POSSIBLE HEALTH EFFECTS OF PYRIDOSTIGMINE BROMIDE ON PERSIAN GULF WAR VETERANS

JOINT HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

AND

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON VETERANS' AFFAIRS

HOUSE OF REPRESENTATIVES

ONE HUNDRED SIXTH CONGRESS

FIRST SESSION

NOVEMBER 16, 1999

Printed for the use of the Committee on Veterans' Affairs

Serial No. 106–28

U.S. GOVERNMENT PRINTING OFFICE

62–452CC WASHINGTON : 2000

For sale by the U.S. Government Printing Office
Superintendent of Documents, Congressional Sales Office, Washington, DC 20402

ISBN 0-16-060723-X

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POSSIBLE HEALTH EFFECTS OF PYRIDOSTIGMINE BROMIDE ON PERSIAN GULF WAR VETERANS

TUESDAY, NOVEMBER 16, 1999

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
JOINT W/
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
COMMITTEE ON VETERANS' AFFAIRS,
Washington, DC.

The subcommittee met, pursuant to call, at 2:30 p.m., in room 334, Cannon House Office Building, Hon. Cliff Stearns (chairman of the subcommittee) presiding.

Present: Representatives Stearns, Everett, Chenoweth-Hage, Buyer, Gutierrez, Hill, Shows, and Evans (ex officio).

Also present: Representatives Peterson and Snyder.

OPENING STATEMENT OF HON. CLIFF STEARNS, CHAIRMAN, SUBCOMMITTEE ON HEALTH

Mr. STEARNS. The House Subcommittees on Health and Oversight and Investigations will come to order. Good afternoon.

As many of you know, the House today will take up a conference report on H.R. 2116, as amended, the Veterans Millennium Health and Benefits Act. Our conference with the Senate last week was a success and this legislation will, in my judgment, improve both the VA health care system and veterans' access to needed care. In demonstration of the fact that veterans' issues are a full-time concern for this committee, our Subcommittees on Health and Oversight and Investigations are also today taking testimony on the most recent scientific finding regarding Persian Gulf illnesses.

Just last year, Congress directed the VA to enter into a contract under which the National Academy of Sciences would conduct a literature review and analysis of all the risk factors which may be associated with health problems experienced by Persian Gulf War veterans. That analysis would be the basis for establishing presumptions of service connected and for recommendations for additional scientific studies. That comprehensive National Academy study is now under way and the first phase is expected to be completed next summer.

As many are aware, the National Academy study would not be the first such scientific review of medical literature relating to the health consequences of Persian Gulf service. Both the Institute of Medicine and the Presidential Advisory Committee on Gulf War

Veterans' Illnesses, for example, published findings on this subject in 1996. Given the focus on the ongoing National Academy study, some people were surprised by published accounts regarding a recent RAND report prepared for the Department of Defense. Some of those accounts indicated that the cause for Gulf War illness may have been found.

As part of our continuing concern about this illness, this committee wants to know just what science can tell us about the causes or likely causes of illnesses affecting so many veterans of the Gulf War. I am somewhat disappointed to learn that the bottom line of this RAND study, 2 years in the works, is that one of the many suspects, a drug used to protect troops against particular nerve agents "cannot be ruled out as a possible contributor to the development of unexplained or undiagnosed illnesses in some PGW veterans."

That conclusion does not seem to take us very far. Matt Puglisi of the American Legion makes that point very effectively in his testimony. He notes that the RAND report's conclusion that more research is needed to answer questions concerning PB and veterans illnesses is quote, maddening to sick Gulf War veterans, end quote. As he points out, quote, above all, these veterans want to become healthy. Short of that, they want answers, end quote.

Clearly our committee shares the same frustrations. In searching for answers, we are fortunate to have with us this afternoon the RAND report's author as well as scientists who have participated in other major studies of risk factors which may be associated with Gulf War illnesses. In addition, we are pleased to have a panel of top government officials responsible for investigation, research, and treatment of Gulf War illnesses as well as representatives from veterans' organizations which have worked so long on these issues.

I appreciate all of you being here today, in particular Dr. Golomb, the author of the RAND report, for traveling across the country to testify. While this is likely to be our last hearing this session, it is an important one and I look forward to all the testimony.

Before calling our first panel of witnesses, I would like to invite the ranking member, Mr. Gutierrez, to make an opening statement and then turn to the chairman, Terry Everett, of the Oversight and Investigation Subcommittee.

OPENING STATEMENT OF HON. LUIS V. GUTIERREZ

Mr. GUTIERREZ. I thank you, Mr. Chairman. The purpose of our hearing today is to consider the possible adverse physical and mental health effects that PB may have had on our veterans who served in the Persian Gulf War. I am eager to hear from the witnesses. My colleagues and I appreciate you taking the time to be with us here today to share with us your findings and perspectives.

PB is a drug used to treat myasthenia gravis, a neuromuscular disorder. In December of 1990, the FDA approved the use of PB as an investigational new drug for use as a nerve agent pretreatment to protect U.S. troops against soman, a chemical warfare agent that the Department of Defense believed the Iraqis may have possessed. PB must be taken before exposure to soman and soldiers who come in contact with this chemical agent must receive postexposure

treatments as well. As many as a quarter of a million U.S. soldiers are believed to have taken PB. That is 250,000 men and women.

Mr. Chairman, thousands of veterans who served in the Persian Gulf War continue to suffer from adverse health symptoms and there is no clear diagnosis for these American men and women. Possible causes of some of the illnesses Gulf War veterans have reported include chemical and biological warfare agents, pesticides, oil well fires, stress, and immunizations.

As Members of Congress, it is our responsibility to continue to hold hearings on this issue and provide the funding necessary for further research on the causes and treatments of all the symptoms we now refer to as Gulf War syndrome. Clearly our efforts to find answers will lead to more questions, but we must continue to be vigilant. Such discoveries are especially important because we must ensure that our efforts to immunize our soldiers from chemical and biological weapons are not making them sick.

Mr. Chairman, as I remember being on the committee and bringing forward people from the Department of Defense and from our fine venerable institutions, I remember them sitting there and saying, well, maybe it is a malaise of our soldiers returning from the Gulf War. Maybe they are making it up. Maybe who knows what happened to them over there but, you know, we really don't think there is any—and for years we fought about this and now every time we investigate the Gulf War and the illnesses, we come up with more and more troubling discoveries.

So I am very happy and delighted that the report has finally been concluded. Obviously the report is not conclusive, but at the same time I think it gives us tremendous information and given what the committee has had to do thus far, I would hope that in the future we would have a little bit more cooperation from the Department of Defense and the Department of Veterans Affairs so that we can deal with these men and women, especially given this dramatic information, as inconclusive as some may say it is today, about having given something that is experimental in nature to 250 men and women without consulting with them, without their consent, and without any posttreatment.

Thank you, Mr. Chairman.

Mr. STEARNS. I thank my colleague. And now the distinguished chairman of the Oversight and Investigation Committee, Mr. Everett.

OPENING STATEMENT OF HON. TERRY EVERETT, CHAIRMAN, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

Mr. EVERETT. Good afternoon. I would like to thank Chairman Stearns for calling this important hearing and asking me to cochair it. I associate myself with Chairman Stearns' opening remarks and those of the ranking member. The issues surrounding the illness of our Persian Gulf War veterans have been controversial and a seeming inability of the government to find out what is causing the illness has been frustrating to all of us. It is certainly understandable that many of our veterans long ago lost confidence in the government's handling of the Gulf War health issues. While much Federally funded research is finally under way, here we are 8 years later with no real answers for our veterans. They deserve

much better than that. The only way to get to the bottom of the questions surrounding PB and the other Persian Gulf health issues is to make sure the right research into the possible causes of veterans illnesses is properly funded, conducted, and coordinated. My hope is that today's hearing will shed some light on whether the research under way maximizes the prospect for helping our Persian Gulf War veterans.

The prepared statements of our witnesses leave no doubt that there are real scientific issues associated with PB. We should not jump to conclusions, nor should we shirk the tasks of seeking the answers. In the meantime, we must ensure Gulf War veterans are receiving the health care and compensation they need without the bureaucratic runaround that, even though they are obviously sick and disabled, the VA can't help them because they don't have a diagnosis.

We are hearing from veterans that some in the VA still haven't gotten the message. We tell them today: Take care of our Persian Gulf War veterans. Thank you, Mr. Chairman.

Mr. STEARNS. I thank my colleague. Now the gentleman from Illinois, the ranking member of the full committee, Mr. Evans.

OPENING STATEMENT OF HON. LANE EVANS, RANKING DEMOCRATIC MEMBER, FULL COMMITTEE ON VETERANS' AFFAIRS

Mr. EVANS. Thank you, Mr. Chairman. This is an important hearing today. It marks the 19th hearing that this committee has held over the past several years concerning Persian Gulf veterans issues. I think we have made clear we leave no stone unturned into looking into the illnesses of these veterans and the delivery of effective health care and compensation for Gulf War veterans.

Our hearing today is about PB. Some DOD studies have indicated that about one-half of the troops who took PB experienced some acute side effects from the drug. More than half of the VA registrants reported taking the drug. PB blocks transmission of messages between nerves and muscles. The RAND Corporation recently reported that PB cannot be ruled out as a potential cause of Gulf veterans illnesses. This is not a new conclusion but deserves greater attention.

There are many troubling questions about giving this potent medication to troops without tailoring it to the individual's medical conditions, size, or medical history. This is a drug that can have extremely dangerous side effects and might even result in death. These are important issues, Mr. Chairman, that I know will be examined at this hearing. I look forward to working with you and the ranking member in the future to pursue this issue.

[The statement of Congressman Evans follows:]

PREPARED STATEMENT OF HON. LANE EVANS

I want to thank the Chairmen of the Health Subcommittee and the Oversight and Investigations Subcommittee for convening this important hearing today. This is the 19th hearing this Committee has held on Persian Gulf War related issues over the last 7 years. I know there will be many more to ensure we leave no stone unturned in examining the potential causes of Persian Gulf Illnesses and in monitoring the federal government's involvement in addressing veterans' needs for health care and compensation.

Our hearing today is about pyridostigmine bromide or PB, one of the many suspected causes of Persian Gulf War Illnesses. PB is a drug that many veterans who served in the Gulf are believed to have taken. Because as many as 250,000 troops took it themselves on command from their unit officers, medical records do not clarify the extent to which they were exposed; neither the amount, nor the frequency of dosages taken over a given period is known for most veterans. As with many potentially risky health exposures in the Gulf, this makes it difficult, if not impossible, to track unit-dose relationships and other key indicators that would help scientists identify its effects on troops.

Some DOD studies have indicated that about half of the troops who took PB did experience some acute side effects from the drug. Animal studies indicate that some conditions and agents, such as stress, insecticides, and insect repellents to which many troops in the Gulf were exposed may enhance the effect of PB. Whether the adverse effects of these drugs resulted in more lasting or chronic conditions is a reasonable question.

We know PB has some serious side effects and we know that people with certain common conditions are not advised to take the medication. Just what does the drug do? PB is a drug that blocks transmission of messages between nerves and muscles. It is not, and does not purport to be a prophylactic in and of itself against the nerve gas, soman. Rather, it is a drug that the Army has deemed to offer some enhancement of effect for the antidote provided for chemical warfare exposure.

The Food and Drug Administration has not approved the drug for pretreatment against nerve-gas exposure. It has been approved for other purposes, most notably treatment of a neuromuscular transmission disorder called myasthenia gravis. It is important that PB be tailored to individual use. It should not be taken if you take certain medications or if you have allergies to chemicals that compose PB. The drug is not to be used or should be used with extreme caution in people with fairly common disorders such as urinary tract infections, asthma or irregular heartbeat.

Side effects (usually associated with excessive dosage of PB) can include nausea, abdominal cramps, increased salivation, diarrhea and contraction of the pupil; in addition, excessive dosage can cause severe muscle weakness, twitching or cramping. Skin rash is another less frequent adverse reaction.

Importantly, the Rand Corporation recently issued a report asserting that PB cannot be ruled out as a potential cause of the illnesses that veterans of the Persian Gulf have. This is not really "new" news; early on in these debates, the Defense Science Board, while minimalizing potential "idiosyncratic" side effects, assumed the benefits of the drug outweighed its risks. In 1997, the GAO described the synergy between PB and other agents to which Persian Gulf veterans were commonly exposed that might explain chronic illness among veterans.

So we seem to have some consensus that PB is an exposure that demands further attention. What I want to know is what can we do to determine, with specificity, what the long-term effects of PB exposure are in populations *without* myasthenia gravis? Can we assess the degree to which this exposure might have damaged individuals' ability to regulate their body chemistry? If so, can we undo the damage? Did likely exposure affect certain subgroups within the population more than others? I am not sure we have any of this information today, but we need to get some definitive answers to these questions and move forward in helping Gulf War veterans.

Because I am also a member of the Committee on Armed Services, I also want to know why more rigorous tests were not done to evaluate the possible risks and potential benefits of this drug in a combat situation. I don't think it's good enough to assume that because this drug helps sick people without too much undue risk, that it won't harm healthy ones. As I understand it, we did not even understand whether troops could perform their duties under the medication. Did we understand if the drug would impair an individual's ability to operate heavy machinery, putting the individual and others at even more risk? There are many troubling questions about giving a potent medication to troops without tailoring it to an individual's medical condition, size, or medical history. This is a drug that can have extremely dangerous health effects, and might even result in death. When FDA waives DOD's responsibility to obtain individuals' informed consent for using experimental drugs, it is DOD's duty to ensure that the benefit of such a treatment at least equals, and preferably outweighs, the potential risks. I am unsure that this was the case in the decision to use PB in the Gulf. It seems that the military had little reason to suspect that the Iraqis had soman in the region and Dr. Golomb's work indicates that the intervention may have been of questionable value even if troops were exposed.

It is also troubling that the decision to order troops to take this medication was left to individual unit commanders' discretion without specific guidance about situations in which it might be more appropriate to expose troops to such a risk to their

personal health. It would have been prudent to require certain precursors to exist to justify this exposure—nearby chemical detections or other military intelligence—to provide more specific guidance to the local officers.

I am eager to hear the testimony of the expert witnesses we have before us today and hopeful that it will shed some light on the many questions that remain about why we have so many sick veterans years after the battles in the Persian Gulf ceased.

Mr. STEARNS. I thank the gentleman. The gentleman from Indiana, Mr. Hill, is recognized for an opening statement.

OPENING STATEMENT OF HON. BARON P. HILL

Mr. HILL. Mr. Chairman, it has been 8 years since the Gulf War and there is still some very basic questions we have not answered that do not seem very close to answering. We still don't know why our soldiers deployed in the Persian Gulf are experiencing a variety of illnesses with overlapping symptoms such as fatigue, joint pain, skin rash, and memory loss, and we don't know exactly where to look for the cause of these still unexplained illnesses.

Today we are discussing one of the many aspects in our search for the cause of health problems associated with the Gulf War service. DOD's and RAND's study, a recent study on the health effects of PB, is far from conclusive. It does not do much more than find that PB is one piece of a puzzle we have not been able to put together yet.

The report indicates that many of our soldiers, perhaps as many as 250,000, as has already been mentioned, deployed in the Persian Gulf took PB tablets. We knew at the time of the Gulf War that PB is the only effective treatment to exposure to the deadly nerve gas soman, but we also knew that if taken in high enough doses PB can cause severe side effects. We knew this and that the Food and Drug Administration restricted its use. We knew this.

The conclusion of this report and of many other reports commissioned by DOD and other groups is that we are not yet able to establish clear causation between substances and chemicals our soldiers faced on the battlefield and the illnesses many of those soldiers have now. It is a very frustrating and time consuming process, but we have to keep searching for the cause or causes of these Gulf War health problems because we owe it to the almost 700,000 Americans who served during Operation Desert Shield and Desert Storm as well as to the millions of soldiers that we may have to deploy on foreign battlefields in the future. And I look forward to hearing the testimony of today's panelists.

Mr. STEARNS. I thank my colleague. The gentleman from Arkansas, Dr. Snyder.

Mr. SNYDER. I have no opening statement. Thank you.

Mr. STEARNS. The gentleman from Minnesota, Mr. Peterson?

Mr. PETERSON. No, thank you.

Mr. STEARNS. The gentlewoman, Mrs. Chenoweth-Hage?

Mrs. CHENOWETH-HAGE. Thank you, Mr. Chairman. I do have an opening statement but due to the time concern, I would just as soon turn it in to be part of the record.

[The statement of Congresswoman Chenoweth-Hage follows:]

PREPARED STATEMENT OF HON. HELEN CHENOWETH-HAGE

Thank you Mr. Chairman. I would like to thank you and other members of the committee for giving me this opportunity to speak. I appreciate everyone for being able to participate in this hearing to find out if pyridostigmine bromide is a cause of Gulf War Syndrome.

I am concerned. Very concerned. It's been 8 years since the end of the Gulf War and we still do not know what's causing the illness among our troops. Recently we have found out that PB *cannot* be ruled out as a cause.

And that is why we are here. We must find out everything we can about the effects of PB and Gulf War Syndrome. To what extent does PB produce symptoms associated with Gulf War Syndrome? How safe is PB? Do the benefits of taking PB outweight the risks involved?

But I am also disappointed with the slow pace of finding a cause to this illness. For untold number of veterans, this illness has disrupted their lives for years. These men and women have to suffer day in and day out. I can only imagine the suffering they endure, both from the physical and emotional pain.

It is my hope that we, Members of Congress and medical professionals, will be able to work together to find answers.

Mr. STEARNS. I would be glad to make it part of the record. Mr. Shows for an opening statement.

Mr. SHOWS. No opening statement. Thank you.

Mr. STEARNS. Mr. Buyer?

Mr. BUYER. No.

Mr. STEARNS. Without further adieu, we will ask the first panel, Dr. Golomb, to come forward and she is accompanied by Dr. Ross Anthony, who is Director of the RAND Center for Military Health Policy Research, and also Dr. Joseph Cassells, Project Director, Institute of Medicine, National Academy of Sciences, and let me welcome you folks here and we are prepared for your opening statement.

Mr. ANTHONY. Before we begin, we will summarize our statement but ask that it be concluded in the record.

Mr. STEARNS. So ordered.

[The prepared statements of Dr. Golomb and Mr. Anthony, with attachment, appears on p. 62.]

STATEMENTS OF BEATRICE ALEXANDRA GOLOMB, M.D., PH.D., CONSULTANT, RAND CENTER FOR MILITARY HEALTH POLICY RESEARCH; AND C. ROSS ANTHONY, PH.D., DIRECTOR, RAND CENTER FOR MILITARY HEALTH POLICY RESEARCH; AND JOSEPH S. CASSELLS, M.D., PROJECT DIRECTOR, INSTITUTE OF MEDICINE, NATIONAL ACADEMY OF SCIENCES

STATEMENT OF C. ROSS ANTHONY

Mr. ANTHONY. Mr. Chairman and distinguished members of the subcommittees, it is a pleasure for us to address you today on RAND's review of the scientific literature as it pertains to pyridostigmine bromide, or PB, and illnesses among Gulf War veterans. Rand is a nonprofit institution that helps improve policy and decision making through research and analysis. At RAND, I am the Director of the Center for Military Health Policy Research, as was mentioned, and co-leader of this particular project. I am joined today by Dr. Beatrice Golomb, who prepared this exhaustive PB study. Dr. Golomb is a RAND consultant, is a physician who also has a Ph.D. In biology specializing in neurobiology. She is a staff physician at the San Diego VA Medical Center and Assistant Professor of Medicine at UC San Diego.

Obviously the opinions and conclusions of this statement today are our own and they do not represent RAND or the agencies that sponsored the research.

I would like to briefly describe for you the context of the study and then turn the podium over to Dr. Golomb, who will summarize her findings.

After the Office of Special Assistant for Gulf War Illnesses was formed, the Special Assistant determined that there was at least two kinds of information that were needed in the office's efforts to leave no stone unturned in looking into possible causes of illnesses among Gulf War veterans. OSAGWI has extensively investigated what happened in the Gulf while RAND was asked to summarize the scientific literature, existing scientific literature, on the health effects of possible causes of illness. It was hoped that combining these sources of information would produce a more complete understanding of illnesses among veterans.

The PB report is the fourth of eight literature reviews published by RAND to date and it differs from others although listening to you, I am hesitant to say this, it differs because it is the first time that we were unable to rule out an agent as a possible contributing factor among illnesses. These findings need to be evaluated very carefully. Even if enough evidence is found that a hypothesis cannot be rejected, this does not necessarily imply that an agent in question is a causal factor but, on the other hand, it also does not imply that it should not be carefully looked at and investigated. It only means that based on the available scientific evidence, the possibility cannot be dismissed. Unfortunately, science sometimes moves more slowly than we all would wish it would go. I would like to turn the podium over now to Dr. Golomb, who will speak about her research.

STATEMENT OF BEATRICE ALEXANDRA GOLOMB

Dr. GOLOMB. Mr. Chairman, and members of the subcommittee, as the committee knows, pyridostigmine bromide, or PB, was the drug taken during the Gulf War by an estimated 250,000 U.S. troops as a pretreatment to protect against nerve agent attack. PB was approved by the FDA in 1955 for treatment of myasthenia gravis, an autoimmune disease that affects the muscles.

During the Gulf War, it was designated an investigational new drug for pretreatment for nerve agent that was supplied to U.S. forces under an FDA waiver of informed consent. Technically, PB is a pretreatment adjunct, a drug that must be taken before exposure to be effective but that can confer benefit only if postexposure treatments are given as well.

RAND was asked to perform a literature review to evaluate whether PB could possibly be related to increased health symptoms in Gulf War veterans. The literature review was used first to identify theories that might link PB to symptoms in ill Gulf War veterans and then to assess the evidence pertaining to these theories. The issue of efficacy of PB as a pretreatment for nerve agent was also addressed but will not be reviewed here due to time constraints.

The identified theories fall roughly into two categories. One set of theories describes mechanisms by which PB may lead—by which

there may be heightened susceptibility to effects of PB in some circumstances so that some individuals might experience effects, possibly toxic effects, while others do not. The second set of theories describes ways PB may actually lead to chronic symptoms. I will discuss these series briefly.

Regarding theories of possible heightened susceptibility to PB, one proposes possible individual differences in processing of PB. Indeed, our review found evidence of differences at many levels. Even supposing the same oral dose of PB which was not uniformly taken, there are sevenfold differences in blood levels of PB in humans from one individual to another. Moreover, for the same blood level of PB, there are manyfold differences in the percent inhibition of an enzyme affected by PB and through which it exerts its action. Thus, depending how long after PB administration one looks, there may be up to 15 to 25 full differences in enzyme inhibition for the same oral dose from one individual to another. Finally, for the same measured enzyme inhibition, there are substantial differences in clinical effects, including toxic effects of PB. These widespread differences in processing of PB from one individual to another could lead to substantial differences in susceptibility to effects of PB, including chronic effects, if any occur.

The second theory notes that whereas ordinarily most PB is excluded from entering the brain by something termed the blood brain barrier, which bars access of many substances, recent evidence from animal studies suggests quite a bit of PB may access the brain under some conditions such as stress, heat, and chemical combinations, conditions to which some Gulf War veterans may have been exposed. This could increase the chance for brain effects of PB to occur. In addition, one study found that PB itself may enhance access to the brain of normally excluded substances, such as infectious viruses.

A third theory notes that toxic effects of PB may be greatly enhanced in some cases in a synergistic fashion by concomitant exposure to other factors like pesticides and nerve agents to which some veterans may have been exposed. These three theories were all found to be viable. That is, they had enough supportive evidence that they could not be rejected.

The other group of theories relate PB to development of actual chronic symptoms. Among theories in this category, literature allowed us to reject one theory, namely bromazine, from the accumulation of the bromide in PB as a likely contributor to illnesses in Gulf War veterans, and the literature was inadequate to seriously evaluate another theory pertaining to multiple chemical sensitivity.

The most important mechanism by which PB may lead to chronic illness suggests that PB may change regulation of a key nerve signalling chemical called acetylcholine. Acetylcholine is known to be vitally involved in regulating muscle action, pain, mood, memory, sleep, and skin function, domains that figure prominently in complaints of ill Gulf War veterans. PB acts by blocking the enzyme that normally breaks down excess acetylcholine. The consequences increased unregulated action by this nerve signalling chemical. The body responds to this inappropriate increase in acetylcholine action by putting into place mechanisms to suppress the excess acetylcholine activity so that signalling cells reduce production and re-

lease of acetylcholine and receiving cells reduce the number of receptors to which acetylcholine combine and the affinity of those receptors for binding acetylcholine there. Moreover, there may be increased breakdown of this chemical.

Since these mechanisms designed to suppress acetylcholine action occur in response to the excess acetylcholine action induced by PB, one might expect that they would go away as PB is withdrawn. But existing evidence from studies in animals suggest that the time courses of these effects differ widely from one another. Some are short lived and unlikely to contribute to chronic effects in ill Gulf War veterans but others are long lasting or permanent, lasting in some instances as long after discontinuation of PB as anyone has looked.

Could these chronic changes in regulation of acetylcholine action relate to chronic symptoms reported by Gulf War veterans? The answer is we just don't know. Much more needs to be understood about the specifics of these changes and how they relate to clinical effects. However, again we do know that acetylcholine is critical to the regulation of muscle action, pain, memory, and sleep, domains that are disrupted in ill Gulf War veterans. Thus, it is possible that disruption of regulation of acetylcholine could produce symptoms of the kind that veterans report.

The major conclusions of the study are we cannot rule out pyridostigmine bromide as a possible contributor to increased health symptoms in some Gulf War veterans. More research is needed to clarify the role, if any, of PB in chronic health effects in ill Gulf War veterans. Some research of this kind is already being funded by the DOD, VA, and HHS.

Finally, further research is needed to determine the effectiveness over the current dose of PB in protecting against soman. The issue now is the complex one, of trading off uncertain health risks but risks now known to be biologically plausible against uncertain gains from use of PB in the warfare setting. Thank you.

Mr. STEARNS. Dr. Cassells.

STATEMENT OF JOSEPH S. CASSELLS

Dr. CASSELLS. Good afternoon, Mr. Chairman and members of the subcommittees. Thank you for the opportunity to discuss the Institute of Medicine's activities involving the war in the Persian Gulf, specifically the health effects of service in that operation. Since the particular focus of this hearing is pyridostigmine bromide and its possible relationship to Gulf War illnesses, I will confine my remarks to that issue.

In 1995, an IOM interim report called "Health Consequences of Service During the Persian Gulf War: Initial Findings and Recommendations for Immediate Action" noted that there was little information at that time about how PB and DEET and permethrin might interact. Further, it was noted that interactions among those compounds are possible and are inadequately studied. In its final report, which came out in 1996, Recommendations for Research and Information Systems, it is noted in regard to PB, and I quote, all of these possible drug interactions cause acute and short-term problems. The committee knows of no evidence of any chronic effect. Furthermore, the report goes on to conclude that the number

and variety of hypotheses call attention to the variety of different types of abnormalities that have been reported and the strong likelihood that no single hypothesis could account for all of these, whether or not the illness resulted from service in the Persian Gulf War.

The Institute of Medicine, at the request of the Department of Veterans Affairs is currently undertaking a literature review of chemical and biological compounds believed to have been present in the Gulf or as a result of the Gulf conflict. Phase one of this study, and Mr. Chairman, you alluded to the study in your opening remarks, phase one of this study is reviewing the literature on pyridostigmine bromide, sarin and cyclosarin, the vaccines botulinum toxoid and anthrax and depleted uranium. Phase two of the study will examine additional exposures.

At this time the IOM has no comment regarding the RAND report other than to note that any new report should be viewed with reservations until it has had careful attention from the rest of the scientific community. Evidence that seems to support a favored idea or hypothesis must be viewed with at least as much caution as evidence against that idea. The RAND report will be included in the literature review that the IOM conducts on pyridostigmine bromide and, as the chairman stated, the report on the phase one reviews will be available in August of next year.

Despite media reports regarding the previous IOM report, noting that the committee is unaware of evidence of chronic effect related to PB does not mean that there is no relationship between PB and the long-term health effect and does not mean that a previous committee has ruled it out. Rather there was not sufficient evidence at the time to determine an association.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Cassells appears on p. 84.]

Mr. STEARNS. I thank the panel. I will start with first sort of an overview. Dr. Golomb, what I hear you say is that several factors may in a synergistic way have made some veterans more susceptible to neurological damage. Is that in a nutshell what you are saying?

Dr. GOLOMB. I guess I would rephrase that to suggest that there is evidence of individual differences and effects from the environment, and we don't yet know whether those factors together with PB could be responsible for illness in some veterans. There is evidence suggesting that that is plausible but the evidence has not yet closed the loop on whether that is a cause.

Mr. STEARNS. Dr. Cassells, do you agree with that, yes or no, what she said?

Mr. CASSELLS. Basically, yes.

Mr. STEARNS. I think many of us are frustrated. I think the members will point this out, because we are actually trying to come up with conclusive evidence. Let me ask Dr. Golomb, your report appears to be a little guarded in its conclusions and I can understand that. In your personal view, your personal view now, what is the likelihood that PB alone or in combination caused Gulf War syndrome?

Dr. GOLOMB. I guess I really can't separate my personal view from my view as a scientist and I would say——

Mr. STEARNS. Let me rephrase the question. Would you take PB yourself?

Dr. GOLOMB. Clearly from doing this report, I have reservations about the possible health effects.

Mr. STEARNS. Now we are getting to understanding what you are saying. You have done the report.

Dr. GOLOMB. Yes.

Mr. STEARNS. You are in Kuwait, Saudi Arabia, and they come to you and say you are going to have to take a PB pill, yourself, today, and you are going to have to continue to do this. My question is would you do it knowing what is in the report?

Dr. GOLOMB. What I would say is the full force of considerations never falls on one in a hypothetical setting and hypothetical answers are known to be poorly correlated with how people actually behave. There are many considerations that would be relevant, whether more evidence has come out regarding the efficacy of PB regarding soman, what the known likelihood would be of soman threat in that particular circumstance, whether additional research has been done into health effects of PB. I would hope before I would have to make that decision more would be known.

Mr. STEARNS. Let me say in all deference to you, I don't mean to put you on the spot, the issue is so serious and many of us are trying to grapple with this that I needed to get some kind of feel for how you felt.

Dr. GOLOMB. I would clearly have reservations.

Mr. STEARNS. That is what I hear and that is a fair answer, and I think you are safe with that answer, too.

Dr. Cassells, why hasn't PB been studied to a greater extent before? Why didn't the Presidential Advisory Committee focus more on PB, and this question might also apply to Dr. Anthony, why after this long a period of time are we suddenly hearing about PB? Maybe you can enlighten me why you folks didn't come to some kind of understanding like she has.

Dr. CASSELLS. Well, as I said, the Institute of Medicine has not taken a position on PB for this current committee report that will be due out in August of next year. We have not earlier ruled out—the Institute of Medicine in its earlier reports did not rule out the effects of PB in possible combination with other things. It simply pointed out there was not sufficient evidence to point to that.

You mentioned the Presidential Advisory Commission report. That report stated that the evidence available at the time of their review did not lead them to conclude that PB simply was the cause of Gulf War illness but specifically stated that there was not enough information about possible interactions with other agents in the Gulf to rule it out and further research needed to be done.

I think the reason that research had not gotten to a particular point with PB, and that was the opening premise of your question, was the fact that it had been approved for use for myasthenia gravis in very much larger doses for a long period of time and I think the assumption was that it was safer and therefore it had not been the subject of research for long term effects. It is purely speculation.

Mr. STEARNS. In all fairness, the Presidential Advisory Committee study on PB devoted only about 3 or 4 pages to the issues,

whereas her report is 300 pages. I don't know how they can make any statement about PB on just 2 or 3 pages.

Dr. CASSELLS. Two or 3 pages of the report is correct but the literature review that led to those 2 or 3 pages was really rather extensive.

Mr. ANTHONY. If I might say, when we came to these issues, we were asked to do a series of literature reviews. Frankly we addressed them with an open mind and with the intent to provide that information to the public, it is true that the Institute of Medicine, the PAC and other people did literature reviews as staff work but never made them available to the public. I think RAND also had the opportunity to take a much closer look at some of these issues.

