distressed, they differ in their brain wave status even at baseline from individuals who are depressed but do not have chemical sensitivity by self-report and from normal people.

We have found also that when tested over repeated sessions with extremely low level exposures, persons with chemical intolerance exhibit sensitization to whatever they are exposed to in the session, in brain waves, heart rate and their blood pressure. These effects are not seen in controls of various types.

We have found also evidence for individual difference susceptibility factors in civilians that parallel those in sensitizable animals who have been studied the most in these areas. These factors of vulnerability include being female, having certain genetic characteristics. In our human research this has been converging on information that they may have family histories of substance abuse even though they themselves cannot tolerate alcohol. We also see spontaneous preference for sucrose, both in animals who are more sensitizable and in the civilians who are reporting this problem, and a baseline hyperreactivity to novel environments.

This kind of work has been pursued in animals and there are animal models demonstrating sensitization to chemicals. And this work is still ongoing, but to my knowledge it has not been directly pursued in terms of Gulf war. Our sense is that sensitization and cross-sensitization could help account for the fact that some veterans have different exposure histories and stress histories during military service, but they end up with similar polysymptomatic conditions.

The mechanism could allow us to explain that multiple interventions could in fact be helpful, coming at this problem from different directions because by removing any eliciting stimulus of any class, be it chemical, stress or otherwise, we might reduce the frequency and severity of the currently sensitized symptoms, but this would not necessarily prove a role for any specific etiologic factor.

In our VA funded study, we are testing the possibility that the chronically ill Gulf veterans are persons who are at least now more

sensitizable than our healthy veterans. We are using extremely low levels of exposure that are not detectable by smell.

In our preliminary analyses of our initial data set, we have found some evidence for sensitization looking at the heartbeat itself during repeated sessions over a period of weeks. These individuals have been receiving, in order to do the sensitization, undetectable levels of jet fuel JP8 versus clean compressed air. We have much further research to do and many other analyses to do before we can say with certainty that this finding will be validated; but we are very encouraged that it has been there from the start of our work when we began to look at our interim analyses.

In conclusion, the phenomenon of sensitization is well documented in basic neuroscience research. It depends on time-related changes in functioning, not structure of nerve cells in response to repeated intermittent stimuli and could help explain the emergence of problems in veterans after they return from the Gulf and the difficulty in identifying particular causes because this phenomenon has both an initiation and an elicitation phase which can be essentially separated.

The stimuli capable of initiating and eliciting sensitized responses are diverse in nature, and they range from chemicals to stress which can cross-sensitize with each other. Some people do sensitize more readily than others. This mechanism deserves further evaluation as a possible mechanism by which a number of Gulf war veterans may have become ill.

Thank you.

Mr. SHAYS. Thank you, Dr. Bell.

[The prepared statement of Dr. Bell follows:]

Committee on Government Reform
Subcommittee on National Security, Veterans Affairs, and International Affairs
United States House of Representatives
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Invited Testimony by

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I have been asked to give my views about the Government's Gulf War research programs and to summarize my own research related to Gulf veterans' illnesses, with a focus on the direction medical science is taking or should be taking, to address the issue. I am currently a VA-funded researcher investigating an area termed neural sensitization as a possible mechanism for development of heightened responsivity to low levels of environmental chemicals in Gulf veterans. I have also been involved in research on possible mechanisms of illness from low level chemicals, primarily funded by private foundations, for almost 25 years. I have published numerous peer-reviewed papers on this subject in civilians, as well as several book chapters and a scientific monograph. Our research group published results of a preliminary study on elevated prevalence of self-reported chemical intolerance in chronically ill Gulf veterans compared with controls in the journal *Military Medicine* in 1998. My work is interdisciplinary, influenced by clinical training in psychiatry and research training in the neurosciences and in multifactorial health outcomes research. I am speaking today as an individual researcher, not as an official representative of the VA or any other agency.

With regard to the issues for medical science and Gulf-related illness, my points are as follows:

- As noted in the GAO report (p. 13), data from several studies on Gulf veterans with unexplained illness suggest convergent themes of multiple, non-specific symptoms in multiple systems of the body ("fatigue, neurocognitive complaints, and musculoskeletal complaints..."). Collectively, these symptoms have pointed to a potentially increased prevalence of controversial, phenomenologically overlapping set of conditions that have, to date, fallen at the outskirts of conventionally-accepted diagnoses. These conditions include chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity (Buchwald and Garrity 1994).

- Civilian research, including our own studies of chemical intolerance, suggests that varying degrees of these conditions may be common in the general population, without reaching a level of severity that merits a clinical diagnosis (Bell et al. 1998b; Jason et al. 1999). Some research on ill Gulf veterans indicates a similar type of continuum. In other words, these may not be conditions that are fully a "case" or not a "case" to the examining physician. Rather, they may be present *to a degree*. This type of problem poses significant, though not insurmountable challenges to epidemiological research approaches, which, as the GAO report indicates, rely on case-ness or non-case-ness. Other, sophisticated statistical approaches are available to deal with this problem (e.g., Mulaik 1998).

- It is likely that most Gulf veterans who have non-controversial, even if rare, diagnoses at a clinical degree of severity have received and/or could receive effective medical care within the VA, DoD, or civilian health care systems. The ability to make some progress in studies of leishmaniasis would be an example of this point.

- However, typically in medicine, when a patient is "subclinical" in severity or appears to have a controversial diagnosis of which the average physician is skeptical or unfamiliar, conventional care has little to offer. This is especially the situation when there is no standardized, widely-available laboratory test to assist in confirming a diagnosis (as in unexplained Gulf-related illnesses in veterans). Overt, diagnosable diseases, not lesser levels of wellness, are the usual domain of conventional medicine.

- If the above argument is valid, then it follows that one factor accounting for the delays in progress with Gulf-related illness research is that the problem may be challenging the field of medicine and medical research in general, which the VA and DoD approaches reflect, to change its prevailing beliefs now, not some time in a distant future, i.e., much sooner and more abruptly than it otherwise would do.

- Studies on unexplained illnesses in Gulf veterans are generating scientific data that logically tell us to take polysymptomatic patients and the controversial conditions of chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity more seriously than ever before, even though the long-standing debates over the validity of the multiple complaints and of the existence of the conditions in civilians remain intense and emotional. Those of us who have worked in this area for many years are well aware of the illogic and frequent lack of objectivity in these debates. This situation could reflect an appropriate conservatism on the part of medicine against accepting every "odd" idea put out for consideration. However, in my view, given the growing weight of evidence, it is more likely a current example of resistance by scientists, even to new ideas with reasonable merit (Barber 1961). This resistance is partly a reflection of social nature of science and scientists in making and acknowledging discoveries.

- The fact that a subset of veterans, who likely were more fit at the time of deployment than the average civilian, nonetheless became ill, offers us an opportunity to understand how these types of health problems can develop. The possibility of multi-causal factors in etiology adds complexity but also may be the appropriate approach to understanding the emergence of illness in veterans with different experiences and different exposures in the Gulf War theater.

- What is crucial to note here, is that much research has previously focused on identifying the original etiological factors in initiating the Gulf illnesses. This work is limited by a myriad of indeterminate variables relating to exposures. It assumes that we must know some specific "cause" if we are to find the appropriate treatment. This is a very reasonable assumption, but it might be limiting our vision in the area of Gulf War treatment research. If these illnesses were classical toxicant-induced processes, research would be showing clearer linkages by now between specific symptoms and possible Gulf exposures. However, most of the polysymptomatic symptoms are not those usually associated with a specific toxicant in the field of toxicology. We are fairly certain that every ill Gulf veteran did not have exactly the same exposures as every other veteran with similar symptoms. A straightforward linkage is not emerging from the available data.

- Even without knowledge of initiating factors, it is still possible to examine the eliciting factors that make a given veteran susceptible to illness, e.g., *current* triggering variables in veterans' illness. My own research on ill Gulf veterans is attempting to test for one possible mechanism by

which polysymptomatic conditions and enhanced susceptibility to environmental chemicals, foods, drugs, and stress could now be elicited, even though we do not know with certainty the possible initiating factors (see below).

- Unfortunately, even assuming that the medical profession were to accept the validity of these subclinical polysymptomatic conditions and controversial diagnoses tomorrow, we then still face the question of treatment. Conventional psychiatry often has effective tools to treat depression and anxiety disorders with which some Gulf veterans have been diagnosed. However, conventional psychiatry has no effective tools with which to treat patients that it labels as having a "somatoform disorder" (a non-etiological, descriptive label for multiple symptoms in multiple systems with no known conventional diagnosis) or, worse, a subclinical collection of symptoms in multiple systems from which many Gulf veterans suffer. Conventional medicine and psychiatry have not made significant advances in understanding the nature of or the treatment for these types of chronic health problems in civilians, let alone Gulf veterans.

- Interventions such as cognitive-behavioral therapy or exercise therapy, which are under study for Gulf veterans with chronic fatigue syndrome-like conditions, are a good start and may prove helpful, but not likely definitive, in resolving the health problems. Even those with treatable psychiatric diagnoses also may have significant persisting chronic symptoms that impair function and quality of life for Gulf veterans, as my VA psychiatric colleagues have previously told me, in their experience. Such anecdotal observations are testable by outcomes research and deserve evaluation. If supported by systematic research, this means that psychiatric treatment will not be a sufficient answer by itself.

- It is far too limited a perspective to focus as much as has been done in various panels on Gulf-related illness on "stress" per se. Stress can interact with many different medical conditions to bring out worse outcomes, but in itself is generally insufficient to explain these conditions as a whole.

- The illogic of emphasizing stress or psychological factors emerges in considering the research finding of increased mortality rates in depressed as opposed to nondepressed heart attack patients (Carney et al. 1999). If depression were believed sufficient as a cause of heart disease mortality, then we should have no reason to study the multiple biological mechanisms of heart disease now under investigation. I doubt that most physicians or cardiac patients would want us to study depression to the exclusion of these other mechanisms. In the least, researchers would probably hypothesize that depression exerts its effects in part by acting via specific biological mechanisms to worsen outcomes. And some heart patients are not depressed, making depression a highly unlikely factor in their outcomes.

- Similarly, not all ill Gulf veterans or civilians with chronic fatigue syndrome, fibromyalgia, or multiple chemical sensitivity have evidence for psychiatric problems (Aaron et al.1996; Fiedler et al. 1996). Furthermore, previous studies on chronic fatigue syndrome even suggest that it is the patients *without* concomitant psychiatric problems who have the poorest neurocognitive function (DeLuca et al. 1997). If this turns out to be the case for Gulf veterans with cognitive difficulties, it will be especially inappropriate to focus on stress and stress-related interventions to the exclusion of other possible treatments.

- How do civilians deal with this situation? A large proportion (e.g., over 80% of fibromyalgia patients - Pioro-Boisset et al. 1996; Schuman et al. 1996) resort to various forms of complementary and alternative medicine (CAM). Even in the general American population, the estimates of utilization rates fall in the range of 40%% (Eisenberg et al. 1998). To my knowledge, it is not

known at what rate ill Gulf War veterans are utilizing CAM, but that alone is worthy of investigation.

- In qualitative research as part of our ongoing VA-funded study of veterans with all types of health problems enrolled in primary care clinics, we have found that veterans seek CAM treatments of many types outside the VA system. They appear generally satisfied with the conventional care, *as measured by their expectations of conventional care*, that their VA primary care providers (PCP) offer, but they describe problems with the limited benefits and unpleasant side effects of pharmaceutical-based medicine. When they perceive limits to the help they can obtain from conventional care, they add various types of CAM to their total program, generally without informing their PCP.

- As you can see, the controversies then compound in complexity. Not only do we have conditions that mainstream medicine as a field does not recognize, but we also have proposed treatments that conventional medicine considers unproven and even potentially unsafe.

- At this moment, we cannot simply declare that ill veterans should obtain particular CAM treatments. There is no body of evidence at this time that any of those are in fact safe or effective for Gulf veterans. As a nation, we are facing the collective dilemma that an individual, desperate patient faces all the time – stop hoping for help and "live with it" indefinitely in a debilitated state or resort now to trying treatments that mainstream medicine largely ignores or rejects.

- At a national level, we can go about this task with scientific rigor, however. We can take a patient-centered rather than disease-centered approach to treatment research for veterans with Gulf War-related illnesses. It is now time to start looking systematically at a range of CAM interventions as possible resources for helping Gulf veterans with their conditions. The scope of CAM, as defined by the NIH National Center for Complementary and Alternative Medicine (NCCAM), includes not only the many controversial interventions that fall under the label of "environmental medicine" or treatments for multiple chemical sensitivity (e.g., comprehensive chemical avoidance with challenge testing, rotation diets – see Miller 1997), but also numerous other nutritional, lifestyle, botanical, mind-body, and energy medicine (e.g., acupuncture) modalities.

- In turn, physicians working in environmental medicine may object to being lumped with some CAM modalities that they themselves consider very strange and beyond rational consideration. Nonetheless, these methods fall into a broad category of treatments considered controversial and unproven by mainstream medicine. Whatever the label, it is time to take a look at these treatments.

- At the CAM conferences and web sites that I have encountered in recent years, it is common to hear claims of major benefit for Gulf veterans made. We need to test those claims. We need to find out what Gulf veterans and civilians with similar health problems are choosing and finding helpful. Then we also need to test those claims for effectiveness in real world situations as patients actually use CAM, i.e., with blended packages of CAM and conventional care, not single interventions in isolation, using appropriate scientific controls.

- With the NCCAM, NIH is fostering a cohort of serious medical researchers around the country who could perform this type of research. I respectfully suggest that it is time to move forward with establishing funding channels to set studies of CAM treatments for veterans with unexplained polysymptomatic Gulf War-related illnesses into motion. Given the methodological difficulties of doing good CAM research (Levin et al. 1997), it is likely that this work will require new collaborations. These would be between VA/DoD and non-VA/DoD investigators, partnering with

CAM providers and researchers, after the model used by the NCCAM to insure that the research team understands all of the parameters with which it must deal to do a good study, i.e., nature of the patient population, the philosophy and features of the CAM intervention(s), and proper scientific design.

- In summary, we should not abandon our current research efforts toward finding the original, albeit multifactorial, etiologies and treatments related to those etiologies. This work is important for avoiding adverse health outcomes after future military operations. However, we can and should invest much more concerted effort toward testing the many CAM treatment possibilities now available (but unproven) for persons with polysymptomatic conditions, including veterans with Gulf War-related illnesses. Without this patient-oriented research, a) mainstream medicine, as reflected in VA and DoD care, will continue to see the patients' multiple symptoms as outside its domain of treatable problems and CAM treatments as outside the scope of "accepted" practice; and b) the ill Gulf veterans will continue to wait in frustration for the availability of properly-studied treatment options.

With regard to my own research on Gulf-related illness, my points are as follows:

- In addition to my emphasis on patient-centered approaches to treatment research, my approach to mechanism research for Gulf War-related illnesses is also patient-centered. We focus on the patient's susceptibility to the environment more than on the environment itself.

- Preliminary research in our own laboratory and in other Gulf War investigators' laboratories suggests that a subset of chronically ill Gulf veterans report newly acquired intolerances for low levels of environmental chemicals that they attribute to their military service (Fiedler et al. 1996). Our data on a randomly chosen, though small, sample Tucson VA-enrolled Gulf veterans revealed that 86% (12/14) of ill Gulf veterans, vs 30% (3/10) of healthy Gulf veterans and 30% (3/10) of healthy era veterans considered themselves "especially sensitive to certain chemicals" (Bell et al. 1998e). The 30% rates in the control groups were similar to those we have observed in general civilian populations (Bell et al. 1998b). In the ill vs healthy Gulf veterans, we also found increased rates of reported multiple chemical exposures (oil well smoke, pesticides, diesel exhaust, raw fuels, insect repellent, paints) during military service (odds ratio 18.7, confidence interval 1.6-223), especially to insect repellents (odds ratio 12.0, confidence interval 1.1-137) and pesticides (odds ratio 12.0, confidence interval 1.3-111). These elevated exposure reports were obtained without asking veterans to attribute health problems to exposures.

- Notably, Miller several years ago found not only similarly high rates of newly acquired chemical intolerance in 59 ill Gulf veterans from Texas (e.g., 78%), but also high rates of newly acquired intolerances to alcoholic beverages, tobacco, foods, and medications. In other words, the intolerances may involve multiple substances with very different chemical structures and different degrees of inherent toxicity. This type of history is similar to those obtained in civilians who report multiple chemical intolerances.

- Conventional toxicology has no easy explanation for this diversity of eliciting factors or for the enhanced low dose reactivity.

- However, the field of pharmacology has studied a phenomenon extensively which can accommodate precisely this diversity of eliciting factors and the enhanced reactivity, i.e., neural sensitization (Antelman 1994; Bell et al. 1992).

- Sensitization is the progressive amplification of response in a host to repeated, intermittent exposures to an initiating stimulus. Once the sensitization is initiated, re-exposures to the same or to other cross-sensitizing stimuli can elicit a heightened response. This process of amplification may reflect changes in the functioning of cells, especially nerve cells, and it does not require immune system involvement.

- As in clinical observations of chemical intolerance, neural sensitization involves separate steps – 1) initiation; 2) elicitation.

- Of note, a sensitized individual at rest in the absence of an eliciting stimulus can function and appear just like a normal, non-sensitized individual. This means that proper studies testing for sensitization must examine subjects not only at rest, but also under stimulus exposure conditions. Furthermore, this research requires at least two testing sessions separated in time by days, not minutes or hours.

- Importantly, stress can cross-sensitize with drugs; drugs can cross-sensitize with chemicals. Endogenous mediators of inflammation or pain can also initiate or foster sensitization. In other words, the sensitized host can experience many diverse stimuli as initiators and as triggers for hyper-reactivity. In some sense, sensitization is a response of the whole organism to the whole environment; it avoids the conceptual and practical limitations of splitting mind from body or one body part from another.

