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/4: S. HRG. 103-984

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# HEARING

BEFORE THE

# OMMITTEE ON VETERANS' AFFAIRS
# UNITED STATES SENATE

ONE HUNDRED THIRD CONGRESS

SECOND SESSION

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MAY 6, 1994

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Printed for the use of the Committee on Veterans' Affairs



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# IS MILITARY RESEARCH HAZARDOUS TO VETERANS' HEALTH? LESSONS FROM WORLD WAR II, THE PERSIAN GULF, AND TODAY

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# IS MILITARY RESEARCH HAZARDOUS TO VETERANS' HEALTH? LESSONS FROM WORLD WAR II, THE PERSIAN GULF, AND TODAY

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**FRIDAY, MAY 6, 1994**

U.S. SENATE
COMMITTEE ON VETERANS' AFFAIRS
*Washington, DC.*

The Committee met, pursuant to notice, at 10 a.m. in room SD–106, Dirksen Senate Office Building, Hon. John D. Rockefeller IV (Chairman of the Committee) presiding.

Present: Senators Rockefeller, Mitchell, Daschle, and Jeffords.

Also present (staff): Jim Gottlieb, chief counsel/staff director; Diana M. Zuckerman, professional staff member; Patricia Olson, congressional science fellow; and John Moseman, minority staff director/chief counsel.

Chairman ROCKEFELLER. This hearing will come to order. I welcome everybody.

## OPENING STATEMENT OF CHAIRMAN ROCKEFELLER

A few months ago, Americans were shocked to learn that our Government had intentionally exposed thousands of U.S. citizens to radiation without their knowledge and without their consent. Although many of us expressed horror at the apparently unethical behavior of our Government, we all were relieved to hear that such experiments had been stopped long ago.

We'd like to think that these kinds of abuses are a thing of the past, but, sad to say, the legacy continues. During the Persian Gulf War, hundreds of thousands of soldiers were given experimental vaccines and drugs, and today we will hear evidence that these medical products could be causing many of the so-called "mysterious illnesses" that those veterans are now experiencing. And for several decades, and continuing today, the testing of chemical and biological agents at U.S. military facilities has put soldiers and civilians at risk.

Today's hearing will examine the results of an intensive 6-month investigation conducted by this Committee's staff, particularly staff members Diana Zuckerman and Patricia Olson. The investigation focuses on Persian Gulf War veterans, but extends from World War II-era veterans to the present. So, while we're focusing on the Persian Gulf War, this is a pattern which has gone on for a long, long time.

The results of our investigation showed a reckless disregard that frankly shocked me, and I think will shock all Americans. The use of

investigational drugs in the Persian Gulf is especially troublesome. The Pentagon did studies on one of these drugs, pyridostigmine bromide, in a cautious way before the war, excluding anyone who might be harmed by the drug. But, after protecting a few hundred men who volunteered for these studies, they threw caution to the winds, ignoring all warnings of potential harm, and gave these drugs to hundreds of thousands of soldiers with virtually no warnings and no safeguards.

If that wasn't bad enough, they administered these drugs and vaccines in such a way that there is a very good chance they would not have even worked for the intended purpose. They would not have protected most soldiers from chemical or biological warfare.

These are very strong statements. I recognize that, and I do not make them lightly.

The situation is unfair from start to finish. It begins with soldiers who are asked to participate in research and take experimental drugs, but are not told what the risks are before, during, or after.

Then, information about the exposures is not included in soldiers' medical records, putting them at an even greater risk. And, when these soldiers leave the service and become veterans, the Department of Veterans Affairs lacks information about the exposures and about any resulting illnesses, making it even more difficult to help those who need help.

Finally, when these veterans become ill, they are unable to get their medical records and other information they need in order to prove that their illnesses are related to their military service.

This situation is clearly thoroughly unacceptable.

Our witnesses today include nationally respected experts and four veterans with very compelling stories of illnesses that seem to have resulted from intentional exposures they experienced while in the military or working for the military. Our witnesses also include scientists and officials from four Federal agencies: the Department of Veterans Affairs, the Department of Defense, the Food and Drug Administration, and the Department of Agriculture.

[The prepared statement of Chairman Rockefeller appears on page 63.]

Chairman ROCKEFELLER. I would like to move now to our first panel. I would ask all of you to come to your places at the witness table. We have here with us Mr. Rudolph Mills, a World War II veteran; Mr. Earl Davenport, who worked at the Dugway Proving Ground both as a military person and as a civilian; and two Persian Gulf veterans, Mr. Neil Tetzlaff and the Rev. Dr. Barry Walker.