I would also point out that the information has become public now, but there was an effort all the way along the way to make whatever we were finding on a draft basis available to decision makers both within DOD and the Congress. So the information was attempted to be available so that in fact if it was needed for decision making, that that was available to the public and to you.

Mr. STEARNS. My last question, Dr. Golomb, let's see if we could maybe bring this down to an understanding here. Gulf War veterans have indicated a variety of problems, neurological symptoms to gastrointestinal problems to joint pains. Would PB alone or in combination be an explanation, a possible explanation for all of those symptoms?

Dr. GOLOMB. It would be a possible explanation for all of those symptoms because all of those domains are influenced by this particular nerve signalling chemical acetylcholine that this review suggests—that evidence suggests might have undergone changed or altered regulation as a result of taking PB in some circumstances.

Mr. STEARNS. My time has expired. The ranking member Mr. Gutierrez.

Mr. GUTIERREZ. Thank you. It is certainly interesting that we have a panel of scientists and experts who are so cautious here this afternoon and I apologize if anybody takes offense to that. But I think that we need to get some answers and everybody is being so careful and so guarded and so cautious and I would hope that we could move forward with this, obviously to get the right answers, but at the same time to use our best judgment so that we can get some answers and be a little clearer on this. And to that point I think it would be useful to have—further explain RAND's role in the production of these series of documents because it is almost like very legalistic. We wrote it, RAND's not responsible, it is our personal opinion, I don't know, I have heard that before. It doesn't sound like a scientist. It sounds like a lawyer trying to get from under his responsibility for his client. Having said that, is it customary for RAND to publish a report done under its review and not stand by its finding? You state that the opinions and conclusions are those of only the authors.

Mr. ANTHONY. That is kind of a standard phrase that is in all RAND testimony. We do stand by the report. And we feel that the research was well done, well conducted, peer reviewed and we believe that to the best of our ability and best of RAND's ability we have ensured a high quality product.

Mr. GUTIERREZ. Doctor, you have obviously done a great deal of work in reviewing the literature on PB exposure and interviewing those who have expertise in this area. This is for Dr. Golomb. We clearly understand that we could research possible human outcomes to PB exposure indefinitely ad infinitum. I am going to ask you to help us non-scientists, lay people here determine how seriously we need to take PB. Will you rate on a scale of one to ten, one being the least certain and ten being the most, the certainty you have that at least some of the chronic illnesses Persian Gulf veterans are confronting today are due to their use of PB?

Dr. GOLOMB. I would probably give it a five to six.

Mr. GUTIERREZ. You stated that chronic effects and chronic illnesses, you are stating from five to six that the chronic effects and chronic illnesses that Gulf War veterans who took PB could be related to PB?

Dr. GOLOMB. There is some evidence consistent with that possibility but there are limitations in that evidence that prevent us from making that statement conclusively.

Mr. GUTIERREZ. And PB is taken for what?

Dr. GOLOMB. For what medical conditions?

Mr. GUTIERREZ. For what medical conditions?

Dr. GOLOMB. The principal medical condition that it is taken for is an autoimmune condition termed myasthenia gravis in which there is damage to the receptors for this nerve signalling chemical acetylcholine so that there is low acetylcholine action in the muscles. Administration of PB raises the acetylcholine action in those individuals toward normal. In those who don't have this condition, rather than normalizing acetylcholine action, PB raises acetylcholine action to abnormal high levels. So effects in individuals with myasthenia gravis can't clearly be extrapolated.

Another reason why extrapolation is problematic is that individuals with myasthenia gravis take PB lifelong. The leading theory in the literature review about how PB might lead to chronic symptoms suggests that it is not PB causing high acetylcholine that leads to the chronic symptoms but the body's response to that, to suppress acetylcholine action by a variety of mechanisms, that leads to problems. That would not show up while PB continued to be given or it may not show up.

Mr. GUTIERREZ. And you take this. Given what we understand that Gulf War veterans confronted, was it necessary for them to take PB?

Dr. GOLOMB. I am really not in a position to address anything but the medical issues. That involves military elements as well.

Mr. GUTIERREZ. So you did a study, the military administered, as you stated, with an FDA waiver.

Dr. GOLOMB. Yes.

Mr. GUTIERREZ. So there was no consent to the 250,000 people.

Dr. GOLOMB. That is correct.

Mr. GUTIERREZ. Otherwise without the waiver you can't administer this so there isn't enough scientific——

Mr. ANTHONY. If I might state, we were not asked and nor did we look into the policy implications of taking PB. The way the report has——

Mr. GUTIERREZ. That is not my question, Dr. Anthony. Forgive me. That thing turns yellow real quickly. See, it just did. And then it turns red even quicker. The question is, and if you don't have the answer, we will ask the people from DOD, is you give this drug to avoid something, to avoid an illness which you have described to us and to avoid these effects but you need to confront, you need to actually have exposure to it. I mean, I don't take a shot for malaria. My doctor if I tell him I am going to L.A. Or maybe New York, he doesn't give me a shot for malaria. He doesn't. If I am not doing construction work and I tell him I don't intend on, you know, putting a nail through my foot, I don't—I mean, in your professional opinion, is there even a need to give this drug, or does somebody just decide, oh, just in case they might come along, this might come along the way and did it come along the way something that they needed to even give the drug for.

Mr. ANTHONY. I think you need to ask DOD that question. The drug is primarily given as a pretreatment for soman, which implies that there was some risk of it being on the battlefield.

Mr. GUTIERREZ. Was there any soman on the battlefield?

Mr. ANTHONY. I am not aware of any but I am also——

Mr. GUTIERREZ. We will ask the people from—that's fine.

Mr. ANTHONY. We didn't have access to any of the classified information so we are not really in a good position to answer the question.

Mr. GUTIERREZ. Mr. Chairman, I just think it is important that if the military is giving 250,000 people something that turns out to be non-existent, we have some serious policy considerations here about what kind of medicines we are giving our military that are out there and then maybe they never even were going to confront it. Anyways, thank you very, very much for your testimony.

Mr. STEARNS. I thank my colleague. He certainly can ask those questions of Dr. Sue Bailey, the Assistant Secretary of Defense for Health Affairs, who is on the next panel two.

Next the chairman of the Subcommittee on Oversight and Investigation, Mr. Everett.

Mr. EVERETT. Thank you, Mr. Chairman. I am going to get a little less technical. I frankly doubt if many members of the panel understood a great deal of what you have said. Does your study answer the question whether the Department of Defense should use PB in the future for the purpose of protecting our troops against attacks with the nerve agent soman?

Dr. GOLOMB. It does not answer that question. It does not address that question. It looks only at whether there could be a link between PB and chronic health effects.

Mr. EVERETT. But your own testimony a little earlier you said that you would have reservations personally.

Dr. GOLOMB. About taking an agent for which there may be chronic health effects.

Mr. EVERETT. About taking PB?

Dr. GOLOMB. Yes.

Mr. EVERETT. There are now over a hundred different research projects on illnesses that could be related to military service in the Persian Gulf War. We have heard today that there are 26 of these research projects looking into PB. Please provide the subcommittee,

if you have the information, a list describing these projects. Also, please answer how do we know these studies are asking the right questions. Who is coordinating the projects so we won't be duplicating them or leaving gaps in these studies? In other words, do we have 26 horses out there running in different directions?

Mr. ANTHONY. Sir, again, we are not the people to ask that question to but I believe Dr. Fran Murphy, who is on the Research Coordinating Committee or was at one point before her recent promotion, can address those questions. The DOD and VA have a complete list of this research but we don't track that at RAND.

Mr. EVERETT. You did this report without access to the other 26 projects going on?

Dr. GOLOMB. We had access to lists of reports that were ongoing at the time the RAND report was being done and I talked to people who were investigators in some of those reports, but naturally the nature of what is being funded and so forth moves forward over time. I have seen a list of the studies that the DOD is currently funding related to pyridostigmine bromide, and those studies do fit into some of the gaps in the literature that we are currently looking at, but there are additional gaps that could profitably be filled by additional research.

Mr. EVERETT. What are they, please?

Dr. GOLOMB. My personal scientific opinion would be that there are two domains in which additional research could very well be profitable. One would be to look specifically at the nature, time course, and possible clinical effects of changes in regulation of the nerve signalling chemical acetylcholine induced by PB and by other acetylcholinesterase inhibitors, which includes pesticides and nerve agents. The other thing that I think could help us pin down causes in illness in Gulf War veterans would be to look, as some people are presently doing, for objective markers of illness in ill Gulf War veterans, changes in blood flow regulation, et cetera, that would allow us then in animal studies to administer different possible causes, like PB in combination with other things or low level nerve agent, or other possible causes, and look for those same objective markers in animals to help trackdown what the most likely probable causes are.

Mr. EVERETT. Did you see any of these benchmarks in the research that you did?

Dr. GOLOMB. There are some such benchmarks currently being explored by Robert Haley in Texas who has some reports suggesting that there are abnormalities in what is called saccadic eye movement, when your eyes move from place to place very quickly. He found that one eye may move a little before another, not in a way that is discernible to the naked aye, but that would be one example, and also there appear to be changes in regulation of blood flow to certain parts of the brain, especially a part called the basal ganglia. That is not inconsistent with PB being a factor because we know that when drugs of PB's class go to the brain, they localize in the basal ganglia. So things like that are lines of research that could help us pin down what the likely causal factors are.

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

Mr. STEARNS. I thank my colleague. The gentleman from Indiana, Mr. Hill.

Mr. HILL. Thank you, Mr. Chairman. I think, doctors, we are all frustrated with this. We spend all this money and we spend all this time and all this energy and we are looking for a bit more clarity in all this and we are not getting it and I guess my question to you is do we need to continue to look at PB and spend more money in determining whether or not this can be a direct cause for Gulf War illnesses?

Dr. GOLOMB. I am not the policy person who makes monetary decisions and I am probably not privy to all the cost-benefit analyses of directing money here or there, but I do think that additional research in this domain would be profitable for us understanding a lot of basic issues about how the nervous system work that would be helpful not only for Gulf War veterans but for other illnesses, and also would be helpful for other possible exposures like organophosphates that have similar mechanisms of action to pyridostigmine bromide.

Mr. HILL. I guess I am asking you a question that maybe you can't answer, but do you think that if we do invest more money, that we can get to a point where it does become clear?

Dr. GOLOMB. I think there are many people who have significant reservations about that. I am slightly more optimistic than many are that with the combination of attacks that I articulated to Mr. Everett I believe it was, that we could get closer to an answer and possibly even have an answer for some or perhaps many Gulf War veterans.

Mr. HILL. Okay. Let me switch gears then and ask another question. Is there any way to screen veterans to see if they are adequately producing and regulating nerve signalling chemicals and, if so, should we invest in screening sick veterans?

Dr. GOLOMB. Currently, there are no good mechanisms for looking at some of the changes, particularly if the changes are occurring in the brain. But it could be possible; if research looked for objective markers of illness, if those markers were found to be produced by PB in animals, then those markers could be used as screens.

Mr. HILL. So we should invest in screening sick veterans?

Dr. GOLOMB. It would potentially be helpful to looking for markers and specific elements of acetylcholine dysfunction that might then be screened for in ill Gulf War veterans.

Mr. HILL. So we should invest?

Dr. GOLOMB. Again, this is an——

Mr. HILL. I am not talking about you making decisions about how much money Congress should spend. I am asking for your recommendation.

Dr. GOLOMB. I would recommend such investment.

Mr. HILL. Thank you, Mr. Chairman.

Mr. STEARNS. I thank the gentleman. Dr. Snyder?

Mr. SNYDER. Thank you, Mr. Chairman. Are we pronouncing your last name right?

Dr. GOLOMB. Golomb.

Mr. SNYDER. Golomb. I appreciate the work you have done and obviously it has gotten a lot of people thinking, which I think is what these kinds of papers are intended to do and what RAND has

intended to do through the years. I wanted to ask you, when did you first start work on this study?

Dr. GOLOMB. I think we looked at the time course earlier today, and July 1997.

Mr. SNYDER. So it has been 2½ years or almost 2½ years that you have been working on it. The comment was made earlier today that you all are being too careful, too cautious, and too guarded. I hope that everybody that works on this stuff will be as careful and as cautious and as guarded as the science takes you. I think we have had too many mistakes made in the past and all kinds of diseases where we tend to overreact, perhaps not the scientists do but some policymakers do. We need to look before we leap.

I wanted to ask the specific question. I was impressed with the difference—the striking difference in blood levels between people taking the same doses. You have sevenfold difference in blood levels and a 15 to 25 difference I guess in efficacy, for want of a better word, of how it affects acetylcholinesterase. Are there other drugs, I mean, common drugs that have that kind of variation in blood level in effect based on the same dose?

Dr. GOLOMB. I actually don't know the answer to that because I haven't been specifically investigating a variety of other drugs. It wouldn't surprise me if there were. There may be drugs that have a better toxic to therapeutic ratio, that is to say a wider range before there are significant adverse effects. I simply don't know the answer to that.

Mr. SNYDER. It seemed pretty striking to think that if Mr. Hill and I were taking the same dose of this drug, that the effect could be 25 times greater in me than in him in terms of how it affected that enzyme, inhibition of enzyme. That seems very striking.

Dr. GOLOMB. To clarify that it depends on how long after PB is given as to whether you get that big of differences but certainly there are a good tenfold differences. We don't really know, you know, if altered regulation is occurring, whether that becomes a problem because you have had high levels of inhibition 2 hours later or 3 hours later. Certainly at 2 hours you can get differences between 50 percent inhibition in one individual and zero percent in another.

Mr. SNYDER. Were there—in your—the written materials we had from you, you talked about the problems of studies having been done on people with myasthenia gravis and then looking at those effects and comparing it to normals. Have there been studies done in the past on pyridostigmine bromide on normals that do not have myasthenia gravis?

Dr. GOLOMB. The military in both the U.S. and Britain have conducted such studies. Typically they have looked to see what degree of enzyme inhibition individuals have before enrolling them and they have excluded those that had particularly high levels of enzyme inhibition. Unfortunately it wasn't possible in the Gulf War setting to individually monitor that and so we really don't have a lot of good information on how individuals who have particularly high rates of acetylcholinesterase inhibition would fare and also the military studies uniformly did not look at long-term health effects and did not monitor for the kinds of health effects that are being experienced by Gulf War veterans.

Mr. SNYDER. So if I got what you are saying, you are saying when the studies on normals were done, people were excluded based on the drug effects on them and it may turn out that those same types of people were the ones that had the—potentially could have had the effects that we now call Gulf War illness.

Dr. GOLOMB. That is correct. But it is also the case for individuals even with more normal or usual percent inhibition, we didn't look at what happened to those people long term. We can't either exclude the possibility that there were health effects in those. We simply don't know whether either group would——

Mr. SNYDER. When you use the phrase long term, what does that mean to you?

Dr. GOLOMB. What it really means to me is long term like the kind we are seeing in Gulf War veterans. It means different things in different contexts. In animal studies, I think the longest in a rat study that anyone looked after stopping PB was 60 days and there were effects still present. Many people would—there are rules of thumb in animal research saying that a week in a rat is like a year, but that is not really fair to say because it is different for every function one looks at. So we don't really know how that would correlate to long term in humans.

Mr. SNYDER. I felt like a rat before and it seemed to go on forever.

The last thing I wanted to say was the—I happened to be, I think, laying in bed the night I saw the CNN news, the day your report was studied. I was really struck by the press reports of your study. I mean, you probably saw them too. Some very dramatic statements being made about what your conclusions were and yet I think your conclusions are very appropriate. You talk about, this is I think your words exactly, a possible contributor that risks are biologically plausible and that further research is needed. I mean, I think you are very clearly sending a message to us and to veterans that there is a whole lot of work that needs to be done, that this is just one baby step on this, an important step and history may show that it is a very important step but I think it is very easy to overreact to one medical study, preliminary literature review of one of these possible contributors. But thank you for your good work.

Mr. STEARNS. I thank the gentleman. The gentlewoman from Idaho, Mrs. Chenoweth-Hage, is recognized.

Mrs. CHENOWETH-HAGE. Thank you, Mr. Chairman. Dr. Golomb, I am very impressed with your testimony and the work that you have done.

Dr. GOLOMB. Thank you.

Mrs. CHENOWETH-HAGE. I want to thank you for bringing it to the committee. Now, based on your testimony and the answers to the questions of the other Members, I think what I understand is that in the case of myasthenia gravis, that acetylcholine is used as a suppressing agent, right?

Dr. GOLOMB. It is a little bit the other way. Myasthenia gravis action of this nerve signalling chemical is abnormally low. What PB does is it abnormally raises that in other people but it raises it toward normal. It normalizes it upward and does with myasthenia gravis.

Mrs. CHENOWETH-HAGE. So based on the reaction of MG patients, it was supposed then that in the case of preventing a reaction to nerve gas, that it would act substantially the same way. Is that what you are telling us? Because in your testimony, it indicates that this was designated an investigational new drug?

Dr. GOLOMB. For the purpose of nerve agent pretreatment. You are right, the presumption was because it had long been given in a specialized population and also I might add that it is also given for some post anesthesia applications where neuromuscular blockers have been given. That is another setting where because of the neuromuscular blockers, acetylcholine action is low and giving PB brings it toward normal. The presumption was because of long-term use in these conditions and particularly myasthenia gravis, at higher doses lifelong that shorter term lower dose use in normals would not be a problem.

Mrs. CHENOWETH-HAGE. But of course your testimony indicates that the variables in different blood levels and body chemicals and chemistry was—there was not substantial time to really understand those variables.

Dr. GOLOMB. I would add that had been known even from individuals with myasthenia, individuals who appeared to have the same degree of illness were known to need widely varying doses of pyridostigmine bromide.

Mrs. CHENOWETH-HAGE. So, Mr. Chairman, I think that what we are hearing is that this drug was given as an investigational new drug. I am shocked. I don't think we need to be investigating new drugs in the course of an impending war giving 250,000 men and women an investigational new drug. I know the FDA is cumbersome and bothersome but this is very disturbing to me and I have seldom heard in my career in Congress a more articulate, astute or brighter person in medicine or any witness. I am stunned by this because I have been involved with veterans who have Gulf War syndrome and it is—I have noticed something else that you indicated in your testimony and that was—there is literature that indicates that PB itself may enhance access to the brain of normally excluded substances such as infectious viruses so that in and of itself causes the long term effect while the effect of the drug itself may be short term, as Dr. Cassells testified. The long-term effect of the suppression that you testified you may not be able to testify directly because you indicated you read it in literature, but I think that is significant and I hope that in your future studies that you can enlighten us more on that because that may be why we are getting some of the contradictions of short term versus long term.

Dr. GOLOMB. I would like to comment in defense of the FDA that they were sufficiently persuaded by the data and myasthenia gravis, that their concerns for an investigational new drug were actually not safety concerns but concerns regarding efficacy. The issues regarding safety were really ones that were brought up later. So at the time they did not perceive safety to be a major issue.

Mrs. CHENOWETH-HAGE. It was still under restricted use, wasn't it?

Dr. GOLOMB. It was FDA approved for those selected conditions in which it had been seen to be effective, and those were myasthe-

nia gravis and the post-neuromuscular blockade conditions. But it's difficult, of course, to do effectiveness studies in humans, and at the time the major concerns resolve revolved around that.

Mrs. CHENOWETH-HAGE. So the suppression of the effects of the soman had not been studied in humans, just on animals?

Dr. GOLOMB. The benefits for soman are generally benefits against lethality, against death. And the literature suggests that there is no evidence to suggest that there are benefits against sublethal effects, that the incapacitating effects would still occur. So performing studies to see at what level of soman there is lethality in humans would clearly be a problem.

Mrs. CHENOWETH-HAGE. I see. Thank you very much.

Mr. STEARNS. I thank the gentlewoman for the questions.

The gentleman from Indiana, Mr. Buyer, who was in the Gulf War and has experience taking PB.

Mr. BUYER. Mr. Chairman, you name it, I had it. I have had the anthrax shots. I took the PB pills. We burned the diesel and JP-5 in our heaters and tents. They fogged us with DEET. They gave us all of the multiple immunizations. I was even in 2 days of the fallout based on Bernie Rostker's study of the chemical fallout from the Khamisiyah, so I got to spend a couple of nice days in that. I think that I have been dipped.

There are a couple of things. I do want to make these comments. I also would like to respond to my colleague from Indiana, Mr. Hill, because he asked a very good question. It would be easy for us to do a little Monday morning quarterbacking years later, but I can tell you at the time—I want to speak for all 200,000 of us that were actually on the desert floor. We had been very well briefed. DOD did a very good job briefing us on Iraq and Iraq's use of chemical munitions, what they had done against Iran in the Iran-Iraq War. Many of us were very prepared, not only for biological but chemical. We were also prepared for tactical nukes to be used in response, if in fact, chemical munitions or biological compounds were used against us.

So we were very prepared on the ground. We anticipated that it would actually happen. It was probably the most frightening thing as a soldier. If there is a bullet out there with your name on it, you accept it as your fate, but don't gas me. So it was our greatest fear, and we took it very seriously. So when you say, how can you actually give such a drug to soldiers—we took it willingly. We wanted to take it. You give me that choice again versus sarin gas in the next room or take these pills, I am going to take them because I know what is going to happen if I go in there with nothing. So we made those choices.

Fortunately, when the first Scuds came in they were nonchemical, they were conventional munitions. After about 5 or 6 days I stopped taking the pills. I don't know what others did.

But that is what makes it so difficult for science. They don't have a specific, detailed, environmental assessment that they can study, or exact numbers of what we were given.

Ma'am, you talked about the individual differences. What an understatement—just given human physiology in itself, let alone all of the numerous combinations and factors that you can do.

So, Mr. Hill, talk about a study—and I can understand the strain on patients, because I am with you, but it is very difficult to come to something concrete. I cringe every time I hear somebody use the term Gulf War syndrome. I just want to jump out of the window. There is no such thing as Gulf War syndrome. It is Gulf War illnesses. It is multifaceted. It is what challenges us to try to find the causal link. Will we ever find it? Maybe not. Why? Because it is so multifaceted and there are so many individual differences, even by gender.

But we should not stop. I guess that would be my advice to my colleague. We can't rest on this one.

I want to complement Bernie Rostker for having the RAND report do this. You, sir, are a tremendous complement to the building across the river for you have done more than any other man or woman I know of on behalf of Gulf War veterans. You take a lot of heat, Bernie, but you are doing the right thing. I don't want to get into questions. I just wanted to make the comment. I want to compliment you on your study. If you are looking for advocates for—further advocates, you have got one.

Mr. STEARNS. I thank the gentleman for a very compelling statement.

I think that we are going to do another short round of second questions, maybe a clarification. My colleagues have indicated they want to do this, so if you would be patient with us.

I just have a clarification, if you don't mind. When my colleague, Mr. Gutierrez, asked you to rate from 0 to 10 the factors, you said 5 or 6. Would that qualify as a maybe——

Dr. GOLOMB. It is a definite maybe.

Mr. STEARNS. So a 6 is a definite maybe; 7 is a——

Dr. GOLOMB. I really hate to even answer those kinds of questions along a continuum where there is so much residual uncertainty.

Mr. STEARNS. Well, you sound very knowledgable in the area. Are there other risk factors that you would rate higher than a 5 or 6, based on your knowledge?

Dr. GOLOMB. Based on my knowledge which, remember, I was designated to do the report on PB, so I don't necessarily have the same degree of knowledge about other risk factors. But I would comment that, for example, in an epidemiological study published by the British this year where they looked at a number of different exposures and their relationship in British Gulf War veterans to CDC-defined Gulf War syndrome, the risk factor that appeared to have the strongest relationship was PB. However, other risk factors also had significant relationships to the development of Gulf War illness. So I could not say that there is another factor that I would perceive as stronger, although one could argue that all acetylcholinestrate inhibitors, which include not only PB but nerve agents and organophosphate and carbamate pesticides, share similar mechanisms of action and could all be linked to similar kinds of health effects.

Mr. STEARNS. Okay. a "definite maybe."

Let me ask you this and see if I understood this. This is following up the gentlewoman from Idaho.

So the FDA approved this drug with the understanding that it would be granted a waiver because, as Mr. Buyer indicated, the dire circumstances that it was better than nothing, so to speak. Mr. Buyer said he would take it, knowing what the alternative was. But looking at this from an experimental scientific outlook and since the military didn't know, as I understand, definitely that this would do the job, would you say this was an experiment on our military? Would you characterize it like that, that they were experimenting with our military with this drug?

Dr. GOLOMB. I certainly don't think that was their perception, because the FDA had not had concerns about safety. So if the residual concerns were just about how effective is it, then they could not have perceived themselves as doing anything except giving what they thought was the only potentially effective countermeasure.

There are issues that have arisen since then regarding safety and effectiveness that might change the balance a little bit, but I certainly, from my understanding of what happened, would not characterize what anyone did as intentional experimentation.

Mr. STEARNS. But looking at it from today, looking from today back, would you characterize it as experimenting?

Dr. GOLOMB. I wouldn't even want to answer that kind of question. First of all, I think this is a little bit of a semantic question; second of all, it is sort of second-guessing people who were making the best decision on the basis of available evidence.

Mr. STEARNS. Let me ask you, in terms of the other countries that were involved, what other countries used PB?

Dr. GOLOMB. The British, Canadians. I talked to someone who did work in Denmark, and they indicated that the Danes used it. Dr. Rostker has talked to individuals in France, and his information is that they were given PB but never given the order to take it. Some individuals there may have taken it, but primarily what we know is the U.S., the British, and the Canadians.

Mr. STEARNS. Their studies are not as conclusive or not as definite maybe as yours?

Dr. GOLOMB. Well, the epidemiological study that emerged was from the British. That is really the best epidemiology that has been published, and that did suggest that PB was the most strongly linked among possible exposures to illness in Gulf War veterans. That was based on self-reported use of PB which has its own problems, and it certainly is the case that the British and Canadians are reporting health symptoms in their Gulf War veterans.

Mr. STEARNS. Did these other countries have to use the same approving authority that we did?

Dr. GOLOMB. I don't know the answer to that. That is not part of what I looked at. My understanding actually—and Dr. Rostker can answer this better, but my understanding in Britain is it is actually approved, but I would have to check on that to be certain.

Mr. STEARNS. My colleague from Indiana says that he believes it has been licensed.

That is my list of questions.

The ranking member, Mr. Gutierrez.

Mr. GUTIERREZ. Thank you. I want to thank Mr. Buyer for his comments about what soldiers are ready to do. I think that is what all of the 250,000 people that took PB were ready to do, and that

causes me a lot of consternation. And so when I raise the issues about people being careful and cautious and guarded—I mean, given the juxtaposition of Mr. Buyer's testimony that he would take it, and knowing what he knows today about PB would take it again, because that is the kind of individual he is, I would hope that we would get some answers. Because it seems that the panel sometimes doesn't want to venture here, doesn't want to venture there, and then we don't get to help the men and women that are out there.

So, at the same time, I think that it is very, very important that, given what Mr. Buyer just said, that I would see the same—not from you, but from the panels that are going to come forward after you—the same kind of commitment, the same kind of dedication, and the same kind of forcefulness in their commitment to serving our veterans who are clearly ill.

And while this evidence is not conclusive, it is certainly leading us in a direction. After 19 hearings, maybe we are finally starting to get to a point where we can say—as Mr. Buyer doesn't want to call it syndrome, I am going to respect what Mr. Buyer says, I wasn't there—these illnesses that our veterans have. It would certainly be good after 19 hearings, and I think your information is going to help us so that this committee doesn't continue—because Mr. Buyer and I remember when we sat on this committee and people would come forward and tell us, well, you know, there might just be malingers, they might be making it up, and they might be looking for an out, a pension.

So it gets real frustrating sitting on this committee after 7 years of examining this, and everybody was all worked up when they came back from the Gulf War and they said they were our best and brightest and most courageous and we had parades and celebrations, all very fitting. And then after the parades and the streets were swept up and everybody went back to work in their regular line of work making America better and stronger, everybody started questioning these people.

I think the information today, had we known it in 1993, maybe would have gotten us quicker to getting and resolving the issues and getting treatment for these people. Because I think that if I walked into my doctor's office today and I had conditions that are being complained of by Gulf War veterans and he asked me a series of questions and he got to ask me did I take PB, he might say, well, I think maybe I know why you feel that way, other than saying, you know, Luis, you are just tired, a little lazy, maybe you want to malinger, maybe we need to send you to a psychologist because really physiologically there is nothing wrong with you. I don't think, given your study, that anybody would say that somebody who feels some of the chronic illnesses that Gulf War veterans are going through would say they are going to need to see a psychologist. They are going to need to see a physician.

So thank you very much.

Mr. STEARNS. Dr. Snyder, second round of questions.

Mr. SNYDER. Thank you, Mr. Chairman. Just one quick question.

What was the normally prescribed milligram dose range of our Gulf War soldiers and what is the normal range prescribed for patients with myasthenia gravis?

Dr. GOLOMB. The dose range for Gulf War veterans was 30 milligrams three times a day. And in general for myasthenia the dosage typically starts at 60 milligrams perhaps three times a day and goes up to potentially 10 times that depending on the individual.

Mr. SNYDER. So I guess—well, I will just make a statement. So that was probably a factor then in the FDA's waiver when they were looking at the substantially lower dose?

Dr. GOLOMB. That is exactly correct.

Mr. SNYDER. Thank you. Thank you, Mr. Buyer, for your comments.

Dr. GOLOMB. Dr. Anthony is suggesting——

Mr. STEARNS. The gentlelady from Idaho, second round? Mr. Buyer?

Mr. BUYER. I have one. I want to thank Mr. Gutierrez for his comments. You are absolutely right.

I remember this in the beginning along with Joe Kennedy, a lot of hard work with a lot of doubters. I still think that we have a long way to go. I really do.

I also, when I think about soldiers, sailors, airmen, and Marines, when they are called to duty, they want whatever is the best in that moment in time—the best armor, the best munitions, the best body armor, whatever you have got that is the best. If what we had were these pills that were the best at the time, we will take it. Because, obviously, you know what happens if you don't and you get hit with nerve agent.

And the Scud that landed on us—I will let you know that the first Scud that landed in Dhahran, it was televised back home as it landed in the desert. It didn't land in the desert. It landed in a John Deere dealership lot that was right across from the street from us. And the concussion was so loud it just shook your entire body. Were we scared? We were scared to death. Absolutely we were scared. Were we glad that we took the pills? You bet.

When you have all of your MOPP gear on, you understand real fear when you know and believe that what just hit across the road from you was chemical. You are scared to death in that chemical suit. I was in it for well over an hour. Did I want to take it off? No, I didn't want to take it off. I may have even doubled up on the pills. I don't know.

One thing that I am thinking about, when I went over to the United Kingdom and met with a lot of my comrades from the U.K. who were also suffering from Gulf War illnesses, was that they immediately pointed to the NAP pills. With it being licensed over there, they have a great concern. Do you have some ongoing studies that you have been doing that would point to some form of causation with these pills and are they concerned about it? Are they considering removing the licensure of the drug? Where does the U.K. stand? Do you know?

Dr. GOLOMB. I don't know the answer to that. I have had contact through Dr. Rostker with individuals in the U.S. who were doing research, but not——

Mr. BUYER. I will ask them that question.

The second question that I have, are you aware of Dr. Haley's work with multiple chemical sensitivity?

Dr. GOLOMB. I am aware of Dr. Haley's work, but I don't think his work is primarily directed at multiple chemical sensitivity.

Mr. BUYER. Well, it is indeed in combination with a lot of other things.

Dr. GOLOMB. Chemical combinations, yes. I am aware of his work, and there are also many others who are doing work on chemical combinations and synergistic toxicity.

Mr. BUYER. We would be also be interested in your ideas about how you can mold a couple of these projects together.

Dr. GOLOMB. Let me comment that looking at interactions among exposures is very difficult because, as the number of potential interactants goes up, the number of interactants goes as 2 to the Nth. I know that doesn't mean much to you right now, but, as an example, if you have 10 possible things interacting, there is over 1,000 possible interactions that one would need to look at. That is the reason, for example, why the FDA does not require when licensing drugs that they be evaluated in combination with other drugs and toxic interactions generally only show up as a result of people in the real world using those agents in combination.