- Mainstream research is looking at sensitization as a possible model for craving in substance abuse, for stimulus hyperreactivity in posttraumatic stress disorder, for development of chronic pain syndromes including fibromyalgia and somatization (Ursin 1993, 1997), and for recurrent episodes in chronic mood disorders (Antelman 1988, 1994).

- Our past research on civilians with multiple chemical intolerances showed that such persons, even though psychologically distressed, are different physiologically in their brain waves from controls with similar types of psychological distress but no concomitant chemical intolerances (e.g., women with depression – Bell et al. 1998d; women with sexual abuse histories – Fernandez et al. 1999). "Somatization" scores (rating multiple symptoms in multiple systems) correlate with a blood biomarker of inflammation called neopterin in women with chemical intolerance in a pattern not seen in depressed or normal controls (Bell et al.1998c). When tested over repeated sessions, persons with chemical intolerances also exhibit sensitization (progressive increases over time) in brain waves (electroencephalographic alpha frequency activity, EEG), heart rate, and blood pressure, i.e., a capacity for sensitization (Bell et al. 1997, 1998a,d; Fernandez et al. 1999) not seen in controls without chemical intolerance.

- We have also found evidence for individual difference susceptibility factors in civilians parallel to those in sensitizable animals. These factors include: female gender, certain genetic strains (i.e., family histories of substance abuse including alcoholism), spontaneous preference for sucrose (sugar), and baseline hyperreactivity to novel environments (Bell et al. 1998b, 1999).

- Several groups of basic neuroscientists, e.g., vonEuler et al. (1994); Sorg et al. (1996, 1998), have developed animal models of sensitization to environmental chemicals. Low level formaldehyde, for example, cross-sensitizes with cocaine (Sorg et al. 1998). Thus, the methodology also exists to test the sensitization model for Gulf War illnesses in animals using various complex combinations of agents and factors that may have been present during the Gulf War.

- If sensitization and/or cross-sensitization were etiological factors in certain Gulf War-related illnesses, then they could account for veterans with different exposure histories and different stress histories during military service ending up with similar polysymptomatic conditions. This mechanism could also help explain the ability of interventions with different emphases to benefit various patients. Removing eliciting stimuli of any class (e.g., chemical or stress) might reduce the frequency and severity of currently sensitized symptoms, without proving a role for the stimulus in the initiation of the illness.

- In our VA-funded study, we are testing the possibility that chronically ill Gulf veterans are persons who are now more sensitizable than are healthy veterans. We are using extremely low level chemical exposures as our probe at levels below olfactory detection (no obvious smell) to avoid patient expectation confounds and to limit symptom provocation. Our outcome measures over three exposure sessions spaced over 3 weeks are more sensitive and objective than symptom reports, i.e., we are looking at physiological responses of the heart and eyeblink to acoustic startle stimuli.

- Preliminary analyses of our interim dataset on approximately 60 veterans suggest that we are seeing sensitization over sessions in ill Gulf vs healthy Gulf and era veterans in the time intervals between heartbeats, as a function of receiving undetectable levels of jet fuel JP-8 versus clean compressed air in the sessions. This is occurring without apparent provocation of subjective symptoms. Earlier analyses controlling for emotional state suggested that anxiety and psychological distress do not explain these findings. Once we have completed a thorough check for more possible confounding variables in our statistical analyses, we plan to submit the data for peer-reviewed publication.

- If our sensitization hypothesis is supported and eventually tested in terms of symptom generation, it would provide a plausible model of mechanism by which Gulf War-related illnesses might have developed. Chemical intolerance, for which there are now validated self-report scales, may be a subjective, clinical indicator of susceptibility to sensitization.

- In conclusion, the phenomenon of neural sensitization is well-documented in basic neuroscience research (Antelman 1988; Ferger et al. 1993; Yoshida et al. 1993). It depends on time-related changes in the functioning, not the structure, of nerve cells in response to repeated, intermittent stimuli. The stimuli capable of initiating and eliciting sensitized responses are diverse in nature, ranging from chemicals to stress, and can cross-sensitize. Some individuals sensitize more readily than do others. Sensitization deserves further study as a possible host mechanism by which a subset of Gulf veterans may have become ill.

Thank you very much for this opportunity to express my views on this important topic.

REFERENCES

Aaron LA, Bradley LA, Alarcon GS, Alexander RW, Triana-Alexander M, Martin MY, Alberts KR. Psychiatric diagnoses in patients with fibromyalgia are related to health care-seeking behavior rather than to illness. Arth Rheum 1996; 39:436-445.

Antelman SM. Time-dependent sensitization as the cornerstone for a new approach to pharmacotherapy: drugs as foreign/stressful stimuli. Drug Devel Res. 1988; 14:1-30.

Antelman SM. Time-dependent sensitization in animals: a possible model of multiple chemical sensitivity in humans. Toxicol Industr Health 1994; 10:335-342.

Barber B. Resistance by scientists to scientific discovery. Science 1961; 134:596-602.

Bell IR, Baldwin CM, Fernandez M, Schwartz GER. Neural sensitization model for multiple chemical sensitivity: overview of theory and empirical evidence. Toxicol Industr Health 1999; 15:295-304.

Bell IR, Baldwin CM, Russek LG, Schwartz GE, Hardin EE. Early life stress, negative paternal relationships, and chemical odor intolerance in middle-aged women: support for a neural sensitization model. J Women's Health 1998a; 7:1135-1147.

Bell IR, Baldwin CM, Schwartz GE. Illness from low levels of environmental chemicals: relevance to chronic fatigue syndrome and fibromyalgia. Am J Med. 1998b; 104(Suppl): 105(3A):74S-82S.

Bell IR, Miller CS, Schwartz GE. An olfactory-limbic model of multiple chemical sensitivity syndrome: possible relationship to kindling and affective spectrum disorders. Biol Psychiatry. 1992; 32:218-242.

Bell IR, Patarca R, Baldwin CM, Klimas NG, Schwartz GE, Hardin EE. Serum neopterin and somatization in women with chemical intolerance, depressives, and normals. Neuropsychobiology 1998c; 38:13-18.

Bell IR, Schwartz GE, Bootzin RR, Wyatt JK. Time-dependent sensitization of heart rate and blood pressure over multiple laboratory sessions in elderly individuals with chemical odor intolerance. Arch Environ Health 1997; 52:6-17.

Bell IR, Schwartz GE, Hardin EE, Baldwin CM, Kline JP. Differential resting qEEG alpha patterns in women with environmental chemical intolerance, depressives, and normals. Biological Psychiatry 1998d; 43(5):376-388.

Bell IR, Warg-Damiani L, Baldwin CM, Walsh M, Schwartz GE. Self-reported chemical sensitivity and wartime chemical exposures in Gulf War veterans with and without decreased global health ratings. Military Medicine 1998e; 163:725-732.

Bell IR, Wyatt JK, Bootzin RR, Schwartz GE. Slowed reaction time performance on a divided attention task in elderly with environmental chemical odor intolerance. Int J Neurosci 1996; 84:127-134.

Buchwald D, Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch Internal Med. 1994; 154: 2049-2053.

Carney RM, Freedland KE, Veith RC, Jaffe AS. Can treating depression reduce mortality after an acute myocardial infarction? Psychosom Med 1999; 61:666-675.

DeLuca J, Johnson SK, Ellis SP, Natelson BH. Cognitive functioning is impaired in patients with chronic fatigue syndrome devoid of psychiatric disease. J Neurol Neurosurg Psychiatry 1997; 62:151-155.

Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC. Trends in alternative medicine use in the U.S., 1990-1997. Results of a follow-up national survey. JAMA 1998; 280:1569-1575.

Fernandez M, Bell IR, Schwartz GER. Sensitization during chemical exposure in women with and without chemical sensitivity of unknown etiology. Toxicol Industr Health 1999; 15:305-312.

Ferger B, Stahl D, Kuschinsky K. Effects of cocaine on the EEG power spectrum of rats are significantly altered after its repeated administration: do they reflect sensitization phenomena? Naunyn-Schmiedeberg's Arch Pharmacol 1996; 353:545-551.

Fiedler N, Kipen HM, DeLuca J, Kelly-McNeil K, Natelson B. A controlled comparison of multiple chemical sensitivities and chronic fatigue syndrome. *Psychosom Med.* 1996; 58:38-49.

Fiedler N, Kipen H, Natelson B, Ottenweller J. Chemical sensitivities and the Gulf War: Department of Veterans Affairs Research Center in basic and clinical science studies of environmental hazards. *Regulat Toxicol Pharmacol.* 1996; 24:S129-S138.

Jason LA, Richman JA, Rademaker AW, Jordan KM, Plioplys AV, Taylor RR, McCready W, Huang CF, Lioplys S. A community-based study of chronic fatigue syndrome. Arch Intern Med 1999; 159:2129-2137.

Levin JS, Glass TA, Kuski LH. Schuck JR, Steele L, Jonas WB. Quantitative methods in research on complementary and alternative medicine. Med Care 1997; 35:1079-1094.

Miller CS. Toxicant-induced loss of tolerance - an emerging theory of disease? Environ Health Perspect 1997; 105 Suppl 2:445-453.

Mulaik SA. Factor analysis and related methods in epidemiological research. Abstract in the June 1999 Dept. of Veterans Affairs Annual Report to Congress on Federally Sponsored Research on Gulf War Veterans' Illnesses for 1998, Appendices, pp. 296-302.

Pioro-Boisset M, Esdaile JM, Fitzcharles MA. Alternative medicine use in fibromyalgia syndrome. Arth Care Res 1996; 9:13-17.

Schuman C, Nicassio PM, Kim J. Predictors of unconventional treatment use in fibromyalgia. Presentation at the Society of Behavioral Medicine, Washington, DC, March 13-16, 1996.

Sorg BA, Willis JR, Nowatka TC, Ulibarri C, See RE, Westberg HH. A proposed animal neurosensitization model for multiple chemical sensitivity in studies with formalin. Toxicology. 1996; 111:135-145.

Sorg BA, Willis JR, See RE, Hopkins B, Westberg HH. Repeated low level formaldehyde exposure produces cross-sensitization to cocaine: possible relevance to chemical sensitivity in humans. Neuropsychopharmacology 1998; 18:385-394.

Ursin H, Endresen IM, Haland EM, Mjellem N. Sensitization: a neurobiological theory for muscle pain. In H Varrey, Merskey H (eds). Progress in fibromyalgia and myofascial pain. NY: Elsevier Science Publishers; 1993; 413-427.

Ursin H. Sensitization, somatization, and subjective health complaints. Int J Behav Med 1997; 4:105-116.

vonEuler G, Ogren S, Eneroth P, Fuxe K, Gustafsson J. Persistent effects of 80 ppm toluene on dopamine-regulated locomotor activity and prolactin secretion in the male rat. NeuroToxicology. 1994; 15:621-624.

Yoshida, K., Morimotor, A., Makisumi, T., Murakami, N. Cardiovascular, thermal, and behavioral sensitization to methamphetamine in freely moving rats. J Pharmacol Exp Ther 1993; 267:1538-1543.

Mr. SHAYS. Dr. Miller.

Dr. MILLER. Thank you. There is an old parable: for want of a nail, the horseshoe was lost; for want of a shoe, the horse was lost; for want of a horse the rider was lost; then the battle, the war and finally the kingdom all for the want of a nail.

This is precisely the situation we find ourselves in today. For want of a paradigm, our veterans are lost in a sea of inconclusive reports, redundant studies, expanding budgets and programs and committees and cries of conspiracy all for want of a paradigm, something to explain the relationship between the exposures they experienced during the Gulf war and the multisystem symptoms that now plague them.

We have veterans seeing different specialists who apply different monikers to their symptoms. The rheumatologist sees them and diagnoses myalgias based on diffuse muscle pain; the neurologist hears head pain and nausea and diagnoses migraine headaches. The pulmonologist finds airway reactivity and diagnoses asthma. The psychiatrist seeing chronic malaise diagnoses depression. The gastroenterologist notes GI complaints and diagnoses irritable bowel syndrome.

Most ill veterans have symptoms involving several organ systems simultaneously. For them there is no unifying diagnosis, no known etiology and no identified disease process. This is not the first time doctors have found themselves baffled by wartime disease. 130 years ago during the Civil War, doctors were faced with a similarly mysterious syndrome characterized by fever. Hundreds of thousands of soldiers died. The doctors did what good epidemiologists do today, they classified the cases. Since the hallmark symptom was fever, they classified the cases by fever type: remittent, intermittent, relapsing.

In doing so, they unknowingly lumped together dozens of unrelated illnesses, everything from typhus and typhoid to malaria and tuberculosis and other diseases. Who would have dreamed it at the time, the germ theory of disease. This war going on between invisible invaders and the body's immune defenses with the only outward sign being literally the heat of battle.

Today, we face this same situation with Gulf war veterans; only this time the hallmark symptom is not as simple as fever. It's the newly acquired intolerances these veterans have been experiencing since the war. Like the mechanic who before the war used to bathe in solvents and now becomes ill after one whiff of gasoline. Or the young woman soldier who recalls how she used to be able to drink any man in her company under the table, but since the war she can't take even one drink without becoming violently ill. The vast majority of sick veterans report these newly acquired intolerances which date from their experiences in the Persian Gulf.

During the past 7 years, I have served as the environmental medical consultant to the Houston VA's regional referral center. Approximately 90 percent of the veterans interviewed described new onset intolerances to everyday chemical exposures which set off their symptoms; 78 percent were intolerant of fragrances, tobacco smoke, gasoline vapors and other chemical inhalants; 78 percent also described food intolerances; 66 percent reported alcohol intolerance; 25 percent were intolerant of caffeine; and nearly 40

percent reported adverse reactions to medications—all since the Gulf war. These intolerances, resulting in flare-ups of symptoms, including fatigue, headaches, GI problems, mood changes, cognitive impairment and diffuse musculoskeletal pain are like the fevers experienced by the Civil War soldiers. They are the outward manifestation of the underlying disease process.

This is not the first time this illness pattern has appeared on the medical landscape. Researchers have described these same new onset intolerances and multisystem symptoms in demographically diverse groups in more than a dozen countries—sheep dippers in the United Kingdom exposed to organophosphate pesticides; radiography workers exposed to x-ray developing chemicals; including glutaraldehyde in New Zealand and other countries; aerospace workers on the West Coast of our country exposed to solvents and plasticizers; and environmental scientists exposed to indoor air contaminants during remodeling at the EPA's own headquarters building in Washington, DC, to name a few.

What ties all these groups together is the common experience of an initiating toxic exposure followed by newly acquired intolerances and multisystem symptoms. These observations provide compelling scientific evidence for a shared underlying disease mechanism, one involving a fundamental breakdown in natural tolerance. This two-step mechanism an initiating toxic exposure followed by newly acquired intolerances that trigger multisystem symptoms has been referred to by the acronym TILT, or toxicant-induced loss of tolerance.

This two-step process is the key to understanding Gulf war illness. It doesn't matter so much which exposure caused the breakdown intolerance, whether it is pesticides, smoke from oil well fires, pyridostigmine bromide or indoor air contaminants. Those things have long since left these veterans' bodies. It is the aftermath of those exposures, the new onset intolerances to low-level chemical exposures which appear to be perpetuating their symptoms. In some cases, it may be difficult to sort out what individual intolerances or triggers may be operating because of a phenomenon called "masking." This occurs when individuals are reacting to so many different exposures that they become a confusion of symptoms.

But the confusion clears for both the patient and the physician when the underlying paradigm is understood, and questions that could not be answered are now answered.

Like why some veterans became ill and others didn't—because individuals react differently to toxic exposures and some have no response at all. Or why researchers have been unable to isolate a single culprit exposure—because the answer to the question, what caused the Gulf war illness, is more likely to be all of the above.

It explains why veterans remain sick almost a decade after the war, long after their initiating exposures. It explains why symptoms wax and wane unpredictably—as their daily exposures are waxing and waning. What can be done to diagnose and treat the chemically intolerant? There is evidence that removing them from the exposures that are affecting them now by putting them in an environmental medical unit will cause their symptoms to subside. The EMU is designed to help patients avoid common low-level ex-

posures. Previous experience shows that within days of entering a facility of this kind, patients will arrive at a clean baseline and their exposure-related symptoms will disappear. During the next 2 weeks, each patient is exposed to potential triggers, such as caffeine, gasoline, perfumes, various foods, medications, and tobacco smoke, one at a time, to determine what is setting them off.

Epidemiological data and literature reviews can only go so far in determining the nature of a new disease process. New paradigms require new approaches and new tools. EMU studies will enable doctors to witness this disease mechanism firsthand and understand Gulf war illness for what it is, while providing a built-in treatment component—one that enables the veterans to understand their disease and emerge less confused, less hopeless, and more in control of their lives.

A validated questionnaire about chemical intolerance is available in the medical literature, and I have enclosed it in this testimony, which the VA and military doctors could use as a first step toward introducing physicians and patients to this paradigm so they can begin to see it for themselves. If we are going to help these veterans what is needed is not more epidemiologic studies and literature reviews, but rather to use a term that Congressman Sanders has used in the past, a Manhattan Project-style approach consisting of EMU studies and other patient-oriented diagnostic and treatment studies.

Mr. SHAYS. Thank you, Dr. Miller.

[The prepared statement of Dr. Miller follows:]

Committee on Government Reform
Subcommittee on National Security, Veterans Affairs and International Affairs
United States House of Representatives
February 2, 2000
Invited Testimony by
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There's an old parable: For want of a nail, the horseshoe was lost; for want of a shoe, the horse was lost; then the rider was lost; then the battle; the war; and finally the kingdom—all for want of a nail.