I want to thank all of you for coming. I know that all of you have been exposed to various experiments, tests, or investigational drugs. I also know that secrecy and lack of information about those exposures may have contributed to your illnesses. Your testimonies represent, in effect, 50 years of experiences that our veterans have endured. You represent many, many folks. Let me assure you that we will listen carefully to what you have to say, and that we really appreciate your being willing to be here and to talk to us.

Because I want to have time for questions, we have asked each of you to try to summarize in 3 minutes. Some of you may not be able to do that. Your entire prepared statements will be made part of the

public record. But in order to have time for questions, if you would try to be as brief as possible, I would be very grateful.

Because this is such a serious hearing and because we want everything to be factual, I am going to administer an oath to each of the panels. So I would ask you to stand and raise your right hand. Do you swear to tell the truth, the whole truth, and nothing but the truth?

[All witnesses responding in the affirmative.]

Chairman ROCKEFELLER. Let the record show that the witnesses have answered in the affirmative.

Mr. Mills, please begin when you are ready. We understand many of your family members are here today, and we welcome them also.

## STATEMENT OF RUDOLPH MILLS, WORLD WAR II VETERAN, FREDERICKSBURG, VA

Mr. MILLS. Mr. Chairman and Senators, my name is Rudolph Mills. In December 1944, my twin brother and I left high school to join the United States Navy. The country was in its third year of World War II and we wanted to serve our country.

In April 1945, a call came for volunteers to participate in what the Navy referred to as gas mask experiments. I stepped forward. I was 17 years old, just out of boot camp, and I guess I would have done anything if they told me it would have helped my country. And it wasn't just me. There were millions of young Americans like me who felt that way.

On April 30, 1945, this was no longer a volunteer situation. I entered a gas chamber for the first of 12 experimental tests. Each test was for 1 hour. It was my understanding that this experiment would determine if people wearing such masks could communicate. I remember the corpsman conducting the tests encouraged me to sing, saying I had a beautiful voice. As I sang or spoke, the edges of the mask would loosen, consequently exposing my face, and I experienced cheek and chin burns.

We were sworn to secrecy and it was not until 45 years later that I learned that I had been 1 of over 4,000 servicemen who were human guinea pigs in tests involving poisonous gases. As I recall, because of the different odors, contrary to my military records, gases present were mustard, lewisite, and phosgene.

Even before my military discharge in 1946, my health began to deteriorate. I began to lose my teeth and experience a chronic sore throat. Within 3 years of my discharge, my tonsils and all teeth had to be removed. I developed a hacking cough when I was in my 20's and was diagnosed with cancer of the larynx in 1970. At the age of 43 I underwent radiation treatments and later surgery to remove part of my voice box and larynx. This left me with difficulty in breathing and the voice you hear today.

It did not occur to me that my exposure to the gases caused my physical problems until June 1991, when I read an article in my hometown paper urging mustard gas volunteers to come forward for compensation. Given that my cancer had affected not only my health, but my career and my family with its associated financial burdens, I came forward.

I don't have time to tell you the whole story, which has left me very depressed and disheartened, but I can tell you that for the past 3 years, I have gotten a royal runaround from VA. I filed a claim which was denied because the particular type of cancer I had was not recognized as being related to mustard gas exposure. But, after the release of other medical studies, I was notified that my laryngeal cancer was in fact linked to mustard gas exposure. Subsequently, I was told that once VA promulgated a new regulation, my case would be reevaluated.

This regulation with its guidance and direction remains in limbo.

I have absolutely no regret about joining the Navy as a young man and doing what was asked of me, for I loved my country then and I love it just as much now, or more. I guess in spite of all that has happened and all that I know now, if I was told that stepping into a gas-filled chamber would help preserve this great country for my grandchildren, I would do it again.

I think, however, that my country has not been fair to me. I was asked to come forward and file a claim. I did so. I was told that silent suffering was over. It is not. They sat back and engaged in their endless bureaucratic games while many of us died off before our cases could be considered. In my opinion, they have acted callously and have not been truthful. If I never get a penny for the fact that I breathed poisonous mustard gas repeatedly into my lungs, that will be all right. But I will never be able to forget that my Government has given such shabby treatment to me and many others like me. That hurts me more than my exposure to the mustard gas. I am surprised and shocked that my Government would allow such as this to occur in this United States of America. Thank you.

[The prepared statement of Mr. Mills appears on page 71.]