There are strategies, and I proposed one in my report, for trying to narrow down the number of studies that would need to be done to evaluate multiple exposures in combination, but it is a difficult problem because of the number of interactions, the rate that the number of interactions goes up with the number of agents.

Mr. BUYER. I guess we are not as moved because we want you to find the difficulty. That is why we try to get science to be exact, although it is very difficult. That is why we are willing to fund it, to look at it so that we can understand it and so we don't run into those problems in the future. If you have some ideas, please share them with us. Not at this moment, but——

Dr. GOLOMB. They are in my report, and I would be happy to make them available as part of the record or however you would like.

Mr. BUYER. Thank you very much. I yield back.

Mr. STEARNS. I thank the gentleman.

I think we have completed our first round of questions for panel one. I want to thank you for your patience and the time that you gave us, and we will look forward to continuing this discussion.

If we could have now the second panel come forward: Dr. Sue Bailey, the Honorable Dr. Bernard Rostker, Dr.—the Honorable Frances Murphy, accompanied by Dr. Brown. If you folks would step forward. We would be pleased to have your opening statements at this point.

STATEMENTS OF DR. SUE BAILEY, ASSISTANT SECRETARY OF DEFENSE FOR HEALTH AFFAIRS, DEPARTMENT OF DEFENSE; HON. BERNARD D. ROSTKER, PH.D., SPECIAL ASSISTANT TO THE DEPUTY SECRETARY OF DEFENSE FOR GULF WAR ILLNESSES, DEPARTMENT OF DEFENSE; HON. FRANCES MURPHY, M.D., M.P.H., ACTING DEPUTY UNDER SECRETARY FOR HEALTH, DEPARTMENT OF VETERANS AFFAIRS, ACCOMPANIED BY MARK A. BROWN, PH.D., DIRECTOR, ENVIRONMENTAL AGENTS SERVICE, DEPARTMENT OF VETERANS AFFAIRS

Mr. STEARNS. We will start with Dr. Bailey.

STATEMENT OF DR. SUE BAILEY

Dr. BAILEY. Thank you.

Mr. Chairman, distinguished members of the committee, as you know soman and tabun are extremely lethal nerve agents suspected to be in the arsenal of our potential adversaries. There are no effective treatments approved by the FDA for exposure to these agents. However, the results of animal tests suggest that the use of PB as a pretreatment, coupled with standard post-exposure treatments may, in fact, be effective.

PB is approved by the FDA as a safe and effective treatment of certain neuromuscular disorders, as you have heard. But it is not approved for marketing as a nerve agent antidote. Therefore, it is classified as an investigational new drug.

DOD submitted to the FDA protocols under INDs and requests for waiver of informed consent for pyridostigmine in the Gulf. PB was considered a potentially useful pretreatment against certain nerve gasses. The Commissioner approved DOD's waiver request of PB, and it was administered to portions of the military personnel in that war.

Since the conclusion of the Gulf War, concerns have been expressed as to whether PB may have contributed to the illnesses we have seen in our Gulf War veterans. Today much of the research now being accomplished on PB is being done under the direction of the Persian Gulf Veterans' Coordinating Board. This Board is composed of representatives from the Departments of Health and Human Services, Veterans Affairs, and Defense. Right now, there are 26 scientific or peer-reviewed projects under way specifically addressing the health consequences of PB as a nerve agent treatment, and the funding for this research is now approaching $20 million.

These studies include evaluations of the interactions of PB with other chemicals such as insecticides or with physiological variables such as heat and stress. Several studies examine the interaction between PB and low-level exposure to nerve agents. Other research addresses susceptibility of certain individuals to PB because of their genetic makeup. Most of these ongoing studies, to date, reveal no definitive link of PB to the illnesses of Persian Gulf veterans, but we will continue with this very important research.

Among the many lessons that we learned from the Gulf War are the need to better validate the presence of lethal chemical and biological warfare agents in the area of deployment and to improve

the process of communicating to our service personnel, their families, and the American public.

In addition to our force health protection measures under way to better ensure these steps are taken, on September 30, 1999, President Clinton signed Executive Order 13139 entitled, "Improving Health Protection of Military Personnel Participating in Particular Military Operations." the Executive Order addresses the President's role under 10 U.S.C. 1107, a law that authorizes the presidential waiver of informed consent for the use of investigational new drugs for force health protection in certain military operations.

Based on 10 U.S.C. 1107, the rule established the standards and criteria the President, the Secretary of Defense, and the Commissioner of the FDA will use to consider the potential need to use an investigational new drug for force protection in a particular military operation without the informed consent of the affected military personnel. These standards and criteria are very detailed and exacting.

The next important action in establishing policy for the use of INDs for force health protection was the issuance by the Secretary of Defense of a directive incorporating the requirements around that Executive Order and the FDA interim final rule. Following involvement of multiple DOD components affected, I expect this to be issued early next year.

Finally, my responsibility as the Assistant Secretary of Defense for Health Affairs is to advise the Secretary on all matters pertaining to the health of our forces. As all of you know, the world has changed. As we consider the threat that our forces now face, we now must consider the horrendous complications wrought by chemical and biological agents. We know that the nerve agent soman is among the chemical agents in the arsenals of countries opposed to the United States of America. Soman is a rapidly lethal nerve agent. Standard treatments for other nerve agents are not effective against soman.

To counter soman, PB in conjunction with protective gear and post-exposure treatment is the best possible measure we have to protect the very lives of America's sons and daughters. PB is an essential element in the military medical defense against the use of soman by those enemy forces. If faced with a decision today to recommend or not recommend the use of PB for the protection of our troops, I would recommend PB be used. Pending FDA approval of PB for this indication, the Department will follow the guidelines of IND usage of PB as established in the statutes and in the Executive Order.

Thank you for the opportunity to meet with you today.

[The prepared statement of Dr. Bailey appears on p. 86.]

Mr. STEARNS. Thank you. Dr. Murphy.

STATEMENT OF HON. FRANCES MURPHY, M.D., M.P.H.

Dr. MURPHY. Mr. Chairman and members of the subcommittees, I appreciate the opportunity to appear before you today to discuss the possible health effects of pyridostigmine bromide on Gulf War veterans.

I am accompanied by Dr. Mark Brown, who is the newly appointed director of VA's Environmental Agents Service.

As you know, U.S. service members may have been exposed to a variety of hazardous materials during the Gulf War. Veterans, their families, and the VA have been concerned about possible health effects from exposure to the drug PB as well as other agents including depleted uranium, oil-well-fire smoke, vaccines, pesticides, chemical and biological warfare agents, and other exposures during the Gulf War.

Numerous independent reviews have previously looked at the existing medical and scientific literature to determine what is known about the health effects of these exposures. The findings have suggested that there is no single unique syndrome that explains all of the illnesses of Gulf War veterans and that some of the exposures at least are unlikely to have caused the health effects that are being experienced in Gulf War veterans.

Based on these findings and the recommendations of the reviews, the Federal Government has funded a broad range of research programs to investigate areas that are not well understood. Nevertheless, in its ongoing efforts to address Gulf War veterans' health problems, VA has been very clear that it has not ruled out any of the exposures as possible causes of Gulf War veterans' illnesses.

This Nation has made a very serious commitment to protect the health and to care for military service members and veterans. VA has supported this commitment by establishing health care programs, compensation and benefits programs and a national research agenda that has focused on the health needs of Gulf War veterans. DOD and HHS has spent almost $134 million over the last 6 years on 145 Federal research projects that are directly related to Gulf War veterans' health issues. The coordination of this research is the primary responsibility of the Interagency Research Working Group which functions under the auspices of the Gulf War Veterans' Coordinating Board.

PB was used as an investigational drug during the Gulf War as a pretreatment to reduce the toxicity of the chemical warfare nerve agent soman. Several external independent scientific committees have reviewed the medical and scientific literature on Gulf War health exposures and have not ruled out the possibility of long-term health effects from taking this drug. In fact, many of them have suggested further research.

Based on these reviews and other information, there is insufficient evidence to conclude that the health effects experienced by Gulf War veterans today are caused by exposure to pyridostigmine bromide during the Gulf War. However, it is clear that additional research is warranted to answer specific outstanding questions about the long-term health effects of pyridostigmine bromide, either alone or in combination with other exposures.

Based upon the recommendations of the previous reviews, the Research Working Group solicited and funded a number of research studies on the potential health effects of pyridostigmine bromide. Twenty-six such studies have been funded with a total estimated cost of almost $20 million. Five of the studies have been completed, and 21 are ongoing.

As you have already heard this afternoon, the RAND report discussed some hypotheses relating to how a brief exposure to pyridostigmine bromide during the Gulf War might affect the

health of Gulf War veterans today. We are fortunate that all of these hypotheses were considered by prior reviews; and, in fact, each of the seven hypotheses are currently being addressed by one or more research studies, which are listed in my full testimony.

As the Chairman noted in his opening statement, VA has contracted with the Institute of Medicine for a new study entitled, "Health Effects Associated with Exposures Experienced During the Persian Gulf War." the first phase will include a complete review of the literature not only on pyridostigmine bromide but on depleted uranium, vaccines, and organophosphate chemical warfare nerve agents. Also, as noted, we expect the results of that study to be available in August of 2000.

To summarize, since 1992 VA has implemented a comprehensive, coordinated set of programs to address Gulf War veterans' health problems. In doing so, we have tried to objectively assess the available published scientific and operational information concerning exposures during Gulf War service and sought the advice of numerous experts. VA is committed to providing quality health care and compensation for service-connected disabilities and to continue to aggressively pursue the answers to health concerns of Gulf War veterans and their families.

That concludes my statement before the committee this afternoon, and Dr. Brown and I would be happy to answer any questions.

[The prepared statement of Dr. Murphy appears on p. 90.]

Mr. STEARNS. Thank you, Dr. Murphy. Dr. Rostker.

STATEMENT OF HON. BERNARD D. ROSTKER, PH.D.

Mr. ROSTKER. Mr. Chairman and members of the committee, I appreciate the opportunity to appear before the Subcommittee on Health and Subcommittee on Oversight and Investigations to report on our efforts to bring forward work of significance for Gulf War veterans.

The Department of Defense and the RAND Corporation recently released the latest in a series of scientific literature reviews on potential health issues affecting Gulf War veterans. This work presents a great deal of information that wasn't available to the decisionmakers during the Gulf War. It is a thorough review of an important issue in the search of Gulf War illnesses. We believe this information is valuable both to Gulf War veterans and the continuing research on pyridostigmine bromide.

Mr. Chairman, the remainder of my remarks have substantially been covered by the first panel and by Dr. Bailey's testimony, so I would ask that the remaining remarks be placed in the record, and I would be happy to take any questions.

Mr. STEARNS. By unanimous consent, so ordered.

[The prepared statement of Mr. Rostker appears on p. 95.]

Mr. STEARNS. Let me open up the questions here.

Just as a general point, Dr. Rostker, does this RAND report get us any closer to understanding the Gulf War illness, in your opinion?

Mr. ROSTKER. I think all of our work gets us closer to that goal which we all share.

When we set out to enter into our investigations, we set forth two broad areas of concern. First, uniquely, my office was in a position to report on what happened in the Gulf, and that is a starting point for our veterans, for their concerns about their health as well as for medical research. It was important that we were able then to focus on things that might be more important than not, and as a result we commissioned RAND to undertake a series of reviews on issues pertaining to the health of veterans. This is one of a series. I think the fact that we are here today talking about it and our research is focused to answer questions that have been raised by the RAND report is an indication that we are, in fact, making progress.

Mr. STEARNS. Paul Sullivan of the National Gulf War Resource Center says in his testimony that last month the Pentagon finally, quote, reversed their longstanding position that PB pills were not associated with Gulf War illness, end quote. Does that surprise you at all?

Mr. ROSTKER. Well, I would suggest that that is incorrect in two regards: One, that would make it sound like we have demonstrated there is a connection; and the first panel, I think, addressed that issue. The second is that we have been saying to committees for the last 2 years, largely informed by the RAND work, that we were not as sanguine as we might have once been concerning this and that we were engaged in a review of our policy considering the use of PB policy articulated in the Executive Order. So I think on those two counts I would have to disagree with Mr. Sullivan.

Mr. STEARNS. Well, let's go on. Mr. Sullivan is going to testify in our third panel that Congress should look at funding immediately aggressive research and treatment into the neurological and other disorders that are related to what we heard on the first panel. Do you not agree with him?

Mr. ROSTKER. I think we are engaged in such research. I am not a physician, so when it comes down to specific issues of which protocol or what treatment regimen, I would have to defer to the physicians.

Mr. STEARNS. Knowing what you know today as a professional, do you think we should have immediate research into this? If you are sitting in my position around the table with other members here, what steps would you take in legislative—or do you think there should be any legislative——

Mr. ROSTKER. I would hope that you continue to support the administration in the funding of the medical research program which includes extensive research on PB. Moreover, I would hope that we would—we the Defense Department and the Veterans' Coordinating Board—would look at Dr. Golomb's paper, review it with an eye towards additional funded research in the area of the effects of PB.

Mr. STEARNS. Dr. Murphy, what do you think is the next steps for us, either for Congress or you folks, in this ongoing research?

Dr. MURPHY. Members of the research working group are currently doing an extensive review of the RAND report on pyridostigmine bromide.

As I had said in my testimony, many of the issues raised in the RAND report are not new. In fact, a lot of the research that is currently being done on pyridostigmine bromide focuses on the ques-

tions that are raised in the RAND report. Clearly, there are additional studies that could be funded to extend that research, and we will seriously consider which ones can potentially focus on those issues.

I would also point out that the IOM study will extend our knowledge in ways that the RAND study did not because it will look at the scientific literature, not just on the basic science and animal studies, but will look at the literature as it relates to human studies and epidemiology and to try to answer the question whether these exposures are, in fact, associated with health effects. The RAND report does not answer that question.

Mr. STEARNS. Good point.

Dr. Bailey, as I understand it, DOD looks to a panel of experts to help them on these research questions. What role has this panel played on previous decision-making on Gulf War research?

Dr. BAILEY. I believe that you are referring to the AFEB, the Armed Forces Epidemiological Board. They provide—they are independent researchers, by the way, even given the name. And they provide me with recommendations about research and review. They are invaluable as a research arm to those of us who work in health affairs and are very focused on the kind of research that we are talking about.

Let me just add, by the way, that there are currently 26 peer review studies under way. Twenty of those are DOD studies. In fact, the majority of those do relate the hypotheses that you have heard discussed here today. So you might have a flavor of that.

Let me just say that you may recall, trying to state in lay terms, that there was discussion of whether or not PB crossed the blood-brain barrier. We have, in fact, six studies that are Federally supported studies under way today that relate to that, the passage through that blood-brain barrier. You hear of individual differences in the reaction. In fact, we have nine studies that deal with that. And interactions with other exposures, which of course are a great concern to us given that the troops in the Gulf were exposed to so many different environmental and deployment exposures. We have 16 studies looking at interactions with other exposures as well.

Mr. STEARNS. You stated earlier that you would still today recommend the use of PB if we went back into the Gulf. Has that been a recommendation from this expert panel or is that—how do you make that statement? Is that just a statement that you feel based upon what research you folks have done? Who is backing that?

Dr. BAILEY. The panel that I mentioned would not be commenting on that particular policy issue. I would be making recommendations in my responsibility as the Assistant Secretary of Defense relating to force health protection. We must balance the risks of medical countermeasures with the risks of facing the consequence of an unprotected exposure to nerve agent attack.

Mr. STEARNS. I thank you. My colleague, Mr. Gutierrez.

Mr. GUTIERREZ. Thank you, Mr. Chairman.

Let me ask, if—we are all for taking every reasonable precaution to protect our troops. But there seems to be some question about the protective value at this point of PB. And it is PB—forgive me if I am wrong, Dr. Bailey or Dr. Rostker, is used against a nerve

agent known as soman? And after the Gulf War, was there any evaluation made whether our troops confronted soman? Did they or didn't they?

Mr. ROSTKER. No, they did not.

Mr. GUTIERREZ. Prior to the Gulf, what steps did DOD take to assure itself of the safety and efficacy of PB as a pretreatment adjunct to soman? Did they take any?

Mr. ROSTKER. During the Gulf War, there was suspicions that soman was in the arsenal of Saddam Hussein. And it was the best judgment at the time that—there was a War Board judgment—not just the United States, but this was the assumed, approved doctrine of all of our allies—that upon indications that nerve agents were possibly to be used and soman could be used that the appropriate way of protecting troops was through the administration of PB.

Mr. GUTIERREZ. So it was in your reasoned and value judgment, of the Department of Defense and the military——

Mr. ROSTKER. Department of Defense, the British——

Mr. GUTIERREZ. This is a great idea. We should use this. There might be soman, but there wasn't any found in the region used.

Let's assume that PB is effective as a pretreatment to soman. How will the Executive Order calling for the direct attention of the President and the Secretary of Defense when there is a decision to use investigational new drugs change current operation? Would guidance to unit commanders be more specific and clear? And what changes would be made?

Dr. BAILEY. Well, as you know, part of our concern about the Gulf War was our ability to track all of the exposures that were occurring with our troops. And our concern today about the use of pyridostigmine bromide is that, first of all, we hope we never have to use it. But, if we do, would we be able to do it with informed consent or would we have to waive that, given the battlefield situation?

I can tell you that a letter went out from me to our surgeons general of each of the services on July 22, 1999, discussing the training about the pyridostigmine bromide as a pretreatment stating that, in fact, we would have updated training information in all of the classes, in all of the pamphlets, manuals and publications that currently provide information on PB.

Mr. GUTIERREZ. I guess the point being that you used all of the best information you had at your disposal at the moment. You thought that soman may be there, so you used it.

I guess that is not the real troubling thing. I guess the real troubling thing is that you knew—you had to waive—you had to get a waiver. You didn't want to go around getting consents because, under normal circumstances, you would have to get consent to use this.

And now that we know that and now that we have this study in which the doctor testified that she wouldn't answer the question, if I recall correctly, whether she would take it or not—but she didn't say I would take it. She didn't sit back there and say, oh, no, there is no problem with it, I would take it. And when a doctor who has studied something for 2½ years says, well, I really don't want to answer that hypothetical, I wouldn't take it, given the fact

that we know that, is this going to help us in terms of the Department of Defense and the Veterans Administration kind of more assertively and more quickly responding to the growing demands of our veterans' population for treatment? And what are we going to do about it, given this study? Does this help at all? Does that change anything?

Dr. BAILEY. Let me just say that I don't want to be quoting Dr. Golomb, but I do believe it was in the testimony that she said she needed more information about the risk as well as the safety and efficacy, the risk of being hit with a lethal nerve agent which within minutes could kill without the pretreatment.

In the same regard, I would say to you that were I in that situation—and I was a member of the Navy Reserves and a general medical officer at the time of that war—I would have taken pyridostigmine. I, like Mr. Buyer, have taken the anthrax shots, and as a member of the Navy armed services I would have also complied because of the——

Mr. GUTIERREZ. I may have a real difficult time arguing with you and Mr. Buyer about what I would or wouldn't take, because the most I have worn is a baseball uniform. The pitchers have always been good so I never got hit. I say that with all sincerity.

But given this, given what we have learned from the Gulf War and given what we know about PB and given all that we know—I mean, they were subjected, it seems to me, to a lot of different drugs, chemical agents, a lot of different treatments. In recent experience, have soldiers ever received so many different types of treatments and then—in a short period of time come back home? Has that happened before and can you explain under what conditions?

Dr. BAILEY. If you were the catcher on that team, you would probably wear a face mask and other protective equipment. That is what we were trying to provide. You figure out what the possible risk is in a certain position and we were putting those troops in harm's way.

Mr. GUTIERREZ. Having said that, but doctors also say do no harm. I am sure my doctor, when he evaluates what risks I am going to take or we go to any professional and you are all professionals, you evaluate the risks versus the consequences. You just don't say, well, we don't know quite what the Iraqis have got, but we are going to just give them everything we think they may possibly throw at them. That is certainly not the situation that we are in. And so I just wanted to ask again, given what our soldiers confronted there—and hindsight is great. With 20/20 you see perfectly. Did our military ever confront a similar situation, and if so, when?

Dr. BAILEY. Let me just say as a physician, first of all, I agree. I attempt to do no harm. But if it is a lethal situation—let's say that I am facing cancer. I may give a patient a cancer drug that could harm the patient, but it is a lethal situation——

Mr. GUTIERREZ. As I stated earlier, Doctor, there is no reason to be defensive, because I will grant you that you did it given the best information that you had. So we agree on that. There is no questioning the integrity of the decision.

I have listened to Mr. Buyer, and if I were to take another position he would clear it up for me real quickly, as I know the gen-

tleman from Indiana would do quickly. That is really not where I am going. You and I are on agreement on that. But has it changed anything given what we learned in terms of how the military makes decisions about what its men and women are going to take in order to protect themselves?

And then my time is over. Thank you.

Dr. BAILEY. Yes, it has changed things, and we are being very specific in looking at the threat and also looking at all of the possible long-term consequences of any medication or pretreatment that we give.

Mr. STEARNS. I thank my colleague.

The chairman of the oversight committee, Mr. Everett.

Mr. EVERETT. I thank my colleague.

Dr. Bailey, did I understand you to say that of the 26 experiments or research projects going on now that 20 of them were in DOD?

Dr. BAILEY. Yes.

Mr. EVERETT. Where are you other six?

Dr. BAILEY. They would be a combination of VA, HHS.

Mr. EVERETT. VA and DOD? Who coordinates this?

Dr. BAILEY. Those are coordinated through VA and DOD. Specifically within the Department of Defense I looked to an organization called ASBREM, which is the armed services biomedical research arm of DOD. That is out of the MINC. They evaluate and manage—in fact, the VA-DOD Military Veteran Coordinating Board will have a research arm or working group that will also be participating. VA may want to add something to that about the coordination of all of these research projects.

Mr. EVERETT. Maybe not. Dr. Murphy.

Dr. MURPHY. Since 1994 we have had an interagency research working group. We feel that group really has served Gulf War veterans well. VA, DOD, and HHS meet on a regular basis to consider any new information such as the RAND report that may have been published and try to analyze that and see how it fits into previous priorities for research. Based on this review they also determine whether there is a need to refocus our research program based on the new information. It has been a good collaboration. For the first time, VA and DOD are sharing information dealing with the issues of active duty members and veterans in a collaborative effort.

Mr. EVERETT. Dr. Murphy, that is pretty much what I was trying to get to. I have been around this place long enough to recognize sometimes we are at cross purposes with each other and we don't even know it. What Dr. Bailey and what you are assuring me is that you have taken steps that there are no duplications within the projects and that is being looked after and we have no gaps developing?

Dr. MURPHY. We make sure that any duplication is minimized and any gaps are filled as much as possible. I would point out that Dr. Bailey and I began working together on these VA/DOD issues in 1994.

Mr. EVERETT. Great. What level of confidence do you have that these current projects that we are discussing here will answer the questions about PB as an antidote for soman? To what end will they answer the question that PB is an antidote for soman?

Dr. BAILEY. I have every confidence that the research is intensive and focussed in the appropriate way. It is being done by the right scientific personnel and with the right scientific methodology. I very much look forward to the outcome of these projects and hope that it will provide us with some of the answers.

Mr. EVERETT. My question was, what was your level of confidence?

Dr. BAILEY. On what scale?

Mr. EVERETT. One to 10 would be fine.

Dr. BAILEY. It is very high that it would answer the questions that I have just described to you. Some of the kinds of things that are being done in those research projects—I mentioned the ones already, but we are also looking at things like neurotransmitter dysregulation, neuromuscular junction effects, and in fact you heard earlier multiple chemical sensitivity mentioned. We are looking at every possible area that will provide us with answers. My confidence level I guess I would say would be an eight.

Mr. EVERETT. Thank you. Are there studies aimed at obtaining FDA approval for PB to be used by DOD?

Dr. BAILEY. We have a new drug application currently with the FDA that is under title 21 of the Federal Code of Regulations that is an application for this to be a licensed product. But none of these research projects in and of themselves would specifically be related to that application.

Mr. EVERETT. What is DOD's informed consent policy on giving military personnel in operations an antidote like PB? Is there an informed consent policy?

Dr. BAILEY. Well, first of all, investigational new drug applications or applying it in deployment settings or military medicine is very—rather rare. So I can think of there are only three times in the last 10 years that we have asked for a waiver of informed consent. That was tick-borne encephalitis and botox and pyridostigmine. So it is very rare that we encounter this.

Mr. EVERETT. What was the policy during the Gulf War concerning PB on informed consent?

Dr. BAILEY. That it would—in fact, we waived—we applied for and received a waiver of the informed consent.

Mr. EVERETT. And that was followed through? The military personnel were informed?

Dr. BAILEY. No, it was waived.

Mr. EVERETT. Waived. I see. I misunderstood you.

Dr. BAILEY. Still, every attempt was made to inform troops and I would share with you—in fact, I have the tablets with me. There was information on the tablets and information provided to the troops, albeit not what we would ordinarily do or would liked to have done or like to do in the future. We would go by all of the regulatory requirements set by the FDA for the use of an IND.

Mr. EVERETT. Should military personnel going to war be allowed to refuse antidotes or inoculations?

Dr. BAILEY. Should they be allowed to——

Mr. EVERETT. Refuse taking inoculations or antidotes for whatever?

Dr. BAILEY. That would adversely affect the ability of having, frequently, successful missions. It would endanger the service member at times and the comrades of that service member as well.

Mr. EVERETT. Thank you.

Thank you, Mr. Chairman.

Mr. STEARNS. Mr. Buyer.

Mr. BUYER. I think Mr. Everett in his last question really went to the heart of the issue. I have to think about this pill along with those who are questioning right now the efficacy of the anthrax vaccine and the anthrax program. I almost see parallels here Dr. Bailey.

Right now, we have a system set up in our military whereby if you don't have your shot record in order you are nondeployable. Why? Because you are a casualty before you begin. I don't know of a commander that wants that.

When I think about these parallels between the PB and anthrax—you have got to be thinking about it, too, Dr. Bailey—we have some tremendous responsibility here. Because shoring up the confidence of our soldiers, sailors, airmen and Marines, that when they are given an order to take a particular drug, obviously they know, if I don't take it, gee, I know what the alternative is, death. Or I guess I will flip the coin and take my chances versus a preinoculation.

It is easy for us to say, well, but it was FDA approved for these types of symptoms, but it wasn't for this, and we can get into the weeds. We can get into the weeds right now with the anthrax. Oh, it doesn't cover all strains of anthrax. You get into these little minutia debates.

I guess I go back to the beginning. Soldiers look at it pretty simple. Is it going to help me? I am going onto the battlefield, and they are going to be throwing this at me, give me everything that we have that will help protect me.

At the same time, we have tremendous responsibilities out there that they need to know. I really believe that they need to know more than what is just written on there. They need to be briefed on what are some of the possible effects. I don't know how you feel about that, but that is where I am sitting right now.

I did not move the legislation to prevent the anthrax program, and I have taken the recent briefing from GAO. There is some competing science out there at the moment. I haven't completely clarified it in my mind, but I am not stopping the program at this point. But there are some parallels out there that I see about the extension of trust and confidence to our soldiers.

I just wanted to make that comment to you because I know that you have got to be sharing that very same feeling.

Dr. Rostker, you have taken on a tremendous project in your years of study, so you will know exactly where different units were at different dates and times. It helps us move the causation. You are taking the tactical side of the house so we can link it to the science. With these—the PB pills, can you tell me about the Navy, the Air Force, the Army, the Marines, who were ordered to take these pills? My sense is that most of us that were on the ground or were forward.

Mr. ROSTKER. You asked the question about the Navy and I am not sure of the answer and we will get that for you.

It is my impression that everyone in theater that was considered to be in harm's way were asked to take the pills. We have a sense that about 250,000 soldiers took the pills. We don't have explicit records. We do not have explicit records to individuals. The best that we can do is answers to survey questionnaires about who took the pills and how often, and we have carried that out a number of times and we continue to——

Mr. BUYER. Are you going to take this endeavor on? You say if you are in theater and in harm's way—I have to assume that if you are in Riad when they were taking Scuds, Iran taking Scuds, KKMC, Bahrain—Bahrain you have got—you had Army and Navy that were there in Bahrain that were taking in Scuds.

Mr. ROSTKER. We know through the various survey instruments there is no population, I believe, that was excluded. Certainly no ground population; Air Force, Army, Navy, that was on the ground, and Marines. And I would have to check on the entire fleet, what the rules were for ships at sea. But there was—the pills were widely distributed and soldiers in all of the units that we know of were required to take them.

Mr. BUYER. All units were required?

Mr. ROSTKER. All the units that we know of through the surveys. We don't find any groupings where there was an entire area where soldiers were exempt from taking it, so we have soldiers forward, in the rear.

Mr. BUYER. Dr. Murphy, when soldiers come in and they want to be on the Gulf War Registry and they fill out a survey, are they asked the question have they taken these pills?

Dr. MURPHY. They were not initially. The original registry was focused primarily when it was designed in 1992 on oil well fires, and when we revised the registry questionnaire in 1994, we did add a whole series of questions on other exposures. Of the almost 20,000 individuals who have responded to the revised registry questionnaire, about 65 percent have reported that they believe they took pyridostigmine bromide.

If I could expand just a little bit on one of the relevant issues related to the question to Dr. Rostker. One of the studies that has not been talked about today that is interesting when you look at issues of whether PB, pyridostigmine bromide, might be related to the health effects in Gulf War veterans is a study that was done by the Canadian Defense Forces.

You may already know that Goss Gilroy was under contract in the Canadian forces to do a survey of their Gulf War veterans. And they were a group that really lends some information to the question of pyridostigmine bromide and health effects. They were part of the naval blockade and they had the ship named the Protector. The crew of that ship rotated out from early in the Gulf War. Some of them served from September through early winter and then they rotated the entire crew out and another group served from December through the Gulf War period, the actual conflict period. Only the conflict veterans on the Protector, that crew took pyridostigmine bromide, and yet the responses to their health status on this questionnaire survey was no different between the

group that we know was not exposed to pyridostigmine bromide and the group who probably took it. So, an interesting piece of information, at least from one group.

Mr. BUYER. Mr. Chairman, I know my light is on. May I have permission to ask one additional question?

Mr. STEARNS. With unanimous consent, go ahead.

Mr. BUYER. Thank you. On the claims of the undiagnosed illnesses, we have got around 8,300, that have been denied; 3,077 have been granted. Dr. Murphy, based on this RAND report, what action will the VA be doing in examining any of these claims that were granted or claims that have been denied with regard to some new information, or are we just going to stand at ease and wait for more research? How are you going to address the undiagnosed illnesses?

Dr. MURPHY. Well, Mr. Buyer, as you and the rest of the committee members are aware, VA doesn't compensate any veteran on the basis of an exposure. We assess disability. All of the symptoms that are reported in the RAND study as potentially being due to health effects from pyridostigmine bromide, are on the list of symptoms that can be compensated under the undiagnosed illness regulations. If a Gulf War veteran reports headaches, memory loss, muscle problems, et cetera, that are related to an undiagnosed condition, are chronic and result in 10 percent or more disability, they can be compensated today as they have been since 1994. So the RAND report really doesn't change the undiagnosed illness compensation or any——

Mr. BUYER. If we took the next study and funded it and actually showed a causal link, you say it would have no impact on the 8,300 cases that have been denied?

Dr. MURPHY. No. You asked the question related to the RAND study. However, the IOM report actually will be informative for VA's compensation policy. The IOM is looking for evidence that health effects might be associated with exposure to pyridostigmine bromide. If their review of the literature shows that there is sufficient evidence of an association or suggestive evidence of an association, the Secretary could create a presumption for conditions that have been found to be associated with PB exposure and grant service-connected disability. That is based on the law that passed last year, Public Law 105–368.

Mr. BUYER. Thank you, Mr. Chairman. I appreciate this hearing.

Mr. STEARNS. Sure. Mr. Hill?

Mr. HILL. Dr. Rostker, I want to make sure I heard you correctly. Did I hear you say that all the units are required to take PB, but only a third did?