This is precisely the situation we find ourselves in today. For want of a paradigm, our veterans are—lost in a sea of inconclusive reports, redundant studies, expanding budgets, programs and committees, and cries of conspiracy—all for want of a paradigm, something to explain the relationship between the exposures they experienced during the Gulf War and the multi-system symptoms that now plague them.

Different specialists apply different monikers to their symptoms.

—The rheumatologist observing diffuse muscle pain diagnoses myalgias.

—The neurologist hearing head pain and nausea diagnoses migraine headaches.

—The pulmonologist finding airway reactivity diagnoses asthma.

—The psychiatrist seeing chronic malaise diagnoses depression.

—The gastroenterologist noting GI complaints diagnoses irritable bowel syndrome.

Most ill veterans have symptoms involving several organ systems simultaneously. For them there is no unifying diagnosis, no known etiology, and no identified disease process.

This is not the first time doctors have found themselves baffled by wartime disease. One hundred and thirty years ago, during the Civil War, doctors were faced with a similarly mysterious "syndrome" characterized by fever. Hundreds of thousands of soldiers died. The doctors did what good epidemiologists do today. They classified the cases. Since the hallmark symptom was fever, they classified the cases by fever type—remittent, intermittent, or relapsing. In doing so, they unknowingly lumped together dozens of

unrelated illnesses—everything from typhus and typhoid to malaria and tuberculosis (Sartin, 1993). Who would have dreamed it—this germ theory of disease? This war going on between invisible invaders and the body's immune defenses, with the only outward sign being—literally—the heat of battle.

Today we face this same situation with Gulf War veterans, only this time the hallmark symptom is not as simple as fever. It's the newly acquired intolerances these veterans have been experiencing since the War. Like the mechanic who before the war used to "bathe" in solvents and now becomes ill after one whiff of gasoline. Or the young woman soldiers who recalls how she used to be able to drink any man in her company under the table, but since the war she can't take even one drink without becoming violently ill. The vast majority of sick veterans report these newly acquired intolerances which date from their experiences in the Persian Gulf.

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This is not the first time this illness pattern has appeared on the medical landscape. Researchers have described these same new-onset intolerances and multi-system symptoms in demographically diverse groups in more than a dozen countries—sheep dippers exposed to organophosphate pesticides in the United Kingdom; radiography workers exposed to Xray developers containing glutaraldehyde, etc. in New Zealand; U.S. aerospace workers on the West Coast exposed to solvents and plasticizers; and environmental scientists exposed to indoor air contaminants at the EPA's own headquarters in Washington, D.C., to name a few (Ashford and Miller, 1998).

What ties all these groups together is the common experience of an initiating toxic exposure followed by newly acquired intolerances and multi-system symptoms. These observations provide compelling scientific evidence for a shared underlying disease mechanism—one involving a *fundamental breakdown in natural tolerance*. This two-step process—an initiating toxic exposure followed by newly acquired intolerances that trigger multi-system symptoms—has been referred to with the acronym "TILT," or Toxicant-induced Loss of Tolerance (Golomb, 1999; Newlin, 1997; Miller, 1999, 1997; Miller et al, 1997).

This two-step process is the key to understanding Gulf War illness. It doesn't matter so much which exposure caused the breakdown in tolerance—be it pesticides, smoke from

the oil fires or pyridostigmine bromide pills; those things have long since left these veterans' bodies. It's the aftermath of these exposures—the new-onset intolerances to low-level chemical exposures—which appear to be perpetuating their symptoms. In some cases, it may be difficult to sort out individual intolerances, or "triggers," because of a phenomenon called "masking." This occurs when individuals are reacting to so many exposures that they become a confusion of overlapping symptoms.

But the confusion clears for both the patient and the physician when the underlying paradigm is understood. And questions that could not be answered, are answered.

Like why some veterans became ill and others didn't—because individuals react differently to toxic exposures; some have no response at all.

Or why researchers have been unable to isolate a single culprit exposure—because the answer to the question "What caused Gulf War illness?" is more likely to be "all of the above."

It explains why veterans remain sick almost a decade after the War, long after their initiating exposures.

It explains why symptoms wax and wane unpredictably—as daily exposures wax and wane.

What can be done to diagnose and treat the chemically intolerant? There is evidence that removing them from the exposures that are affecting them by putting them in an environmental medical unit (EMU), will cause their symptoms to subside. The EMU is an environmentally controlled in-patient hospital unit designed to help patients avoid common, low-level exposures. Previous experience shows that within days of entering the EMU, patients will arrive at a "clean baseline," and their exposure-related symptoms will disappear. During the next two weeks, each patient is exposed to potential triggers—such as caffeine, gasoline, perfume, various foods, medications, and tobacco smoke—one at a time, to determine what is setting them off.

Epidemiological data and literature reviews can only go so far in determining the nature of a new disease process. New paradigms require new approaches, and new tools. EMU studies will enable doctors to witness this disease mechanism firsthand and understand Gulf War illness for what it is, while providing a built-in treatment component—one that enables veterans to understand their disease and emerge less confused, less hopeless, and more in control of their lives.

A validated questionnaire (attached) is available in the medical literature which VA and military doctors could use as a first step toward introducing physicians and patients to this paradigm so they can begin to see it for themselves.

If we are going to help these veterans, what is needed is not more epidemiologic studies or literature reviews, but, rather, a Manhattan Project-style approach consisting of EMU studies and other patient-oriented diagnostic and treatment studies.

References

Ashford NA, Miller CS, 1998. Chemical Exposures: Low Levels and High Stakes. New York: John Wiley and Sons, New York. 440 pp.

Golomb, BA. 1999. Pyridostigmine bromide. A review of the scientific literature as it pertains to Gulf War illnesses. Vol.2. RAND, Santa Monica, CA.

Miller CS. 1999. Are we on the threshold of a new theory of disease? Toxicant-induced loss of tolerance and its relationship to addiction and abdiction. Toxicology and Industrial Health 15:284-294.

Miller CS. 1997. Toxicant-induced loss of tolerance: An emerging theory of disease? Environmental Health Perspectives 105(Suppl 2):445-453.

Miller C, Ashford N, Doty R, Lamielle M, Otto D, Rahill A, Wallace L. 1997. Empirical approaches for the investigation of toxicant-induced loss of tolerance. Environmental Health Perspectives 105(Suppl. 2):515-519.

Newlin, D. 1997. A behavior-genetic approach to multiple chemical sensitivity. Environmental Health Perspectives 105(Suppl. 2): 505-508.

Sartin, JS. 1993. Infectious diseases during the Gulf War: the triumph of the "Third Army." Clinical and Infectious Diseases 16:580-584.

Figure 1. Exposures that may initiate TILT or trigger symptoms

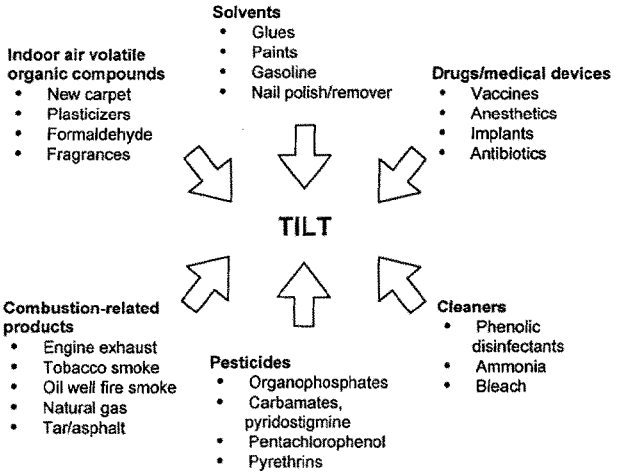
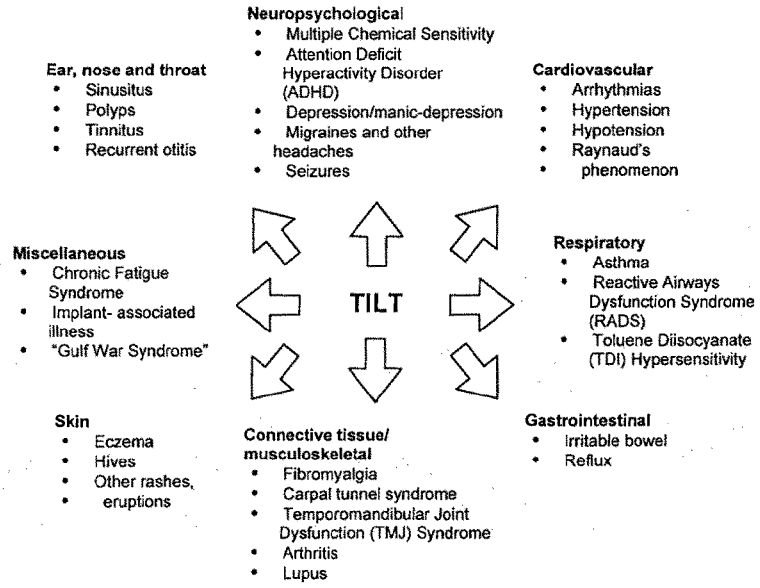


Figure 2. Conditions that may have their origins in TILT



The QEESI©

The Quick Environmental Exposure and Sensitivity Inventory (QEESI©) was developed as a screening questionnaire for multiple chemical intolerances (MCI). The instrument has four scales: Symptom Severity, Chemical Intolerances, Other Intolerances, and Life Impact. Each scale contains 10 items which are scored from 0 = "not a problem" to 10 = "severe or disabling problem." A 10-item Masking Index gauges ongoing exposures that may affect individuals' awareness of their intolerances as well as the intensity of their responses to environmental exposures. The QEESI© can be used for:

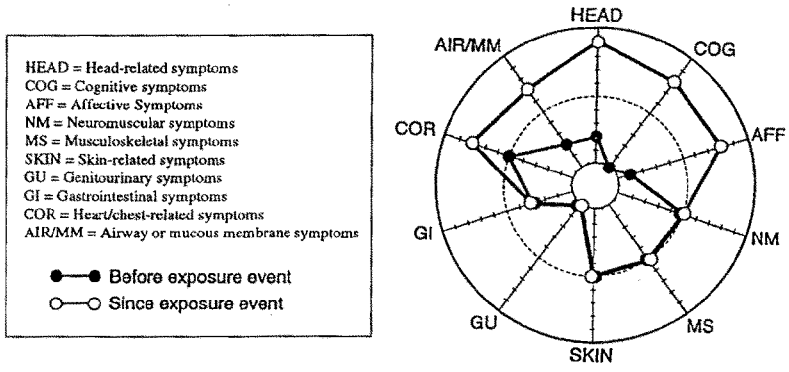
(1) Research, to characterize and compare study populations and to select subjects and controls.

(2) Clinical evaluations, to obtain a profile of patients' self-reported symptoms and intolerances. Patients can be asked to complete a QEESI© at intervals in order to follow the course of their illness over time or in response to treatment or exposure avoidance.

(3) Workplace or community investigations, to identify and provide self-assessment information to individuals who may be more susceptible or who report new intolerances. Affected employees should have the option to discuss the results with investigators or their personal physicians.

Individuals whose health problems began or became worse following a particular exposure event can fill out the QEESI© using one color of ink to illustrate how they were before the event, and a second color to illustrate how they have been since the event. On the cover of the QEESI© is a "Symptom Star" (Figure 1) which provides a graphical representation of patients' responses on the Symptom Severity Scale.

Figure 1. QEESI Symptom Star illustrating symptom severity in an individual before and after an exposure event (e.g., pesticide application, indoor air contaminants, chemical spill)



For additional copies of the QEESI©, contact Claudia S. Miller, M.D., M.S., University of Texas Health Science Center at San Antonio, Department of Family Practice BCT 150, 7703 Floyd Curl Drive, San Antonio, Texas 78229-3900. Phone: (210) 567-7760; fax: (210) 567-7764; email: millercs@uthscsa.edu. For further information see Chemical Exposures: Low Levels and High Stakes by Nicholas A. Ashford and Claudia S. Miller, John Wiley & Sons, 1998 (1-800-225-5945).

Interpreting the QEESI©

In a study of 421 individuals, including four exposure groups and a control group, the QEESI© provided sensitivity of 92% and specificity of 95% in differentiating between chemically intolerant persons with multiple chemical intolerances (MCI) and the general population (Miller and Prihoda 1999).

Cronbach's alpha reliability coefficients for the QEESI©'s four scales—Symptom Severity, Chemical Intolerances, Other Intolerances and Life Impact—were high (0.76-0.97) for each of the groups, as well as over all subjects, indicating that the questions on the QEESI© form scales showing good internal consistency. Pearson correlations for each of the four scales with validity items of interest, i.e., life quality, health status, energy level, body pain, ability to work and employment status, were all significant and in the expected direction, thus supporting good construct validity.

Information on the development of this instrument, its interpretation, and results for several populations have been published (Miller and Prihoda 1999a,b). Proposed ranges for the QEESI©'s scales and guidelines for their interpretation appear in Tables 1 and 2 below:

Table 1. Criteria for low, medium, and high scale scores

Scale/Index	Score Low	Medium	High
Symptom Severity	0-19	20-39	40-100
Chemical Intolerance	0-19	20-39	40-100
Other Intolerance	0-11	12-24	25-100
Life Impact	0-11	12-23	24-100
Masking Index	0-3	4-5	6-10

Table 2. Distribution of subjects by group using "high" cutoff points for symptom severity (≥ 40) and chemical intolerances (≥ 40), with masking low or not low (< 4 or ≥ 4)

Degree to Which MCI is Suggested[2]	Risk Criteria[1] Symptom Severity Score	Chemical Intolerance Score	Masking Score	Percentage of Each Group Meeting Risk Criteria Controls n=76	MCS - No Event n=90	MCS – Event n=96	Implant n=87	Gulf War Veterans n=72
Very suggestive	≥ 40	≥ 40	≥ 4	7	16	23	39	45
Very suggestive	≥ 40	≥ 40	< 4	0	65	66	36	4
Somewhat suggestive	≥ 40	< 40	≥ 4	3	1	2	16	26
Not suggestive	≥ 40	< 40	< 4	0	0	2	3	6
Problematic	< 40	≥ 40	≥ 4	7	3	1	1	0
Problematic	< 40	≥ 40	< 4	3	13	4	2	0
Not suggestive	< 40	< 40	≥ 4	68	1	0	2	18
Not Suggestive	< 40	< 40	< 4	12	1	2	1	1
				100	100	100	100	100

[1] Subjects must meet all three criteria, i.e., Symptom Severity, Chemical Intolerance, and Masking scores, as indicated in each row of this table.
[2] "Very suggestive" = high symptom and chemical intolerance scores.
"Somewhat suggestive" = high symptom score but possibly masked chemical intolerance
"Not suggestive" = either (1) high symptom score but low chemical intolerance score with low masking, or (2) low symptom and chemical intolerance scores.
"Problematic" = low symptom score but high chemical intolerance score. Persons in this category with low masking (<4) may be sensitive individuals who have been avoiding chemical exposures for an extended period (months or years).

References:

Miller CS, Prihoda TJ: The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. *Toxicology and Industrial Health* 15:370-385, 1999a.

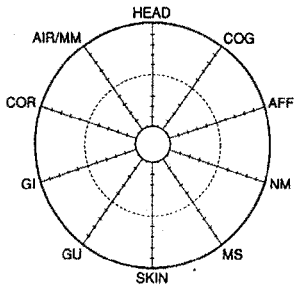
Miller CS, Prihoda TJ: A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients and persons with multiple chemical sensitivity. *Toxicology and Industrial Health* 15:386-397, 1999b.

Quick Environmental Exposure and Sensitivity Inventory V-1

(QEESI)©

The purpose of this questionnaire is to help identify health problems you may be having and to understand your responses to various exposures. If your health problems began suddenly or became much worse after a particular exposure event, such as a pesticide exposure or moving to a new home or office building, complete pages 1-3 describing how you are now, then go back through these same questions a second time, and identify how you were before the exposure event. After you have completed all of the items on pages 1-5, fill in the "target" diagram below.

Symptom Star



Instructions: After completing pages 1 through 5, unfold page 3 so that it lies just to the right of this page. Place a small dot on the corresponding spoke for each symptom item on page 3. Connect these points. For "before and after " scores (described above), use two different colors.

CHEMICAL EXPOSURES

The following items ask about your responses to various odors or chemical exposures. Please indicate whether or not these odors or exposures would make you feel sick, for example, you would get a headache, have difficulty thinking, feel weak, have trouble breathing, get an upset stomach, feel dizzy, or something like that. For any exposure that makes you feel sick, on a 0-10 scale rate the severity of your symptoms with that exposure. For exposures that do not bother you, answer "0." Do not leave any items blank.

0 = not at all a problem
5 = moderate symptoms
10 = disabling symptoms

For each item, circle one number only:

1.	Diesel or gas engine exhaust	0 1 2 3 4 5 6 7 8 9 10
2.	Tobacco smoke	0 1 2 3 4 5 6 7 8 9 10
3.	Insecticide	0 1 2 3 4 5 6 7 8 9 10
4.	Gasoline, for example at a service station while filling the gas tank	0 1 2 3 4 5 6 7 8 9 10
5.	Paint or paint thinner	0 1 2 3 4 5 6 7 8 9 10
6.	Cleaning products such as disinfectants, bleach, bathroom cleansers or floor cleaners	0 1 2 3 4 5 6 7 8 9 10
7.	Certain perfumes, air fresheners or other fragrances	0 1 2 3 4 5 6 7 8 9 10
8.	Fresh tar or asphalt	0 1 2 3 4 5 6 7 8 9 10
9.	Nailpolish, nailpolish remover, or hairspray	0 1 2 3 4 5 6 7 8 9 10
10.	New furnishings such as new carpeting, a new soft plastic shower curtain or the interior of a new car	0 1 2 3 4 5 6 7 8 9 10

Total Chemical Intolerance Score (0-100): ____

Name any additional chemical exposures that make you feel ill and score them from 0 to 10:

_____

_____

_____

_____

_____

OTHER EXPOSURES

The following items ask about your responses to a variety of other exposures. As before, please indicate whether these exposures would make you feel sick. Rate the severity of your symptoms on a 0-10 scale. Do not leave any items blank.