Chairman ROCKEFELLER. Thank you very, very much, Mr. Mills. And now, Mr. Davenport.

## STATEMENT OF EARL P. DAVENPORT, VETERAN AND FORMER EMPLOYEE, DUGWAY PROVING GROUND, TOOELE, UT

Mr. DAVENPORT. My name is Earl Davenport. I was employed by the U.S. Government for about 23 years until I retired in 1993. The nature of my career is chemical and biological testing both for the Army and the Navy.

I entered the Army in 1958 and was stationed at Dugway Proving Ground through 1960, where I worked as a supply clerk delivering supplies out into the toxic field test areas.

In 1960, I was discharged from active duty. In 1962, I went to work at Dugway as a civilian as a decontamination equipment operator. I worked with a variety of agents—VX, GB, GD, mustard, the whole bit of chemical agents, plus I worked with biological agents.

At that time, the biological and chemical tests were conducted in open air using many of the delivery systems out there. This required military and civilians to wear protective clothing and also take biological shots. We weren't told what the shots were; they just told us that they were to build up our immunity to the agents that we were testing, which were things like tularemia, VEE, anthrax, and Q-fever.

When I questioned them about the shots, they told me that I received hazard pay and that was part of the job. So we had to take them if we wanted to work there. The hazard pay at that time was 6 cents an hour.

Like many workers at Dugway, I never doubted the judgement of my superiors who briefed us on hazards of the job. But I assumed that if they were wrong, the Government would be responsible for protecting the workers. Now I wonder if I was wrong.

On July 13, 1984, I was involved in a test the Army was conducting using a laser system that would detect nerve gas. I was operating a sprayer, blowing a fog of nerve gas simulant called DMMP, dimethyl methylphosphonate, into the path of the laser beam. During the test I noticed a sudden shift in the wind and the nerve gas blew back on me. I cut the sprayer off but before I could get my mask on, it was all over my face, all over my hair, I could taste it on my lips. Anyway, I got saturated with this DMMP. I secured my area and left the test site. At that time I was checked out by a medic and seemed to be OK. I reported to the supervisor and filled out the accident report. I was told that if I felt any different, to go up to the base hospital.

I wasn't really too concerned with the simulant. I trusted the Army's assurance that DMMP was "practically nontoxic," according to the material safety data sheet that was available at that time. It also stated that DMMP irritated mucous membranes, the respiratory system, prolonged contact with the skin would cause burns and blisters, and maybe irritate the skin. The Dugway safety office told us to wear a military protective mask, rubber gloves, and aprons. So working with a live agent before, this wasn't really a big concern with me at the time.

The day after the accident I felt a little bit different. I was wheezing and coughing and spitting up mucous. After about 2 weeks, my condition didn't improve so I went to the Dugway Army Hospital. I was given cough syrup and antibiotics and was diagnosed as having bronchitis. But after 3 or 4 weeks, there was still no improvement in my condition. I was sent to the University of Utah for another evaluation. There they diagnosed me as having a mild exacerbation of chronic obstructive pulmonary disease by irritant effect of DMMP.

Over the years, my condition got worse. I seemed to get colds and bronchitis more frequently, and shortness of breath, especially at high altitudes. In 1988 I suffered a heart attack. And by 1992, I was missing about 6 days a month of work due to illness. Twice I was taken from Dugway Proving Grounds by ambulance to the hospital for breathing problems and heart problems. The days I felt the worst were when they were testing at Dugway and firing simulants into the air. It bothered my lungs real bad.

At that time, I was considered a health risk. I was having a lot of problems and taking a lot of time off. Because of the medication I was taking, the doctors suggested that I might be a safety hazard, and I was removed from the biological and chemical work out there. And in 1993, I was urged by my doctor to take an early retirement.

I was very concerned about my health and being sprayed with this DMMP, especially with my past history of working with chemical and biological agents and the possibility of unknown low-level exposures.

Also, there were the shots I had been given. I did some research on the DMMP and found that the Government had underestimated the health hazard.

The Army memo issued 3 months before the laser test said a study was underway on the cancer-causing potential of DMMP. In 1986, the Surgeon General confirmed that DMMP was a mild carcinogenic and harmful to male reproduction. The memo recommended using a different simulant, but they still told us to continue wearing the protective mask.