Mr. ROSTKER. I don't know that. There was general release of PB. We don't have a unit-by-unit accounting. The decisions to use PB were quite decentralized. We believe, based upon the stocks used, that about 250,000 soldiers took PB, but we do not have an accounting, unit by unit, of which soldiers took PB or which did not. General units where PB was given, it would—the soldiers were instructed to take PB and supplies of PB were made available to them.

Mr. HILL. So I misheard you? Did I mishear you when you said only a third took it?

Mr. ROSTKER. About 250,000 we believe took PB.

Mr. HILL. But everybody was required to take it?

Mr. ROSTKER. I can't—I cannot say that. I don't know what the actual release was to each individual unit.

Mr. STEARNS. Mr. Hill, I think it is a very good question you have. How many people didn't take it, do you know?

Mr. ROSTKER. The estimates that have come out of the Gulf War, based upon the stockage and the amount used, was 250,000 soldiers took it. We have no direct accounting.

Mr. STEARNS. So that means roughly 250,000 did not take it?

Mr. ROSTKER. Would mean more than that did not take it. Two-thirds did not take it.

Mr. HILL. But I guess I will turn to Dr. Bailey on this, because you are the one that made the comment earlier in your testimony that by not taking it, you are actually putting other soldiers in danger; is that correct?

Dr. BAILEY. That could be correct ,given a specific situation. I think what you are hearing here, though, when we say that all across the theater that there were no exceptions as far as who was forward-deployed or where they were in theater, that doesn't mean that everyone was commanded to take it. It was a very discrete command given when the risk was considered to be high, and so there may have been areas where it was commanded and areas where it was not.

Mr. HILL. Well, clearly, though, there was some—there were an awful lot of people who were commanded to take it who didn't take it; and that then, based upon your testimony, is endangering other soldiers?

Mr. ROSTKER. I don't think we can say that. We don't have an accounting explicitly of who was told to take it and who was not told to take it. It was distributed around the battlefield and it was decentralized, as best we know, in terms of who was instructed to take it and who was not. We have not done—I can't directly report to the committee the command procedures of who took it and who did not, so I wouldn't want to leave you with the impression that there were soldiers who did not take PB when they were ordered to take it. I think the situation that Congressman Buyer describes is more accurate, but we have anecdotal information. We do not have a specific inquiry on the orders to take PB.

Mr. HILL. Let me—I want to make clear I want to understand clearly what you are telling me. You are not telling me that soldiers disobeyed orders?

Mr. ROSTKER. No, not at all.

Mr. HILL. Let me switch gears. Let me ask the question if we in fact discover that in future studies that PB does cause these side effects and these problems for our soldiers, is there any help that we can give them? Is there any treatment that we can give them that you know of, or is this something that they just have to live with all the rest of their lives and the only way to help them is through some kind of compensation?

Dr. MURPHY. At this point, there is no recognized illness related to PB or treatment for any of the potential effects, neurologic effects that might result from this. It would require randomized clinical trials to develop a treatment for these conditions.

Mr. HILL. Bear with me here a little bit, because one of the things, Dr. Bailey, that you said, that even though there are unanswered questions about PB and whether it shouldn't—you know, it shouldn't necessarily exclude it from future use—tell me what happens to a soldier who is exposed to soman without having taken PB? What happens to that soldier and however long a period of time?

Dr. BAILEY. You have heard a lot of talk about acetylcholine. The PB binds to the acetylcholinesterase but that is temporary and reversible. Binding by the nerve gas soman is irreversible and kills within minutes.

Mr. HILL. Within minutes?

Ms. BAILEY. It can kill within minutes.

Mr. HILL. So I take the PB and nothing happens to me.

Dr. BAILEY. You have to have taken the PB ahead of time, which is why we would command that it be given if we feel the threat is high.

Mr. HILL. If you know that there is going to be some side effects from all of this—I will get back to the line of questioning over here a minute ago—do you think that the military has an obligation, does it have a duty to inform the soldier that there is going to be possible side effects from taking PB or any other?

Dr. BAILEY. Whenever possible. Again in the use of an IND, if you do not have a waiver of informed consent, you conform to the regulations of the FDA and you do inform, orally and in a written form, about the possible side effects. And, yes, that is something that we would certainly do. We would follow all of the regulations of the FDA in the use of an IND, and that would include PB if there were no waiver of informed consent.

Mr. HILL. I see my time has run out, Mr. Chairman.

Mr. STEARNS. I think if any members want to go a second round.

Mr. EVERETT. Mr. Chairman, I would have additional questions for this panel.

Mr. SNYDER. Mr. Chairman, I never got a first round.

Mr. STEARNS. I am sorry. Mr. Snyder.

Mr. SNYDER. Thank you. I wanted to ask Dr. Bailey, a while ago Dr. Golomb and I were trying to think of a drug that had such variation if two people took the same dose; and I may have come up with one: Coumadin. I have certainly had people go off the charts and that is why we test for blood levels so frequently. In view of some of some of this information about the variation in blood levels and so on, has that led to any questions or research or the possibility of looking down the line where there may be a way of evaluating people for, oh, you are a high reactor or something, and we can't give you the drug or we have to give you lower doses; has that been part of your thinking or looking at in the future?

Ms. BAILEY. Clearly, I think it is one of the potentials we have here in terms of the research that is being done. We are concerned about the effects of any medication and pretreatment we give. If we could titrate the amount to be a lesser amount that would be safer and still be efficacious, we certainly would do so, and I think the research has the possibility of providing that.

I should tell you that in the FDA applications, there were human studies done since 1984 that showed very little difference between

gender, weight, or exposure to heat. But it is one of the things that we are now looking at again and concluding what is the amount that would give us the appropriate efficacy and protect against the deadly nerve agent and be the lowest possible dose that we could give and therefore the safest.

Mr. SNYDER. And, Dr. Murphy, in answer to Mr. Hill's question about was there a specific treatment, I assume that in your answer you are saying there is no one thing we can give you and make it all go away, but you certainly have symptomatic treatments. Where somebody has sleeplessness, you have ways of trying to deal with that; is that correct? It is not a hopeless situation for a constellation of symptoms that falls under this rubric we call Gulf War illnesses?

Dr. MURPHY. I think one of the things that we do have is very good symptomatic treatment for a number of complaints of Gulf War veterans, but in terms of curative treatment, we would have to look more carefully at.

Mr. SNYDER. One final question just for clarification. You mentioned the ship, and there was no difference; but my guess is the numbers would be pretty small to be—it would be doubtful it would be statistically significant; is that a fair statement? Is that an anecdotal? You described it as a piece of information.

Dr. MURPHY. I don't remember the exact numbers of the crew members, but it was under——

Mr. SNYDER. Thank you all. Thank you, Mr. Chairman.

Mr. STEARNS. I thank the gentleman. I didn't mean to overlook him because he gives great questions. We always appreciate his perspective, particularly as a doctor.

Before we go further, Dr. Bailey, you said you have a piece of paper which shows—talks about PB and was given to every serviceman when he got it. Do you mind if we have a copy of that; and I would like to make it part of the record.

Ms. BAILEY. I would be glad to give that to you. I should also tell you one of the problems with what was given was that there was good information on the sleeve. But some of the information was on the blister pack itself, so as you took the pills, you were losing some of the information. We have changed it and put it on the sleeve. The point being that we really want to get as much possible information out to the troops as we can. And there is extensive information on here today and an insert, and we will provide you with all that information.

Mr. STEARNS. If possible, we will just have a staff take it and make a copy. Can we make a copy?

Dr. BAILEY. It is hard to copy but if you can do that.

Mr. STEARNS. Mr. Buyer.

Mr. BUYER. Mr. Hill, maybe it is one of these things of instant death versus chronic illnesses.

Mr. HILL. I understand.

Mr. BUYER. That is a horrible choice, but at the same time we need to become comfortable whether or not it is causing the chronic illnesses. So we don't really need to jump—it is easy to jump to that conclusion. That is what is eager for us to say here today.

I have got three things I would like to cover. One is who is coordinating with Canada and the United Kingdom with regard to

their research projects to ensure there is not redundancy? Who is doing that?

Dr. MURPHY. I actually am on the Gulf War Advisory Committees for both Canada and the Medical Research Council in the U.K. We also have Colonel John Graham, who happens to be in the audience, who is actually stationed here in the U.S. and has an office with our Gulf War Coordinating Board in the VA Headquarters Building, so there is constant communication.

Mr. BUYER. Are you with the U.K.?

Colonel GRAHAM. I am a British army medical officer posted to Washington.

Mr. BUYER. That is great. Years ago I met with Nicholas Songs back when he wasn't too sure about all this either.

Colonel GRAHAM. You met with me too, sir, briefly.

Dr. MURPHY. I would also mention that we have an ongoing interaction with the Australian Department of Veterans Affairs and have been giving them advice on their Gulf War veterans programs. In fact, I was just on the phone with some of them this morning.

Mr. BUYER. I know this is rather unusual, but could I ask the British officer a question?

Will you be a little nervous if you were to stand up and speak on behalf of the U.K.?

Mr. STEARNS. I have to tell you we have had a hearing where we brought to the table different people in the audience, but I want the gentleman from England to understand that we can have him come at another time. He is not required to answer any questions.

Colonel GRAHAM. I would be happy to come another time or indeed answer questions for the record if you want to submit them afterwards.

Mr. BUYER. Would you be able to give us——

Mr. STEARNS. Mr. Buyer, maybe the appropriate way—and I think he is hinting at this—is if you would be kind enough to send him the questions, he would like to answer them in writing rather than being put on the spot at this point, without preparation.

Mr. BUYER. Mr. Chairman, you are so kind. We appreciate the coordination between the U.K. And the United States. We are great allies. And you owe the Chairman something.

Dr. Rostker, you are the one that when the President's Advisory Committee said it is A, you said, "but it doesn't look right, smell right, feel right." your instincts didn't—you didn't feel comfortable there. So you went with your instincts and said, no, we are going to take another step. Now that you have taken that next step, tell me about your instincts about how you feel, your comfort here, and where do you go next? I am telling you, you could have stopped right there but you didn't.

Mr. ROSTKER. We made a commitment when we took on this issue and created the Office of the Special Assistant to, in the words of the President, leave no stone unturned. And in all candor, when we commissioned, we commissioned the RAND work, and the report from the President's Advisory Committee came out several weeks later. It was a matter of weeks. And I had a discussion with the chairman of the President's Advisory Committee who suggested the RAND work would be duplicative; that they had researched all

of these issues, but she could not provide me with anything more than the 2-paragraph summary that was in the Presidential report.

I felt that I could not meet my charter, accepting someone else's work, so we commissioned the RAND work on that and on a number of other areas where we felt it would inform certainly our work and hopefully the work of others in the field.

RAND has reported so far on stress, on depleted uranium, on oil well fires and, as we said in the press conference, this was the first time that RAND did not reach a conclusion that the subject of their inquiry was not likely related to unexplained illnesses. I think we made the right call.

I truly lose sleep over the issues that we have discussed here because, just as you understand from your times as a combat soldier, it falls on us to get this right. It would be terrible if we ordered soldiers to take a pill that eventually resulted in their harm. It would be equally terrible if we denied them the full protection that was our best assessment at the time. That is, the latter is what we did. I think we made the right decision. We do need to answer these questions for the future.

DOD truly is a learning organization and these lines of inquiry are terribly important so we get it right for the future, but that doesn't mean that we made a mistake in the past. We truly believed, on the best data available, that we were protecting our soldiers.

Mr. BUYER. Thank you, Dr. Rostker. Thank you, Mr. Chairman.

Mr. STEARNS. Thank you, Mr. Buyer. Dr. Snyder? Mr. Hill?

Dr. Rostker, I think your final comments are very appropriate and I think it—I think most of us pray that you do have—will be able to make the right decision considering the magnitude of it. And I think we are going to see something, someday, somewhere like the Gulf War again, and so these decisions will have to be made again. And America's young men and women are looking to you, Dr. Bailey and Dr. Murphy and others, for that right decision. And we here in Congress can only look back in hindsight and try to, in our small way, to try to understand it better and to try to legislate to protect and do no harm.

And I think we have no more questions. We want to thank the second panel.

And now we will have the third panel if they will come forward. Panel number 3 is Mr. Matthew Puglisi, Director of Veterans Affairs and Rehabilitation, the American Legion; Mr. Paul Sullivan, Executive Director of the National Gulf War Resource Center; and also we have invited Denise Nichols, Vice Chairwoman of the National Vietnam and Gulf War Veterans Coalition.

We are pleased to have all of you folks and we are prepared for your opening statement. Let's start with Mr. Puglisi. Would you start with your opening statement?

STATEMENTS OF MATTHEW L. PUGLISI, DIRECTOR OF VETERANS AFFAIRS AND REHABILITATION, THE AMERICAN LEGION; PAUL SULLIVAN, EXECUTIVE DIRECTOR, NATIONAL GULF WAR RESOURCE CENTER; AND DENISE NICHOLS, VICE CHAIRWOMAN, NATIONAL VIETNAM AND GULF WAR VETERANS COALITION

STATEMENT OF MATTHEW L. PUGLISI

Mr. PUGLISI. Thank you, Mr. Chairman and members of the committee. Thank you for the opportunity to offer testimony regarding the possible health effects of the drug pyridostigmine bromide, or PB, on veterans who served in the Persian Gulf War. Thousands of Gulf War veterans continue to suffer symptoms associated with the military service in the Persian Gulf. The American Legion has consistently urged that all possible causes and all adverse health outcomes related to Gulf War veterans be investigated. It is imperative that we understand what has made these veterans ill and what particular illnesses they suffer from. We are all here today to help improve their health and the well-being of their families.

The recently released report on PB by RAND, which is the event that sparked today's hearing, is one component of a vast $100 million-plus research effort investigating Gulf War veterans' illnesses. Unfortunately, the RAND PB report does not answer the question regarding PB's possible association with Gulf War veterans' illnesses. Rather, it argues that questions concerning PB and veterans' illnesses remain unanswered and merit further investigation.

This finding is maddening to sick Gulf War veterans. Above all, they want to become healthy. Short of that, they want answers. Those answers are no closer today, however, than they were at the end of the Gulf War. Although the report did not answer the most pressing question regarding PB, it raised some other ones regarding PB's effectiveness as a nerve agent pretreatment and its safety. This aspect of the report validates the American Legion's long-held position against PB's use as a nerve agent pretreatment.

The American Legion continues to urge the Department of Defense to suspend its policy of using PB until its efficacy and safety are proven. DOD maintains that it will only order U.S. troops to take PB in an event that there is an imminent threat of attack of soman against those troops. Legislation signed last year requires that the President authorize the use of PB by U.S. troops. One would imagine that DOD would have to be very confident in future intelligence assessments to ask the President to issue such an order.

Given all that we have learned about chemical weapons, their use in past wars, and their non-use in the Gulf War, is PB really a viable defense against a soman attack? The evidence suggests otherwise. "morale is to materiel as three is to one." so said Napoleon, a man who knew a little something about how to win battles. PB could undermine troops' morale in future wars and their confidence in their commanders at the very moment when their mental state is most critical. And I think no one said it more eloquently than Congressman Buyer regarding how troops feel at the moment before a chemical attack and how they approach the risks and the dangers that are inherent in military service, especially in combat.

But commanders will not issue PB in a future war in a vacuum, and this gets at Mr. Buyer's comment regarding some of the similarities between the controversy of the anthrax vaccination program and this issue. I think that hits the nail on the head. Young Americans, aware of Gulf War veterans' illnesses, Agent Orange, and the controversy over the anthrax vaccination program, will be ordered to take a drug whose effectiveness and safety are under serious scrutiny.

DOD argues that operation requirements may require that PB be issued. Yet it may very well be the height of folly to order troops to ingest the drug that is being investigated for its role, if any, in Gulf War veterans' illnesses while the same troops await attack with a chemical weapon that can kill them in minutes. Commanders need a rational doctrine that takes into account history and human warfare, not one that ignores the two.

During the hours before the bullets fly, troops need as much certainty as their commanders can muster, not further uncertainty and added risk.

The RAND PB report outlines several hypotheses that merit an investigation regarding PB's possible link to Gulf War veterans' illnesses. It is encouraging to learn that scientific studies underway are investigating these hypotheses and the American Legion remains hopeful that these studies may answer the outstanding questions regarding PB's safety.

In the meantime, it is imperative that Congress maintain an active role in overseeing the Federal Government's response to Gulf War veterans' illnesses. Only through active oversight will disabled Gulf War veterans' health have a chance to improve.

This concludes my statement, Mr. Chairman, and I would be happy to answer any questions.

[The prepared statement of Mr. Puglisi appears on p. 99.]

Mr. EVERETT [presiding.] Thank you, Mr. Puglisi. Mr. Sullivan.

STATEMENT OF PAUL SULLIVAN

Mr. SULLIVAN. MR. Chairman, members of the subcommittee, thank you for the opportunity to testify on behalf of the National Gulf War Resource Center regarding the adverse health effects of pyridostigmine bromide, an investigational new drug given to as many as 250,000 U.S. soldiers during the Gulf War in 1991. In hindsight, the history of the Gulf War may show the well-intended use of PB pills backfired, resulting in an untold number of U.S. Gulf War casualties. Similarly, the demolition of Iraqi chemical warfare agent stockpiles, the use of depleted uranium ammunition, and the presence of other toxins could very well represent the world's largest friendly-fire incidents all rolled into one never-ending conflict.

The mission of the National Gulf War Resource Center is narrow: It requests our government to determine why so many of our comrades are ill and disabled, to provide medical treatment to those in need, to provide compensation to the disabled, and to learn from mistakes made in the Gulf War so that future toxic exposures and illnesses may be reduced or prevented.

The Resource Center is here today to restate our justifiable anger and disappointment at the Pentagon for failing to admit earlier

that PB pills cannot be ruled out as associated with some of the illnesses reported among some Gulf War veterans. The DOD has possessed some of this information for years. Gulf War veterans have been aware of the possible side effects since 1991 due to our battlefield experience taking the pills.

Once the decision to use PB was made, the U.S. Government accepts responsibility for the consequences of the health of the U.S. soldiers. The military remains for the most part unresponsive to calls by Gulf War veterans for more research and treatment not only on PB pills but on other matters including oil well fire particulate matter, depleted uranium radioactive toxic waste, the anthrax vaccine, and low-level chemical warfare agents, among others.

What we would like to do instead of discussing the history is to urge Congress to review three main issues. The first is to consider funding immediate and aggressive research and treatment into the neurological and other disorders found believed related to PB. This includes, as was mentioned, synergistic effects of PB and other toxins and the possible genetic predisposition of some veterans to be at higher risk for adverse effects to some toxins, as was found by Dr. Robert Haley, a researcher with the University of Texas Southwestern Medical Center at Dallas. The Resource Center strongly supports full funding of the Gulf War illnesses research in an agenda developed by the Centers for Disease Control and Prevention earlier this year.

Second, the National Gulf War Resource Center would urge Congress to hold hearings on the VA's role in granting direct service connection for any new conditions science associates with taking PB pills, either alone or in combination with other toxins. Once direct service connection is established, then Gulf War veterans should be provided appropriately with existing symptom-based treatment or any new treatment modalities found to provide any relief.

Third—and this is very important for the long term—the Resource Center urges Congress to investigate a major lesson from this PB controversy. After Congress began funding PB research in 1993, adverse effects were subsequently found. Congress should consider funding additional specific research into the adverse effects of the anthrax vaccine, oil well fire particulate matter, and other Gulf War toxins.

Specifically in 1993, Congress funded research on inhaled, ingested, and embedded depleted uranium. DU is a radioactive toxic waste used as ammunition. However, the DOD chose to research only embedded depleted uranium shrapnel. The Resource Center urges Congress to investigate the failure of the Pentagon to research inhaled and ingested DU in accordance with Public Law 103-160. The bill was introduced by Representative Evans and Representative Buyer. Mr. Evans was here earlier and Mr. Buyer is here now.

On April 15, 1999, Bernard Rostker in his dual role as Under Secretary of the Army and Special Assistant for Gulf War Illnesses was asked by the Resource Center to conduct research on inhaled DU. Rostker publicly refused, saying there was, quote, "no need," end quote, to conduct research on inhaled DU.

In a 1999 report prepared for DOD, RAND recommended more research into depleted uranium. Several peer-reviewed, published research reports from the Armed Forces Radiobiology Research Institute, part of the Pentagon, recommended research into the possible links between cancer and depleted uranium. The Resource Center asked Congress to hold hearings on how Bernard Rostker and Army Colonel Eric Daxon may have undermined the intent of Congress. The Resource Center believes objective, independent research on inhaled and ingested depleted uranium must begin soon.

In conclusion, the Resource Center finds that the military failed to collect data regarding PB exposures, ignored the claims made by Gulf War veterans and scientists regarding PB pills for years, and delayed research into the adverse effects of PB. So we thank Dr. Golomb for her work with RAND that was ordered by the Pentagon after so much public outcry.

The preliminary findings now strongly suggest problems associated with PB pills, thus vindicating Gulf War veterans and scientists such as James Moss and others. Additional research and treatment must be launched in earnest. This concludes my testimony.

I ask that a letter dated November 5, 1999, sent from the Military Toxics Project to Representative Lane Evans be included in the record, Mr. Chairman.

Mr. EVERETT. Without objection. Thank you, Mr. Sullivan.

[The prepared statement of Mr. Sullivan, with attachments, appears on p. 103.]

Mr. EVERETT. Ms. Nichols.

STATEMENT OF DENISE NICHOLS

Ms. NICHOLS. Good afternoon, Chairmen Stearns and Everett and committee members and staffers and those in attendance today.

The National Vietnam and Gulf War Veterans Coalition, composing 102 grassroot organizations, are glad to be here today and welcome the opportunity to testify to you. We welcome the recent release of the OSAWGI RAND Report on Pyridostigmine Bromide. We wish to point out that the information presented in this report in 1999 has been openly available since 1994.

Senator Rockefeller, in his Senate Veterans' Affairs Committee report in 1994, discussed pyridostigmine bromide. There was some discussion in the Presidential Advisory Committee investigation. Last year's Senate Veterans' Affairs report referenced it, and I believe their chapter had a lot of influence from Dr. Jim Moss. We also have had the Shays committee hearing in the House Government Reform Human Relations Committee that went on for 3 years.

So if not stronger recommendations to continue studying, the information has been there. We would like to encourage you that in January when you come back into session that you continue these hearings on pyridostigmine bromide and bring those experts that have testified before. We need to have stronger interaction between the House and Senate and the different committees to coordinate the information that is being presented.

The Gulf War vets sometimes have a feeling that we are repeating information at different time periods and it gets very frustrating for them. We repeatedly listed all the exposures that occurred in theater. We have also been quite open in saying that the response to our illness has not been treated in the urgent emergency manner as is necessary. These illnesses are neurological and immune system in nature.

I can say as a nurse with over 20 years of experience and a master's degree, that what we veterans are seeing is truly an emergency situation that has not been dealt with in the manner that it should be. These illnesses are devastating and warrant the strongest actions that we can mount as a Nation. This is not about runny noses and feeling poorly. This is about extreme fatigue and muscle weakness that interferes with the ability of people to live a normal life and to support a family. We are talking about illnesses like ALS, Parkinson's, like multiple sclerosis, aggressive cancer, and documented brain stem damage. We are talking about memory loss, to the extent that the Gulf War veterans become disoriented and lost in driving around their hometowns that they have known for a lifetime. It is about having blackouts while driving. It is about normal 20, 30, 40, and 50-year-olds that are not able to function as walking adults and head their families. It is about deaths at an early age. It is about family members who are also showing illnesses with the same symptoms as their Gulf War veteran spouses.

One question I have that I will put in here is how can PB be passed to family members and have them showing symptoms? We in the last months have lost one of these wives, 2 weeks ago. That was getting the same answers and tentative diagnosis as MS-like and sarcoidosis as her husband the veteran was receiving. She died.

These are people, veterans that should be in the prime career-building and family-building time of their lives. That is why this situation should be treated differently than we have traditionally treated post-war illnesses. We should already have learned the lessons well from the atomic vets and Agent Orange veterans. We need to treat these veterans with a new "gold standard," as I call it. Compensation shouldn't be a battle to be fought with your government after you have served that same government with no question asked.

We have experts who have been with the veterans since early 1993. Dr. Jim Moss testified on pyridostigmine bromide in 1994; Dr. Abou-Donai who did studies utilizing hens at Duke university; Dr. Thomas Tiedt who came forward at a Presidential Advisory Committee and at the Shays committee, who was part of the U.S. Army Medical Research team in the 1980s that warned even then that this drug should not be utilized. We have Dr. Hailey and Dr. Baumzweiger who have also come forward to testify on brain stem and immunological immune system damage that Gulf War vets are exhibiting. We welcome other funding of research studies.

We would most likely—we would like to most strongly recommend that clinicians like Dr. Baumzweiger and other clinicians be funded fully, quickly, so Gulf War veterans can seek effective treatment and care. We also want the extension granted for family

members that are affected past the current deadline of December 1999.

Dr. Rivijani out at the Presidential Oversight Committee in Seattle said quit chasing for Agent X. It is probably all of the above in combination. We would like to recommend that those veterans who are Gulf War era veterans who did not serve in theater who were given shots or dealt with equipment returning from the Gulf, and who are experiencing the same symptoms, be included in the registry and provided care just as the Gulf War veterans who served in theater. They need to be placed on the registry and coded as non-deployed.

We also must not forget our veterans who served in theater as early as 1988 and then, after the Gulf War, 1991. They too are suffering from these symptoms, as well as our civilian contractors that served both in theater and out, who have reported in as ill. We have categories of people in theater who didn't take pyridostigmine bromide that are reporting ill. We have those that are reporting ill that took the tablet over a limited time as compared with others who took pyridostigmine bromide over a longer period of time. So we still have not found the magic bullet.

I have said all along, as well as other experts have said, that it is a combination and synergistic combination of all of the various exposures. We now come to a time that we must ask and push for a blanket compensation under an emergency immediate category for these veterans. I have prepared a point paper before and presented it to the Oversight Board and to the Institute of Medicine. I am including it today as an appendix. It is kind of a road map of simple-point things that we can do to take care of our vets better. One of those 36 points is meant to meet the emergency needs of these veterans. If FEMA can meet the needs of civilians in natural disaster situations, why can't we utilize an approach like that to help our Nation's Gulf War veterans, many of them out there unable to support their family, not getting VA compensation——

Mr. EVERETT. Ms. Nichols, are you close to summing up?

Ms. NICHOLS. Yes, I am. As a nurse, I would like to say we have the patients gathered. They are in the triage area. They are bleeding. I can't say do no further harm. It is time to start taking action and providing some kind of care, treatment; and yes, we welcome other hearings and funding, but those patients are here and they are bleeding, sir, and they are dying. So we must move forward rapidly. Thank you.

Mr. EVERETT. Thank you.

[The prepared statement of Ms. Nichols appears on p. 121.]

Mr. EVERETT. Before I proceed any further, let me do a little housekeeping here, I am going to submit the remarks of Honorable Corinne Brown who is the Ranking Member of the Investigations Oversight Subcommittee. I will make sure that is a part of the record.

[The statement of Congresswoman Brown follows:]

PREPARED STATEMENT OF HON. CORRINE BROWN

Chairman Stearns, Chairman Everett, Ranking Members Evans and Gutierrez, I am pleased to have this opportunity to examine yet another aspect of the Gulf War illnesses, which have taken such a toll on American veterans. This mixture on diag-

nosed, undiagnosed and misdiagnosed maladies has wasted so much of the vitality of these gallant men and women, who thought they had come home unscathed from a war we seemed to have won at little cost. My heart is with them in their disability and pain.

What we used to call "Gulf War Syndrome" is turning out to be a series of rare, hard-to-diagnose, overlapping illnesses of a debilitating nature that are environmentally linked. For a number of years, medical science looked for a single explanation, checking symptoms against possible exposures. Now it seems clear that a number of toxins and other causes affected some veterans not at all, and others in differing ways.

A newly-written report on the illness-related claims of Persian Gulf War veterans, for example, released recently by the Ranking Democratic Member of the House Veterans Affairs Committee, Congressman Lane Evans of Illinois, points to several potentially useful areas for further research into the unusual illnesses of Gulf War veterans. We are concerned that there has been little analysis and research involving the various groups of veterans who have filed claims with the Department of Veterans Affairs (VA) related to undiagnosed illnesses.

Our staff has updated information concerning the disposition of these claims, and the results stand out like highway markers. The report is drawn from data supplied by VA's Veterans Benefits Administration. VA's data show that:

- Veterans who were potentially subject to toxic agents at the port of A1 Jubayl and the Khamisiyah pit are more likely to file a claim for service-connected disability benefits than other veterans serving during the conflict or in the Gulf after it ended.
- Khamisiyah veterans are more likely to be receiving a disability pension based on a permanent and total disability which VA has determined is unrelated to military service than other Gulf veterans.
- Women service members in all groups who served in the Gulf are more likely to be service-connected for undiagnosed illnesses than their male counterparts.

Why are Khamisiyah veterans almost twice as likely to be permanently and totally disabled than other Gulf War veterans? Does this suggest that some mechanism associated with the conflict period is responsible for these illnesses? Women veterans in all groups have a higher rate of compensable service-connected undiagnosed illnesses than their male counterparts. Why?

Likewise, Representative Lane Evans, along with Representative Bob Filner of California, Ranking Democrat on the Subcommittee on Veterans' Benefits and Senator Russ Feingold (D-WI), recently wrote to Secretary of Defense William Cohen, expressing concern about Depleted Uranium (DU). Recent findings from a study by the General Accounting Office (GAO) that Mr. Evans commissioned cast doubt on the accuracy of Department of Defense studies to reconstruct the exposure of Persian Gulf War veterans to DU. GAO found clear indications that some veterans may have received far greater exposures than have been assumed. Errors in methodology caused the Army to significantly underestimate probable exposure, GAO found.

We must focus attention on the needs of these veterans. I commend the VA for improving its ability to provide better information concerning the claims filed by Gulf War veterans. I remain concerned, however, that many Gulf veterans are still having their claims denied, particularly claims associated with undiagnosed or poorly defined disabilities.

I am concerned about the narrow focus of the RAND study, but we do need to know more about pyridostigmine bromide. I hope today's hearing helps us in thinking about what we need to learn next.

Mr. EVERETT. We have some tough practical issues when trying to defend our troops—excuse me just a second. A little more housekeeping. I am sorry.

How do we defend these troops, especially when we know that we are against an adversary that uses nerve agents like soman, or any other lethal chemical weapons? In that respect, I will ask each of you, do you believe it was appropriate for the Department of Defense to use PB for the purpose of protecting our troops in the Persian Gulf from the nerve agent soman, based on what was known then, not what is known now but what was known then, and also the fact that we knew that the Iraqis used chemical agents and

killed a number of people before? We can start anywhere. Mr. Puglisi, we will start with you and just move down the line.

Mr. PUGLISI. Sure. Mr. Chairman, looking back, I think there is a consensus amongst those who have testified, amongst those on the committee, that based on the information that was available in 1990 and 1991, there doesn't seem to be any reason why PB should not have been used, given the threat and given what was known about PB at that time. But it is important to remember that the Iraqis chose not to use chemical weapons because of threats the U.S. made in the case that they did use chemical weapons and not because of our chemical protective gear or the use of PB. They didn't know whether or not our troops were getting PB but they certainly knew, as they were told by Secretary of State Baker, that they would pay an awful price if they used chemical weapons. And it is our argument that the best defense that troops then and today have against chemical weapons is a credible threat by the United States to respond disproportionately to any use of chemical weapons, and not any kind of measures that we can take individually with troops.

Mr. EVERETT. Mr. Sullivan.

Mr. SULLIVAN. Mr. Chairman, you asked a very important question. The National Gulf War Resource Center's position on the use of the pills is that it was well-intended. The Pentagon was trying to do the best thing possible in the worst case scenario of war. Was it appropriate at the time? Yes, I would concur with Matt on that.

There is one thing that is different that the National Gulf War Resource Center did. In 1997, we supported the Chemical Weapons Convention, which was the treaty to basically stop producing and proliferating chemical weapons, and we believe that the best way to prevent having to force the soldiers to take the pills is to remove the threat from the battlefield all together. That is why we supported that treaty and it is now the law of the United States.