0 = not at all a problem
5 = moderate symptoms
10 = disabling symptoms

For each item, circle one number only:

1.	Chlorinated tap water	0 1 2 3 4 5 6 7 8 9 10
2.	Particular foods, such as candy, pizza, milk, fatty foods, meats, barbecue, onions, garlic, spicy foods, or food additives such as MSG	0 1 2 3 4 5 6 7 8 9 10
3.	Unusual cravings, or eating any foods as though you were addicted to them; or feeling ill if you miss a meal	0 1 2 3 4 5 6 7 8 9 10
4.	Feeling ill after meals	0 1 2 3 4 5 6 7 8 9 10
5.	Caffeine, such as coffee, tea, Snapple, cola drinks, Big Red, Dr. Pepper or Mountain Dew, or chocolate	0 1 2 3 4 5 6 7 8 9 10
6.	Feeling ill if you drink or eat less than your usual amount of coffee, tea, caffeinated soda or chocolate, or miss it altogether	0 1 2 3 4 5 6 7 8 9 10
7.	Alcoholic beverages in small amounts such as one beer or a glass of wine	0 1 2 3 4 5 6 7 8 9 10
8.	Fabrics, metal jewelry, creams, cosmetics, or other items that touch your skin	0 1 2 3 4 5 6 7 8 9 10
9.	Being unable to tolerate or having adverse or allergic reactions to any drugs or medications (such as antibiotics, anesthetics, pain relievers, x-ray contrast dye, vaccines or birth control pills), or to an implant, prosthesis, contraceptive chemical or device, or other medical, surgical or dental material or procedure	0 1 2 3 4 5 6 7 8 9 10
10.	Problems with any classical allergic reactions (asthma, nasal symptoms, hives, anaphylaxis or eczema) when exposed to allergens such as: tree, grass or weed pollen, dust, mold, animal dander, insect stings or particular foods	0 1 2 3 4 5 6 7 8 9 10

Total Other Intolerance Score (0-100): ____

SYMPTOMS

The following questions ask about symptoms you may have experienced commonly. Rate the severity of your symptoms on a 0-10 scale. Do not leave any items blank.

0 = not at all a problem
5 = moderate symptoms
10 = disabling symptoms

For each item, circle one number only:

1	Problems with your muscles or joints, such as pain, aching, cramping, stiffness or weakness?	MS 0 1 2 3 4 5 6 7 8 9 10
2	Problems with burning or irritation of your eyes, or problems with your airway or breathing, such as feeling short of breath, coughing, or having a lot of mucus, post-nasal drainage, or respiratory infections?	AIRWAY 0 1 2 3 4 5 6 7 8 9 10
3	Problems with your heart or chest, such as a fast or irregular heart rate, skipped beats, your heart pounding, or chest discomfort?	CCR 0 1 2 3 4 5 6 7 8 9 10
4	Problems with your stomach or digestive tract, such as abdominal pain or cramping, abdominal swelling or bloating, nausea, diarrhea, or constipation?	GI 0 1 2 3 4 5 6 7 8 9 10
5	Problems with your ability to think, such as difficulty concentrating or remembering things, feeling spacey, or having trouble making decisions?	COG 0 1 2 3 4 5 6 7 8 9 10
6.	Problems with your mood, such as feeling tense or nervous, irritable, depressed, having spells of crying or rage, or loss of motivation to do things that used to interest you?	AFF 0 1 2 3 4 5 6 7 8 9 10
7.	Problems with balance or coordination, with numbness or tingling in your extremities, or with focusing your eyes?	NM 0 1 2 3 4 5 6 7 8 9 10
8.	Problems with your head, such as headaches or a feeling of pressure or fullness in your face or head?	HEAD 0 1 2 3 4 5 6 7 8 9 10
9.	Problems with your skin, such as a rash, hives or dry skin?	SKIN 0 1 2 3 4 5 6 7 8 9 10
10.	Problems with your urinary tract or genitals, such as pelvic pain or frequent or urgent urination? (For women: or discomfort or other problems with your menstrual period?)	GU 0 1 2 3 4 5 6 7 8 9 10

Total Symptom Score (0-100): ____

MASKING INDEX

The following items refer to ongoing exposures you may be having. Circle "0" if the answer is NO, or if you don't know whether you have the exposure. Circle "1" if the answer is YES, you do have the exposure. Do not leave any items blank.

Circle "0" or "1" only:

1.	Do you smoke or dip tobacco once a week or more often?	NO=0 YES=1
2.	Do you drink any alcoholic beverages, beer, or wine once a week or more often?	NO=0 YES=1
3.	Do you consume any caffeinated beverages once a week or more often?	NO=0 YES=1
4.	Do you routinely (once a week or more) use perfume, hairspray, or other scented personal care products?	NO=0 YES=1
5.	Has either your home or your workplace been sprayed for insects or fumigated in the past year?	NO=0 YES=1
6.	In your current job or hobby, are you routinely (once a week or more) exposed to any chemicals, smoke or fumes?	NO=0 YES=1
7.	Other than yourself, does anyone routinely smoke inside your home?	NO=0 YES=1
8.	Is either a gas or propane stove used for cooking in your home?	NO=0 YES=1
9.	Is a scented fabric softener (liquid or dryer sheet) routinely used in laundering your clothes or bedding?	NO=0 YES=1
10.	Do you routinely (once a week or more) take any of the following: steroid pills, such as prednisone; pain medications requiring a prescription; medications for depression, anxiety, or mood disorders; medications for sleep; or recreational or street drugs?	NO=0 YES=1

Masking Index (0-10):
(Total number of YES answers) ____

IMPACT OF SENSITIVITIES

If you are sensitive to certain chemicals or foods, on a scale of 0-10 rate the degree to which your sensitivities have affected various aspects of your life. If you are not sensitive or if your sensitivities do not affect these aspects of your life, answer "0." Do not leave any items blank.

0 = not at all
5 = moderately
10 = severely

How much have your sensitivities affected:

1. Your diet	0 1 2 3 4 5 6 7 8 9 10
2. Your ability to work or go to school	0 1 2 3 4 5 6 7 8 9 10
3. How you furnish your home	0 1 2 3 4 5 6 7 8 9 10
4. Your choice of clothing	0 1 2 3 4 5 6 7 8 9 10
5. Your ability to travel to other cities or drive a car	0 1 2 3 4 5 6 7 8 9 10
6. Your choice of personal care products, such as deodorants or makeup	0 1 2 3 4 5 6 7 8 9 10
7. Your ability to be around others and enjoy social activities, for example, going to meetings, church, restaurants, etc.	0 1 2 3 4 5 6 7 8 9 10
8. Your choice of hobbies or recreation	0 1 2 3 4 5 6 7 8 9 10
9. Your relationship with your spouse or family	0 1 2 3 4 5 6 7 8 9 10
10. Your ability to clean your home, iron, mow the lawn, or perform other routine chores	0 1 2 3 4 5 6 7 8 9 10

Total Life Impact Score (0-100): ____

For additional copies of the QEESI, call 210-567-7760. For more information about this questionnaire, refer to Chemical Exposures: Low Levels and High Stakes (2nd Edition) by Nicholas A. Ashford and Claudia S. Miller, John Wiley & Sons, Inc., 1998. To order, call toll-free 1-800-225-5945.

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Biosketch

Claudia S. Miller, M.D., M.S., is an Associate Professor in Environmental and Occupational Medicine in the Department of Family Practice of the University of Texas Health Science Center at San Antonio. She is board-certified in Allergy/Immunology and Internal Medicine, and has a Master's degree in Public Health/Environmental Health. Her research interests include the health effects of low level chemical exposures, pesticides, indoor air pollution, and Gulf War veterans' illnesses. Dr. Miller has held appointments to several federal advisory committees, including the National Advisory Committee on Occupational Safety and Health, the National Toxicology Program Board of Scientific Counselors, and the Department of Veterans Affairs Persian Gulf Expert Scientific Advisory Committee. She is co-author of the WHO-award-winning *New Jersey Report on Chemical Sensitivity* and a professionally acclaimed book, *Chemical Exposures: Low Levels and High Stakes* (Ashford, NA and Miller, CS, John Wiley and Sons, Inc. 1998, New York).

Mr. SHAYS. Dr. Urnovitz.

Dr. URNOVITZ. Thank you. I am grateful to the committee for allowing me the opportunity to review the GAO report and for inviting me to present my views and recommendations on research directions for Persian Gulf war-related illnesses, or Gulf War Syndrome.

My name is Dr. Howard Urnovitz. I received my doctorate degree in microbiology and immunology from the University of Michigan in 1979. My entire CV is submitted with my written testimony. I currently hold the position of scientific director of the Chronic Illness Research Foundation as well as my current position as the chief science officer of a publicly traded biomedical company.

With respect to my views on government research programs concerning Gulf War Syndrome, I concur with the GAO report that many of the research objectives identified by the research working group of the Persian Gulf veterans coordinating board have not been reached. Some of the government-funded epidemiological studies, particularly those of the Centers for Disease Control and Prevention and the University of Texas Southwestern have been very meaningful.

Most of the government-funded research conducted thus far has focused on trying to quantify exposures with little or no data, identifying single exposure agents as the sole causative factor, or summarizing the research of others. The identification of the range of toxic exposures would assist greatly in determining the array of causative factors associated with Gulf War Syndrome. Today we are already have a great deal of information on the potential exposures during the Gulf war. Unfortunately, since a significant amount of the data was not collected, we will never know with any degree of certainty what the extent and combination of the exposures were in the case of each individual patient.

Further, identification of these exposures alone will not reveal the disease mechanisms involved in the progression of these illnesses. Identifying the disease mechanism has been the focus of our research. I recommend that Congress strongly encourage the Department of Defense, the department of Veterans Affairs and the department of Health and Human Services to fully acknowledge nongovernment-funded published peer-reviewed independent research to further expand the total information base on Gulf War Syndrome. I am concerned that we in the independent research community do not have a structure for free dialog with government agencies and researchers. To exclude these contributions to science is not productive.

The GAO report recognizes medical science's conventional approach to chronic illnesses. The paradigm continues to be a search for a single causative agent. The weakness in this conceptual approach is that most chronic diseases are multi-factorial. The single causative agent approach was formulated long before science recognized that the human body can sustain damage at the cellular and molecular level from a variety of physical, chemical, and biological insults and long before we determine the vast arrays of hazardous materials to which these veterans were exposed. Assigning any one entity as the causative agent will impede any progress in designing medical control or treatment of a chronic disorder.

I thank the subcommittee for recognizing the contributions my colleagues and I have made to the Gulf War Syndrome medical literature. It is my hope that our unique approach to understanding Gulf war illnesses may serve as a platform for research into other chronic ailments. My colleagues and I approach Gulf War Syndrome like most other chronic illnesses by asking the follow question: What is common among people who suffer from chronic diseases? For brevity, I will summarize our research findings published in six peer-reviewed papers in 1999 on four different diseases. One of these papers is attached to my written testimony.

It would appear that the human body has a mechanism for confronting toxic exposures. We all know that we are given our physical characteristics from genetic material, or genes, one set of genes received from each parent. What we learned by simultaneously studying Gulf War Syndrome, cancer, AIDS and multiple sclerosis is that genes have the ability to reshuffle and create new genes. We reasoned that these new genes are used to adapt to the toxic environment in which we live. It seems that there are confounding events that turns this reshuffling mechanism from a normal protective process to a disease state.

One of the next phases in our research plans is to determine what events trigger these reshuffled genes to convert from helpful to harmful. Through a research blood test we recently developed, we have been able to identify material in the sera of patients suffering from chronic illnesses that likely play a critical role both as a marker of the illness and as a mechanism for the reshuffling.

This discovery of the reshuffling process resulted from the identification and analysis of a type of nucleic acid, RNA, found in the serum or plasma of Gulf war veterans. It took us several years to break the code on just one RNA molecule that we were able to isolate. It has been our goal to collect RNA from as many veterans with Gulf War Syndrome and control and clone, decode and catalog the reshuffled genes with respect to patient symptomology. This approach should allow us to group ailments according to the pattern of each gene sequence.

The modern marvel of mapping the normal human genome is close to completion. We plan to initiate our own program, mapping the detours that the human genome takes with respect to toxic exposure and chronic disease. The ensuing catalog of reshuffled genes should assist in establishing diagnostic protocols and tailoring treatments for each patient. The single greatest obstacle to achieving this goal with respect to veterans has been the lack of sufficient private-sector funding for research into an issue that most people believe is the responsibility of the government.

I include supporting testimony from my colleague, Professor Luc Montagnier, whose laboratories with 4 decades' experience of evaluating the biomedical and medical significance of RNA, led the research effort into discovering the AIDS-associated viruses: HIV–1, 2, and group O. We jointly concur that to understand the origin of diseases associated with RNAs in Gulf War Syndrome, a major effort must be launched on understanding a family of genes referred to as retroelements. Retroelements make up over 6 percent of the genes in the human body and appear to be central to the origin of disease-associated RNA.

I would like to state for the record that it is my professional opinion that the clues to solving significant medical problems in the world today, cancers, AIDS, heart and liver diseases, auto-immune and neurologic disorders, vaccine safety, chemical injuries and military-associated ailments lie in the blood of these veterans who suffer from Gulf War Syndrome and possibly in the blood of their families. Once we break and catalog the code of reshuffled RNA, we may finally have a clear direction on how to treat chronic illnesses in general. The Gulf war veterans will become heroes again for a second time.

I ask that the full text of my statement along with the prepared statement from my colleague, Professor Montagnier, be submitted for inclusion in the hearing.

[The prepared statement of Mr. Urnovitz follows:]

TESTIMONY OF HOWARD B. URNOVITZ, PH.D.

FEBRUARY 2, 2000

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON GOVERNMENT REFORM

SUBCOMMITTEE ON NATIONAL SECURITY, VETERANS' AFFAIRS AND INTERNATIONAL RELATIONS

I am grateful to the Committee for allowing me the opportunity to review the GAO report on "Gulf War Illnesses: Management Actions Needed to Answer Basic Research Questions" and for inviting me to present my views and recommendations on research directions for Persian Gulf War Related Illnesses or GWS, Gulf War Syndrome. My name is Dr. Howard B. Urnovitz. I received my doctorate degree in Microbiology and Immunology from the University of Michigan in 1979. My entire CV is submitted with my written testimony. I currently hold the position of Scientific Director of the Chronic Illness Research Foundation as well as my current position as Chief Science Officer and Director of a publicly traded biomedical company.

With respect to my views on government research programs concerning GWS, I concur with the GAO report that many of the research objectives identified by the Research Working Group of the Persian Gulf Veterans' Coordinating Board have not been reached. Some of the government-funded epidemiological studies, particularly those of the Centers for Disease Control and Prevention and the University of Texas Southwestern have been very meaningful. Most of the government-funded research conducted thus far, however, has focused on trying to quantify exposures with little or no data, identifying single exposure agents as the sole causative factor, or summarizing the research of others. The identification of the range of toxic exposures would assist greatly in determining the array of causative factors associated with GWS. Today, we already have a great deal information on the potential exposures during the Gulf War. Unfortunately, since a significant amount of the data was not collected, we will never know with any degree of certainty what the extent and combination of the exposures were in the case of each individual patient. Further, identification of these exposures alone will not reveal the disease mechanisms involved the progression of these illnesses.

Identifying the disease mechanism has been the focus of our research. I recommend that Congress strongly encourage the Department of Defense, the Department of Veterans' Affairs and the Department of Health and Human Services to fully acknowledge non-government funded, published, peer-reviewed independent research to further expand the total information base on GWS. I am concerned that we in the independent research community do not have a structure for free dialog with government agencies and researchers. To exclude these contributions to science is not productive.

The GAO report recognizes medical science's conventional approach to chronic illnesses. The paradigm continues to be a search for a *single* causative agent. The weakness in this conceptual approach is that most chronic diseases are multifactorial. This single causative agent approach was formulated long before science recognized that the human body can sustain damage at the cellular and molecular level from a variety of physical, chemical, or biological insults, and long before we

determine the vast arrays of hazardous materials to which these veterans were exposed. Assigning any one entity as the causative agent will impede any progress in designing medical control of a chronic disorder.

I thank the Subcommittee for recognizing the contributions my colleagues and I have made to the GWS medical literature. It is my hope that our unique approach to understanding Gulf War Illnesses may serve as a platform for research into other chronic ailments. My colleagues and I approach GWS like most other chronic illnesses by asking the following question: what is common among people who suffer from chronic illnesses? For brevity, I will summarize our research findings published in 6 peer-reviewed papers in 1999 on four different diseases. One of these papers is attached to my written testimony.

It would appear that the human body has a mechanism for confronting toxic exposures. We all know that we are given our physical characteristics from genetic material or genes; one set of genes received from each parent. What we learned by simultaneously studying GWS, cancer, AIDS and multiple sclerosis is that the genes have the ability to "reshuffle" and create new genes. We reason that these new genes are used to adapt to the toxic environment in which we live. It seems that there are confounding events that turns this reshuffling mechanism from a normal protective process to a disease state. One of the next phases in our research plan is to determine what events trigger these reshuffled genes to convert from helpful to harmful.

Through a research blood test we recently developed, we have been able to identify material in the sera of patients suffering from chronic illnesses that likely play a critical role both as a marker of the illnesses and a mechanism for the reshuffling. This discovery of the reshuffling process resulted from the identification and analyses of a type of nucleic acid, RNA, found in the serum or plasma of GWS veterans. It took us several years to break the code on just one RNA molecule that we were able to isolate. It has been our goal to collect RNA from as many veterans with GWS and clone, decode and catalog the reshuffled genes with respect to patient symptomology. This approach should allow us to group ailments according to the pattern of each gene sequence. The modern marvel of mapping the normal human genome is close to completion. We plan to initiate our own program mapping the detours that the human genome takes with respect to toxic exposure and chronic disease. The ensuing catalog of reshuffled genes should assist in establishing diagnostic protocols and tailoring treatments for each patient.

The single greatest obstacle to achieving this goal with respect to the veterans has been the lack of sufficient private sector funding for research into an issue that most people believe is the responsibility of the government.

I include supporting testimony from my colleague, Prof. Luc Montagnier. Prof. Montagnier's laboratories, with 4 decades experience with evaluating the biological and medical significance of RNA, led the research effort into the discovery of the AIDS associated viruses: HIV-1, HIV-2 and HIV-1 group O. We jointly concur that to understand the origin of the disease associated RNAs in GWS, a major effort be launched on understanding a family of genes referred to as retroelements. Retroelements make up over 6% of the genes in the human body and appear to be central to the origin of disease associated RNA.

I would like to state for the record that it is my professional opinion that the clues to solving significant medical problems in the world today: cancers, AIDS, heart and liver diseases, autoimmune and neurologic disorders, vaccine safety, chemical injuries, and military associated ailments, —lie in the blood of these veterans who suffer from GWS and possibly in the blood of their families. Once we break and catalog the code of the reshuffled RNA, we may finally have a clear direction in how to treat chronic illnesses. The Gulf War veterans will become heroes again for a second time.

I ask that the full text of my statement along with a prepared statement from my colleague Professor Montagnier be submitted for inclusion in the record of the hearing.

WRITTEN TESTIMONY OF LUC MONTAGNIER, M.D.

FEBRUARY 2, 2000

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON GOVERNMENT REFORM

SUBCOMMITTEE ON NATIONAL SECURITY, VETERANS' AFFAIRS AND INTERNATIONAL RELATIONS

Mr. Chairman, my name is Dr. Luc Montagnier. I received a medical degree from Paris University in 1960. My CV is submitted along with my written testimony. I currently hold the position of Distinguished Professor at both Queens College in New York and at the Institut Pasteur in Paris. I also serve on the Scientific Advisory board of publicly traded company along with Howard B. Urnovitz, PhD, who was invited to testify before this committee today.

I have been involved in the study of the biological properties of RNA for nearly four decades. I first published the observation of the existence of double stranded RNA in replicating viruses in 1963 and within cells in 1968. I also led the team that discovered the RNA viruses: HIV-1, HIV-2 and HIV-1 group O.

I have been following the interesting work of Urnovitz and his colleagues. They have reported on the detection of RNA molecules in the blood of veterans with Gulf War Syndrome (GWS) which seems to be specific for the disease. I am aware of their ability to detect similar blood RNA molecules in several other chronic diseases. We should remember that the role of RNA in the process of life was first recognized just 37 years ago. Since 1963, RNA has been shown to be self-replicated, spliced, edited, reverse-transcribed and to be endowed with enzymatic activity. This new observation suggests that RNA may also be involved in the process of disease. It is my opinion that the detection and identification of blood-borne RNA is an important contribution to the field of medicine that will result in our further understanding of the nature of chronic disease and chronic disease progression.

I have reviewed Dr, Urnovitz's published research and the testimony prepared for presentation to this Committee and strongly advise that future research on Gulf War Syndrome should include the study of the detected genetic material, i.e., novel RNA in the sera of these veterans. I have agreed to provide my advice, drawing upon my experience and research into RNA to assist this research team in this matter. I foresee that the study of GWS may have major consequences for other chronic diseases.

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RNAs in the Sera of Persian Gulf War Veterans Have Segments Homologous to Chromosome 22q11.2

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Reverse transcriptase PCR (RT-PCR) was used for polyribonucleotide assays with sera from deployed Persian Gulf War veterans with the Gulf War Syndrome and a cohort of nonmilitary controls. Sera from veterans contained polyribonucleotides (amplicons) that were obtained by RT-PCR and that ranged in size from 200 to ca. 2,000 bp. Sera from controls did not contain amplicons larger than 450 bp. DNA sequences were derived from two amplicons unique to veterans. These amplicons, which were 414 and 759 nucleotides, were unrelated to each other or to any sequence in gene bank databases. The amplicons contained short segments that were homologous to regions of chromosome 22q11.2, an antigen-responsive hot spot for genetic rearrangements. Many of these short amplicon segments occurred near, between, or in chromosome 22q11.2 Alu sequences. These results suggest that genetic alterations in the 22q11.2 region, possibly induced by exposures to environmental genotoxins during the Persian Gulf War, may have played a role in the pathogenesis of the Gulf War Syndrome. However, the data did not exclude the possibility that other chromosomes also may have been involved. Nonetheless, the detection of polyribonucleotides such as those reported here may have application to the laboratory diagnosis of chronic diseases that have a multifactorial etiology.

During the Persian Gulf War approximately 700,000 individuals were exposed to genotoxic hazardous materials (GHM) (42, 42a, 51). The GHMs to which these individuals were exposed included low-level chemical warfare agents, investigational drugs (including pyridostigmine bromide, which is used as a prophylactic agent against nerve agents), organophosphate, carbamate, and other pesticides and insect repellents. Other occupational and environmental contaminants included low levels of nuclear and electromagnetic radiation, toxic combustion products from oil-well fires, diesel exhaust products, and airborne particulates. A significant proportion of the Persian Gulf War veterans (GWVs) developed a pattern of symptomatic health disorders that have been referred to as Persian Gulf War-Related Illnesses (42). The pattern of illness is reasonably consistent: rash, fatigue, muscle and joint pain, headache, irritability, depression, unrefreshing sleep, gastrointestinal and respiratory disorders, and cognitive defects (22). These Gulf War Syndrome (GWS) disorders were recently defined as a clinical entity (16).

We elected to test for polyribonucleotides in the sera of GWVs on the basis of several considerations. Most GWVs received oral poliovirus vaccine before deployment to the Persian Gulf. Persistent enterovirus infection has been implicated in the chronic fatigue syndrome (18), one of the major health disorders of GWS. Clements et al. (8) reported that enterovirus-related sequences persisted in the sera of patients with the chronic fatigue syndrome. The availability of primers (14) to the nontranslated sequences of most enteroviruses and to the P2-P3 junction of oral polioviruses provided a means to test whether enterovirus sequences persisted in the sera of GWVs. We used a reverse transcriptase (RT) PCR (RT-PCR), described in this report, to detect amplicons (RT-PCR amplicons [RPAs]) in the sera tested. We report that amplicons that were 750 bp or larger occurred in the sera of GWVs but not in the sera of healthy nonmilitary controls. Two amplicons (of 414 and 714 bp) unique to GWVs were sequenced. They contained short segments homologous to regions of chromosome 22q11.2, a hot spot for genetic rearrangements and mutations.

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MATERIALS AND METHODS

RT-PCR. Sera from peripheral blood specimens were obtained after the provision of informed consent from 24 veterans with GWS (Rheumatology Clinic, Veterans Affairs, Northern California Health Care System, Martinez, Calif.) who had been deployed to the Persian Gulf approximately 5 years previously. The major signs and symptoms in the 24 GWVs with GWS were rash ($n = 20$), muscle and joint pain ($n = 20$), headache depression irritability ($n = 19$), gastrointestinal and respiratory disorders ($n = 18$), chronic fatigue syndrome ($n = 17$), posttraumatic stress disorder ($n = 12$), and cognitive losses ($n = 6$). Combinations of these symptoms occurred in all but one veteran. Blinded serum samples from 50 healthy nonmilitary subjects were obtained from life insurance applicants (Osborn Laboratories, Lenexa, Kans.). For the most part, the subjects were matched by age, sex, and race. They ranged in age from 26 to 56 years. All sera were separated from clots immediately after blood was drawn and were used for RT-PCR within 48 h. To prevent cross contamination, separate facilities dedicated to specimen processing, PCR amplification, and amplicon detection were used. RNA from 0.25 ml of the sample was extracted in a laminar flow hood with 0.75 ml of TRIZOL LS reagent (Gibco BRL, Gaithersburg, Md.). RNA was precipitated with 10 μg of RNase-free glycogen as a carrier. Both methods were performed as specified by the manufacturer. Precipitated RNA was washed once with 70% ethanol by centrifugation at 4°C, resuspended in 10 μl of RNase-free distilled water, and added to 17 μl of the RT mixture (GeneAmp RNA PCR kit; Perkin-Elmer, Norwalk, Conn.) containing $MgCl_2$ (5 mM), 1× PCR Buffer II, RNase inhibitor (2.5 U), murine leukemia virus RT (2.5 U), random hexamer primers (2.5 μM), and 1 mM each dATP, dGTP, dCTP, and dTTP. Poliovirus Sabin type 1 RNA (National Institute for Biological Standards and Control, Hertfordshire, United Kingdom) was used as a positive control. RT was omitted from the reaction mixture for the negative control. The RT mixture was incubated for 10 min at 22°C, 30 min at 42°C, and 5 min at 95°C with a Perkin-Elmer thermocycler. The RT mixture was then added to the top of a hot-start PCR, with a melted Ampliwax bead (Perkin-Elmer) used as the barrier. The 70 μl of the top PCR mixture contained 1× PCR Buffer II and Amplitaq (2.5 U). The 30 μl of the bottom PCR mixture contained 1× PCR Buffer II, 2 mM $MgCl_2$, and the appropriate primer pairs (15 μM). Primers from the enteroviral nontranslated region (primer PG01 [5′-AAGCACTTCTGTTTCC-3′] and primer PG02 [5′-CATTCAGGGGCCGGAGGA-3′]) and the poliovirus viral protein region (P2-P3 junction of poliovirus types 1 and 2; primer PG03 [5′-GAAATGTGTAAGAA

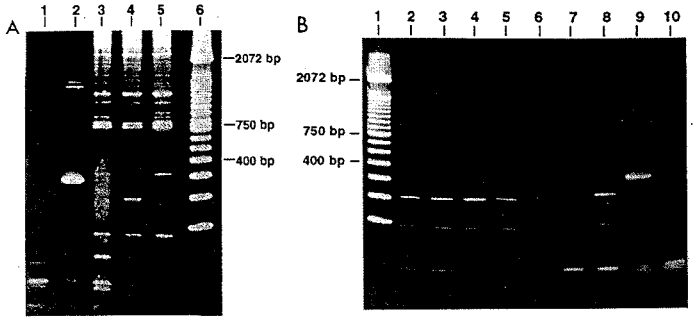

FIG. 1. Nucleotide bands (amplicons) in sera from GWVs and nonmilitary controls. (A) Results for representative samples from three different veterans. Lane 1, poliovirus without RT as a negative control; lane 2, poliovirus-positive control; lane 3, serum from veteran 1; lane 4, serum from veteran 2; lane 5, serum from veteran 3; lane 6, 100-bp ladder. (B) Results for representative samples from seven different nonmilitary controls. Lane 1, 100-bp ladder; lanes 2 to 8, sera from seven healthy controls, respectively; lane 9, poliovirus-positive control; lane 10, poliovirus without RT as a negative control.

CTGTCA-3'] and primer PG04 [5'-GTAACAATGTTTCTTTTAGCC-3']) were used as primer pairs or in a multiplex combination. After 35 cycles of amplification (1 min at 94°C, 2 min at 48°C, and 1 min at 72°C), 8 μl of the PCR mixture was electrophoresed with a precast 6% polyacrylamide gel in TBE buffer (45 mM Tris, 45 mM boric acid, 1 mM EDTA) (NOVEX, San Diego, Calif.) for 30 min at 200 V. The gels were stained for 20 min in a 0.5-μg/ml ethidium bromide solution and were photographed under UV light.

Cloning and sequencing. Sera from three different veterans were processed on three different days. The PCR products were run on and excised from a 2% NuSieve GTG low-melting-point agarose gel (FMC BioProducts, Rockland, Maine). The bands were blunt-end cloned with the Prime PCR Clorer Kit (5 PRIME-3 PRIME, Inc., Boulder, Colo.) according to the manufacturer's specifications. Sequence analysis was performed with the automated sequencer from ABI PRISM (Operon Technologies, Inc., Alameda, Calif.).

Statistical analysis. A 2-by-2 contingency analysis (see Table 1) was done by using Graphpad InStat software (Graphpad Program Software, San Diego, Calif.).

GenBank Search. All GenBank and EMBL searches were done with the DNASTAR Lasergene CD-ROM and software (release 103, November 1997; DNASTAR, Madison, Wis.). Homology searches were performed with 2 through 6 k-tuples with window sizes of 11 to 100 nucleotides (nt). Homology searches for 14 nt or higher were done by starting with position 1 and continuing through to the last 14-nt segment of each amplicon. All sequences with 100% homology were recorded and are presented in Table 2.

Nucleotide sequence accession numbers. The sequences of the 414- and 759-nt sequences derived from sera from patients with GWS were placed in the GenBank database under accession nos. AF100637 and AF100636, respectively.

RESULTS

Sera from 24 deployed GWVs and 50 serum samples from healthy nonmilitary controls were tested for RPAs. Figure 1A shows the presence of multiple bands in the sera from GWVs. The pattern was typical for most veterans, i.e., the occurrence of several bands in the 300- to 750-bp regions accompanied by discrete bands with sequences longer than 2,000 bp. These band patterns were detected by RT-PCR but not by direct PCR, implicating the presence of RNAs and not DNAs in the sera. Figure 1B shows a representative gel in which sera from seven healthy nonmilitary controls were tested. Only a few distinct bands were found. There were no bands larger than 450 bp. The results for 24 veterans and 50 healthy controls (Table 1) indicate the differences in the occurrence of RPAs in the two cohorts.

Two bands in the gel regions of ca. 400 and 750 bp that occurred only in the sera of GWVs were isolated, cloned, and sequenced. Figure 2 presents the consensus sequence data for isolates from three different veterans. Each of the 414- and 759-nt sequences from the three different isolates had approximately 99% homology. The 414 and 759-nt GWS sequences contained several initiation and stop codons (open reading frames) that could code for small polypeptides. Neither the 414- nor 759-nt sequences had direct homologies to sequences in GenBank. In analogous studies with sera from approximately 30 patients with active multiple myeloma (13), we detected RPAs that were related to chromosome 22q11.2. We therefore elected to search the chromosome 22q11.2 database for homologies to the 414- and 759-nt sequences. Several short segments of 15 nt (15mer) and 14 nt (14mer) were found. Table 2 shows that three 15mer and eight 14mer segments of the 759-nt sequence had 100% homology to sequences in chromosome 22q11.2. One 14mer segment, from positions 377 to 390 (Fig. 2 and Table 2), was identical for GWVs 2 and 3 but

TABLE 1. Occurrence of polyribonucleotide bands in sera from GWVs and nonmilitary controls

Band[a]	Band size (bp)	No. (%) positive		P value[b]
		GWVs (n = 24)	Nonmilitary controls (n = 50)	
EV NTR	297[c]	14 (58)	21 (42)	0.22
Polio P2/P3	565[d]	10 (42)	11 (22)	0.10
	200	2 (8)	15 (30)	0.043
Non-EV	350	4 (17)	0 (0)	0.0092
	450	17 (71)	19 (38)	0.0125
	750	12 (50)	0 (0)	<0.0001

[a] EV NTR, enterovirus nontranslated region; EV, enterovirus; Non-EV, nonenterovirus.

[b] See Materials and Methods for description of statistical analysis.

[c] The PG01-PG02 primer pair detects a 297-bp band from the nontranslated region of a majority of enteroviruses.

[d] The PG03-PG04 primer pair detects a 565-bp band of the P2-P3 junction of the oral poliovirus vaccine strains, Sabin types 1 and 2.

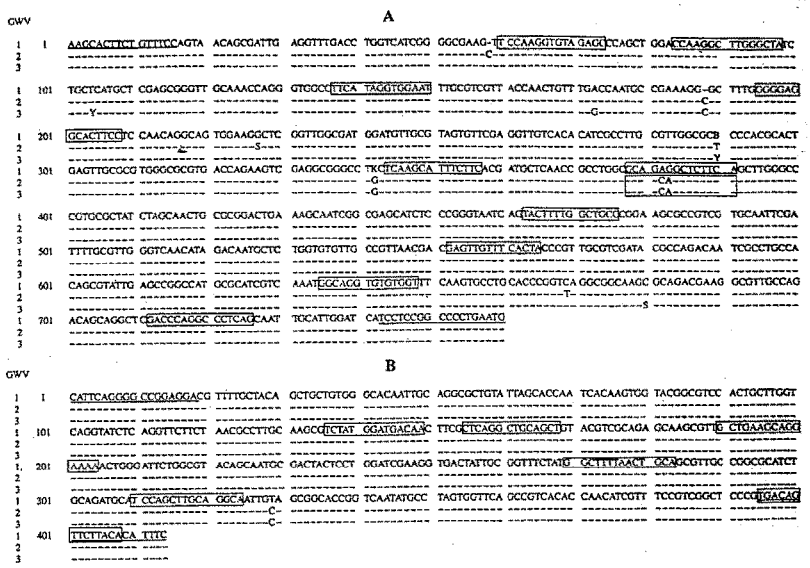

FIG. 2. Sequences of the 759-nt (A) and 414-nt (B) RPAs derived from the sera from three different GWVs. Boxed sequences denote 22q11.2 homologies (Table 2). Enteroviral primers are underlined.

differed by two nucleotides for GWV 1. The 14mer from GWVs 2 and 3 had 100% homology with a segment in the sequence with GenBank accession no. HSF4G12. The 14mer from GWV 1 had 100% homology with a segment in the sequence with GenBank accession no. HSN38E12. The gene sequences from GenBank accession nos. HSF4G12 and HSN38E12 are both located on chromosome 22q11.2. Six of 11 RPA segments were located either within an Alu region (12), between Alu and other repeat regions, or as segments flanking an Alu region. Five 759-nt segments occurred only in the chromosome 22q11.2 region. Two 14mers of the 759-nt sequence were located proximal to the immunoglobulin lambda light-chain variable-region genes. For the 414-nt sequence, there were two 15mer and four 14mer segments that also had 100% homology within the 22q11.2 region. However, these six segments also occurred at sites on other chromosomes. Interestingly, unique 15mer segments were not found in any chromosomal region other than 22q11.2.