Part of the problem of the Gulf War soldiers—and I am one of those who was on the front lines—I was a cavalry scout when they gave us the pills. We took them right away. We didn't think about the Nuremberg Code. We didn't think about a whole lot of other things. We just wanted to live. But in retrospect, after the war, I went back to college and then I went and got a degree in political science and started studying international relations, and I started to realize that it was some American companies and Western European companies that we believe negligently sold dual-use chemicals as well as technology to Iraq that allowed them to be a threat in the first place. So it is a very complicated answer involving the Pentagon trying to do the best at the time, but also we painted ourselves in the corner.

Mr. EVERETT. Thank you. Ms. Nichols.

Ms. NICHOLS. I think everybody in the fog of war, the best decisions were made with the best information available at the time. I believe some of the research that had been done in the eighties, like Dr. Tiedt's research, was not circulated, evaluated quickly enough. We have got to change that so that as research is being done, it is pushed out there to the community, to the commanders, to make decisions maybe better in the future.

But I think the thing we can say is that at the time, the commanders, people in charge of the troops, made the best decision they could. Since then we have seen reality.

Mr. EVERETT. Let me ask each of you this. If we deployed our military today against an enemy that we knew had and would use this deadly agent soman, would you suggest that they use PB?

Mr. PUGLISI. Mr. Chairman, again, in——

Mr. EVERETT. I am not saying we need a great deterrent and wipe them off the face of the Earth. That may or may not work. I don't think we can depend on that working every time.

Mr. PUGLISI. It worked in 1991 and may very well work again.

Mr. EVERETT. It could or could not. That is not the question I am asking you. I am asking you, would you suggest if we are facing an enemy that we know has used it and will use it, has demonstrated they would use it, would you suggest using PB?

Mr. PUGLISI. Based on the research that has been done to date, and Dr. Golomb did a good job in sort of outlining it, we don't know if PB is effective as a nerve agent pretreatment adjunct. We think it is, but we don't know that it is.

Mr. EVERETT. Therefore your answer would be?

Mr. PUGLISI. And we would not support the issuance of PB in the future, no.

Mr. EVERETT. Thank you. Mr. Sullivan?

Mr. SULLIVAN. Mr. Chairman, the Resource Center doesn't have an official position on the use of PB now. We do have a position on the use during the conflict period of 1990-91 in the Gulf War, and that was that it was a mistake. I would like to preface that by adding something. Once the decision to use PB was made, the U.S. Government accepted the responsibility for the health care consequences, so I would argue that if the decision is going to be made, that Congress and the VA and the DOD all be cognizant of the long-term consequences of such a decision, because I am glad I am alive today and we took the pills back then; but there is also the flip side of where would all those generals be today if we just now learned that there was a pill out there that could have helped some people? So again, you raise a very important question. We can say in hindsight that it was a mistake, and we definitely want the Pentagon to make much better and judicious use of such drugs in the future.

Mr. EVERETT. I really have to wonder, you know, if it did not happen the way it did and we did not have a PB pill out there or use it and we had casualties, what the public reaction would have been against the Department of Defense not using the PB.

Mr. PUGLISI. The Department of Defense has rightly pointed out that very thing; that if they had made that decision, then the question would have come up afterwards.

Mr. EVERETT. Some liability there I would say also. Ms. Nichols?

Ms. NICHOLS. Interesting that you put me on the spot here on that question, because as a nurse——

Mr. EVERETT. All of you understand these are very hard questions.

Ms. NICHOLS. As a nurse, I took the pills. I believed. I took the pills, took the anthrax, all those things, just like Congressman Buyer. Now having done the reading, would I take them? Would

I pass the order on to my troops as I did in the past? There is doubt in my mind and I have to say that out loud. I know that the decision at the time was made with the best information, but what we know now, no. I have one individual that I know of out of my unit that didn't take the pills and she is not having the problems I physically am having and others that did take the pills. But I also know others that didn't take the pills that are sick also, so——

Mr. EVERETT. There is some question in your mind?

Ms. NICHOLS. Oh, yes, sir.

Mr. EVERETT. My time has run out. Dr. Snyder.

Mr. SNYDER. Thank you, Mr. Chairman. By way of explanation—by the way, since your panel began, we have had a slow diminishing of our staff and members here because there is a bill, veterans' bill coming up on the House floor that is either being discussed right now or is about to be discussed. We apologize for that. But it was very important to the Chairman of the committee to go to it.

I don't have a question, but in Mr. Sullivan's statement, there was a number of comments made about depleted uranium. And Dr. Rostker, if we could have the staff prepare questions for Dr. Rostker for the record, just to give him a copy of Mr. Sullivan's statement and ask him to comment for the record, and we share that with this panel also. Thank you all for your testimony today.

Mr. EVERETT. Now my classmate and very favorite cleanup hitter in Congress, Mr. Buyer.

Mr. BUYER. Thank you, Mr. Chairman. I think that is very prudent, Dr. Snyder, because I think Dr. Rostker has felt that some recent research has shown that some of the fears about the use of depleted uranium are subsided. I think your question is very prudent so everybody could know and learn that information.

Ma'am, you said we still have not found the magic bullet. I concur with you. But there is no such thing as the magic bullet. It is more like a shotgun shell of birdshot and that is what we are trying to find is the birdshot that is out there. It is a lot of different things.

To the American Legion, did you just make up American Legion policy on the spot? Or did you come here with American Legion policy and espouse it? You answered the Chairman's question. I just want to be very clear because I am part of that American Legion, and I don't ever remember having been informed that that is American Legion policy. Would you clarify for me and make me feel comfortable?

Mr. PUGLISI. Sure, Mr. Buyer. Like everybody involved in this issue regarding Gulf War veterans' illnesses, but particularly regarding PB, its relationship perhaps or not with the illnesses Gulf War veterans have today and its potential use again in the future, there has been a lot of debate within the American Legion, as there has been within other circles, regarding what is known about PB, what is not known, what is known about its effectiveness and what is not known, and its potential use in the future. And the American Legion, as you know, Mr. Buyer, is a Democratic organization. At our national convention for the last several years——

Mr. BUYER. Have they voted on a resolution saying that PB——

Mr. PUGLISI. We do not support the use of PB as intervention pretreatment adjunct. The American Legion does not say that PB is causing Gulf War veterans' illnesses because, as we all know, we just don't know whether or not there is a relationship. But the American Legion doesn't support its use and, as you know, within the American Legion, there are retired generals and admirals. There are the people who, like Dr. Bell and others from the Department of Defense, have to make those god-awful decisions that are really on the horns of a dilemma, as you pointed out earlier. It is chronic long-term health effects versus perhaps instant death. That is a tough decision to make.

Commanders, as you know, make those very difficult decisions all the time in combat. Do I send out this patrol? Do I clear this minefield now? Do I wait? Any kind of decision that the commander makes has risks for troops. Even wearing a helmet and flak jacket in a desert environment has some risks. We are not trying to put ourselves in the place of those who make those decisions or pretend we are those people, but as the Nation's largest veterans' organization, we felt it was important that we not stand on the sidelines.

Mr. BUYER. I am rather surprised that the American Legion would take that position. I just want you to know that for the record. I am surprised, and I will respect Mr. Sullivan because I perhaps agree with your answer a little bit more. The American Legion has always been one not only that stood up for the veteran but also balanced the national security interests of the Nation when they passed and exercised these judgments, and that position rather surprises me that the American Legion would take that position.

If, in fact, as a Nation we are going to say that we are going to continue along with the PB pills, same with the anthrax, and our research is not conclusive, this research basically says that it cannot be excluded from the realm of possibility—that is basically what this is saying—that is pretty broad. There is no causal link. So when there is no causal link, and Dr. Rostker's advice to us is fund the further research, we need the greater understanding, I concur.

In the meantime, the responsibility is to protect the soldier, the sailor, the airman and the marine as much as possible. Even if perhaps, it is that painful judgment of instantaneous death versus a chronic illness. If we as a Nation say that the best protection we give is chronic illness versus death, then we are saying we have no widow; and what we will do is take care of you when you come home. Aha. Therein lies the second part of the question. If that is the judgment that we as a country are going to take, then how have we done on the second part of the equation?

The committee took A very radical approach to this question after having faced the pains of the Vietnam era. This committee exercised the judgment in the early 1990s and said we are not going to wait, like in the Vietnam era, for science to prove our compassion. Our compassion for the veteran is real and the science will have to catch up with it. So we passed legislation to gain access to the Gulf War veterans immediately, even though many didn't believe that there was such a harm physiologically; it was all men-

tal, if you recall that early on. Then Joe Kennedy and I took radical—not just the two of us, but the entire committee took a radical move. Compensation for undiagnosed illnesses? Pretty radical. Very radical for this town.

It has been very difficult. It has been very difficult for all of us. It has been difficult for my comrades, and difficult for the leaders of these organizations. I recognize that because it tries the virtue of your patience.

But as we have to exercise compensation, America's Treasury is based on something that is concrete, that is why it is painful. It is. I just want you to know that. It is hard for me. I wish we could do as you are asking, ma'am, but we are not going to be able to do it— especially with the speed for which you are asking, with the broad reach that you are doing with a broad brush—because we are trying to move it within a system that has a logic, that has compassion, is very thoughtful, and there is compensation and there are links.

Because it is so difficult to say—there are individuals who have become ill and their illness—they may have become ill had they never gone to the Gulf; you know that as a nurse. They may already have come down with cancer. But what has happened is that everyone who has become sick is automatically saying it is because of the Gulf War. And it is very difficult then for us to come in and to try to sort that out. It is very difficult.

Ms. NICHOLS. Let me parallel this, if I could have just a moment.

Mr. BUYER. Sure.

Ms. NICHOLS. When we talk about heart disease and you all know—I hope a lot of you have had CPR training, but we talk about the risk and there is material put out by the Heart Association looking at your risk factors. And if you had hereditary problems, smoke, cholesterol problems, they all add up. Let us say that our vets—we will give an example of cardiac. Maybe they would have developed cardiac problems anyway. But maybe because of the added whatever happened in the Gulf War, that they developed it sooner. Per se, another risk factor that created them to have cardiac problems earlier than they would have otherwise. So you can't prove a negative.

Mr. BUYER. Ma'am, excuse me. If there are preexisting conditions, perhaps. But what is difficult for us here as a committee when we exercise policies and the VA has to then come up with their rules and procedures, is that it has to be based on something, it needs to be concrete. I just want you to know it has to be. So I just want to share that. Did you have another comment?

Ms. NICHOLS. I have one comment here. According to Medical Management, U.S. Army of Chemical Casualty Handbook, December 1995, over 50 percent of the individuals who took PB had admitted to bad health effects. Over 50 percent. And that was published in 1995 and that was forwarded to me by Dr.—Major Doug Rokke who isn't here today. But he wanted me to point that out to you all. Fifty percent.

Mr. BUYER. Thank you, ma'am. I have one last one, Mr. Chairman, if I may.

To the American Legion, has the American Legion taken a position on the anthrax and the anthrax program?

Mr. PUGLISI. Yes, we have Mr. Buyer. We support the use of the anthrax vaccine based on all the available evidence but we have addressed—we have been made aware of some concerns by legionnaires who have taken the vaccine and some who have refused the vaccine. There are some implementation problems at the local unit level with the anthrax vaccine. So we are not calling into question the safety, the efficacy of the anthrax vaccine or the threat or the need to use it. What we are calling attention to are some local units' problems that are occurring because there are some commanders and medical officers who aren't implementing that program as their guidance——

Mr. BUYER. I am fully aware of those particular cases. I just want you to know that we try to be very consistent in our logic in how we come to judgment on both of the programs. I just want to share that with you.

Mr. PUGLISI. If I can comment, Mr. Chairman just on some of the earlier comments by Mr. Buyer. There are some similarities in the perceptions regarding PB and the anthrax vaccination program and I highlighted that in my testimony. But there are some differences between this drug and the vaccine. The vaccine has been approved by the FDA to protect someone against getting anthrax and it has been used by folks who are exposed to anthrax. No one has gotten anthrax from the vaccine. People who use the vaccine haven't gotten anthrax. And given the threat and how spores—anthrax in its form is a spore, it is very persistent and it could perhaps be easily spread. So it is a different threat.

Mr. BUYER. I will correct you for a moment, if I may. If the anthrax is actually placed on your skin, then it is FDA approved. If it is airborne through air assault, it is not FDA approved. So now have you soldiers out there that are confused because it is being sold as if they do an air assault by plane, and it covers this many thousands of square acres, this is how much troops that could get anthrax; and don't worry, you have taken a vaccine that will protect you. Aha. Have we?

Then there is confusion among the American public by saying now we are giving a vaccine to troops that is not FDA approved. Wait a minute. See how people get confused. It is FDA approved for one type but not for the other. But as a soldier, if I am going into the theater and I know they are going to drop anthrax on me, give me the vaccine. You know, give me the vaccine. And there is the pain that we all endured in those judgments. Would you concur with what I have said?

Mr. PUGLISI. Absolutely, Mr. Buyer. I think that describes it very accurately.

Mr. BUYER. Thank you, Mr. Chairman. I appreciate your contributions to this hearing, all three of you.

Mr. EVERETT. Well, you know, it has been kind of a long hearing. And I would like to assure this panel as well as the other panels, first of all, we appreciate you being here. And secondly, I know that you are asked to wear difficult hats but this committee is also. We have had 19 hearings. And in some cases they have been pretty tough hearings. The hats that we have to wear sometimes are not pleasant for us to wear. We have to make decisions of compassion,

on compensation, but unfortunately also based on something concrete. If we don't make them, who will make them?

But I will say to you that we have wandered around in this darkness for a long time and we sure would like to see the light, light a candle, all of us would, and this committee is on record with that. Hopefully, we will get to the end of this and we will see that our veterans are taken care of the way the American public wants them taken care of and the way this committee and your organizations want them taken care of.

Thank you all for appearing. The hearing is adjourned.

[Whereupon, at 5:41 p.m., the subcommittee was adjourned.]

APPENDIX

Statement of Representative Luis Gutierrez
House Committee on Veterans' Affairs
Joint Health and Oversight and Investigations Hearing:
Possible Health Effects of Pyridostigmine Bromide on Persian Gulf War Veterans
November 16, 1999

I thank the chairmen. The purpose of our hearing today is to consider the possible adverse physical and mental health effects pyridostigmine bromide, or PB, may have had on our veterans who served in the Persian Gulf War. I am eager to hear from the witnesses. My colleagues and I appreciate you taking the time to be with us here today to share with us your findings and perspectives.

PB is a drug used to treat myasthenia gravis, a neuromuscular disorder. In December of 1990, the FDA approved the use of PB as an investigational new drug for use as a nerve agent pre-treatment to protect U.S. troops against soman, a chemical warfare agent the Department of Defense believed that the Iraqis may have

possessed. PB must be taken before exposure to soman and soldiers must receive post-exposure treatments as well. As many as a quarter of a million U.S. soldiers are believed to have taken PB.

Mr. Chairmen, thousands of veterans who served in the Persian Gulf War continue to suffer from adverse health symptoms, and there is no clear diagnosis for these American men and women. Possible causes of some of the illnesses that Gulf War veterans have reported include chemical and biological warfare agents, pesticides, oil well fires, stress and immunizations. As Members of Congress, it is our responsibility to continue to hold hearings on this issue and provide the funding necessary for further research on the causes and treatments of all the symptoms we now refer to as Gulf War Syndrome. Clearly, our efforts to find answers will lead to more questions, but we must continue to be vigilant. Such discoveries are especially important because we must ensure that our efforts to immunize our soldiers from chemical and biological weapons are not making them sick.

Statement of Congressman Christopher H. Smith
Tuesday, November 16, 1999
Joint Hearing of the Subcommittee on Health and Subcommittee on Oversight and Investigations
Possible Health Effects of Pyridostigmine Bromide on Persian Gulf War Veterans

Mr. Chairman, I join my colleagues today in expressing my support for the need to find concrete answers to Persian Gulf War illnesses. PB has been one of many substances theorized as having some possible link to the medical problems of the Persian Gulf War veterans. PB works by blocking the nerve agent, such as soman, from binding to and inhibiting a major neurotransmitter (or nerve-signal-regulating enzyme).

Last year, Congress directed the Department of Veterans' Affairs to enter into a contract with the National Academy of Sciences whereby they would conduct a literature review and analysis of all the risk factors which may be associated with health problems experienced by Persian Gulf War veterans. That analysis would be the basis for establishing presumptions of service-connection and for recommendations for additional scientific studies. This study is now underway and is expected to be completed next summer.

Concurrently, the RAND National Defense Research Institute is under contract with the Department of Defense to conduct its own scientific literature review regarding subjects that could be plausible causes of some of the illnesses Gulf War veterans have experienced. On October 19, RAND released a lengthy report on PB. The RAND report characterizes existing research on the questions of PB as a possible source of chronic symptoms as being in its infancy. It concluded that PB cannot be ruled out as a contributor to illness in Persian Gulf War veterans. RAND also concluded that PB's effectiveness in protecting humans against nerve agents is uncertain. The report also recommends numerous avenues for further research.

Today's hearing on the possible health effects of pyridostigmine bromide (PB) is timely and should provide momentum for the ongoing research as well as a future legislative response. I thank our witnesses today for coming before the Health and Oversight Subcommittees and I look forward to hearing and reviewing their testimony.

Testimony of

Beatrice Alexandra Golomb, M.D., Ph.D.
C. Ross Anthony, Ph.D.

RAND

Before

The Sub-Committee on Health, and
The Sub-Committee on Oversight
Committee on Veteran's Affairs
U.S. House of Representatives

November 16, 1999

Mr. Chairman and distinguished Members of the Sub-Committees, it is a pleasure for us to address you today on RAND's review of the scientific literature as it pertains to pyridostigmine bromide (PB) and illnesses among Gulf War veterans. RAND is a nonprofit institution that helps improve policy and decision making through research and analysis. At RAND I am the Director of the Center for Military Health Policy Research and Co-Leader of this project. I am joined today by Dr. Beatrice Golomb, who prepared this exhaustive new PB study. Dr. Golomb, a RAND consultant, is a physician who also has a Ph.D. in biology specializing in neurobiology. She is a staff physician at the San Diego VA Medical Center, an Assistant Professor of Medicine at the U.C. San Diego, and a Research Associate Professor in the University of Southern California's Psychology Department. This statement is based on a variety of sources, including research conducted at RAND. However, the opinions and conclusions expressed are those of the author and should not be interpreted as representing those of RAND or any of the agencies or others sponsoring its research.

I would like to describe briefly the context for this study. Dr. Golomb will then summarize her research findings.

After the Office of the Special Assistant for Gulf War Illnesses (OSAGWI) was formed in late 1996, the Special Assistant determined that there were at least two key kinds of information that were needed in the office's efforts to leave no stone unturned in looking into the possible causes of illness among Gulf War veterans. OSAGWI has extensively investigated what happened and what exposures occurred in the Gulf while RAND was asked to summarize the scientific literature on the health effects of possible causes of illness. It was hoped that combining these sources of information would produce a more complete understanding of illnesses among veterans.

The PB report is the fourth of eight literature reviews published by RAND to date. Literature reviews on the health effects of wartime stress, oil well fires, and depleted uranium were published previously; while reviews on chemical and biological warfare agents, pesticides, immunizations, and infectious diseases are to follow. The PB report differs from the other reviews to date, in that we are unable to rule out an agent as a possible contributing factor to illnesses among some veterans. As Dr. Golomb will explain, she exhaustively examined seven hypotheses and found enough supporting evidence that she was not able to dismiss PB as a potential contributing factor.

These findings must be interpreted carefully. Even if enough evidence is found that a hypothesis can not be rejected, this does not necessarily imply that the agent in question is a causal factor. It only means that, based on the available scientific evidence, the possibility cannot be dismissed. Also note that although this report has clear policy implications, RAND was not asked to and did not examine the policy issues related to PB and its use.

Dr. Golomb will now summarize her study for you.

PB Report Background

Mr. Chairman and Members of the Sub-Committees, over the past several years, I have looked extensively at the scientific information as it relates to pyridostigmine bromide.

As the Committee knows, pyridostigmine bromide was a drug taken during the Persian Gulf War by an estimated 250,000 U.S. troops as a pretreatment to protect against the nerve agent soman. PB was approved by the Food and Drug Administration in 1955 for treatment of myasthenia gravis, an autoimmune disease that affects the muscles, and it is also approved for certain post-anesthesia applications. During the Gulf War, it was designated an "investigational new drug" for pretreatment for soman and was supplied to U.S. forces under a FDA waiver of informed consent with the possibility of an Iraqi nerve agent attack in mind. Technically, PB is a "pretreatment adjunct"—a drug that must be taken before exposure to be effective but that only confers benefit if post-exposure treatments are given as well.

RAND was asked to perform a literature review to evaluate whether PB could plausibly be related to increased health symptoms experienced by Persian Gulf War (PGW) veterans. I examined over 10,000 titles, 6,000 abstracts, several thousand papers and reports, interviewed over 80 people, and reviewed dozens of declassified British studies and reports. This extensive review has resulted in the lengthy report before you, which includes more than 1,000 citations.

The literature review was used first to identify theories that might link PB to symptoms in ill PGW veterans, and then to assess the evidence pertaining to these theories. (In addition, the issue of efficacy of PB as a pretreatment for nerve agent was addressed, but will not be reviewed here due to time constraints.) A total of 7 theories were identified that pertain to a link between PB and health effects. Each has its own chapter in the report, but two are closely related and will be discussed together.

These theories fall roughly into two categories each containing three theories.

- The first group of theories describes possible mechanisms that may produce heightened individual susceptibility to effects of PB in some circumstances – so that some individuals might experience effects, including perhaps toxic effects, while others do not.

- The second group of theories describes ways that PB may actually lead to chronic symptoms, perhaps selectively in those with heightened susceptibility.

I will discuss each of these theories briefly.

Theories on Individual Susceptibility

Regarding theories of possible heightened susceptibility to PB, one theory proposes that there may be widespread individual differences in processing of PB. Indeed, our review found evidence of differences at many levels. First, the desired dose of PB was not taken by all the veterans in the approved manner; some took more and many took less. However, even supposing the same oral dose of PB, there are 7-fold differences in the resulting steady-state blood level of PB in humans. Moreover, for the same blood level of PB, there are many-fold differences in the percent of enzyme inhibition induced by PB; thus depending when after PB administration one looks, there may be up to 15 to 25 fold differences in enzyme inhibition for the same oral dose. Finally, for the same measured enzyme inhibition, there are widespread differences in clinical effects, including toxic effects of PB. These widespread differences in processing of PB from one individual to another could potentially lead to substantial differences in susceptibility to effects of PB, including chronic effects if any occur.

The second theory notes that whereas ordinarily most PB is excluded from entering the brain by what is termed the "blood brain barrier," which bars access of many substances, some of the recent evidence from animal studies suggests that quite a bit of PB may access the brain under some conditions, such as stress, heat, and chemical combinations. These are conditions to which some PGW veterans may have been exposed, thus increasing the chance for brain effects of PB to occur. In addition, there is literature that indicates PB itself may enhance access to the brain of normally excluded substances, such as infectious viruses.

A third theory notes that toxic effects of PB may be greatly enhanced, in some cases in a synergistic fashion, by concomitant exposure to other factors like pesticides and nerve agent, to which some veterans may have been exposed.

These three theories, which describe mechanisms by which some individuals may have increased susceptibility to effects of PB – due to differences in processing, differences in environmental exposures, or combinations of these – were all found to be viable (i.e. had enough supporting evidence that they could not be rejected).

Mechanisms Linking PB with Chronic Symptoms

Of the theories in this category, the literature allowed us to reject bromism (from accumulation of the bromide in PB) as a likely factor in illnesses in Gulf War veterans, and the literature was inadequate to seriously evaluate multiple chemical sensitivity.

The most important theory regarding mechanisms by which PB may lead to chronic illness – perhaps selectively in those with heightened susceptibility – suggests that PB may change regulation of a key nerve signaling chemical called "acetylcholine" (ACh). ACh is known to be vitally involved in regulating muscle action, pain, mood, memory, and sleep, domains that figure prominently in complaints of ill PGW veterans.

PB acts by blocking the enzyme that normally breaks down excess ACh. The consequence is increased, unregulated action by this nerve-signaling chemical. The body responds to this inappropriate increase in ACh action by putting into place mechanisms to suppress the excess ACh activity. Thus, signaling cells may reduce production and release of ACh, and may withdraw nerve terminals from receiving cells. Receiving cells may reduce the number of receptors to which ACh may bind, and reduce the affinity of these receptors for binding to the signaling chemical. And there may be increased breakdown of ACh.

Since these mechanisms designed to suppress ACh action occur in response to the excess ACh action induced by PB, one might expect that they would go away as PB is withdrawn. But in fact, existing evidence from studies in animals suggests that the timecourses of these effects differ widely from one another. Some are short lived, and are unlikely to explain chronic illness in PGW veterans. However other effects are long lasting or permanent, lasting in some instances as long after stopping PB as anyone has looked.

Could such long lasting or permanent changes in regulation of ACh action relate to chronic symptoms reported by PGW veterans? The answer is, we don't know; much more needs to be understood about the specifics of these changes, and what their relation may be to clinical effects. However we do know that ACh is critical to regulation of muscle action, pain, memory, and sleep – domains that are disrupted in ill PGW veterans; thus it is plausible that chronic changes in regulation of ACh could produce symptoms of the types veterans report.

Conclusions

Three major conclusions emerged from the study:

- We can not rule out pyridostigmine bromide as a possible contributor to the increased health symptoms in some Gulf War veterans.

- Further research is needed to determine the effectiveness of the current dose of PB in protecting against soman.

- More research is needed to clarify the role, if any, of PB in chronic health effects in ill PGW veterans. Some research of this kind is already being funded by the DoD, VA, and HHS.

The issue now is the very complex one of trading off uncertain health risks – but risks now known to be biologically plausible – against uncertain gains from use of PB in the warfare setting.

Attachment:

Attachment

Executive Summary

A Review of the
Scientific Literature
As It Pertains to
Gulf War Illnesses

Volume 2
PYRIDOSTIGMINE BROMIDE

Beatrice Alexandra Golomb

National Defense Research Institute RAND

PREFACE

This literature review, one of eight commissioned by the Special Assistant to the Deputy Secretary of Defense for Gulf War Illnesses, summarizes the existing scientific literature on the health effects of pyridostigmine bromide that may have affected service members who served in Operations Desert Shield and Desert Storm. The eight RAND reviews are intended to complement efforts by the Defense Department and other federal agencies as they attempt to understand the full range of health implications of service in that conflict.

While many veterans have reported an array of physical and mental health complaints since the war, it is not yet clear the extent to which veterans are experiencing either higher-than-expected rates of identifiable illnesses with known etiologies or any other illnesses from as yet unidentified origins.

The other seven RAND literature reviews deal with chemical and biological warfare agents, depleted uranium, pesticides, oil well fires, immunizations, infectious diseases, and stress. The topics of these reviews all represent plausible causes of some of the illnesses Gulf War veterans have reported.

These reviews are intended principally to summarize the scientific literature on the known health effects of given exposures to these risk factors. Where available evidence permits, the reviews also summarize what is known about the range of actual exposures in the Gulf and assess the plausibility of the risk factor at hand as a cause of illnesses. Statements related to the Gulf War experience should be regarded as suggestive rather than definitive, for much more research both on health effects and exposures remains to be completed before more definitive statements are made. Recommendations for additional research where appropriate are also made.

These reviews are limited to literature published or accepted for publication in peer-reviewed journals, books, government publications, and conference proceedings. Unpublished information was occasionally used, but only to develop hypotheses.

This work is sponsored by the Office of the Special Assistant and was carried out jointly by RAND Health's Center for Military Health Policy Research and the Forces and Resources Policy Center of the National Defense Research Institute. The latter is a

federally funded research and development center sponsored by the Office of the Secretary of Defense, the Joint Staff, the unified commands, and the defense agencies.

SUMMARY

Pyridostigmine bromide (PB) is a drug, often given as a tablet, that has been approved since 1955 by the U.S. Food and Drug Administration for treatment of myasthenia gravis, a disease characterized by weakness and fatigability of the muscles. During the Persian Gulf War (PGW), PB was used as an "investigational new drug" (IND) by the U.S. military and some other allied forces as a pretreatment adjunct to protect military personnel from death in event of attack with the nerve agent soman. (IND status conferred by the FDA does not permit unrestricted use but may, as in this case, have conditions attached.) PB is called a pretreatment adjunct because it must be given before exposure to be effective. Also, it is not effective alone but only confers benefit if postexposure treatments are given as well.

PB is used primarily to protect troops against attack by one particular nerve agent, soman. During the PGW, Iraq was known to have nerve agents, including sarin, and had weaponized them by putting them into rockets, bombs, and missile warheads. While it was not known whether Iraq had militarized the nerve agent soman, it was known that the former Soviet Union had soman, and there were concerns, particularly since the fragmentation of the former Soviet Union, that Iraq may have purchased soman. Iraq used chemical weapons against Iran and the Kurds. Because of the possibility that Iraq had soman, coalition troops were provided with PB, to be used for protection when the threat of chemical warfare was deemed high. Evidence from that time and subsequent to the PGW suggests that Iraq had weaponized the nerve agents sarin, cyclosarin, and perhaps tabun and VX, but no evidence uncovered suggests they had soman or had weaponized it.

This report examines issues surrounding the safety and to a lesser degree the effectiveness of PB. The sections on safety consider seven hypotheses of how PB might lead to negative health effects. Each hypothesis is investigated to determine if it can be rejected as a possible causal factor. If sufficient evidence cannot be marshaled to rule out a hypothesis, this does not imply that it is necessarily a causal factor, only that the possibility cannot be dismissed.

HOW PB PROTECTS AGAINST SOMAN EXPOSURE

To understand how PB protects against soman requires understanding the action of nerve agents. Nerve agents act by irreversibly binding to, and inhibiting, the normal action of acetylcholinesterase (AChE), an enzyme. Acetylcholine (ACh) is a major neurotransmitter, or nerve-signaling chemical, and acts as a signaling chemical both in the brain and elsewhere in the body; for example, it is the main signaling chemical used by nerves to tell muscles to contract. AChE breaks down ACh in the synapse, the area where a nerve sends signals to another nerve, or to a muscle (see Figure S.1). Thus, AChE serves a critical role in regulating nerve signaling to other nerve cells or to muscle cells. When AChE is inhibited by a nerve agent, an excessive accumulation of ACh occurs in the synapse, followed by excessive binding of ACh to the receptors on the receiving cell (see Figure S.2). Consequently, cells are overstimulated. This condition leads to an array of possible symptoms based on ACh binding to different types of receptors.

For most nerve agents, postexposure treatment confers adequate protection from death with amounts of nerve agent that are presumed likely in warfare. The postexposure treatments in use by the military are atropine and pralidoxime (also called "2PAM"). Atropine antagonizes (blocks) the effects of ACh at one type of receptor, and pralidoxime pulls the nerve agent off the AChE, restoring the action of AChE to normal. In addition to PB, troops were given three "Mark I" kits containing injections of both atropine and pralidoxime for use after a nerve agent attack (Army and possibly Marines) or were given individual injectors of these agents (Air Force and Navy).

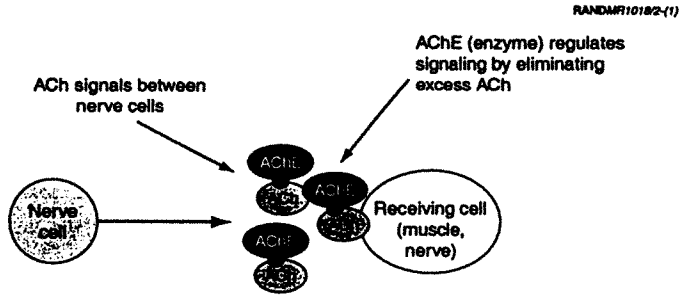

Figure S.1—How Normal Neurotransmission Works

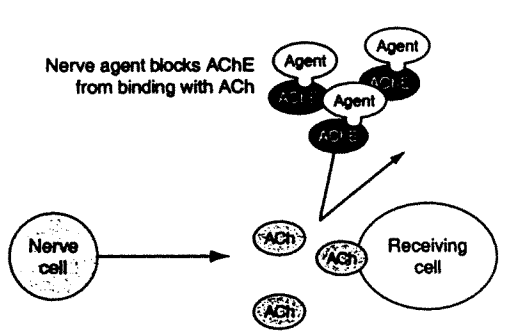

Figure S.2—Nerve Agent Blocks AChE Enzyme

Unfortunately, in the case of soman, a reaction termed "aging" takes place in the nerve agent–AChE complex within only minutes of exposure. Once this reaction has taken place, pralidoxime can no longer pull the nerve agent off the AChE molecule. Thus, troops would not have enough time to administer pralidoxime before AChE is permanently inactivated, which could ultimately result in death. Aging also happens with other nerve agents, but it takes hours to occur after sarin, cyclosarin, tabun, or VX exposure, which allows troops adequate time to administer pralidoxime before aging has taken place, helping to restore AChE action. Animal evidence suggests that to ensure adequate protection against death in the event of a soman attack, PB pretreatment must be employed.[1]

PB acts—it is thought—by reversibly binding to (and, incidentally, inhibiting) the AChE on the site where the nerve agent would bind, thus blocking soman from permanently inactivating the AChE (see Figure S.3). As soman is cleared from the body, PB spontaneously leaves the AChE and restores functional

[1]PB may also slightly raise the protection against the nerve agent tabun in rodents, although good primate data are not available, and the increase in protection against tabun is substantially more modest. This is important because any potential side effects of use of the agent must be weighed against the far smaller number of personnel who could be exposed in a realistic battle scenario to more LD_{50}s (lethal doses for 50 percent of subjects) of tabun than after-exposure treatment alone could protect against, but fewer than PB plus after-exposure treatments could protect against. Moreover, this assumes that people will respond as rodents do. But extrapolation of oxime effects from guinea pigs to primates is problematic; primates may be more oxime-sensitive than guinea pigs so that PB may confer no advantages or possibly reduce protection efficacy.

x Pyridostigmine Bromide

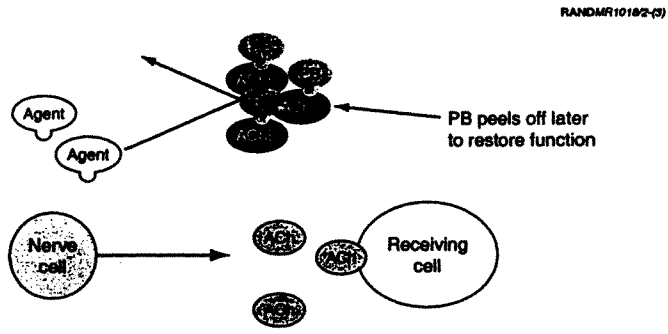

Figure S.3—PB Prevents Nerve Agent from Binding to AChE Enzyme

AChE. The dose of PB used by troops, 30 mg each eight hours, is chosen to inhibit 20 to 40 percent of the AChE. The goal is to ensure that at least this proportion of AChE is relatively safe from permanent inactivation in case of exposure to soman, while allowing enough residual AChE activity (60–80 percent) to prevent significant side effects and to allow personnel to adequately carry out their functions. It is believed that to protect most troops from death by amounts of soman that might realistically occur in a combat setting, a person must be able to withstand approximately five times the normal lethal dose. This level of protection has not been achieved with postexposure treatments alone (that is, with atropine and pralidoxime) but requires use of PB as a pretreatment adjunct in tests in nonhuman primates.

HOW EFFECTIVE IS PB?

The dose of PB needed to protect humans against the effects of soman is not clear and may be higher than previously thought. Tests done in primates to determine the protection by PB against soman have used higher doses of PB (three to 50 times as high on a mg/kg basis), as well as higher doses of atropine (four times as high on a mg/kg basis) than those actually used in humans for nerve agent protection. In addition, these tests commonly have given the equivalent of all three atropine-pralidoxime postexposure treatments at once. Higher doses of PB are given to achieve a similar percentage of AChE inhibition, while the higher doses of atropine are given on the grounds that the nonhuman primates tested are this much "less sensitive" to the effects of atropine. The extrapolation of these data to humans then rests on the assumption that the percentage of AChE inhibition is the exclusive relevant "measure" of the "pharmacologically equivalent" dose of PB (with an analogous argument for atropine), which may or may not

be so. According to the only identified study (Smith, 1981)[2] that directly compared the ability of PB to protect against the effects of soman in human and primate muscle tissue, 10 times as high an in vitro dose of PB was needed in humans as in monkeys to provide comparable protection (whereas we give only one-tenth the oral dose to achieve a comparable AChE percentage inhibition). These data arouse concerns about the validity of extrapolation from primate data to humans. It is known that the protective ability of PB, atropine, and oximes vary widely from one species to another.

In monkeys and to a lesser extent in other animals, PB protects against the lethal effects of the nerve agent soman; but it does not prevent severe incapacitation of the animals from high doses of the nerve agent. So even if data signifying protection in primates at higher doses of PB do extrapolate to humans at lower doses, troops are likely to be incapacitated in the presence of a soman attack. Moreover, in animal studies, PB appears to reduce somewhat the protection (conferred by postexposure atropine and pralidoxime) against lethal effects of some other nerve agents, such as sarin and cyclosarin. This apparent reduction in protection still provides for high protection in some animals (with "protective ratios," characterizing protection against lethal effects, that are still several times higher than the fivefold protection that has been designated as desirable). However, no direct evidence ensures that the increased vulnerability to death (*reduced* protection) that PB may bring for such nerve agents as sarin leaves high or "adequate" (fivefold) protection intact in humans. Again, substantial interspecies differences have been seen, with changes not only in magnitude but also in the sign (direction) of the effect of PB, and testing of protection by PB against lethal effects of nerve agents in humans cannot, of course, be done.

IS PB SAFE? SAFETY CONSIDERATIONS OF USING PB

The short-term side effects of taking PB—which also may occur with exposure to any nerve agent—are those of AChE inhibition and the resulting excess of ACh action. These effects may include muscle twitching, muscle spasms, weakness or paralysis, and secretions from glands. Consequences may include difficulty in breathing, cramping, feeling of urge to urinate or frequent urination, tearing, runny nose, salivation, increased bronchial secretions, diarrhea, and sweating.

PB is normally largely excluded from entry to the brain by the "blood-brain barrier," which bars access to the brain of many chemicals and organisms that circulate in the blood. If PB gains entry to the brain, adverse effects can result from the binding of PB to ACh receptors in the brain. These effects may include confusion, emotional changes such as depression, sleep alterations, and difficulties with concentration and memory.

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[2]Source citations for other references in the "Summary" can be found in the corresponding chapters of the main body of this report.

This report explores whether PB—with this panoply of *acute* effects—could plausibly have contributed to *chronic* symptoms reported by ill PGW veterans. Far higher doses of PB, used for far longer times (typically lifelong) have been employed for decades to treat patients with myasthenia gravis, and this has been assumed by many to indicate that lower-dose, briefer use in nerve agent pretreatment will be safe. However, data from patients with myasthenia might not extrapolate completely to those taking PB for other purposes. For one thing, PB is used in patients with myasthenia gravis to restore nicotinic cholinergic function (at least in the muscles) *toward* normal. In those without myasthenia gravis, PB raises ACh function *away* from normal. Thus, extrapolating evidence of safety from patients with myasthenia gravis is somewhat analogous to assuming that, since high doses of insulin are tolerated—or even necessary—in some patients with diabetes (to bring their blood sugar toward normal), therefore a smaller dose of insulin should surely be safe in those without diabetes. We know this is not the case and that smaller doses of insulin given to normal individuals can cause adverse effects and even death. There are other important reasons PB may not be safe for nonmyasthenic individuals, which are discussed later.

HYPOTHESES RELATING PB USE TO ILLNESSES IN PGW VETERANS

A literature review was performed to identify hypotheses or theories that might link PB to illnesses in PGW veterans and to evaluate evidence pertaining to these hypotheses. Hypotheses are divided into two categories: those that may explain how some individuals may have had heightened susceptibility to PB and those that purport to link exposure to PB—perhaps enabled by such heightened susceptibility—to development of chronic illnesses.

Hypotheses regarding heightened susceptibility to effects of PB include the following:

- Stressful or other special conditions may allow PB to breach the blood-brain barrier and penetrate the brain, producing effects that would not "normally" occur.
- Individual differences in physiology may lead to widely different levels of and susceptibility to PB.
- Interactions between PB and other chemicals may produce toxicity greater than that produced by either alone.

Hypotheses that propose mechanisms by which PB exposure could produce subsequent chronic symptoms include the following:

- The bromide in PB may accumulate in the body, leading to development of a condition termed bromism, which can produce many neuropsychiatric symptoms.

- Exposure to AChE-inhibiting agents, such as PB, may promote a "syndrome" termed "multiple chemical sensitivity" with symptoms similar to those reported by PGW veterans.
- PB may lead to chronic effects on the neuromuscular junction.
- PB may lead to abnormal regulation of the ACh neurotransmitter system.

Several other considerations, including possible effects of PB on sleep and serotonin, are also discussed. The evidence appears to be adequate to dismiss one hypothesis of PB as a significant contributor to illness—that of bromism—but is insufficient to rule out the other hypotheses as possible explanations of how PB might have contributed to PGW illnesses.

HYPOTHESES REGARDING HEIGHTENED EFFECTS OF PB

Blood-Brain Barrier: Does PB Cross the Blood-Brain Barrier During Conditions of Stress?

The permeability of the "blood-brain barrier" in PGW veterans may have been enhanced due to stress and other conditions of war, permitting increased access of PB to the brain. Moreover, PB itself may increase the access of other agents to the brain. Data demonstrating breach of the blood-brain barrier, consequently allowing increased access of PB to the brain in conditions of stress, comes from recent limited research conducted on rodents. However, human data suggest a possible increase in central nervous system (CNS) side effects of PB during the war compared to peacetime, which could also reflect increased access of PB to the brain during stressful circumstances.

The degree to which the blood-brain barrier may have been compromised in conditions of stress may influence the possible contribution of several other hypotheses. For example, dysregulation of the brain's cholinergic system is less likely to result from PB use unless PB gains access to the brain—or other AChE inhibitors do so, perhaps facilitated by PB. (In fact, however, changes in cholinergic function occurring in the periphery could have central consequences).

Individual Differences: Do Physiologic Differences Influence Susceptibility to PB?

Individual differences in susceptibility may also contribute to a connection between PB and chronic illnesses. How is it, if PB is a contributor to chronic illnesses in PGW veterans, that some PGW veterans who took PB became ill, while others who took a similar amount did not? Individual differences of many kinds play a role in the effect of PB on the body. First, differences occurred in the dose of PB actually taken by troops. Moreover, different absorption of PB pills from the gut into the blood; differences in

chemical structure, in efficiency of action, and in available amounts of enzymes that clear PB from the blood; and differences in other factors all may lead to different PB blood levels. Furthermore, differences in AChE inhibition occur even for the same blood level of PB. Finally, differences in toxic effects may occur even if individuals experience the same degree of AChE inhibition, perhaps reflecting individual differences at baseline in elements of the complex ACh system.

Altogether, these factors provide substantial opportunity for differences in effect from the "same" oral dose of PB from one individual to another. From a clinical standpoint, individual differences in *acute* susceptibility to PB obviously occur and are reflected in differences in side effects individuals experienced in response to PB. There is limited evidence that the acute susceptibility differences may arise from mechanisms relevant to differences in chronic symptoms in PGW veterans—one study finds a relation between certain chronic illness "syndromes" in ill PGW veterans and self-reported adverse acute response to administration of PB. If PB is a contributor to chronic illnesses in some PGW veterans, then individual differences in susceptibility could play a role in determining which individuals are affected.

Interactions with Other Exposures: Do Interactions Between PB and Other Exposures Enhance the Toxicity of Effects?

Another factor that may play a role in the connection between PB and illnesses in PGW veterans involves possible interactions between PB and other exposures. Animal studies indicate that additive or even synergistic toxicity—that is, toxic effects from a group of chemicals that are more than the sum of the toxic effects from the individual chemicals—may occur with PB and other exposures that some veterans may have experienced. These may include pesticides and insect repellents, as well as caffeine, perhaps nerve agents, and chemicals released by the body itself in conditions of stress.

The degree to which these interactions between PB and other exposures may play a role in PGW veterans is unclear for several reasons. First, we do not have good data regarding who received which exposures, complicating any epidemiological studies to determine the effect of these interactions. Second, the data from animal studies are difficult to extrapolate to PGW veterans because extremely high doses of both PB and the interactants have been used in studies in animals—doses many times higher than those experienced by PGW veterans.

Addressing the question of whether important synergistic effects would occur with lower doses of interactants—more comparable to those administered to PGW veterans—is not simple. There is no good way to assess whether low doses in animals produce effects comparable to those reported by ill veterans. In the existing animal studies, relatively crude measures, such as gross incoordination in walking, or death, are often employed because it is difficult to test animals for more-subtle effects. If lower doses are studied, more-sensitive measures will need to be found. Nonetheless, because evidence of

synergistic toxicity exists, interactions between PB and other agents or exposures remain a possible avenue by which increased effect or toxicity of PB may have occurred in some veterans.

HYPOTHESES PROPOSING A LINK BETWEEN PB AND DEVELOPMENT OF CHRONIC SYMPTOMS

Bromism: Does Accumulation of the Bromide from PB Produce Bromism?

Bromism is a condition characterized by neurological and psychiatric symptoms and caused by the accumulation of bromide in the body. It has been suggested that PB administration during the PGW may have led to this condition. However, bromism emerges as an unlikely cause of chronic illness, because the cumulative doses of bromide ingested in PB pills by most PGW veterans were too small to cause bromism, and the time-course of illness in many ill PGW veterans is too long to be typical of this condition, which usually abates within days to months of discontinuing exposure to bromide. Although it is conceivable that bromism could have contributed to illnesses for some rare veterans with special circumstances, bromism is highly unlikely as a significant contributor to illnesses in most ill veterans.

Multiple Chemical Sensitivity (MCS): Does PB Lead to MCS?

MCS is a putative symptom complex involving multiple self-reported "sensitivities" or adverse subjective responses to low levels of a host of apparently unrelated foods and chemicals. Symptoms may include headaches, difficulty concentrating, memory impairment, and musculoskeletal and abdominal complaints. MCS is not universally accepted as a syndrome by scientists or clinicians. It lacks a widely accepted case definition, and no objective technique has been identified to distinguish those who report symptoms from those who do not. Since MCS itself is not universally accepted or well understood, it is poorly positioned to explain illnesses in PGW veterans.

Still, there are several intriguing similarities. First, symptoms reported by patients with MCS are not confined to chemical sensitivities; and other symptoms, such as musculoskeletal symptoms and headaches, are reportedly similar to those described by ill PGW veterans. Second, some ill PGW veterans report that they have developed new chemical sensitivities since their return from the PGW. Third, many or most ill PGW veterans and MCS patients experienced exposures to AChE-inhibiting drugs or chemicals prior to developing their symptoms. Moreover, the genesis of MCS has been proposed to relate to excessive ACh activity, or reduced AChE activity, which may presumably have been experienced by PGW veterans exposed to PB. At present, because of limitations noted above, MCS cannot serve as an explanation for illnesses in any PGW veterans. However, it can be hoped that ongoing research into each condition (MCS and illnesses in

PGW veterans) will advance understanding of possible cholinergic mechanisms for both, whether or not these conditions are found to converge.

Neuromuscular Junction (NMJ) Effects: Does PB Produce NMJ Changes?

Nerves signal to muscles using ACh at the neuromuscular junction (NMJ), and this signaling causes the muscles to contract. Administration of high doses of AChE-inhibiting drugs, such as PB, has been shown in animals to produce destructive changes to the muscle tissue and to produce pre- and postsynaptic changes in the NMJ—that is, changes that occur both at the side of the signal-sending nerve cell and at the side of the signal-receiving muscle cell. These changes begin after a single dose of PB. Though some destructive effects begin to recede even if use of PB is continued, partially restoring the appearance of the muscle and of the NMJ, this restoration has not been complete in all cases, even long after administration of PB has been stopped. Thus, chronic—and perhaps permanent—changes take place.

Findings at the NMJ are important for two reasons. First, some of the symptoms reported by PGW veterans include musculoskeletal problems and fatigue, to which the effects of PB at the NMJ might contribute. Second, the NMJ is the most accessible cholinergic synapse, and it is therefore the easiest one to study. Researchers have hoped that effects evident at the NMJ will accurately reflect effects at acetylcholinergic synapses in the brain. In some instances, but not others, this hope has been borne out. Additional and different processes play important roles in brain synapses.

Neurotransmitter Dysregulation: Does PB Alter Regulation of Neurotransmitters, Particularly ACh?

Abnormal regulation of neurotransmitter systems may occur following the administration of drugs that act on these systems. "Downregulation," in this case the (hypothesized) attenuation or suppression of the acetylcholinergic system following use of such AChE-inhibiting drugs as PB, is an instance of dysregulation. That is, during and after PB use, effects may occur that counteract the abnormally high activity of ACh induced by PB. Changes consistent with downregulation have been demonstrated in the NMJ with drugs like PB. Moreover, some evidence suggests that dysregulation changes may also occur in the brain, when AChE-inhibiting chemicals gain access to it. These changes have been demonstrated in animals, using AChE inhibitors that readily gain access to the CNS, and typically at doses that achieve higher levels of AChE inhibition than expected for doses to which veterans were exposed. These may include both changes that enhance and that depress ACh action, with different effects occurring for different components of the ACh system and in different parts of the brain. Different effects may also occur with widely differing time-scales, from very brief to long-term or perhaps permanent. They may involve changes in production, packaging, and release of the neurotransmitter; changes in the number of receptors for ACh, in the "affinity" of these receptors for ACh (the avidity

with which ACh attaches), and in their response to ACh; and changes in production and degradation of the enzymes that regulate breakdown of ACh.

By hypothesis, symptoms described by PGW veterans could be manifestations of a prolonged dysregulation effect from PB use. But this hypothesis has not been directly substantiated by data. *If* PB gains access to the brain, discontinuing PB exposure might lead to symptoms of low (or altered) ACh activity. However, little basic science has been done to characterize the time-course of dysregulation changes, and more needs to be understood about the doses and the durations of use that might produce it—recalling that individual differences are surely at play. Clinically, ACh is known to play an important role in memory, sleep, and pain, as well as muscle action, and the most prominent symptoms reported by PGW veterans include problems with memory, sleep, pain, and fatigue. Moreover, studies have been done in which drugs that boost ACh function, particularly nicotinic function, have specifically benefited memory, pain, fatigue, diarrhea, and sleep apnea. (Sleep apnea is a specific sleep abnormality that has been reported among ill PGW veterans). These findings, indicating the selective benefit of ACh-enhancing drugs for problems that figure prominently in complaints of ill PGW veterans, are consistent with the possibility that these symptoms in PGW veterans could derive from ACh downregulation (or, more generally, dysregulation) resulting from use of PB. However, they are not proof of this hypothesis. In addition, these studies showing benefit to these symptoms from ACh-enhancing drugs have not been done in ill PGW veterans, and it is unknown whether ill veterans would derive similar benefit. At present, the idea of neurotransmitter dysregulation as an explanation for illnesses in some PGW veterans is speculative. Research is needed to clarify what role, if any, such dysregulation might have in the development of chronic symptoms.

Chronic Effects

Some literature suggests the possibility of chronic effects by AChE inhibitors generally, including PB. Data regarding chronic effects, particularly from low-dose exposures that do not produce acute symptoms, are meager and studies are frequently of poor quality. Some studies fail to demonstrate such abnormalities on neuropsychological or other tests in persons with prior AChE exposures. Other studies report chronic changes in nerve and muscle function, EEGs, regional cerebral blood flow, or neuropsychological tests, typically following exposure to AChE-inhibiting pesticides or to nerve agents.

Still other studies have evaluated whether ill PGW veterans indeed have chronic neurological abnormalities. The findings of these studies have been mixed. Differences in findings may reflect both the strategy for selecting ill veterans and the character of the tests performed. If chronic effects are present, they could be missed by failing to properly identify cases and controls or by performing tests that are not sensitive to the specific deficits that ill veterans may have. Of course, if chronic neuropsychological effects are

not present in PGW veterans more often than in others, then neither PB nor any other exposure will need to be invoked as an explanation.

A few small studies of chronic neuropsychological findings in ill PGW veterans suggest that selected ill veterans have statistically lower scores on neuropsychological tests than do healthy controls. Although it appears that *some* ill veterans do have mildly diminished neurocognitive function, the extent to which an excess number of veterans do so remains to be clarified. The reductions in function that have been observed do not appear to relate to one or a small number of neurocognitive abilities. However, since the acetylcholinergic system plays a prominent role in many functions of the brain, abnormalities resulting from the disruption of the ACh system might be expected to span many functions. An additional important issue is whether such impairment, if present, is related to use of—or an adverse response to—PB. One study suggested a connection between adverse acute response to PB and current neuropsychological syndromes in Gulf War veterans. Moreover, a recent study from Britain found that self-report of exposure to PB was strongly and significantly linked to current CDC-defined Gulf War illness among British veterans. These and other completed works are limited by the use of self-reporting to determine exposure to PB. Individuals who are ill may remember use of PB differently from individuals who are not ill. (Self-report appears to be the best gauge of use available because records of who received PB, who took PB, and how much they took, were not maintained. Moreover, in the British study, risk ratios were not materially different for troops for whom records were available to confirm risk-factor status, compared to the group as a whole, suggesting against a major role for recall bias.) In short, there is suggestive evidence that some AChE inhibitors may cause chronic neurological changes. There is some objective evidence that chronic neurological changes exist in some ill PGW veterans compared with healthy controls. There is limited evidence that development of some types of chronic neuropsychological changes may be linked to acute response to administration of PB. Consequently, one cannot rule out the possibility that long-term effects of PB might occur and might participate in the production of neuropsychological and other deficits reported by some PGW veterans.

Other Effects

PB's effects on hormones, sleep, the serotonergic and other neurotransmitter systems, and the observation of increased deaths from accidents in PGW veterans after the war may merit additional study. Many PGW veterans report difficulties with sleep. Sleep is prominently regulated by the ACh and serotonin/melatonin systems, both of which might be influenced by PB. Sleep apnea may be particularly common in ill PGW veterans, and some studies outside the PGW population suggest that sleep apnea may respond to nicotine (a "nicotinic" acetylcholinergic agent), consistent with proposed dysregulation of the ACh system in ill PGW veterans. PB may mimic serotonin, providing another avenue for association between PB use and sleep difficulties in PGW veterans. Disruption of sleep, in turn, has been shown to have a role in some pain syndromes. Moreover, sleep

disruption is strongly linked to susceptibility to motor vehicle accidents, and epidemiologic studies show an increase in death by motor vehicle accidents in PGW veterans. (Other neurological characteristics that some researchers are investigating in subsets of ill PGW veterans may also dispose them to increased risk of accidental death, perhaps independent of sleep difficulties. For instance, abnormalities in eye movement coordination if confirmed could retard reaction times, which could translate to increased risk when at the wheel.)

LIMITATIONS OF THIS REVIEW AND FUTURE DIRECTIONS

The combined literature related to PB, to PGW illnesses, and particularly to acetylcholinergic function is quite extensive. Although this document is far from being a complete evaluation of each of these areas, it does present a much more thorough discussion of the acetylcholinergic system and its relation to possible mechanisms of illness than have previous discussions of PB as a contributor to illnesses in PGW veterans. Certainly, all possible issues have not been addressed, and it is hoped that future efforts can build on the foundation laid here.

Several issues important to military use of PB were reviewed but are not discussed in detail in this report, including data regarding the efficacy of PB as a nerve agent pretreatment adjunct, data on acute physiological and performance effects of PB, and information about acute side effects outside the warfare setting. (Limited information on the acute effects of PB is included in Appendix B.) While important to the future military use of PB, these data do not directly address the development of chronic illnesses in PGW veterans.

Concern regarding PB as a possible source of chronic symptoms is relatively new, and research in this area is in its infancy. Human data regarding chronic effects are mostly observational, and these epidemiological studies are complicated by lack of a consistent clinical case definition distinguishing which PGW veterans should be counted as ill or as neurologically symptomatic as a result of their involvement in the PGW. The lack of good data regarding who received which exposures hinders study as well. When both the exposure and the outcome are not well characterized, it is doubly difficult to evaluate clearly the connection between PB exposure and an adverse outcome. While some experimental data related to short-term PB effects are available from studies using non-war volunteers, such studies have not looked at long-term effects and have not entailed conditions of high stress and interactions with other exposures that may have conditioned susceptibility to PB in the PGW. Most experimental studies relating to toxic effects, and involving stress and drug interactions, are done in animals at relatively high doses, and the degree to which this evidence extrapolates to humans is unknown.

The findings reported here, in which it is concluded that PB cannot be excluded as a contributor to illness in PGW veterans, differ from conclusions of some prior investigating bodies, such as the Presidential Advisory Committee and the Institute of

Medicine. Three significant factors contribute to these differences. First, a more extensive literature review, and particularly a more in-depth examination of the ACh system, has been performed. Second, the approach to evaluation of evidence differs. Some prior reports appear to have interpreted the evidence as though absence of proof that PB contributed to illness constitutes proof that it did not. Finally, new evidence has become available that provides additional rationale for concern regarding PB—evidence not available to previous groups. Similarly, our own findings are provisional and subject to change as new evidence emerges.

CONCLUSIONS

Two major conclusions emerge from this review of the scientific literature, one pertaining to the safety and one to the effectiveness of PB. First, PB cannot be ruled out as a possible contributor to the development of unexplained or undiagnosed illness in some PGW veterans. Of the hypotheses considered, the evidence permits the rejection of only one—bromism. The others remain scientifically viable. By their nature, these hypotheses are not mutually incompatible.

Second, uncertainties remain concerning the effectiveness of PB in protection of humans against nerve agents. Most data on effectiveness of PB in primates derive from studies using higher doses, and how well these extrapolate to lower dose use in humans remains ambiguous. Finally, some literature, again mostly based on animal studies, indicates that use of PB may reduce somewhat the effectiveness of postexposure treatment for some nonsoman nerve agents. The extent and importance this reduction would have in humans is unknown.

These findings based on the scientific literature raise many questions and have important implications relating to the use of PB in military deployments. Clearly, substantially more research into the effectiveness of PB for humans is needed—and quickly. Meanwhile, the issue is a complex one, involving trading off uncertain health risks—but risks now shown to be biologically plausible—against uncertain gains from use of PB in the warfare setting.

Statement of Joseph S. Cassells, M.D., M.P.H.
Institute of Medicine

Good afternoon, Mr. Chairman, and distinguished members of the subcommittee. Thank you for the opportunity discuss the Institute of Medicine's (IOM) activities involving the war in the Persian Gulf, specifically the health effects of service in that operation. Since the particular focus of this hearing is pyridostigmine bromide and its possible relationship to Gulf War Illnesses, I will confine my remarks to that issue.

In 1995, an IOM Interim Report, *Health Consequences of Service During the Persian Gulf War: Initial Findings and Recommendations for Immediate Action"* noted that there was little information about how PB, DEET, and permethrin might interact. Further, it was noted that interactions among those compounds are possible and are inadequately studied. (p15, Finding 12)

In the 1996 Final Report, *Health Consequences of Service during the Persian Gulf War: Recommendations for Research and Information Systems,* it is noted with regard to PB, "All of these possible drug interactions cause acute and short-term problems. The committee knows of no evidence of any chronic effect." Furthermore, the report goes on to conclude that "the number and variety of hypotheses call attention to the variety of different types of abnormalities that have been reported and the strong likelihood that no single hypothesis could account for all of these, whether or not the illnesses result from service in the Persian Gulf War."

The IOM, at the request of the Department of Veterans Affairs, is currently undertaking a literature review of chemical and biological compounds believed to have been present in the Gulf or as a result of the Gulf conflict. Phase 1 of this study

is reviewing the literature on pyridostigmine bromide, sarin/cyclosarin, vaccines (botulinum toxoid and anthrax) and depleted uranium. Phase 2 will examine additional exposures.

At this time, the IOM has no comment regarding the RAND report, other than to note that any new report should be viewed with reservations until it has had careful attention from the rest of the scientific community. Evidence that seems to support a favored idea or hypothesis must be viewed with at least as much caution as evidence against that idea. The RAND report will be included in the literature review on pyridostigmine bromide. The report on the Phase 1 reviews will be available in August of next year

Despite media reports regarding the previous IOM report, noting that the committee is unaware of evidence of chronic effect related to PB, doesn't mean that there is no relationship between PB and a long-term health effect and does not mean that a previous IOM committee ruled it out. Rather, there was not sufficient evidence at the time to determine an association.

RECORD VERSION

The
Use of the Drug Pyridostigmine Bromide as it relates to Gulf War Veterans

STATEMENT BY

Dr. Sue Bailey
Assistant Secretary of Defense for Health Affairs

Submitted To

SUBCOMMITTEES ON HEALTH AND
OVERSIGHT AND INVESTIGATIONS
COMMITTEE ON VETERANS' AFFAIRS

FIRST SESSION, 106TH CONGRESS

November 16, 1999

NOT FOR PUBLICATION
UNTIL RELEASED BY THE
SUBCOMMITTEES ON HEALTH
AND OVERSIGHT AND INVESTIGATIONS,

INTRODUCTION

Chairman and Distinguished Committee Members, I am Dr. Sue Bailey, Assistant Secretary of Defense for Health Affairs. I am honored to appear before your Committee today to address your questions about the Department of Defense (DOD) use of the drug pyridostigmine bromide as it relates to Gulf War veterans.

Soman is an extremely lethal nerve agent, suspected to be in the arsenal of potential adversaries. There is no effective treatment approved by the Food and Drug Administration (FDA) for exposure to these agents. However, the results of animal tests suggest that use of pyridostigmine bromide (PB) as a pretreatment adjunct, coupled with standard post-exposure treatments, may be effective. PB is approved by the FDA as safe and effective treatment of certain neuromuscular disorders, but it has not been approved for marketing as a nerve agent antidote, and is therefore classified as an "investigational new drug" for this medical purpose.

As noted in the Federal Register notices concerning 21 CFR Part 50, "During the months preceding the Persian Gulf War, DoD had discussions with the FDA regarding the potential use of specific investigational products in military personnel serving in the Gulf. It was thought that the products discussed represented the best preventive or therapeutic treatment for diseases endemic to the area and in providing protection against possible chemical or biological weapons. DoD requested the assistance of FDA in allowing the use of these products in certain battlefield or combat-related situations in which they considered obtaining informed consent "not feasible."

On December 28, 1990, DoD submitted protocols under IND's and requests for waiver of informed consent for pyridostigmine bromide 30-milligram (mg) tablets to the Food and Drug Administration. Pyridostigmine bromide was considered a potentially useful pretreatment against certain nerve gases. The Commissioner approved the Department's waiver requests for pyridostigmine bromide 30-mg tablets on December 31, 1990. This product was administered to portions of the military personnel who participated in Operation Desert Storm War.

Concerns have been expressed as to whether PB may have contributed to Gulf War veterans' illnesses. Reviews conducted by the Institute of Medicine and the Presidential Advisory committee on Gulf War Veterans' Illnesses did not consider PB a likely cause. The recent RAND study concludes that medical research to date has not ruled out some hypotheses of PB as a possible contributor. The RAND study requires further independent review. I have asked the Armed Forces Epedimiology Board to review the research merit of the recommendations posited in the study.

Much of the research now being accomplished on PB is being done under the direction of the Persian Gulf Veterans Coordinating Board. This Board is composed of representatives from the Departments of Health and Human Services, Veterans Affairs and Defense. Right now, there are 26 scientific, peer-reviewed research projects underway specifically addressing the health consequences of PB as a nerve agent pretreatment. The funding for this research is approaching $20 million.

These studies include evaluations of the interactions of PB with other chemicals such as insecticides or with physiological variables such as heat and stress. Several studies examine the interactions between PB and low level exposure to nerve agents. Other research addresses susceptibility of certain individuals to PB because of their genetic make-up. These on-going studies, to date, reveal no definitive results to link PB to the illnesses of our Gulf Veterans. But, we must continue with this very important research.