DISCUSSION

The pattern of RPAs (polyribonucleotides) found in sera from GWVs was distinct from that found in sera from the nonmilitary cohort. Moreover, RPAs larger than 450 bp did not occur in the sera from healthy controls. The frequencies of occurrence of RPAs homologous to the poliovirus P2-P3 junction sequences and the enteroviral nontranslated region were not significantly different in the two groups (Table 1). The gels shown in Fig. 1 disclosed many bands larger than 2,000 bp in the sera of GWVs. No attempt was made to resolve or to characterize them at the molecular level. Such studies are in progress. Analysis of the 414- and 759-nt sequences showed that they are not related and that the 414-nt sequence is not a degradation product of the 759-nt sequence.

In attempting to understand the pathogenesis of GWS, the challenge has been to explain the diversity of the signs and symptoms typical of the disorder. A traditional approach of invoking a single cause is not applicable because it fails to accommodate three basic considerations. First, the etiology of the disease is multifactorial (49). Thus, different groups of signs and symptoms very likely have different causes. Second, exposure to environmental genotoxins during the Persian Gulf War likely caused an interaction among causative factors, thus affecting expression of signs and symptoms in given individuals. Third, and consistent with multifactorial diseases in general, the genetic and physiologic diversity of the affected population is in accord with the spectrum of disease expression seen. These concepts are known to be relevant to a number of chronic multifactorial diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and insulin-dependent diabetes mellitus. For such diseases it has been essential to identify the individual causative factors, to weigh the contributions of each to the overall clinicopathologic picture, to determine how they interact in various population

TABLE 2. Segment homologies among GWS RPAs and human chromosome 22q11.2

RPA, sequence, and position	GenBank accession no.	22q11.2 GenBank sequence	Segment location	No. of other 100% matches
759-nt RPA				
15mers				
59–73	HSU07000	809–823	Between two Alu regions	0 human, 0 nonhuman
83–97	HSCN37F10	36332–36346	Between MIR and Alu	0 human, 0 nonhuman
711–725	HS322B1	45987–46001	Between AluSx and MIR	1 human, 0 nonhuman
14mers				
11–24	D86998	23151–23164	Between V2–8 and V1–3	2 human, 2 nonhuman
136–149	U30597	227965–227978	Between two Alu regions	0 human, 8 nonhuman
194–207	HSE78G1	29369–29382	Between two Alu regions	0 human, 3 nonhuman
343–356	HSN44A4	1460–1473	In AluY	9 human, 25 nonhuman
377–390 (GWV 1)	HSN38E12	19903–19916	Between AluSx and repeat region	2 human, 3 nonhuman
377–390 (GWV 2 and 3)	HSF4G12	39069–39082	Between two repeat regions	18 human, 22 nonhuman
462–475	HSN20A6	17205–17218	Near flanking repeat region	4 human, 1 nonhuman
551–564	AC000068	14136–14149	No description	0 human, 2 nonhuman
634–647	D87021	17508–17521	Between V2–7 and V2–6 light-chain genes	15 human, 7 nonhuman
414-nt RPA				
15mers				
190–204	AC002475	1301–1315	No description	23 human, 1 nonhuman
310–324	HSN74G7	10657–10671	Between Alu repeat and repeat region	3 human, 0 nonhuman
14mers				
136–149	HS65B7	4097–4110	Inside MIR repeat	4 human, 0 nonhuman
155–168	HSE78G1	35878–35891	Between repeat regions	18 human, 2 nonhuman
270–283	HSE146D10	522–535	Between repeat regions	4 human, 2 nonhuman
395–408	HSE116C6	9265–9278	Between Alu and repeat region	1 human, 14 nonhuman

[a] Sequences from a survey of consensus sequences with 100% homology to the designated RPAs from sera from GWVs with GWS (GWS RPAs) were divided into human and nonhuman categories according to the GenBank definition of the entry. MIR, mammalian-wide interspersed repeat.

groups, and to evaluate the effects of different environmental influences.

The notions outlined above reflect our approach to an analysis of GWS. First, we sought to determine whether enterovirus infection could be a contributory factor in the pathogenesis of GWS. Molecular studies that have used PCR technologies have indicated persistent enterovirus infection in myalgia and myositis (54), dermatomyositis and polymyositis (5, 43), neuromuscular disease (28, 37), and the chronic fatigue syndrome (18). The signs and symptoms of these disorders are common in GWS. Moreover, enterovirus infection is known to cause a variety of immunologic and autoimmune disorders (9, 17). Immunologic disorders appear to make up an important component of the signs and symptoms of GWS. Studies of immunologic abnormalities in GWS, similar to those done for the chronic fatigue syndrome (4), appear to offer an important approach in an analysis of the pathogenesis of the disease.

To the best of our knowledge this is the first report of the occurrence of nonviral RPAs in the sera of subjects with a multifactorial chronic disease. We consider four central questions: (i) the possible origin(s) of the polyribonucleotides (amplicons) found in sera, (ii) the possible role(s) of chromosome 22q11.2 in the pathogenesis of the GWS, (iii) whether environmental genotoxins may have played a role in its pathogenesis, and (iv) the possible diagnostic value of detecting RPAs in the sera of patients with chronic diseases.

Identification of the possible origin(s) of the RPAs in sera is an important consideration. Since the occurrence of nonenterovirus RPAs in the sera of GWVs and controls was unexpected, we were concerned that they might have been PCR artifacts. Specific steps had been taken to minimize this possibility (see Materials and Methods). Two separate lines of evidence indicate that the RPAs described here were not artifactual in origin: (i) we developed a non-PCR, total RNA assay that independently confirmed that RNA species occur in the sera of patients with chronic diseases; and (ii) studies of approximately 30 patients with active multiple myeloma and 152 healthy controls by the described RT-PCR assay disclosed the occurrence of unique RPAs, e.g., GenBank accession no. AF018254, in test sera. Accordingly, our data suggest that individual chronic diseases may be characterized by the consistent occurrence of unique RPAs in the sera of patients with the individual chronic diseases.

An explanation of how polyribonucleotides could persist in the sera without being degraded is also needed. A reasonable account comes from the work of Wieczorek et al. (52), who reported that RNAs in the sera of patients with a variety of malignancies persisted as RNase-resistant RNA-proteolipid complexes. Salmon and Seligmann (45) referred to the occurrence of RNAs in the sera of patients with multiple myeloma. We recently confirmed and extended these findings (13). We detected a 705-bp segment homologous to the flanking region of the peroxisome proliferator-activated receptor exon 4 sequence located on chromosome 22q11.2. We are testing whether RPAs found in sera were derived from diverse tissue and cellular origins. These experiments are based on the clinical observation that immunologic abnormalities appear to be commonplace in GWS. In addition, Koga et al. (25) reported that uninfected thymocytes from healthy humans contained elevated amounts of heterodisperse RNA. Such heterodisperse RNA may be released into the circulation as a result of thymocyte apoptosis. Presumably, such RNAs would be protected from RNase degradation because of a physical association with cellular debris, as described by Wieczorek et al. (52). This

hypothesis takes into consideration the evident immunologic dyscrasias that are observed in patients with GWS and that presumably occur because of underlying disorders in immune regulation.

None of the RPA sequence data disclosed homologies to enterovirus or poliovirus sequences. Since only a fraction of the RPAs observed in gels were sequenced, we do not exclude the possibility that some of them were enterovirus related. We assume that the RPAs that were sequenced are direct transcripts of recombinant sequences, although direct experimental proof is still required. Both the 414- and 759-nt RPAs, which were found only in the sera from the three GWVs tested, had short 14mers or 15mers (Table 2) that were 100% homologous to chromosome 22q11.2 segments. These findings suggest that abnormalities in chromosome 22q11.2 are involved, either directly or indirectly, in the pathogenesis of GWS. This does not mean that chromosomal regions other than 22q11.2 are not involved. Nonetheless, it appears that the GWS may be added to the list of diseases in which abnormalities in chromosome 22q11.2 are involved. These include the recently defined chromosome 22q11.2 deletion syndrome (46, 48), juvenile rheumatoid arthritis-like polyarthritis (47), idiopathic thrombocytopenic purpura (29), and hypoparathyroidism (3). In fact, deletion from chromosome 22q11 is the most common microdeletion (36). Interestingly, up to 60% of subjects (36, 53) with such deletions suffer from behavioral or psychiatric disorders. Also of note, chromosome 22 appears to be involved in the so-called Goldenhar complex (21, 24), a birth defect possibly associated with GWS (19). The mechanisms involved in embryonic development and 22q deletion disorders are now being defined at the molecular level (33).

The occurrence of hot spots for genetic deletions, translocations (6), and rearrangements, e.g., immunoglobulin lambda light chains (15, 44), in chromosome 22q11.2 is recognized widely. Such hot spots may be particularly sensitive to adverse genotoxic effects of environmental GHMs encountered during service in the Persian Gulf War. Studies with animal models (2) suggest that combined or multiple exposures to GHMs may have a synergistic genotoxic effect, thus causing some of the symptoms seen in GWS.

The juxtaposition of the detected RPA sequences with Alu sequences in chromosome 22q11.2 also may be relevant to the pathogenesis of GWS. The contemporary notion that Alu sequences are "junk DNA" is not consistent with the accumulating evidence that Alu sequences become transcriptionally active when cells are exposed to physiologic insults such as infection with DNA viruses (10, 40) or human immunodeficiency virus type 1 (23, 25) or when cells are induced to express heat shock proteins (7). Liu et al. (32) reported that cells stressed by exposure to cycloheximide or puromycin "rapidly and transiently increased the abundance of Alu RNA." We postulate that the expression of RNAs of Alu sequences, their flanking regions, and their recombinants in response to GHMs may be a supplemental mechanism for detoxification of GHMs (11, 38). Such Alu-Alu recombinants are generated by both extrachromosomal and chromosomal genetic mechanisms (20, 27, 31, 35, 39, 41). In addition, Makalowski et al. (34) described the role of Alu sequences in generating diverse proteins. Such diverse proteins may also contribute to autoimmune reactivities in patients with GWS and possibly other chronic disorders.

The possible roles of the detected RPAs in the pathogenesis of GWS are unknown. Nonetheless, their occurrence makes available markers that can be studied for possible pathophysiologic effects. The biological activities of such molecules can be significant. Krieg (26) reported that specific CpG Alu-rich DNA (30) sequences in the plasma of patients with systemic lupus erythematosus may play an important role in the pathophysiology of the disease. Interestingly, chromosome 22 is rich in CpG islands. In addition, Abken et al. (1) reported that novel mouse cytoplasmic DNA sequences immortalized human lymphocytes in vitro. Such studies provide a paradigm for GWS.

The patterns of the occurrence of RPAs in the sera of GWVs and healthy controls are sufficiently distinct to suggest possible future diagnostic applications. Sufficiently large numbers of subjects need to be studied (50) to determine the sensitivities and specificities of such tests. Our studies of patients with active multiple myeloma (13) suggest that patients with individual chronic multifactorial diseases may have unique RPAs in their sera. Validated tests for such putative surrogate markers may aid in the diagnosis of such diseases or in the evaluation of responses to therapeutic modalities.

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REFERENCES

1. **Abken, H., R. Hegger, C. Butzler, and K. Willecke.** 1993. Short DNA sequences from the cytoplasm of mouse tumor cells induce immortalization of human lymphocytes in vitro. Proc. Natl. Acad. Sci. USA 90:6518–6522.
2. **Abou-Donia, M. B., K. R. Wilmarth, K. F. Jensen, F. W. Oehme, and T. L. Kurt.** 1996. Neurotoxicity resulting from coexposure to pyridostigmine bromide, DEET and permethrin: implications of Gulf War chemical exposures. J. Toxicol. Environ. Health 48:35–56.
3. **Adachi, M., K. Tachibana, M. Masuno, Y. Makita, H. Maesaka, T. Okada, K. Hizukuri, K. Imaizumi, Y. Kuroki, H. Kurahashi, and S. Suwa.** 1998. Clinical characteristics of children with hypoparathyroidism due to 22q11.2 microdeletion. Eur. J. Pediatr. 157:34–38.
4. **Barker, W., S. F. Fujimura, M. B. Fadem, A. L. Landay, and J. A. Levy.** 1994. Immunologic abnormalities associated with the chronic fatigue syndrome. Clin. Infect. Dis. 18:S136–S141.
5. **Bowles, N. E., C. A. Sewry, V. Dubowitz, and L. C. Archard.** 1987. Dermatomyositis, polymyositis, and coxsackie-B-virus infection. Lancet i:1004–1007.
6. **Calasanz, M. J., J. C. Cigudosa, M. D. Odero, C. Ferreira, M. T. Ardanaz, A. Fraile, J. L. Carrasco, F. Sole, B. Cuesta, and A. Gullon.** 1997. Cytogenetic analysis of 280 patients with multiple myeloma and related disorders: primary breakpoints and clinical correlations. Genes Chromosomes Cancer 18:84–93.
7. **Chu, W. M., R. Ballard, B. W. Carpick, B. R. G. Williams, and C. W. Schmid.** 1998. Potential Alu function: regulation of the activity of double-stranded RNA-activated kinase PKR. Mol. Cell. Biol. 18:58–68.
8. **Clements, G. B., F. McGarry, C. Nairn, and D. N. Galbraith.** 1995. Detection of enterovirus-specific RNA in serum: the relationship to chronic fatigue. J. Med. Virol. 45:156–161.
9. **Craighead, J. E., S. A. Huber, and S. Sriram.** 1990. Animal models of picornavirus-induced autoimmune disease: their possible relevance to human disease. Lab. Invest. 63:432–446.
10. **Darlix, J. L., E. Khandjian, and R. Weil.** 1984. Nature and origin of the RNA associated with simian virus 40 large tumor antigen. Proc. Natl. Acad. Sci. USA 81:5425–5429.
11. **Davies, H. G., R. J. Richter, M. Keifer, C. A. Broomfield, J. Sowalla, and C. E. Furlong.** 1996. The effect of the human serum paraoxonase polymorphism is reversed with diazoxon, soman and sarin. Nat. Genet. 14:334–336.
12. **Deininger, P. L.** 1989. SINEs: short interspersed repeated DNA elements in higher eucaryotes, p. 619–636. In D. E. Berg and M. M. Howe (ed.), Mobile DNA. American Society for Microbiology, Washington, D.C.
13. **Durie, B. G. M., W. H. Murphy, and H. B. Urnovitz.** GenBank accession no. AF018254. Unpublished data.
14. **Egger, D., L. Pasamontes, M. Ostermayer, and K. Bienz.** 1995. Reverse transcription multiplex PCR for differentiation between polio- and enteroviruses from clinical and environmental samples. J. Clin. Microbiol. 33:1442–1447.
15. **Frippiat, J. P., S. C. Williams, I. M. Tomlinson, G. P. Cook, D. Cherif, D. Le Paslier, J. E. Collins, I. Dunham, G. Winter, and M. P. Lefranc.** 1995. Organization of the human immunoglobulin lambda light-chain locus on chromosome 22q11.2. Hum. Mol. Genet. 4:983–991.
16. **Fukuda, K., R. Nisenbaum, G. Stewart, W. W. Thompson, L. Robin, R. M. Washko, D. L. Noah, D. H. Barrett, B. Randall, B. L. Herwaldt, A. C. Mawle,**

and W. C. Reeves. 1998. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. JAMA **280:**981–988.
17. **Garzelli, C., F. Basolo, D. Matteucci, B. S. Prabhakar, and A. Toniolo.** 1989. Picornavirus-induced immunosuppression, p. 193–200. In S. Specter, M. Bendinelli, and H. Friedman (ed.), Virus-induced immunosuppression. Plenum Press, New York, N.Y.
18. **Gow, J. W., and W. M. H. Behan.** 1991. Amplification and identification of enteroviral sequences in the postviral fatigue syndrome. Br. Med. Bull. **47:**872–885.
19. **Haley, R. W.** 1998. Point: bias from the "healthy-warrior effect" and unequal follow-up in three governmental studies of health effects in the Gulf War. Am. J. Epidemiol. **148:**315–323.
20. **Harteveld, K. L., M. Losekoot, R. Fodde, P. C. Giordano, and L. F. Bernini.** 1997. The involvement of Alu repeats in recombination events at the alpha-globin gene cluster: characterization of two alphazero-thalassaemia deletion breakpoints. Hum. Genet. **99:**528–534.
21. **Herman, G. E., F. Greenberg, and D. H. Ledbetter.** 1988. Multiple congenital anomaly/mental retardation (MCA/MR) syndrome with Goldenhar complex due to a terminal del(22q). Am. J. Med. Genet. **29:**909–915.
22. **The Iowa Persian Gulf Study Group.** 1997. Self-reported illness and health status among Gulf War veterans. A population-based study. JAMA **277:**238–245.
23. **Jang, K. L., M. K. L. Collins, and D. S. Latchman.** 1992. The HIV tat protein increases the transcription of human Alu repeated sequences by increasing the activity of the cellular transcription factor TFIIIC. J. Acquired Immune Defic. Syndr. **5:**1142–1147.
24. **Kobrynski, L., D. Chitayat, L. Zahed, D. McGregor, L. Rochon, S. Brownstein, M. Vekemans, and D. L. Albert.** 1993. Trisomy 22 and facioauriculovertebral (Goldenhar) sequence. Am. J. Med. Genet. **46:**68–71.
25. **Koga, Y., E. Lindstrom, E. M. Fenyo, H. Wigzell, and T. W. Mak.** 1988. High levels of heterodisperse RNAs accumulate in T cells infected with HIV and in normal thymocytes. Proc. Natl. Acad. Sci. USA **85:**4521–4525.
26. **Krieg, A. M.** 1995. CpG DNA: a pathogenic factor in systemic lupus erythematosus? J. Clin. Immunol. **15:**284–292.
27. **Lehrman, M. A., J. L. Goldstein, D. W. Russell, and M. S. Brown.** 1987. Duplication of seven exons in LDL receptor gene caused by Alu-Alu recombination in a subject with familial hypercholesterolemia. Cell **48:**827–835.
28. **Leparc-Goffart, L., J. Julien, F. Fuchs, I. Janatova, M. Aymard, and H. Kopecka.** 1996. Evidence of presence of poliovirus genomic sequences in cerebrospinal fluid from patients with postpolio syndrome. J. Clin. Microbiol. **34:**2023–2026.
29. **Levy, A., G. Michel, M. Lemerrer, and N. Philip.** 1997. Idiopathic thrombocytopenic purpura in two mothers of children with DiGeorge sequence: a new component manifestation of deletion 22q11? Am. J. Med. Genet. **69:**356–359.
30. **Li, J. Z., and C. R. Steinman.** 1989. Plasma DNA in systemic lupus erythematosus. Characterization of cloned base sequences. Arthritis Rheum. **32:**726–733.
31. **Li, L., and P. F. Bray.** 1993. Homologous recombination among three intragene Alu sequences causes an inversion-deletion resulting in the hereditary bleeding disorder Glanzmann thrombasthenia. Am. J. Hum. Genet. **53:**140–149.
32. **Liu, W.-M., W.-M. Chu, P. V. Choudary, and C. W. Schmid.** 1995. Cell stress and translational inhibitors transiently increase the abundance of mammalian SINE transcripts. Nucleic Acids Res. **23:**1758–1765.
33. **Lorain, S., J. P. Quivy, F. Monier-Gavelle, C. Scamps, Y. Lécluse, G. Almouzni, and M. Lipinski.** 1998. Core histones and HIRIP3, a novel histone-binding protein, directly interact with WD repeat protein HIRA. Mol. Cell. Biol. **18:**5546–5556.
34. **Makalowski, W., G. A. Mitchell, and D. Labuda.** 1994. Alu sequences in the coding regions of mRNA: a source of protein variability. Trends Genet. **10:**188–193.
35. **Marcus, S., D. Hellgren, B. Lambert, S. P. Fallstrom, and J. Wahlstrom.** 1993. Duplication in the hypoxanthine phosphoribosyl-transferase gene caused by Alu-Alu recombination in a patient with Lesch Nyhan syndrome. Hum. Genet. **90:**477–482.
36. **McCandless, S. E., J. A. Scott, and N. H. Robin.** 1998. Deletion 22q11: a newly recognized cause of behavioral and psychiatric disorders. Arch. Pediatr. Adolesc. Med. **152:**481–484.
37. **Muir, P., F. Nicholson, M. K. Sharief, E. J. Thompson, N. J. Cairns, P. Lantos, G. T. Spencer, H. J. Kaminski, and J. E. Banatvala.** 1995. Evidence for persistent enterovirus infection of the central nervous system in patients with previous paralytic poliomyelitis. Ann. N. Y. Acad. Sci. **753:219–232.**
38. **Nebert, D. W.** 1997. Polymorphisms in drug-metabolizing enzymes: what is their clinical relevance and why do they exist? Am. J. Human Genet. **60:**265–271.
39. **Nystrom-Lahti, M., P. Kristo, N. C. Nicolaides, S. Y. Chang, L. A. Aaltonen, A. L. Moisio, H. J. Jarvinen, J. P. Mecklin, K. W. Kinzler, B. Vogelstein, A. de la Chapelle, and P. Peltomaki.** 1995. Founding mutations and Alu-mediated recombination in hereditary colon cancer. Nat. Med. **1:**1203–1206.
40. **Panning, B., and J. R. Smiley.** 1995. Activation of expression of multiple subfamilies of human Alu elements by adenovirus type 5 and herpes simplex virus type 1. J. Mol. Biol. **248:**513–524.
41. **Pousi, B., T. Hautala, J. Heikkinen, L. Pajunen, K. I. Kivirikko, and R. Myllyla.** 1994. Alu-Alu recombination results in a duplication of seven exons in the lysyl hydroxylase gene in a patient with the type VI variant of Ehlers-Danlos syndrome. Am. J. Hum. Genet. **55:**899–906.
42. **Presidential Advisory Committee on Gulf War Veteran's Illnesses.** 1996. Final report. U.S. Government Printing Office, Washington, D.C.

42a. **Presidential Advisory Committee on Gulf War Veteran's Illnesses.** 1997. Special report. U.S. Government Printing Office, Washington, D.C.

43. **Rosenberg, N. L., H. A. Rotbart, M. J. Abzug, S. P. Ringel, and M. J. Levin.** 1989. Evidence for a novel picornavirus in human dermatomyositis. Ann. Neurol. **26:**204–209.
44. **Roth, D. B., and N. L. Craig.** 1998. VDJ recombination: a transposase goes to work. Cell **94:**411–414.
45. **Salmon, S. E., and M. Seligmann.** 1974. B-cell neoplasia in man. Lancet **ii:**1230–1233.
46. **Smith, C. A., D. A. Driscoll, B. S. Emanuel, D. M. McDonald-McGinn, E. H. Zackai, and K. E. Sullivan.** 1998. Increased prevalence of immunoglobulin a deficiency in patients with the chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/Velocardiofacial syndrome). Clin. Diagn. Lab. Immunol. **5:**415–417.
47. **Sullivan, K. E., D. M. McDonald-McGinn, D. A. Driscoll, C. M. Zmijewski, A. S. Ellahban, L. Reed, B. S. Emanuel, E. H. Zackai, B. H. Athreya, and G. Keenan.** 1997. Juvenile rheumatoid arthritis-like polyarthritis in chromosome 22q11.2 deletion syndrome (DiGeorge anomalad/velocardiofacial syndrome/conotruncal anomaly face syndrome). Arthritis Rheum. **40:**430–436.
48. **Thomas, J. A., and J. M. Graham, Jr.** 1997. Chromosome 22q11 deletion syndrome: an update and review for the primary pediatrician. Clin. Pediatr. **36:**253–266.
49. **Urnovitz, H. B., and W. H. Murphy.** 1996. Human endogenous retroviruses: nature, occurrence, and clinical implications in human disease. Clin. Microbiol. Rev. **9:**72–99.
50. **Urnovitz, H. B., J. C. Sturge, and T. D. Gottfried.** 1997. Increased sensitivity of HIV-1 antibody detection. Nat. Med. **3:**1258.
51. **U.S. Senate (J. J. Tuite, principal investigator).** 1994. United States dual-use exports to Iraq and their impact on the health of the Persian Gulf War veterans, p. 229–243, 362–379. In Senate hearing document no. 103–900 and appendices. U.S. Government Printing Office, Washington, D.C.
52. **Wieczorek, A. J., C. Rhyner, and L. H. Block.** 1985. Isolation and characterization of an RNA-proteolipid complex associated with the malignant state in humans. Proc. Natl. Acad. Sci. USA **82:**3455–3459.
53. **Yan, W., L. K. Jacobsen, D. M. Krasnewich, X. Y. Guan, M. C. Lenane, S. P. Paul, H. N. Dalwadi, H. Zhang, R. T. Long, S. Kumra, B. M. Martinm, P. J. Scambler, J. M. Trent, E. Sidransky, E. I. Ginns, and J. L. Rapoport.** 1998. Chromosome 22q11.2 interstitial deletions among childhood-onset schizophrenics and "multidimensionally impaired." Am. J. Med. Genet. **81:**41–43.
54. **Yousef, G. E., D. A. Isenberg, and J. F. Mowbray.** 1990. Detection of enterovirus specific RNA sequences in muscle biopsy specimens from patients with adult onset myositis. Ann. Rheum. Dis. **49:**310–315.

Mr. SHAYS. Before I ask my questions, I want to thank Mr. Chan for staying and hearing other witnesses and also Dr. Feussner and Dr. Mazzuchi and Dr. Foster. It is appreciated that you listen to the other witnesses.

I am struck by the fact that if you had testified 4 years ago, it would almost seem like you were speaking a foreign language, and it doesn't seem so foreign to us today so there is some kind of progress here.

I think the thing that I recognized, the most astounding thing that I felt was beginning to understand why our veterans were faced with this kind of lack of sympathy and lack of receptivity to their illnesses. We had no doctors in VA except a few occupational therapy-types that were thinking the way that you are thinking. They are competent doctors, but they weren't involved in occupational hazards.

So I guess what I would ask, it seems to me what you are suggesting is we are making some progress. You are here and there are others who have testified before you, but that the paradigm that we are using is still wrong.

Dr. URNOVITZ. That's correct.

Mr. SHAYS. And all three of you have been able to make your case, some who sit on the board.

Where do you all disagree with each other?

Dr. MILLER. Can I say maybe what the context here is?

Mr. SHAYS. Yes.

Dr. MILLER. There are some very specific mechanisms that can relate to the continuing symptoms that the veterans are having, and it might be on the basis of genetic changes or neurosensitization. There are many specific mechanisms including inflammation that people have proposed to explain some of these ongoing health problems.

With respect to the intolerances that people have now, we don't understand the underlying mechanism any more than we did back when people had the germ theory of disease. They didn't know how cholera, for example, operated; but they had a particular concept which could be tested.

I think it is important to keep in mind if there were this initial event, exposure, and people develop intolerances, we can intervene without knowing the specific mechanisms. In fact, when people recognized if you washed your hands or wore gloves going from one child-bearing to the next, one birth to the next, you wouldn't transmit child bed fever; but people didn't know about the germs that caused child bed fever. They had this crude theory of disease, but it allowed them to operate in a way that prevented the transmission of disease.

If we have in mind there is a toxic exposure for at least some people, and they lose tolerance for other common exposures, what we can do is minimize the exposures that they are having currently and start to prevent any unnecessary exposures in future wars, and maybe identify early some of the susceptible people that I think both Dr. Bell and Dr. Urnovitz alluded to.

Mr. SHAYS. One of the things that I concluded over time was that there was no incentive to get into the field that you are getting into

for a variety of reasons. Economically there didn't seem to be an incentive. How did each of you get into this area?

Dr. URNOVITZ. I actually tried to tell you 4 years ago, and I ran out of time then.

I got involved because my mom died 30 years ago of cancer, and I have been trying to figure out why. There is no single causative agent.

We were born in Detroit, which I love dearly. However, it was a toxic exposure. We were exposed to many chemicals getting rid of Japanese beetles. We were given 26 monkey viruses in vaccines. We were living in one of the greatest economic growth centers of the world in manufacturing. There is no single cause.

I have been trying to figure out how cancer works. I have been trying to do that for 3 decades and the germ theory I reject for chronic illnesses. It is great for the acute bugs; we can cure them. We can cure them with doxycycline, no problem. We are talking about chronic diseases. These take decades to develop.

You must reject the germ theory. Just like we had to reject the single atomic theory and go to quantum mechanics to understand relativity, you have to start a new paradigm.

You can't start the Manhattan Project until some Einstein writes some Roosevelt a letter saying we just split the atom. That letter has never been written; that is why we don't have the Manhattan project for these chronic diseases. We are trying to write that letter to you.

You asked originally what is the difference between our testimonies, nothing. There is nothing mutually exclusive here. What Dr. Miller said, I agree completely. She describes the different phases of these diseases. They are multiphasic as well as multifactorial. Throw out the book. Start over again and start with the fact that we are living in a toxic environment. We are trying to keep up with a toxic environment. We love the modern marvels of science. I love them, faster computers. But the thing is, we are not going to give them up. We love our modern marvels, and we are not going to give them up. Medicine has to keep up. We have to figure out how we can keep up with the changes in the toxic environment that we live in, and we are going to constantly add pollutants to our environment, and we are going to constantly have our genes rearranged.

The treatments that we come up with for Gulf War Syndrome will be used throughout all aspects of medicine. I am sending this message out to the private sector, because that is where we get money from. We can build products, both diagnostic and pharmaceuticals, to help us keep up with modern medicine if we all recognize as a medical and scientific community that our genes do rearrange in response to toxic exposures.

That is what Gulf War Syndrome taught us. We gave 28-year-olds the biggest whopping dose of toxic exposures I can think any human ever got, and that is Gulf War Syndrome.

Mr. SHAYS. How did you get in this field?

Dr. MILLER. First, to amplify on one statement and that is about the different theories of disease. The importance of rejecting what we have in the past and what we are seeing, these characteristics

in these individuals, does not fit the germ theory. It does not fit the immune theory of disease, our classic theories of disease.

So just as when the germ theory came along, we need to have a new model that does fit observations by physicians and others, what is going on with the patients. I want to say that is absolutely right, you have to reject what you have right now. The problem is with epidemiology. Classically, it developed out of looking at infectious diseases and looking at patterns of illness, and it doesn't work as well in this situation.

The paradigm here is in-depth talking with patients, 4 to 6 hours with a patient, trying to figure out what they are saying and they are all reporting these intolerances. There is a thread of a hallmark symptom and you can make sense if you spend the time. But veterans are shuttled from specialty clinic to specialty clinic, and no one has time to put together what is really going on with them, and it takes time to get these kinds of histories, and the VA has not had the physicians to do that.

If I could just say how, I worked before I went to medical school as what is called an industrial hygienist looking at people in work places who got ill and noticed that there was a subset that continued to be sick, whether it was in a sick building or after pesticide exposure and out of interest in that went to medical school and trained in allergy and immunology and found that I had gone into the wrong specialty. I don't know what specialty this is any more but—and this led me into research, writing the New Jersey report on multiple chemical sensitivity and some other—many papers on the subject, and finally the Gulf war veterans came along years after we were seeing this in civilians and the pattern looks the same. It looks identical.

Mr. SHAYS. With Dr. Kaiser and the VA, basically we were being told that low exposure did not lead to injury or death and yet in my own environment as a State legislator, I was passing laws right and left to prevent there being exposure to low-level chemicals because we ultimately felt like it would lead to injury or death. I spent so many years of my life trying to protect workers from a bad environment.

Dr. MILLER. There is a reason. When you talk about low-level exposures in terms of a toxicologist's view of it and what would affect people that were healthy to begin with, that is one thing. When you attack people who had been exposed and lost normal tolerance, now they can't tolerate—one alcoholic drink, they can't tolerate. They can't tolerate medications they took for years. Remember the guys who took decongestants many times before the Gulf war, and now one tablet makes them feel strung out for many days. There is a fundamental loss of tolerance, and now you have thrown into something that is orders of magniture less tolerant than what you started with. So when EPA talks about low levels of exposure, they are talking in the average general population, and these people are on a different scale.

Dr. BELL. Before I address the question of how I got into it, I would like to amplify on some of the other comments. I believe that part of the issue is that science in general has taken a very productive direction toward reductionism, which means finding as simple an answer as one can control all of the variables for. This is an

issue where we have been forced by the nature of the phenomenon to deal with multiple variables in interaction. There are statistical techniques for doing this and methodological approaches in science for doing it, but it is not the prevailing way science has been done and certainly not medical research. It is not easy to do, and it is very expensive frequently because when there are multiple variables, you require even more subjects than you would for other kinds of studies, and you have less absolute certainty that what you have found is the answer because frequently it is in fact a multifactorial answer.

This means that in terms of us all saying these various points that factors such as nutrition, factors such as genetics and factors such as environment all interplay and you will hear people in science adamantly proclaiming that any one factor is a major issue having controlled for all of these other variables, and in fact that is valuable information. But the whole picture in terms of what happened to the individual requires an understanding that they can interplay and interact, and that is not something that is typically looked at in a lot of research.

In terms of my own interest, as Dr. Miller was alluding to, the kind of things I did as a graduate student in neuroscience, I was working with a group of patients who have narcolepsy, a sleep disorder where they fall asleep against their will at undesirable times; and I listened to what they said. And what they told me is when they ate certain foods, they fell asleep. And that led me to meet with doctors who were working in food and chemical sensitivity, and I became fascinated by its potential usefulness as an area to study within clinical neuroscience; and I pursued it from that perspective for many years.

Mr. SHAYS. Thank you. Thank you for your patience. You have the floor.

Mr. SANDERS. Thank you, Mr. Chairman. I just want to thank and congratulate all three of you for the extraordinarily important work you are doing. Some day I think you will get the recognition that you deserve. Maybe not tomorrow, but it will come. What you are doing is extremely important.

It seems to me—I got into this, Mr. Chairman, because a constituent of mine in Montpelier, VT, was made ill by exposure to a coffin, and her children were made ill. I didn't believe her, and we investigated it and so forth and so on, and I think the coffin industry has perhaps changed how they manufacture the product.

I have met with hundreds of Gulf war veterans in the State of Vermont who, as I said before, cannot tolerate being around perfume. Mechanics, just as you described, Dr. Miller, used to work as mechanics, they no longer can do their job. They suffer short-term memory loss, nausea, et cetera.

Let me—and I happen to accept the paradigm that you are throwing out. We are living in an increasingly toxic environment, and it is hard not to believe that all of us have suffered as a result of that and those folks over in the Gulf suffered even more, and I want to underline the statement that all of you made that the research taking place on Gulf war illness will have an enormous impact on the general society as well.