On September 30, 1999,President Clinton signed Executive Order 13139, entitled "Improving Health Protection of Military Personnel Participating in Particular Military Operations." This Executive Order addresses the President's role under 10 U.S.C. 1107, a law that authorizes a Presidential waiver of informed consent for the use of investigational new drugs for force health protection in certain military operations. Supporting the E.O. is a new regulation issued by the FDA on October 5, 1999, the interim final rule. Also based on 10 U.S.C. 1107, this rule establishes the standards and criteria both the President and the Secretary of Defense will use to consider the potential need to use an investigational new drug for force protection in a particular military

operation without the informed consent of the affected military personnel. These standards and criteria are very detailed and exacting. The next important action in establishing policy for the use of investigational new drugs for force health protection will be the issuance by the Secretary of Defense of a DoD Directive incorporating the requirements of 10 U.S.C. 1107, the Executive Order, and the FDA interim final rule. Following involvement of multiple DoD components, I expect this to be issued early next year.

My responsibility as the Assistant Secretary of Defense for Health Affairs is to advise the Secretary on all matters pertaining to the health of our forces. As all of you know, the world has changed. As we consider the threats our forces face, we now must consider the horrendous complications wrought by chemical and biological warfare agents. We know that the nerve agent soman is among the chemical agents in the arsenals of countries opposed to the United States. Soman is a rapidly lethal nerve agent. Standard treatments for other nerve agents are not effective against soman. PB as a pretreatment coupled with standard post-exposure treatments may well protect our forces. If faced with a decision today to recommend or not recommend the use of PB for the protection of our troops, when under a confirmed high threat of the use of soman, I would recommend PB be used. To counter soman, PB, in conjunction with protective gear and post exposure treatment, is the best measure we have to help protect the lives of America's sons and daughters. PB is an essential element in the military medical defense against use of soman by enemy forces. Because PB is not FDA-approved for this indication, the Department will follow the guidelines for IND usage of PB as established in the statutes, the Executive Order, and the FDA's interim final rule on standards and criteria.

Thank you for the opportunity to discuss this issue with you. I would be pleased to answer any questions you may have.

Statement of
Frances M. Murphy, M.D., M.P.H.
Acting Deputy Under Secretary for Health
Department of Veterans Affairs
Before the
Subcommittees on Health and Oversight & Investigations
Committee on Veterans' Affairs
U. S. House of Representatives

November 16, 1999

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Mr. Chairman and members of the Subcommittees, I appreciate the opportunity to appear before you to discuss the possible health effects of the drug pyridostigmine bromide (PB) on veterans who served in the Gulf War.

As you know, U.S. service members may have been exposed to a variety of hazardous materials during the Gulf War. Veterans, their families, and the VA have been concerned about possible health effects from exposure to the drug PB, as well as to other agents including depleted uranium, oil-well-fire smoke, vaccines, pesticides, chemical and biological warfare agents, and psychological and physiological stress. Numerous independent reviews have looked at the existing medical and scientific literature to determine what is known about health effects from these exposures. The findings have suggested that there is no single unique syndrome that explains the symptoms and illnesses of all Gulf War veterans and that some exposures are unlikely to cause health effects. Based on the findings and recommendations of these reviews, the Federal government has funded a range of significant research programs to investigate areas that are less well understood. Nevertheless, in its ongoing efforts to address Gulf War veterans' health problems, VA has not ruled out any of these exposures as possible causes of Gulf War veterans' illnesses.

This Nation has made a serious commitment to protect the health of, and to care for, military service members and veterans. VA has supported this commitment by establishing health care programs, compensation and benefits programs, and a national research agenda that is focused on the health needs of Gulf War veterans. VA, DOD, and HHS have spent about $134 million over the last six years on 145 federal research projects that are directly related to Gulf War veterans' health issues. The coordination of this research is the primary responsibility of the Interagency Research Working Group, under the auspices of the Persian Gulf Veterans Coordinating Board.

PB is an FDA-approved treatment for the chronic muscle disorder myasthenia gravis and has been used for that purpose for over 40 years. PB was used as an unapproved, investigational drug during the Gulf War as a pre-treatment to reduce the toxicity of the chemical warfare nerve agent soman. Several external independent scientific committees have reviewed the medical and scientific literature on Gulf War health exposures and have not ruled out the possibility of long-term health effects from taking this drug. These reviews, conducted by teams of scientists, physicians, public health specialists, veterans and others, include the 1994 "NIH Technology Assessment Workshop"; the 1996 Institute of Medicine, "Report of the Committee to Review the Health Consequences of Service During the Persian Gulf War"; the 1996 "Presidential Advisory Committee on Gulf War Veterans' Illnesses"; and independent scientific reviews contracted by the Committee on Veterans' Affairs, U.S. Senate, reported in its 1998 "Report of the Special Investigation Unit on Gulf War Illnesses".

Based on these reviews and other information, there is insufficient evidence to conclude that the health effects experienced by Gulf War veterans today are related to exposure to PB during the Gulf War. However, additional research is needed to answer specific outstanding questions about the long-term effects of PB, either PB exposure alone or in combination with exposure to other risk factors, such as pesticides.

Based upon these recommendations, which predate the recent RAND report, the Interagency Research Working Group solicited and funded a number of research studies on potential health effects of PB. Twenty-six such studies have been funded with a total estimated cost of approximately $20 million. Five of the studies have been completed and 21 are ongoing.

The RAND report declared that its conclusion that PB cannot be excluded as a contributor to illnesses in Gulf War veterans differs from conclusions of some prior investigating bodies, such as the Presidential Advisory Committee and the Institute of Medicine. We think that this statement overstates the differences. The other investigating bodies have not ruled out PB as a possible cause of or contributor to the illnesses that some Gulf War veterans are reporting. The RAND report differs in some important ways from the previously described, independent scientific and medical literature reviews. But, in the most critical aspects, the reports are similar. All of them concluded that further research on possible health effects from PB is warranted. The earlier reviews were focused on whether scientific evidence existed that suggested PB was likely to be associated with health problems, while the recent RAND review focused on whether PB could be excluded as a possible cause of health problems.

As you know, the RAND author discussed seven hypotheses relating to how a brief exposure to PB during the Gulf War might affect the health of Gulf War veterans today. We are fortunate that all of those hypotheses were also considered by the prior reviews. In fact, each of the seven hypotheses is currently being addressed by one or more of the 26 Federally sponsored research studies. The following table lists the seven hypotheses raised by the RAND investigator and the number of studies that address each. Some studies address more than one hypothesis.

RAND Investigator's Hypothesis	# Federally Sponsored Studies
Blood-brain barrier passage with stress	6
Individual differences in reaction	9
Interactions with other exposures	16
Bromism	1
Multiple chemical sensitivity related	1
Neuromuscular junction effects	4
Neurotransmitter dysregulation	4

The RAND report is only the latest in an ongoing, intensive effort to improve our understanding of Gulf War health issues. In this regard, VA has contracted with the Institute of Medicine (IOM) for a new study entitled "Health Effects Associated with Exposures Experienced During the Persian Gulf War". This ongoing effort will provide a comprehensive review and analysis of the scientific and medical literature on health effects associated with known Gulf War exposures. VA contracted for this study in June 1998 and thereafter Congress supported this effort with legislative mandates in P.L. 105-368 and P.L. 105-277.

The first phase of the IOM study will include a complete review of scientific literature related to health effects associated with exposure to depleted uranium, vaccines, organophosphate chemical warfare nerve agents, and PB. This report is scheduled to be completed in August 2000.

To summarize, since 1992 VA has implemented a comprehensive, coordinated set of programs to address Gulf War veterans' health problems. In doing so, we have objectively assessed the available published scientific and operational information concerning exposures during Gulf War service and sought the advice of numerous experts. Clearly, in examining the scientific literature, it is important to keep an open mind and consider all information. However, that should not be equated to giving the same weight to subjective and anecdotal reports as to

scientifically designed, replicated research results. American veterans served honorably in the Gulf War and deserve the best health care and research program addressing their health problems that the Nation can provide. VA is committed to providing quality health care and compensation for service-connected disabilities and continuing to aggressively pursue answers to the health concerns of Gulf War veterans and their families.

This concludes my statement. My colleagues and I would be happy to answer any questions.

Statement of
The Honorable Bernard Rostker
Special Assistant to the Deputy Secretary of Defense
For Gulf War Illnesses
Before the House Committee on Veteran's Affairs
November 16, 1999

Mr. Chairman I appreciate the opportunity to appear before the Subcommittee on Health and Subcommittee on Oversight and Investigations to report on our efforts to bring forward work of significance for Gulf War veterans.

The Department of Defense and RAND Corporation recently released the latest in a series of scientific literature reviews on potential health issues affecting Gulf War veterans.

This work presents a great deal of information that wasn't available to decision-makers during the Gulf War. It is a thorough review of an important issue in the search for answers to Gulf War illnesses. We believe this information is valuable both to Gulf War veterans and in the continued research on pyridostigmine bromide (PB).

The RAND paper examines the safety and effectiveness of pyridostigmine bromide (PB), as used during the Gulf War as a pretreatment to protect military personnel from the nerve agent soman. The work was performed to identify hypotheses or theories that might link PB to illnesses in Gulf War veterans.

Two major conclusions emerge from this review of the scientific literature, one pertaining to safety and one to the effectiveness of PB as used as a pretreatment against soman. The report concludes that while medical research has not established PB as a cause of Gulf

War illnesses, it cannot be ruled out as a possible contributor to the development of illnesses in some Gulf War veterans.

The paper also concludes that further research is needed to determine the effectiveness of the current dose of PB against soman. At this time, a very active research program is continuing on all the hypotheses identified by RAND. The Department has asked the Armed Forces Epidemiology Board, an outside panel of distinguished medical experts, to evaluate the RAND review and advise DoD on whether present research directions should be altered.

This review will also be evaluated by the Institute of Medicine as part of its review and assessment of published scientific literature related to exposure of Gulf War veterans and any associations with health effects. We have already forwarded copies of this report to the IOM and clearly understand they are going to expedite their review of this work.

The Department has participated in a comprehensive and collaborative research effort to more fully understand the nature of the illnesses. From FY94 through FY99 more than $134 million has been invested for research on illnesses among Gulf War veterans. To date, over 26 peer-reviewed studies with funding in excess of $20 million, address the health consequences of PB use for nerve agent pretreatment. The Persian Gulf Veterans Coordinating Board has given priority to studies on PB, either alone or in combination with other exposures.

Pyridostigmine bromide is an FDA-approved drug for the civilian use of treating myasthenia gravis, a neuro-muscular disorder. However, PB is considered to be an investigational drug when used

as a pre-treatment against chemical warfare agents because FDA has not licensed PB for that use. FDA rules, with a few narrow exceptions, require that investigational drugs be administered with the informed consent of the person being treated. For the Gulf War, FDA waived the informed consent requirement for the administration of PB because if concurred with DoD's assessment that informed consent was not feasible and that withholding treatment would be contrary to the best interests of military personnel.

We've learned a lot from our experience with PB in the Gulf War. In 1998, the Strom Thurmond National Defense Authorization Act for Fiscal Year 1999 established specific criteria for granting a waiver of informed consent for the use of investigational drugs in a particular military operation. Specifically, only the Secretary of Defense can request a waiver and only the President can grant a waiver of informed consent under certain circumstances. On September 30, 1999, the President issued executive order 13139 which clearly states the procedures he will use in considering a waiver request from the Secretary of Defense. It also sets requirements for DoD to follow in documenting the investigational drug's use, communicating health risk information to the troops and monitoring the health effects of the investigational drug.

In considering the future use of PB we must always balance the risks of war, to include the potential for use of deadly nerve agents such as soman with the possible side effects from the drugs. Currently, PB is thought to be an essential part of the medical protection our troops will have available if the extremely lethal soman nerve agent is found to be a credible threat.

The primary author of the paper, Dr. Beatrice Golomb, joins us here today to discuss the findings with committee members. With that, I'm pleased to answer any questions you may have.

MATTHEW L. PUGLISI
ASSISTANT DIRECTOR, VETERANS AFFAIRS AND REHABILITATION DIVISION
THE AMERICAN LEGION
BEFORE A JOINT HEARING OF THE
SUBCOMMITTEE ON HEALTH
AND
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATION
COMMITTEE ON VETERANS' AFFAIRS
UNITED STATES HOUSE OF REPRESENTATIVES
ON
PYRIDOSTIGMINE BROMIDE

Messrs. Chairmen and members of the Subcommittees:

Thank you for the opportunity to offer testimony regarding the possible health effects of the drug pyridostigmine bromide (PB) on veterans who served in the Persian Gulf War. Thousands of Gulf War veterans continue to suffer symptoms associated with their military service in the Persian Gulf. The American Legion has consistently urged that all possible causes and all adverse health outcomes related to Gulf War veterans be investigated. It is imperative that we understand what has made these veterans ill, and what particular illnesses they suffer from. We are here today to help improve their health, and the well-being of their families.

The recently released report on PB by RAND, which is the event that sparked today's hearing, is one component of a vast $100 million research effort investigating Gulf War veterans' illnesses. Unfortunately, the RAND PB report does not answer the question regarding PB's possible association with Gulf War veterans' illnesses. Rather, it argues that questions concerning PB and veterans' illnesses remain unanswered and merit further investigation.

This finding is maddening to sick Gulf War veterans. Above all, they want to become healthy. Short of that, they want answers. Those answers are no closer today, however, than they were at the end of the Gulf War.

Although the report did not answer the most pressing question regarding PB, it raised some other ones regarding PB's effectiveness as a nerve agent pre-treatment, and its safety. This aspect of the report validates The American Legion's long held position against PB's use as a nerve agent pre-treatment. The American Legion continues to urge the Department of Defense to suspend its policy of using PB as a nerve agent pre-treatment until its efficacy and safety are proven.

Background

Weapons of Terror

The first use of chemicals as a weapon of war occurred in the ancient world. The Spartans burned wood, pitch and sulfur under the walls of besieged cities in 431 BC for the purpose of choking the defenders and easing the difficulty of the assault. "Greek Fire," a flaming mixture spewed at enemy ships and fortifications, was employed for over a thousand years in the Mediterranean. Union troops burned wood saturated with sulfur under the parapets outside of Charleston during their siege of that Confederate city. It was the Germans during World War I, however, who introduced the world to chemical warfare on an industrial scale.

On April 22, 1915, near Ypres, France, 5,000 cylinders filled with chlorine gas were opened all along the front of the German trenches when the wind was blowing towards the British lines. Thousands of casualties resulted as the British were unsuspecting and unprotected. The panic caused by gas attacks that followed, however, was out of proportion to the toxicity and lethality of the chemical weapons used.

By war's end, 31.4 percent of hospital admissions in France for American soldiers were due to chemical weapons. Only two percent of battle deaths, however, were caused by these weapons. One can compare this to the 25 percent of American battle deaths caused by high explosive artillery shells and 10 percent from bullets. Similar casualty and death figures were reported by the other combatants as well. These numbers make clear that chemical weapons filled the hospitals, but not many of the graves, of the First World War. Yet both British and American reports written during and after the war make clear that the weapon troops feared most were chemical weapons. What makes this fact all the more astonishing is that the same British soldiers who fled in panic near Ypres in 1915, many leaving behind their equipment and weapons, marched headlong into machine gun and artillery fire before and after that event. On July 1, 1916

at the Battle of the Somme 20,000 British soldiers were killed before the end of that bloody day. These men showed that they were much more willing to face great risk of getting torn to shreds by bullets and shrapnel, than the much smaller risk of dying from exposure to poison gas.

The ancient Greeks, the Zulu and the Samurai overcame the basic human instinct to flee from mortal danger, and this quality made them all fearsome warriors. By World War One, millions of men in massed armies bravely, or foolishly, were slaughtered as they ignored the temptation to run from certain death. Most humans, however, have not overcome the fear of invisible dangers. Men have shown time and time again that they will march straight into lances, arrows, bullets and minefields. Many cannot, however, overcome their very rational, yet visceral, fear of poison gas. It was the fear of chemical weapons, not their lethality, that made them effective weapons during World War I.

Soman: Lethal and Terrible

Chemical nerve agents attack the nervous system by attaching to enzymes critical to living. Nerve agents (among them sarin, cyclosarin, tabun, VX and soman) attach to acetylcholinesterase (AChE). AChE regulates acetylcholine (ACh), an enzyme which signals other nerve cells to "fire," or muscles to contract. Without AChE, ACh builds up in the synapses and causes twitching, seizures, paralysis and possibly death if the dose received is great enough.

Once exposed to nerve agents, one can inject two antidotes that must be used in tandem: antropine and pralidoxime (known as 2 PAM by troops in the Persian Gulf). Most nerve agents require hours in order to permanently bind to AChE. This should therefore allow an individual to develop symptoms and inject themselves with atropine and 2 PAM in time to save their lives. Soman, however, behaves differently from the other nerve agents. By the time an individual develops the symptoms of soman poisoning, it is too late to inject themselves with the antidotes. This characteristic of soman's, combined with its ability to kill via inhalation or contact with the skin, make it a fearsome and effective weapon if one is exposed to sufficient doses of it. It would appear that unlike the chemical weapons of the First World War, nerve agents, particularly soman, may live up to human's fears of poison gas.

PB as a Nerve Agent Pre-Treatment: Unknown Efficacy and Safety

PB is a drug used to treat myasthenia gravis, a disease marked by muscle weakness and fatigue. It has been in use for this purpose for over 40 years. Research in animals suggests that PB can delay the lethal effects of soman, and allow an individual to inject themselves with antropine and 2 PAM before the onset of severe symptoms and death. All things being equal, this would suggest that PB could be an integral component in any defense against attack with soman.

In the real world however, one cannot hold all other factors constant as in a laboratory. Tests done in primates of PB's effectiveness as a nerve agent pre-treatment utilized very high doses of PB, atropine and 2 PAM, and their extrapolation to humans is a matter of controversy. Furthermore, exposures in a lab can never mimic exposures on a battlefield, with swirling air and inefficient means of delivery (artillery and rockets). PB's effectiveness as a defense against soman for humans is therefore unknown.

In spite of this the US adopted the policy of using PB as a soman pre-treatment in 1986.

The Gulf War

The history of the Gulf War is well known to this Committee, and it therefore does not bear a detailed retelling. The aspects of this history that have a bearing on the topic of this hearing, however, are the role of the Food and Drug Administration (FDA) in PB's use, and the Iraqi's decision not to use chemical weapons.

FDA

In December 1990 FDA approved the use of PB as an investigational new drug (IND) for use as a nerve agent pre-treatment. DoD believed that the Iraqis may have possessed soman (they did not, as it turns out) and urged FDA to approve PB's use. FDA initially balked because PB's effectiveness for the use intended for it by DoD was unknown. FDA, however, was ultimately reluctant to shoulder the burden of being on the wrong side of history if the Iraqi's unleashed a massive soman attack and American troops died because they were not issued PB.

Iraq did not use any of their chemical weapons during the Gulf War. The Iraqis did not realize that US troops were taking PB, nor is there any evidence that they were impressed by our chemical protective masks or suits. Iraq apparently decided not to use chemical weapons because of how the United States would have responded to such an attack, not to any of our chemical defenses.

The Apocalypse as CW Defense

On January 9, 1991 Secretary of State James Baker met with Iraqi Foreign Minister Tariq Azziz in Geneva and handed him a letter from President Bush for Saddam Hussein. The letter stated that if the Iraqis attacked American forces with chemical weapons, among other "unconscionable acts," Saddam and Iraq would "pay a terrible price." The Iraqis interpreted that as a threat to overthrow the Saddam Hussein regime.

Senior national security and foreign policy leaders in the Bush Administration since the Gulf War have suggested that the "terrible price" ranged from annihilation of Iraq's civilian infrastructure, to the bombing of dams near Baghdad. US doctrine simply states that any use of weapons of mass destruction (which includes chemical, biological and nuclear weapons) against the United States or its forces will be met with an "overwhelming and disproportionate response." Whatever form the US response to Iraq's use of chemical weapons would have taken, two things are clear: first, the United States in 1991 had the capability to raise the level of violence against Iraq to apocalyptic levels; second, the Iraqis believed the US had the will to carry out the threats contained in President Bush's letter.

US CBW Doctrine

The Actual Threat May Not Warrant the Current Policy

DoD maintains that it will only order US troops to take PB in the event that there is an imminent threat of attack with soman against those troops. Legislation signed last year requires that the President authorize the use of PB by US troops. One would imagine that DoD would have to be very confident in future intelligence assessments to ask the President to issue such an order. Given all that we have learned about chemical weapons, their use in past wars, and their non-use in the Gulf War, is PB really a viable defense against a soman attack? The evidence suggests otherwise.

"Overwhelming and Disproportionate Response"

Somalia, Beirut and Kosovo notwithstanding, the United States has shown the world in this century that it will use weapons of mass destruction and mass air bombardments to protect the lives of its GIs as it pursues it war aims. This historical fact, combined with its policy of disproportionate response to an attack with weapons of mass destruction, appear to be the most effective defense that US troops have against a chemical weapons attack.

Weapons of Terror

The key characteristic of chemical weapons remains, in spite of the introduction of nerve agents, the fear of them. My own experience in the Persian Gulf would probably have been familiar to a junior officer serving on the Western Front in 1917 in this regard: more time was spent reassuring the several Marines under my charge regarding an attack with chemical weapons than reassuring them regarding the risks from mines, shrapnel and bullets. The irony was that we were never attacked with chemical weapons, and those casualties we did suffer resulted from high explosives similar to those found in World War I.

"Morale is to Material as Three is to One."--Napoleon

PB could undermine troops' morale in future wars, and their confidence in their commanders, at the very moment when their mental state is most critical. Commanders in a future war will not issue PB in a vacuum. Young Americans, aware of Gulf War veterans' illnesses, Agent Orange and the controversy over the anthrax vaccination program, will be ordered to take a drug whose effectiveness and safety are under serious scrutiny. DoD argues that operational requirements may require that PB be issued. Yet it may very well be the height of folly to order troops to ingest a drug that is being investigated for its role, if any, in Gulf War veterans' illnesses while these same troops await attack with a chemical weapon that can kill them in minutes. Commanders need a rational doctrine that takes into account history and human nature, not one that ignores the two. During the hours before the bullets fly, troops need as much certainty as their commanders can muster, not further uncertainty and added risk.

Chemical Weapons Are Difficult to Use Effectively on Modern Battlefields

In order to allow a human to be exposed to enough soman to kill him or her, one must somehow deliver it to where that person is. Fixed trench positions and surprise allowed the Germans to use thousands of canisters in 1915 for the first modern gas attack. Artillery shells were the most practical method for the remainder of the war, but they certainly were not the most efficient. Unless one can mass artillery, rockets or aircraft bombs on a concentration of troops, one may not poison enough troops to have a significant impact (besides the fear such an attack would likely cause). It is true that very little soman can cause death in a human. However, spreading the soman across a battlefield, or even concentrating it on a segment of it, is easier said than done

particularly with the US Air Force bombing everything that moves. Unless a future adversary can stop a US military operation dead in its tracks for a significant duration with a massive, accurate, exquisitely well coordinated soman attack (with the wind blowing in the ideal direction, at the ideal velocity, and for the ideal duration), even the most foolish of despots would realize the potential US retaliation was not worth whatever gain was realized. Saddam Hussein is often ridiculed for his poor judgment. He may have poor judgment, but it was still good enough in 1991 prevent him from using chemical weapons.

Suspend PB Policy Until Its Safety and Efficacy Are Known

The RAND PB report raises more questions than it answers. One question it does not raise explicitly is why would DoD issue PB again before the questions regarding its efficacy and safety are answered.

The weight that commanders bear before they lead troops into battle is enormous. The services, the Joint Chiefs of Staff, and the Office of the Secretary of Defense are obligated to lesson that weight as much as possible before the fighting begins. They must acquire the best weapons and equipment money can buy, they must provide commanders with the best trained troops possible, and they must develop policies that assure victory and minimize the risk of defeat and unnecessary casualties.

PB's effectiveness as a soman pre-treatment in humans is unknown, and its long term safety is in question. Until and unless those issues are addressed adequately it is the judgment of The American Legion that PB not be issued to US troops.

Leave No Stone Unturned

The RAND PB report outlined several hypotheses that merited investigation regarding PB's possible link to Gulf War veterans' illnesses. It is encouraging to learn that scientific studies underway are investigating these hypotheses, and The American Legion remains hopeful that these studies may answer the outstanding questions regarding PB's safety. In the meantime, it is imperative that Congress maintain an active role in overseeing the federal government's response to Gulf War veterans' illnesses. Only through active oversight will disabled Gulf War veterans' health have a chance to improve.

That concludes my statement, Messrs. Chairmen. I would be happy to answer any questions at this time.

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Testimony
of
Paul Sullivan
Executive Director

Before the
House Veterans' Affairs Committee
Subcommittee on Health
&
Subcommittee on Oversight and Investigations

November 16, 1999

NATIONAL GULF WAR RESOURCE CENTER, NOVEMBER 16, 1999
TESTIMONY BEFORE THE HOUSE VETERANS' AFFAIRS COMMITTEE

I. Introduction

Chairman, members of the subcommittee, thank you for the opportunity to testify on behalf of the National Gulf War Resource Center regarding the adverse health effects of pyridostigmine bromide, an investigational new drug (IND) given to as many as 250,000 U.S. soldiers during the Gulf War in 1991.

Each time humans engage in warfare, almost everyone suffers, even some who at first may appear to have survived without visible injury or illness. Amid the chaos of gunfire since the start of the Gulf War in 1990, some laws regarding human rights and medical experimentation have fallen short, fallen silent, or been disregarded. In hindsight, the history of Gulf War may show the well-intended use of PB pills backfired.

Similarly, the demolition of Iraqi chemical warfare agent stockpiles, the use of depleted uranium ammunition, and the presence of other toxins could very well represent the world's largest friendly fire incidents all rolled into one never-ending conflict.

Today, the NGWRC urges Congress, based on new information released by the Department of Defense (DoD), to reexamine the utility of current research and benefits laws that have failed to adequately address Gulf War veterans' illnesses.

The mission of the NGWRC is very narrow: request our government to determine why so many of our comrades are ill and disabled, to provide medical treatment to those in need, to provide compensation to the disabled, and to learn from mistakes made in the Gulf War so that future toxic exposures and illnesses may be reduced or prevented.

II. NGWRC Position on the Need for Research and Treatment

The NGWRC is here today to re-state our justifiable anger and strong disappointment at the Pentagon for failing to admit earlier that PB pills cannot be ruled out as associated with some of the illnesses reported among Gulf War veterans. The DoD has possessed this information for years. Gulf War veterans have been aware since 1991 due to our battlefield experience with PB.

The military remains, for the most part, unresponsive to calls by Gulf War veterans for more research and treatment, not only on PB pills, but on other matters, including oil well fire particulate matter, depleted uranium radioactive toxic waste, the anthrax vaccine, and low-level chemical warfare agent exposures, among others.

The NGWRC urges Congress to review three main issues:

1. Consider funding immediate and aggressive research and treatment into the neurological and other disorders found believed related to the PB pills. This includes synergistic effects of PB and other toxins, and the possible genetic predisposition of some veterans to be at higher risk, as was found by Dr. Robert Haley.

Of the 25 studies launched by the VA and DoD on PB, more than 20 remain on-going. Research shows there may be a connection between PB and Gulf War illnesses. The NGWRC strongly supports full funding for the Gulf War illnesses research agenda developed by the Centers for Disease Control and Prevention earlier this year. Appropriate and effective treatment remains a top priority.

2. Consider hearings on the VA's role in granting direct service-connection for conditions science associates with taking PB pills, either alone or in combination with other toxins. This would follow the intent of Congress when it passed the "Persian Gulf War Veterans Act of 1998," Public Law 105-277. Once direct service-connection is established, then Gulf War veterans should be provided promptly with existing symptom-based treatment and any new treatment modalities found to provide relief.

3. The NGWRC urges Congress to investigate a major lesson from the PB controversy. After Congress funded PB research in 1993, adverse effects were subsequently found. Congress should consider funding additional specific research into the adverse effects of the anthrax vaccine, oil well fire particulate matter, and other Gulf War toxins.

In 1993, Congress funded research on inhaled, ingested, and imbedded depleted uranium (DU). DU is a radioactive toxic waste used as ammunition. However, the DoD chose to research only imbedded DU shrapnel. The NGWRC urges Congress to investigate the failure of the Pentagon to research inhaled and ingested DU in accordance with Section 271 of PL 103-160, enacted on November 30, 1993.

On April 15, 1999, Bernard Rostker, in his dual role as Undersecretary of the Army and the Special Assistant for Gulf War Illnesses, was asked by the NGWRC to conduct research on inhaled DU. Rostker publicly refused, saying there was "no need" to conduct research on inhaled DU.

In a 1999 report prepared for DoD, RAND recommended more research into depleted uranium. Several peer-reviewed, published research reports from the Armed Forces Radiobiology Research Institute (part of DoD), recommended research into the possible links between cancer and depleted uranium. The NGWRC asks Congress to hold hearings on how Bernard Rostker and Army Colonel Eric Daxon may have undermined the intent of Congress. The NGWRC believes objective, independent research on inhaled and ingested DU must begin soon.

III. Conclusion

The NGWRC finds that the military failed to collect data regarding PB exposures, ignored the claims made by Gulf War veterans and scientists regarding PB pills for years, and delayed research into the adverse effects of PB. After much hesitation, and only after dozens of Congressional hearings and public outcry by disabled veterans, did the Pentagon begin research into PB pills.

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The preliminary findings now strongly suggest problems associated with PB pills, thus vindicating Gulf War veterans and scientists such as James Moss and others. Additional research and treatment must be launched in earnest.

The NGWRC urges Congress to press the VA for immediate regulations for direct service-connection for all PB-related conditions. The NGWRC also urges Congress to apply the lesson learned regarding PB to DU and other toxins: once research was launched into PB, some of the mystery of Gulf War illnesses was unlocked.

This concludes my testimony. I ask that a letter dated November 5, 1999 sent from Dan Fahey of the Military Toxics Project to Representative Lane Evans, the Ranking Member of the House Veterans' Affairs Committee, be included in the record.

Thank you. I will be happy to answer any of your questions.

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Attachment #1: NGWRC Position on the Required Use PB Pills

The NGWRC is not testifying today to cast blame on the individuals who may be responsible for the decision to take the pills, the failure to keep records, or the failure to launch research on PB pills when veterans first began experiences problems.

The NGWRC is not here to debate the issue of human rights and the Nuremberg Code prohibiting the use of experimental drugs on unknowing participants. The NGWRC position remains clear: the use of PB is a mistake, and the possible adverse effects have been well documented and accepted – with the notable exception of the DoD.

Even Dr. Galomb, writing for the Pentagon and RAND, asserts the continued use of PB may be problematic, and she claims the PB

> **... issue is a complex one, involving trading off uncertain health risks – but risks now shown to be biologically plausible – against uncertain gains from use of PB in the warfare setting [xxxiii].**
>
> **...there remain some concerns regarding the efficacy of PB in protection against nerve agent threats. For some nerve agents, such as sarin, evidence was not adequate to exclude a possible harmful effect by use of PB as a pretreatment [277].**

The NGWRC stands by our May 1996 conclusion that the on-going use of PB pills is a "mistake." The recent RAND report cannot rule out a link between the PB pills and Gulf War illnesses.

Furthermore, the RAND report calls into question the effectiveness of PB against soman, and highlights the possible adverse effects of PB when sarin is present.

Although these critical issues should be addressed and resolved, they are not the focus of our testimony today.

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Attachment #2: Historical Perspective of PB use by the NGWRC

At the start of the Gulf War, the Department of Defense, in a reasonable attempt to protect U.S. troops against the chemical warfare agent soman, may have unintentionally injured or disabled some of us by ordering the use of PB pills. The DoD estimates between 250,000 and 300,000 U.S. troops took the PB pills.

In August 1990, Iraq invaded Kuwait, and U.S. troops were deployed to the region. The military learned that Iraq was armed with the same chemical warfare agents (some supplied by U.S. and other nations) that Iraq had previously used against Kurds inside Iraq, including soman, sarin, cyclosarin, mustard, and others.