I remember in my office there was a woman who actually was a nurse. She was visiting a patient. She went into the bathroom and the woman had used heavy duty detergents, and she was ill as a result. I have heard this a dozen different times, and I cannot believe but that these anecdotes are true.

Mr. Chairman, you will remember the major from Connecticut, the pilot, who became ill after jogging at a military base after they had sprayed with some pesticide.

Dr. URNOVITZ. Dr. Donnelly came down with Lou Gehrig's disease.

Mr. SANDERS. His feeling is that he was hit right after they had sprayed. That is a coincidence, perhaps; but I have heard too many of these stories.

Let me ask some specific questions, if I might. Before I do, let me tell you a story. The story was that I took one researcher, one gentleman whose views are not different from yours because I felt so strongly about this about 5 or 6 years ago, I took him up to Jesse Brown, who was then head of the VA. He made his case and Brown was interested. I urged him to submit a grant for funding, and he said they will never fund me. I said please do it. He did it. And not only was he rejected, he got a letter back which he sent to me which basically said are you crazy. You are a quack and a fraud. You don't have any peer reviews, and they insulted him. Not a rejection, but an insult.

It seems to me that one of the problems is that people are living in different paradigms. You can have a scientist coming here and people saying you are crazy; we don't accept what you are doing. In fact, many of the definitions that you are using are not accepted by large numbers of physicians and scientists in this country. We are living in two different worlds, and I think honest people are rejecting you because they think you are crazy.

I think our challenge is how do we introduce in the Congress an acceptance or at least a willingness to fund and take seriously this research. Let me start off with a question to all three of you—and I know the answer will be different—but basically what kind of response have you gotten from the government in terms of requests for funding the research that you all are doing?

Dr. URNOVITZ. Congressman Sanders, I only play in the sandbox with people that like me. I don't bother going to places that don't understand the theory. We have gone to the private sector for funding. I can't tell you the great honor I have by having Dr. Montagnier submit a written testimony, knowing the ramifications. This is probably one of the greater scientists in the world today.

I think that we should recognize an important factor of how discovery is made in the world. I have thought about this for 3 decades.

Discovery is made in small groups of people, 5, 10 people just passionate, living, breathing new ideas. I come from the San Francisco Bay area where the standard issue is a Diet Coke, cheeseburger and working at your computer for 3 days in a row; and those are the kinds of people who make discoveries.

I just don't know what the wisdom is in asking agencies that collect data, regulate data and disseminate information, to do discovery and that is Health and Human Services and they do the first

part very well. I don't know if it is really proper for us to do discovery and legislate to make discoveries. Maybe if we thought about it from the terms of who is successful and gets up in Sweden and gets these little Nobel Prizes, it is people in small discovery groups and academia, private research, occasionally a federally funded agency; but it is the small groups.

And I ask Congress to think about maybe the resource management is where we need to think about this. How can you create an environment for discovery that we then take that information and the CDC has to verify it and the FDA has to regulate and the NIH has to vet it.

I think discovery should be made in small groups and we should find some way to do that and maybe we should take it out of the executive branch and put it in Congress so we separate that power and balance it a little bit more. That's the short answer.

Mr. SANDERS. Have you particularly gone to the government for funding?

Dr. URNOVITZ. I have not because it just doesn't make sense to me to think outside the box and then ask the box to fund it. So I've gone to the private sector it's just an observation of a few years.

Mr. SANDERS. Basically you've given up, and you don't think——

Dr. URNOVITZ. I never started. I go where the money goes. The money is in biotechnology. The money is in venture capitals. And venture capitalists have a long view that they'll wait 10 years for a product. I've successfully taken three products to the FDA. A urine test for AIDS which is exciting. It's an epidemiologic tool. It's unfortunate the People's Republic of China will adopt it first as their mainstream AIDS test because—well, that's another hearing. Let's just talk about the fact that the—we were proud we have our co-author Jim Fuite, whom the committee knows very well has handed out our papers to everybody. We know that they're there. We're just waiting every day with bated breath to hear how we can work with the VA and DOD to introduce these tests.

You know, what's going to happen—may I predict on the record under oath what's going to happen with your mycoplasma study? I don't need data to tell me how things are going to happen. You're going to find out it's worse than you thought because some veterans are going to do very well on this doxycycline program but it may be the fact is we know that the doxycycline also inhibits RNA formation.

What's going to happen is a year from now you're going to sit here going well why are only 25 percent of the people responding? Are they the only ones who have mycoplasma. I hope I put a little seed in your brain under oath that there are other ways that doxycycline works.

So I ask that you look at the bigger picture here and that we take control of it. The problem is I have no way of getting that dialog except every 4 years sitting here and telling you my thoughts on things of how to tell the Federal Government about other research programs that are out there, a vast array of literature we're not quoting at all. So there are two different worlds. There is the greatest physicians in the world and they are probably in this country and they're doing medicine and health care better than

anywhere else in the world, but I never expected them to read the literature and do the discovery work. That's what I do. How do I get my work into their hands. There's only one way I know to do that and that's put it in the peer review journals.

Mr. SANDERS. Thank you.

Dr. MILLER. The kind of research we talked about with using an environmental medical unit doesn't have the same commercial potential. So going to a private donor for this is virtually impossible. So we've turned to various Federal agencies. I've testified to Congress not 4 years ago but probably 7 or 8 years ago going forward. I think I testified to different groups including the Presidential committee, IOM, CDC, all kinds of groups 10 times in the last 8 years.

And it's been on the same thing, just looking what are the observations in these veterans, look at the common thread, the new onset of intolerances is an important clue just as fever is an important clue to infectious diseases, let's pursue the clue. But it doesn't go any further than that. In fact, Congress not only has heard about this but they actually authorized funding for an environmental medical unit in 1993.

And then it went through a series of a progression. And in the long run the funds were diverted elsewhere. And I know Congressman Sanders has done some things even more recently, and he can describe those better than I in terms of trying to get agencies perhaps to work together to find funding for this kind of treatment. And it's actually dual-research, treatment, and diagnosis—three things in one, in trying to sort out what is getting on with the Gulf war veterans.

There was a time when some of the Federal agencies like NIEHS had an interest in supporting research but there was no facility and they couldn't fund a facility. And so there was this effort, initial effort to get the funding just for the facility. But as you know, there isn't an environmental medical unit yet. We've submitted, I think, three or four times through VA and DOD, and the kinds of reviews that you get back are confused.

People don't understand it. They are operating out of old paradigms, and they will say this is still controversial. That's the purpose of the study. Yes, it's controversial. We have to study to settle the controversy because it's one that is costing not only veterans but civilians huge sums of money. And they'll say it's too costly. And of course when I found out how much money has been spent on research in reviewing literature, I'm very sad to hear that this is not worthy of funding.

I think it's going to take this kind of Manhattan-style project to make this area happen, and I'm also worried about playing in the sandbox with people that don't like me, that it's very difficult having worked closely with a number of Federal agencies on this issue trying to get them to use questionnaires and so on. It has not happened yet after this long a period of time. And I don't see the willingness yet to have it transpire, and I don't see a home for this right now. I wish I did.

Dr. BELL. I have tried for many years to be funded through Federal agencies. I started with NIH and so on. When the Office of Alternative Medicine was originally set up, I was very enthusiastic

and thought that this would be a particular opportunity; and when I spoke with them at that time early in their existence, they basically said this isn't controversial enough. And they discouraged me from applying because I wasn't studying some of the even more controversial areas within the area of a complementary and alternative medicine. I don't know where they would stand at this point. I have not made any further attempts to apply through that agency.

Generally the reviews that come back are "I don't like this area. I don't like multiple chemical sensitivity." Frequently I do not get thoughtful scientific critiques of the actual work. That's what happens when I get rejected.

I have to say that after several attempts of being funded by VA, we were—we did attempt to be funded for an environmental hazard center that had a focus on chemical sensitivity; and we were not funded. It was the time when the VA was very much emphasizing or at least the overall research effort was emphasizing epidemiology, and that was not our strength. Our strength was in the chemical sensitivity question.

I applied twice for the funding that I currently have through a merit review at the VA and got very favorable reviews both times and eventually did get the funding. I have applied to the DOD because I feel that my EEG work while not specific and not as elegant as some of the work with functional MRI and so on, would allow us to find some biomarker that's very inexpensive and noninvasive to identify people who might be at risk for chemical sensitivity. This might be a way of identifying personnel before they are put in harm's way. That was favorably reviewed but not funded.

And one of the issues often is any of this is my reading of the way the reviews go at this point in time. This is an interesting area. They're beginning to take us a little more seriously scientifically, but it's not a priority topic to them because there are so many other areas that they feel are stronger scientifically. And so as the way the field is going, they don't feel that they want to invest the limited resources that are available in that particular direction.

Mr. SANDERS. My last question, Mr. Chairman. As you heard from previous panels, I've been concerned that we have not developed treatment protocols, and that's what the veterans want. If you had the money and the resources, what treatments—could you develop treatments that actually might improve life for veterans who are ill right now? Dr. Miller, why don't you start on that.

Dr. MILLER. The approach would be straightforward. It would be using a controlled environment to take patients, have them go into this controlled hospital environment, spend the first week getting to baseline, a clean baseline. This is not—I want to draw a bright line here between an environmental medical unit and exposure chamber. This is not a chamber like they have in North Carolina or at Robert Wood Johnson. Those are strictly for maybe a few hours exposing people to a substance.

I'm talking about an inpatient hospital facility sort of a treatment progression. Patients will stay in there for about 3 weeks, the

first week getting to clean baseline, the next couple of weeks testing them to single foods and common low level chemical exposures.

Mr. SHAYS. Would you define clean baseline?

Dr. MILLER. Clean baseline means you've gotten them away from all the usual low level fragrances, disinfectants, other things that might be present in the air.

Mr. SHAYS. It takes a week to go through their system?

Dr. MILLER. That's right. It takes about a week. This is by reports by many, many physicians now that they'll get to a clean baseline after about a week. So that any exposure related symptoms from volatile organic chemicals for example would decrease at that point to the point where you get them so they're feeling better, and this is what patients report and then you can challenge.

Mr. SHAYS. Your second week is?

Dr. MILLER. The second and third weeks would be reintroducing foods and then very judicious low-level exposures.

Mr. SANDERS. What we would have learned about that is to say to that patient you better stay away from A, B, and C.

Dr. MILLER. That's right. They would have identified their specific triggers and the information we have now is the people that avoid exposures that set off their symptoms gradually regain tolerance, and then they can——

Mr. SANDERS. Do you have the concern that there may be tens of thousands of veterans who every day are sticking their heads into things that are simply making their illness recur?

Dr. MILLER. This is what the veterans tell me. Many of them have gone off—tried to get away from these things, but it's been difficult. I had a call only the week before I came to testify from a mother whose son was at the San Antonio VA and he's extremely ill, multiple, multiple diagnoses; and she was begging to get into the environmental medical unit. I had to tell her there is no environmental medical unit right now. There just isn't one. So veterans and their families have heard about this idea. They recognize these intolerances in themselves; and yet they have no recourse, nowhere to go.

Mr. SANDERS. You're telling us that you have a treatment that you think certainly deserves to be reviewed and you think could be successful?

Dr. MILLER. That's correct. It would give you insight not only to the underlying mechanisms but it would provide treatment and diagnosis.

Mr. SANDERS. To the best of our knowledge that is not being done by the government right now?

Dr. MILLER. There is no place in the government or any research center doing this work.

Mr. SANDERS. Dr. Urnovitz and Dr. Bell.

Dr. URNOVITZ. This is what I'm doing from the funding source we're raising right now. It's a parallel track. What we're going to do—you've alluded to it. The AIDS deaths have dropped. We're all very excited about it. It's been a very, very hard road to go and we're excited about it but let's look at how that worked. It worked because of the fact that we had drugs that could knock out the virus in tissue culture, what's called AZT. Didn't work. The AIDS deaths weren't dropping.

What was the single event that got the AIDS deaths to drop? They had a marker to shoot for. Remember I said outside the box, this is out of the box thinking that some very clever physicians did about 10 years ago by having a marker called the viral load test which by the way measures RNA in the blood except this RNA is the virus HIV–1.

All of a sudden they realized that AZT alone in mono therapy isn't bringing the virus load down. That's when they said maybe if we combine a bunch of therapies together, throw in some protease inhibitors, guess what happened. The viral load went undetectable. Guess what one of the by-products of that was. The AIDS deaths dropped.

In other words, you've got to find a viable marker. The squalene antibody is solid work. Professor Bob Garry, I know him personally. He's a world class scientist. We talked privately about this. This is an antibody that may also be an autoimmune antibody. It's a marker. It's not going to be the cause of Gulf War Syndrome. It is a marker and should be put into the panel of things that we test for to see if it includes or not includes certain patterns.

You need a biomarker first. Before you go out and you start treating Gulf war vets, you're going to need a biomarker. I can't tell you at this point whether this RNA in the blood is the biomarker. We're going to proceed in that way.

I will tell you we have submitted a paper in multiple myeloma, a cancer, based on what we found in Gulf War Syndrome. Out of 30, 20 who have active disease have the marker, and 1 out of 30 who are in remission do not have the marker. This doctor then started to prescribe a drug called Biaxin, a different type of antibiotic and those people that responded lost the marker in their blood. Those who did not——

Mr. SANDERS. What you're saying when you have a marker you know what you're shooting for.

Dr. URNOVITZ. When you have a marker, you know what to shoot for. Right now we're flying a plane with no windows on it. We have no idea where we're going and all roads get us there to reiterate what Congressman Shays said. You have a marker you know now how to tailor the treatment, and it's not going to be the same. My recommendation is—well, let me tell you what I'm doing and then if you wish to work with us, we'd be happy to do so.

We're going to use combination therapies to knock the RNA expression out. We're going to use things that are antibiotics which, by the way, evolved or co-evolved with RNA. We're going to use those. We're going to use things that induce things called interferons in the cell. We're going to add interferons, and we're going to physically remove the RNA from the body. We're looking at combination therapies right now to remove this marker.

I personally know that things like doxycycline in some cases was a miracle. Some people are alive and working and paying taxes today because of that. Lots of people are not. So what does that mean? It means that this individual responded to the therapy. That's all it means.

Why? That's where we need to get at the root of this. It will require what we learned in the AIDS epidemic which by the way is exciting but it's not done. No one is cured. The reason why is we've

got to get rid of the other RNA in the blood of people with AIDS. That's what we found and will be publishing this summer. We need to take an approach that gets rid of all of these markers to get people back on the health track so they can start living their lives all over again. We need to find those markers.

Mr. SANDERS. Are you optimistic that some day we will?

Dr. URNOVITZ. It will happen.

Mr. SANDERS. Dr. Miller.

Dr. BELL. I would agree with what the other two speakers have said in general. However, one can also take the point of view as one would in complementary and alternative medicine that indeed the patient's vulnerability is what has to be focused on.

One can take a very innovative approach, such as Dr. Urnovitz has done, but we can also be concerned that when we intervene in any particular mechanism, that we may imbalance other mechanisms. There are long-standing systems of alternative medicine that are available starting with the work that's been done more recently in environmental medicine.

Again, the controversial work that's available, it provides a foundation for giving the patient a way to begin rebuilding their health. In reality, in clinical practice when you work with people over many years, you find they need more than avoidance. They have to start with avoidance. The patients will identify that as the central thing that helps them.

However, as I said in terms of the multiple vulnerabilities, frequently they go after other things in alternative medicine to the extent they can tolerate them. And that's one of the advantages of the avoidance technique, that gradually over time there's a certain amount of ability to regain the ability to tolerate things because these are individuals where even if they're found, for example, to have a nutritional deficiency, they can't tolerate the vitamins no matter how cleanly prepared they are and how few contaminants and other problems or source problems they might have.

But eventually it's a sequential treatment process and so what one starts with is the foundation and then one builds from there. When they get the nutrition, when they get some of these other kinds of interventions, then they begin to again handle more and more things. At that point I've also—in the early stages of treatment, I've also referred patients successfully for treatment such as acupuncture which can be used without the use of any chemicals and so on and which is frequently capable of being titrated to the sensitivity of the patient.

These kinds of approaches are in themselves controversial. I haven't heard of them necessarily being studied in Gulf war, but I wouldn't be surprised if we had many roads to the same answers and there would be ways of strengthening the individual.

Dr. MILLER. I just want to point to Allison Johnson's book that was handed out earlier that she surveyed and other people have surveyed many chemically intolerant patients and as Dr. Bell mentioned, sort of the fundamental, the basis of their improvement starts with avoiding things that set off symptoms—chemicals, foods, medications, and so on and hopefully they get to a point where they can regain some tolerance and try other things.

I also want to say in terms of biomarkers, biomarkers are very important. We don't have them yet. We don't know how many years right now they are away. I hope it's next month, frankly, that we have biomarkers. But when we don't have biomarkers, we still have the ability to put people in a controlled environmental, get them to a clean baseline, challenge them in a blind way to see if symptoms recur.

It's just like again with the germ theory, at first we could do prevention and had not identified the first germ, the first microorganism. Cholera was being treated in London by shutting off certain water sources that were contaminated, 30 years before Koch discovered the bacterium that causes cholera.

Mr. SANDERS. I would just conclude, Mr. Chairman. I have to run upstairs. Once again, I feel refreshed having listened to this testimony. And I think we should be embarrassed, frankly, that after the expenditure of over $120 million, that we are not doing more to support this entire line of research which I think is breathtaking and just enormously important for not only Gulf war veterans but for the American people in general. And I just would hope that we're going to work together to support folks like this and just thank you again very much for your testimony.

Mr. SHAYS. Thank you. I concur with his remarks. I think it's been a fascinating three panels and with the three of you. And thank you very much. I have a feeling though, it won't be another 4 years before we meet again. Thank you. This hearing is adjourned.

[Whereupon, at 2:40 p.m., the subcommittee was adjourned.]