In late December 1990, the DoD requested a waiver from the Food and Drug Administration (FDA) so the military could order U.S. troops to take investigational new drugs (INDs), including PB pills. The use of PB pills was needed because Iraq was able to obtain dual-use technology and equipment as well as pre-cursor chemicals from the U.S. and other nations needed to manufacture weapons of mass destruction.

As part of the request for the waiver to order the use of an FDA approved drug for a non-FDA-approved purpose, the DoD wrote,

> **In all peace time applications, we believe strongly in informed consent and ethical foundations ... but military combat is different.**

Then, starting January 17, 1999, when Iraq began launching SCUD missiles and the U.S. began bombing Iraqi chemical weapons manufacturing, storage, and deployment sites, U.S. troops were ordered to begin taking PB pills.

As part of the FDA waiver, the DoD agreed to keep records documenting who took the PB pills and to determine the long-term effects, if any, of taking the PB pills. As pointed out in many sources, some soldiers, under the belief that "if one PB pill is good, then several more are better," took unknown amounts of PB pills for unknown lengths of time.

In early 1991, the first public hint of a serious problem surfaced as thousands of Gulf War veterans reporting unusual symptoms to private healthcare providers as well as to the DoD and VA. DoD research in 1991 was limited to whether PB interfered with the combat mission – not on the long-term health consequences. Congress responded promptly to the unusual illnesses in 1992 and 1993 and required the DoD and VA to establish registries for the unusual illnesses.

In December 1994, the Senate Veterans' Affairs Committee sounded a loud alarm on the PB pills. Many non-DoD scientists, including James Moss, a former Department of Agriculture scientist, claimed there may be a problem associated with the use of PB pills at the same time other toxins were present.

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Led by Senator John Rockefeller, the panel's staff reached a firm conclusion that

> **... pyridostigmine bromide pretreatment makes individuals more vulnerable to other nerve agents, such as VX and Sarin.**

Sarin, cyclosarin, and mustard agents were released into the air as a result of post-cease fire demolitions efforts by U.S. troops, including two such incidents at Khamisiyah, Iraq on March 4 and March 10, 1991. Many others remain under DoD investigation.

Shortly after Senator Rockefeller's report was released, the DoD and VA began additional medical research into the PB pills, with total appropriations of $20 million since 1994. This is commendable, yet DoD failures between 1990 and 1994 cost years of precious time for Gulf War veterans seeking answers and treatment.

More disturbing information was released in April 1996, as research conducted by Mohamed Abou-Donia at Duke University was published in New Scientist to

> **... suggest that an anti-nerve gas [PB] pill taken by many of the troops may have interfered with the body's natural defenses against the toxic effects of an insecticide and an insect repellent they routinely used to protect against disease-carrying flies and mosquitoes. A year ago, the researchers reported that chickens exposed to relatively low levels of all three chemicals developed nerve damage. Last week ... the researchers outlined a possible mechanism behind the damage.**

There were other official warnings, too. Later in 1996, the National Academy of Science's Institute of Medicine, in their report, "Health Consequences of Service During the Persian Gulf War," found

> **A third hypothesis that there were synergistic reactions among some combination of PB pesticides, and insect repellents used by the troops. It has been known for many years that the simultaneous or sequential administration of two anti-AchE drugs can have an additive or even synergistic effect.**

And then there were more warnings in 1996, as the Presidential Advisory Committee on Gulf War Veterans' Illnesses concluded

> **Ongoing federally funded studies should help the scientific community draw conclusions about the synergistic effects of PB and other risk factors.**

Congress continued working on the issue of PB pills, and in August 1998, the Senate Veterans' Affairs Committee, under the leadership of Chairman Arlen Specter and Senator John Rockefeller, published a scathing report on Gulf War illnesses, confirming

> **DoD kept no records to document who took PB and how much was taken despite FDA's requirement to do so. DoD believes that about 250,000 personnel took at least some PB during the deployment.**
>
> **... PB may also interact with pesticides and potentially create adverse health effects at lower doses of these agents, although the health consequences of such multiple exposures are unknown.**

The 1998 Senate report also contains a lengthy report prepared by James Moss on the "Possible Potentation of Pyridostigmine Bromide by Pesticides." Moss was one of the first non-Pentagon researchers to raise awareness on the potential adverse role of PB pills in 1994.

In early 1999, Richard A. Rittig, working for the RAND Corporation at the request of the Department of Defense, concluded

> **The DoD Gulf War experience in the use of PB [pills] ... was characterized by poor record keeping, inadequate data collection, and other violations of the terms agreed to in the FDA waivers.**

Simply put, this means that research into the long term effects of PB pills will be seriously hampered by the lack of data – information such as how many troops took the pills, how many were taken, over what period of time were the pills taken, and what other toxins may have been present at the time the pills were taken.

All that remains now, unfortunately, is the memory of the some veterans who have reported illnesses. In a very sad irony, many Gulf War veterans who took PB pills also report memory problems, further complicating an already difficult research situation.

This is why Congress wisely passed Public Law 103-446, thus providing healthcare and other benefits to Gulf War veterans with undiagnosed or not clearly defined illnesses. The law, enacted 1994, presumes that lay evidence presented by a Gulf War veteran as to exposure and current medical condition should be believed.

Then, last month, the Department of Defense reversed their long-standing position that PB pills were not associated with Gulf War illnesses. Beatrice Alexandra Golomb, working for RAND Corporation at the request of the Pentagon, found

> **1. PB cannot be ruled out as a possible contributor to the development of unexplained or undiagnosed illness in some [Gulf War] veterans [xxxiii].**
>
> **2. In summary, present evidence cannot exclude a role of PB as a contributor to chronic illnesses in [Persian Gulf War] veterans**

mediated through several possible pathways, individually or in concert [277].

Thus, after almost nine years, with ill Gulf War veterans in the lead followed by non-military scientists and a White House commission, the Pentagon finally woke up and listened to reasonable concerns about the possible dangers of PB pills.

On October 20, 1999, Dr. Joyce Lashof, ex-dean of the Berkeley School of Public Health and former chair of the Presidential Advisory Committee on Gulf War Veterans' Illnesses, was interviewed by the San Francisco Chronicle. In response to the Pentagon's about-face on PB pills, she declared

We left the same door open.... It's a real illness. People are sick.

The NGWRC believes that now is the time, in light of this dramatic shift in military policy on PB pills, for the VA, DoD, HHS, and non-government scientists to take aggressive, immediate action to benefit ailing Gulf War veterans, including more research, developing treatment, and exploring other Gulf War toxic exposures with vigor and rigor.

NATIONAL GULF WAR RESOURCE CENTER, NOVEMBER 16, 1999
TESTIMONY BEFORE THE HOUSE VETERANS' AFFAIRS COMMITTEE

Attachment #3: Public Law 103-160, Signed into Law on November 30, 1993

SEC. 271. RESEARCH ON EXPOSURE TO DEPLETED URANIUM BY MILITARY PERSONNEL WHO SERVED IN THE PERSIAN GULF WAR.

(a) GRANT TO SUPPORT RESEARCH ON THE EFFECTS OF DEPLETED URANIUM- From the funds appropriated or otherwise made available in fiscal year 1994 for research, development, test, and evaluation for the Department of Defense, the Secretary of Defense is authorized to make a competitive award of a grant in the amount of $1,700,000 to a medical research institution for the purpose of studying the possible health effects of battlefield exposure to depleted uranium, including exposure through ingestion, inhalation, or bodily injury. The selection of the institution to which the grant is awarded shall be made in accordance with established defense acquisition procedures.

(b) RESEARCH PROGRAM- The research to be conducted at the facility for which a grant is made under subsection (a) shall explore the possible short-term and long-term health effects of exposure to depleted uranium, including exposure through ingestion, inhalation, or bodily injury, and the individual susceptibility of service personnel to such exposure. Such research shall focus on (but not be limited to) persons who may have been exposed to depleted uranium while serving on active duty in the theater of operations during the Persian Gulf War. The specific objectives of the study shall include investigation of the pathology of depleted uranium fragments under controlled conditions, including--

(1) assessment of the toxico-kinetic properties of the various chemical forms of depleted uranium that could be inhaled, ingested, or imbedded;

(2) examination of whether there are depleted uranium cancer induction mechanisms similar to those observed in Thorotrast-specific liver cancers;

(3) determination of whether the radiogenic effects described in paragraphs (1) and (2) occur and, if so, at what fragment densities and latent periods;

(4) assessment of long-term, low-dose-rate irradiation of specific tissues, such as those of the nervous system;

(5) determination of the potential for chronic nephrotoxicity as a function of the organ exposed to depleted uranium; and

(6) conduct of pathological studies of tissue surrounding depleted uranium particles.

(c) REPORTS TO CONGRESS- Not later than October 1, 1994, and annually thereafter for the period that research described in subsection (a) is being carried out under the grant made under this section, the Secretary shall submit to the congressional defense committees a report on the results of such research during the year preceding the report.

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Funding Statement
November 16, 1999

The National Gulf War Resource Center, Inc. (NGWRC) has not received any Federal grant or contract during the current or previous two fiscal years

The NGWRC is registered with the Secretary of the Senate and the Clerk of the House of Representatives.

The NGWRC was founded on June 28, 1995 in the District of Columbia, and it was incorporated on November 21, 1995 in the District of Columbia.

The NGWRC received our certification for non-profit status as a 501(c)(3) from the Internal Revenue Service on March 31, 1997.

Further information regarding the NGWRC should be addressed to our Washington, DC headquarters.

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PAUL SULLIVAN
Executive Director

Paul Sullivan was appointed Executive Director of the National Gulf War Resource Center (NGWRC) in August 1997. From June 1995 until August 1997, he served on the NGWRC Board of Directors.

In his role as Executive Director, Mr. Sullivan serves as the chief executive officer and spokesperson for the NGWRC, a coalition of sixty grassroots organizations providing advocacy for Gulf War veteran-related issues, especially Gulf War illnesses.

Formed in 1995 by seventeen grassroots groups, the National Gulf War Resource Center became the first organization based in Washington, D.C. dedicated solely to Gulf War veterans' concerns, especially Gulf War illnesses. The NGWRC maintains a national presence in our nation's capital advocating Gulf War veterans' concerns through a grant from Vietnam Veterans of America.

Mr. Sullivan previously served as the President of the Gulf War Veterans of Georgia, a grassroots group he helped organize, from 1994 to 1996, and as Vice President from 1996 until 1997. As a representative of the Gulf War Veterans of Georgia, he helped organize the National Unity Conference in Dallas, Texas, in March 1995, which served as the genesis for the formation of the NGWRC in June 1995.

Starting in 1993, Mr. Sullivan and others conducted research and then publicized documents (most notably Central Command's Nuclear, Biological, and Chemical incident reporting log) that assisted in forcing the Department of Defense to disclose that as many as 100,000 American soldiers may have been exposed to low-levels of chemical warfare agents during the Gulf War

In 1994, Mr. Sullivan provided assistance with preparing the first outline and draft of a *Gulf War Syndrome Self Help Guide* to assist veterans when filing claims for healthcare and other benefits with the Department of Veterans Affairs. More than 21,000 free NGWRC *Self Help Guides* have been distributed to veterans, veterans service organizations, legislators, the press, and the public. In 1999, Mr. Sullivan co-wrote, along with Charles Sheehan-Miles, the NGWRC National Secretary, the Third Edition of the *Self Help Guide for Gulf War Illnesses*.

During the Gulf War, he served in the U.S. Army as a Cavalry Scout (Armored Reconnaissance Specialist) with the 1st Armored Division. After leaving the service, he earned a Bachelor of Arts degree in Political Science from the State University of West Georgia.

Mr. Sullivan and his wife, Danielle, live in Fairfax, Virginia with their three-year old daughter, Erin. He is also a Life Member of Veterans of Foreign Wars Post 2681 as well as a member of the Associates of Vietnam Veterans of America.

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November 5, 1999

The Honorable Lane Evans
2335 Rayburn House Office Building
Washington, DC 20515

Dear Congressman Evans:

I write to call to your attention an intentional violation of a bill you submitted, which later became public law, that called for research on the health effects of inhaled and ingested depleted uranium dust, which is a suspected cause of Gulf War veterans' illnesses.

In 1993, you submitted HR 2481, which called for research on the health effects of exposure to depleted uranium through "ingestion, inhalation, or bodily injury." HR 2481 was subsequently incorporated into HR 2401, the Defense Authorization Bill, which later became Public Law 103-160 (on November 30, 1993). Section 271, Subtitle E, Title II of PL 103-160 called upon the Department of Defense to provide funding to study the health effects of inhaled, ingested, *and* implanted DU.

Since 1993, the Department of Defense has initiated only three research projects on depleted uranium: two conducted by the Armed Forces Radiobiology Research Institute examining DU fragments in rats; and one study at the Baltimore, MD VA Medical Center designed to study a subgroup of the veterans wounded by DU fragments in the Gulf War.

Despite the fact that the Pentagon admitted, in January 1998, that "thousands" of veterans may have inhaled or ingested depleted uranium dust on Gulf War battlefields, no research on inhaled or ingested depleted uranium has ever been undertaken by the Department of Defense, in a blatant violation of your intention and Public Law 103-160.

New information indicates Colonel Eric Daxon, U.S. Army Medical Corps, made a decision, on his own, that no research on inhaled depleted uranium would be conducted. Last week, at a meeting meeting on DU at the United Nations, journalist Scott Peterson (Christian Science Monitor) gave me the transcript of a telephone interview he did with Col. Eric Daxon on December

14, 1998.

In this interview, Eric Daxon makes the following statement:

"And you know to me, it is really disturbing that folks are still pushing for studies of [DU] inhalation. I was the guy who basically decided not do that in 1994, and focus the AFRRI research effort and the follow-up on the embedded fragments because of everything that has already been done in inhalation." Emphasis added.

If he is quoted correctly, Daxon took it upon himself to prohibit research on inhalation of DU. If the research had been conducted, as ordered by Congress, we may have a better understanding today of the role of DU in veterans' health problems.

I strongly encourage you to investigate this matter. Further, I stand ready to assist your office in whatever way possible. I can be contacted at (202) 232-1880.

Sincerely,

Dan Fahey
National Organizer

Cc: The Honorable Russell Feingold
The Honorable Bob Filner
The Honorable William S. Cohen
Steve Fox, U.S. General Accounting Office
Paul Sullivan, National Gulf War Resource Center

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May 3, 1999

Honorable William Cohen
Secretary of Defense
1000 Defense, The Pentagon
Washington, DC 20301

Dear Secretary Cohen:

The National Gulf War Resource Center, representing 58 grassroots groups concerned about the health effects of Gulf War service, has lost all confidence in the ability of the Office of the Special Assistant for Gulf War Illnesses (OSAGWI) to be candid and credible on this issue.

As a result of recent false and misleading statements about depleted uranium (DU) made by Army Undersecretary Bernard Roskter, the NGWRC demands that Roskter be removed immediately as the DoD Special Assistant for Gulf War Illnesses.

Rostker claims there are no significant health problems related to DU exposure. Scientific research shows his claims are false, as many serious medical problems are related to DU, including the presence of DU in the semen of Gulf War veterans. Rostker, in contrast to a recent RAND report, refused to consider new medical research into the health effects of DU among soldiers.

Furthermore, Rostker is unable to verify that required DU training for soldiers or military medical personnel has taken place. This is unacceptable. Rostker is AWOL for leadership and accountability purposes regarding Gulf War illnesses because he may be spending too much time as Army Undersecretary.

Therefore, because DU is currently in use in the Gulf War and the Balkans War, the NGWRC demands high-level accountability for uranium radioactive toxic waste exposures and Gulf War illnesses. The NGWRC demands the President issue an executive order requiring soldiers and military medical personnel be provided DU training, demands soldiers and veterans be presumed to have the highest levels of DU exposure, and demands soldiers and veterans be given medical screenings and

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any needed follow-up healthcare associated with DU exposures.

Furthermore, new, independent research must be launched at once for this significant, widespread health hazard.

We would appreciate a prompt reply to our demands for action on this issue.

Sincerely,

Copy

Paul Sullivan
Executive Director

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June 15, 1999

Honorable William Cohen
Secretary of Defense
1000 Defense, The Pentagon
Washington, DC 20301

Dear Secretary Cohen:

On May 3, 1999, the NGWRC wrote you asking for the removal of Bernard Roskter as the Special Assistant for Gulf War Illnesses. You have not replied.

However, on May 28, 1999, the NGWRC was sent a letter from Bernard Rostker wherein he claimed you asked him to reply. His reply is not satisfactory.

In Rostker's letter, he fabricated an outside endorsement of his work. In the letter, Rostker claimed former Senator Warren Rudman "endorsed" Rostker's self-described "premature" report on the adverse health effects of poisoning from depleted uranium radioactive toxic waste contamination during the Gulf War.

A thorough reading of Senator Rudman's official response to Rostker dated February 2, 1999 shows Rostker's depleted uranium report is, "incomplete," "misleading," "not clearly written," and "contains contradictory information." This is not an "endorsement." This is harsh criticism of Rostker's unprofessional work.

In another matter, in a June 15, 1999 briefing by the Armed Forces Radiobiology Research Institute before the National Academy of Sciences, AFRRI found:

* Depleted Uranium "induces oconogenes known to be involved in carcinogenesis." In simple terms, DU radioactive toxic waste appears to be linked to cancer by AFRRI scientists. In contrast, Rostker claims exposure to DU is not medically significant.

* "Conclusion: Strong evidence exists to support detailed study of DU carcinogenicity." In simple terms, AFRRI scientists want long-term research into the adverse health effects caused by exposure to depleted uranium radioactive toxic waste. The NGWRC supports this view (expanded to included inhaled DU). In contrast, on April 15, 1999 Rostker told the NGWRC he would not recommend DU research into possible links between cancer, respiratory problems, and reproductive outcomes among Gulf War veterans. Rostker said there was "no need."

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Once again, the NGWRC demands the immediate removal of Rostker, the start of DU training, the start of documenting DU exposures, the start of providing medical screenings for DU exposures, and the start of healthcare for the long-term effects of all types of DU exposure, especially inhaled and ingested DU.

We also request a reply from you, not the employee who continues to fail in his duties to soldiers and veterans.

Sincerely,

- Cpy -

Paul Sullivan
Executive Director

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Testimony Before the Health/Oversight Subcommittees November 16th

National Vietnam & Gulf War Veterans Coalition

Denise Nichols-Vice Chair

USAFR(ret) RN,MSN

Gulf War Veteran Flight Nurse

Good Afternoon, Chairmen Stearns and Everett, Committee members, staffers, and those in attendance today. The National Vietnam and Gulf War Veterans Coalition, composing 102 member groups of Vietnam and Gulf War veterans is honor to appear today in front of this committee.

We welcome the recent release of the OSAWGI Rand Report on Pyridostigmine Bromide. WE wish to point out that the information presented in this report in 1999 has been openly available since 1994. Senator Rockefeller in his Senate Veterans Affairs committee report in 1994, the Presidential Advisory Committee on Gulf War Illnesses, and last year's Senate Veterans affairs report, 1998 have all come to the same conclusion if not stronger conclusions that this FDA, investigational new drug, pyridostigmine bromide had some part to play in Gulf War Illnesses.

We Gulf War veterans have repeated listed all the exposures that occurred in theater. We have also been quite open in saying that the response to our illnesses have not been treated in the URGENT EMERGENCY manner as is necessary. These illnesses are neurological and immune system in nature. I can say as a nurse with over 20 years of experience that what we veterans are seeing is truly an emergency situation that has not been dealt

with in the manner it should be. These illnesses are devastating and warrant the strongest actions that we can mount as a nation. This is not about runny noses and feeling poorly. This is about extreme fatigue that interferes with the ability of people to live a normal life and to support a family. We are talking about illnesses like ALS, Parkinsons, Multiple Scelorsis, Aggressive Cancers, and Brain Stem Damage.

We are talking about memory loss to the extent that Gulf War Veterans become disoriented and lost in driving around their hometowns that they have know a life time. It is about having blackouts while driving. It is about normal 20-30-40- and early 50 years olds that are not able to function as working adults.

It is about deaths at an early age, it about family members who are also showing illnesses with the same symptoms as their gulf war veteran

spouses. WE in the last month lost one of these wives that was getting the same answers and tentative diagnoses as MS and Scarcodosis as her husband the veteran was receiving. These are people, veterans, that should be in the prime career building and family building time of their lives. This is why this situation should be treated differently than we have traditionally treated post war illnesses. We should have already learned the Lessons well from atomic veterans and agent orange veterans. We need to treat veterans with a new Gold standard! Compensation should not be a battle to be fought with your government after you served that same government with no questions asked.

We have experts that have been on the veterans side since early in 1993. These experts include Dr Jim Moss who testified on pyridostigmine bromide in 1994, Dr Abou-Donai who did studies utilizing hens at Duke University, Dr Tiedt who came forward at a Presidential Advisory Committee and was

part of the U S Army Medical Research team in the 1980s that warned even then that this drug should not be utilized, and Dr Hailey and Dr Baumzweiger who have also come forward to testify on the brain stem and the neurological immune system damage that Gulf War Veterans have been exhibiting.

We welcome further funding of research studies. We would like to most strongly recommend that clinicians like Dr Baumzweiger be funded fully quickly so more Gulf War veterans can seek EFFECTIVE Treatment and CARE. We also would want the extension granted for family members that are effected past the current deadline of December 1999.

We also wish to recommend that those veterans who are Gulf War era veterans who did not serve in theater who were given shots or dealt with equipment returning from the Gulf and who are experiencing the same

symptoms be included in the registries and provide care just as the Gulf War veterans who served in theater. They need to be placed on the registry and coded as nondeployed. We also must not forget our veterans who served in theater as early as 1988 and then after the gulf war(Operation Desert Storm 1991) they too are suffering from these symptoms. As well as our civilian contractors that served both in theater and out who have reported in as being ill.

WE have categories of people that were in theater who did not take the pyridostigmine bromide that are reporting ill. We have those that are reporting ill, that took the tablets over a limited time as compared with others who took the pyridostigmine bromide over a longer period of time. So we still have not found the magic bullet. I have said all along as well as other experts that it is a combination and synergistic combination of all the various exposures.

We now come to a time that we must ask and push for a Blanket compensation under an emergency Immediate Category for these veterans. I have prepared a point paper that I have presented to the Presidential Oversight Board and to the Institute of Medicine I am including that today as an appendix to my testimony.

One of the 36 points on the point paper is the need to meet the emergency needs of these veterans. If FEMA can meet the needs of our civilians in Natural Disaster situations, why can't we utilize that approach to help our Nation's Gulf War Veterans?

We hope that you will follow this valuable hearing today with complete hearings in January at the start of legislative business for 2000 that will include testimony from the witnesses we have mentioned in this testimony and plus veterans and civilians that have been affected that are identified in

this testimony as also being ill, because until we do these action items we are not fully addressing the complete needs of our Gulf War Veterans.

Until we add in these other categories of people affected we will not have a complete picture of the illnesses and all its potential causes.

I would welcome the opportunity now to answer your questions related to my testimony or to the attachment titled POINT PAPER ON GULF WAR ILLNESSES.

Thank you for this opportunity today and we hope to be invited again in the future to participate in person at these hearings.

Statement of

SIDNEY DANIELS
Deputy Director
National Legislative Service
Veterans of Foreign Wars of the United States

to the

COMMITTEE ON VETERANS' AFFAIRS
SUBCOMMITTEE ON HEALTH and
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
U.S. HOUSE OF REPRESENTATIVES

with respect to

PYRIDOSTIGMINE BROMIDE (PB)

WASHINGTON, DC **NOVEMBER 16, 1999**

MESSRS. CHAIRMEN AND MEMBERS OF THE SUBCOMMITTEES: Thank you for the opportunity to present the views of the Veterans of Foreign Wars of the United States with respect to Pyridostigmine Bromide (PB) as a possible cause for Gulf War Undiagnosed Illnesses.

We need to state that we appreciate the candor and forthrightness by Dr. Rostker, Department of Defense Special Assistant for Gulf War Illnesses, during the October 20, 1999, Pentagon briefing on the RAND Report concerning PB and a possible causal relationship to undiagnosed illnesses suffered by Gulf War veterans. There can be no doubt that a viable Force Health Protection Program is critical in assuring our national security goals and objectives. DoD's position on the RAND Report initially seems to confirm the Secretary of Defense's intentions to fulfill the President's mandate on this issue.
This report reveals that a link cannot be discounted between the drug pyridostigmine bromide, a drug administered to protect an estimated 250,000 troops during the Gulf War, and undiagnosed illnesses among veterans of this war. PB was given to troops because it was the only suspected medication available to protect humans against Soman, a deadly nerve agent known to be available to Saddam Hussein and actually present in the Gulf region before and during the war. At that time, the risks associated with the possible use of Soman were considered a far greater danger than the possible health consequences of administering PB.

The RAND Report suggests PB may hypothetically cause lasting effects in some humans with symptoms including but not limited to difficulty sleeping, mood swings, muscle fatigue, and memory loss, all similar to the type reported by Gulf War veterans. However, Dr. Rostker notes that no definitive cause for the illness has yet been found and because the research is inconclusive to date, it will continue.

Subsequently, we sent a letter to Secretary Cohen stating that, with the findings that a possible link cannot be fully discounted, our primary concern is now the related, on-going medical and scientific research be continued, and indeed intensified. We are aware that 22 of the current 25 federally sponsored, PB related research studies are through the Department of Defense (with the other three by the Department of Veterans Affairs).

This on-going medical research is important and critical because the RAND Report actually has no impact on veterans in the processing of claims for compensation (and attendant health care). Service connection is granted for identified disabilities or illnesses and no medical or scientific evidence is specified currently to indicate that any certain disability or illness is directly linked to the ingestion of PB.

If a relationship is eventually identified through such research, then the Secretary of Veterans Affairs should quickly establish a presumption of service connection for the identified illnesses. This process is actually in place through VA's contract with the National Academy of Sciences but any recommendation by the academy will only be as good as the current medical and scientific information available at their time of review. Meanwhile, our ill veterans are not getting better and some likely are presently not eligible for mandated medical treatment by the VA; nor are they receiving proper compensation.

Messrs. Chairmen, this concludes my statement and I will be happy to address any questions you may have.

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Statement of

VIETNAM VETERANS OF AMERICA

Submitted For the Record by

William T. Frasure
Deputy Director
Government Relations Department

Before the
House Veterans Affairs Subcommittee on Health and Oversight & Investigations

Regarding

Pyridostigmine Bromide (PB) And Its Health Effects On Gulf War Veterans.

November 16, 1999

Vietnam Veterans of America **Pyridostigmine Bromide (PB) And Its Health Effects On Gulf War Veterans.**

Vietnam Veterans of America appreciates this opportunity to present our views regarding pyridostigmine bromide (PB) and its health effects on Gulf War veterans.

Pyridostigmine Bromide was essentially an experimental drug administered to approximately 250,000 U.S. troops during the Gulf War to counter the chemical agent soman. In light of the hard intelligence that DoD had in August of 1990 indicating that Iraq had in its possession soman, sarin, cyclosarin, mustard gas, and other chemical agents, the administration of PB pills was certainly a reasonable measure of protection at the time. VVA wants to make it clear that we are not focusing on DoD's decision to administer the PB pills. VVA's concerns center on the possible long term adverse health effects stemming from PB, and the care provided to Gulf War veterans experiencing PB related symptoms by the Department of Veterans Affairs.

In December of 1990, DoD requested a waiver of informed consent from the Food and Drug Administration (FDA) granting the military the legal authority to administer PB. One of the conditions of the FDA waiver was that the military had a responsibility to keep records regarding the administration of the PB pills and to determine the long term effects of PB.

Up until very recently, DoD has maintained that PB is not a causal factor for Gulf War undiagnosed illnesses. Since 1991, when thousands of Gulf War veterans first started exhibiting similar, undiagnosed conditions, DoD has, in fact, possessed information that clearly shows that PB pills ***cannot*** be ruled out as a causal factor. Recently, Dr.Galomb of the RAND Corporation (hired by the Pentagon to study various aspects of Gulf War undiagnosed illnesses to include PB) stated that the PB:

...issue is a complex one, involving trading off uncertain health risks-but risks now shown to be biologically plausible-against uncertain gains from use of PB in the warfare setting [xxxiii].

Dr.Galomb further states that:

...there remain some concerns regarding the efficacy of PB in protection against nerve agent threats. For some nerve agents, such as sarin, evidence was not adequate to exclude a possible harmful effect by use of PB as a pretreatment [277].

There is varied scientific evidence from different studies, both government and non-government, showing that PB makes individuals more vulnerable to other nerve agents, such as VX and Sarin. These agents were released into the air during demolitions of Iraqi munitions bunkers on March 4 and March 10, 1991. (Many other demolitions remain under DoD investigation.)

It has also been shown that PB, when taken by a person who is exposed to insect repellant and insecticides, creates a harmful, debilitating effect on the person's immune system

Vietnam Veterans of America **Pyridostigmine Bromide (PB) And Its Health Effects On Gulf War Veterans.**

In 1996, a Duke University study stated that:

an anti-nerve gas (PB) pill taken by many of the troops may have interfered with the body's natural defenses against the toxic effects of an insecticide and an insect repellant they routinely used to protect against disease carrying flies and mosquitoes.

Also in 1996, both the Institute of Medicine (of the National Academy of Science) and the Presidential Advisory Committee on Gulf War Veterans' Illnesses concluded that further research is needed in regards to the synergistic effects of PB and other risk factors and agents.

It is now known that DoD did not keep records documenting who took PB and other relevant variables (amount, etc.) despite their clear obligation to do so. A RAND Corporation report has stated that:

The DoD Gulf War experience in the use of PB (pills)...was characterized by poor record keeping, inadequate data collection, and other violations of the terms agreed to in the FDA waivers.

VVA strongly urges Congress to fund additional research regarding the synergistic effects of PB and other toxins must begin now. Research clearly shows that a connection between PB and Gulf War illnesses is likely.

Furthermore, VVA urges the Congress to hold hearings regarding VA's role in granting direct service connection for conditions associated with the ingestion of PB. Public Law 105-277, the "Persian Gulf War Veterans Act of 1998" has paved the way for the VA to establish direct service connection for conditions associated with PB and a myriad of other toxins and exposures associated with Gulf War undiagnosed illnesses.

VVA urges Congress to note that once PB research was funded, adverse effects of the drug were found. We believe there should be additional research on the possible long term adverse effects of the anthrax vaccine, oil well fire particulate matter, Depleted Uranium, and other known toxins present in the Gulf War theater.

VVA finds it troubling that DoD failed to accurately gather data regarding the administration of PB to its troops. We ask these fundamental questions that have yet to be answered: Why did DoD ignore the claims made by thousands of Gulf War veterans and scientists regarding PB? Why did DoD delay research on the adverse effects of PB?

In conclusion, VVA strongly urges Congress to demand that DoD put a final and complete halt to their dilatory tactics regarding ***all*** research and progress on Gulf War undiagnosed illnesses. Congress must also ensure that the VA abides by the intent and spirit of PL 105-277 and establishes immediate regulations for direct service connection for all PB-related conditions.

Again, VVA thanks the House Veterans' Affairs Committee for holding this important hearing.

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A Not-For-Profit Veterans Service Organization Chartered by the United States Congress

William T. Frasure
Deputy Director of Government Relations

Bill Frasure became Deputy Director of Government Relations in February, 1999. He is responsible for a host of legislative activities regarding veterans' issues. From February, 1996 through January, 1999, Bill Frasure served on the national staff of the Veterans of Foreign Wars (VFW) as a Legislative Special Assistant. He is a veteran of the Persian Gulf War, having served in the U.S. Army from 1989-1991. Bill Frasure graduated from the University of Connecticut in 1995 with a B.A. in Political Science.

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VIETNAM VETERANS OF AMERICA
Funding Statement
November 16, 1999

The national organization Vietnam Veterans of America (VVA) is a non-profit veterans membership organization registered as a 501(c)(19) with the Internal Revenue Service. VVA is also appropriately registered with the Secretary of the Senate and the Clerk of the House of Representatives in compliance with the Lobbying Disclosure Act of 1995.

VVA is not currently in receipt of any federal grant or contract, other than the routine allocation of office space and associated resources in VA Regional Offices for outreach and direct services through its Veterans Benefits Program (Service Representatives). This is also true of the previous two fiscal years.

For Further Information, Contact:
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