In 1988, a Dugway safety officer reported that "DMMP has been determined to be a mild carcinogen and potent renal toxin. Because of these hazards, there is a grave concern over the release of DMMP into the environment and the exposure of personnel to liquid and vapors," he wrote. "A safer simulant should be substituted for the outdoor testing." He also said the standard respirator mask wasn't sufficient to protect against DMMP. He recommended that the chemical be used only in a test chamber, and even then, personnel handling DMMP should wear a mask hooked up to a separate oxygen supply.

Dugway safety officials confirmed that DMMP was used extensively as a simulant for chemical agents until 1988, when the Army Surgeon General reviewed studies identifying it as a suspected carcinogen. So they just use it in the chambers now.

Since 1988, the use of DMMP has been reduced. That is because, "The recommended exposure limit required protective clothing criteria and engineering controls that were so stringent that DMMP lost most of its value as a simulant," Dugway's public affairs office said in a written response to Desert News about DMMP.

Although the Army clearly miscalculated the health hazards of DMMP for several years, the Government concluded my health problems were caused because I smoke and not because of any exposure to DMMP.

While talking to other employees at Dugway, I discovered that many of them were also having health problems similar to mine. We decided to have a meeting and discuss our individual health problems. While we were talking, we discovered that at least 29 of the people, including myself, who had worked with chemicals and biological testing at Dugway and had received the shots had also had heart attacks, and 12 of them had died. Another 13 had serious problems such as cancer, MS, and Q fever. Many of us feel we could not depend on Dugway for much help. Many of our records requested could not be found or were not available. The shots we had all taken during the 1960's were of special interest, but we were unable to get records of just what they were.

We all have grave concerns about our health and what we may have been exposed to while working at Dugway. We cannot get answers to our questions, and we do not know what to tell our doctors to help in our treatment. We need answers about the shots we took and the rest of it so we can tell our doctors, so maybe they can treat us. One gentleman I worked with has got MS and the doctor indicated to him that there was some kind of chemical additive in his spinal fluid that he cannot identify. So if they could provide this

partner of mine with some kind of information on those shots, it might save his life. He is now in a wheelchair.

That's the end of my statement. Thank you.

[The prepared statement of Mr. Davenport appears on page 74.]

Chairman ROCKEFELLER. Mr. Davenport, I thank you very much.

I also want to recognize that two of our Committee members are here, Senator Daschle and Senator Jeffords. Senator Daschle, do you have any comments you want to make?

Senator DASCHLE. Mr. Chairman, let me just commend you for this hearing and your leadership. I am impressed with the extensive degree to which we have been able to bring people from all over the country to address this issue. And I certainly thank all those who are about to present their testimony today. I hope this will be the first in a series of opportunities for us to better understand the implications of many of our policies of the past. I commend you for this hearing in particular.

Chairman ROCKEFELLER. Thank you, Senator. And as those of us on the Committee know, you have been on the warpath for many years on Agent Orange and other subjects.

Senator Jim Jeffords from Vermont.

Senator JEFFORDS. Yes, Mr. Chairman. I have a statement I would like to make part of the record. I would like to proceed for about a minute, if that is all right.

Chairman ROCKEFELLER. Please.

## OPENING STATEMENT OF SENATOR JEFFORDS

Senator JEFFORDS. Mr. Chairman, almost 6 months ago the Committee first opened discussions relating to Persian Gulf War veterans and the illnesses they have encountered since they returned from the Gulf War. It is disturbing that we gather here again today with little new information on the causes of these illnesses.

While this issue has been widely discussed and researched in the last 6 months, there are still no concrete answers; in fact, there are probably more questions. But one thing is clear, some of our Persian Gulf War veterans are suffering because of unknown illnesses. I want to be sure that this Government does all that it can and is able to do to determine why it is happening and how we can help.

We ask our veterans to risk the ultimate sacrifice for our country, and they accept. Now it is our turn to make sure that those suffering because of their service are given the best treatment and our full attention. I was a Member of the House of Representatives when the Government was trying to determine service connection for men and women exposed to Agent Orange in the Vietnam War. I saw these veterans and their families suffer because of the red tape and bureaucracy in our Government, with many veterans dying in the time it took for the compensation to be awarded to them. This cannot happen again.

I have long believed that veterans should be able to be given the benefit of doubt under these circumstances, Mr. Chairman, and I hope that we can develop a satisfactory process and policy in this matter now. Thank you, Mr. Chairman.

[The prepared statement of Senator Jeffords appears on page 68.]

Chairman ROCKEFELLER. Thank you, Senator Jeffords. I can assure you that we intend to do that.

I will also enter into the record a statement by Senator Daniel Akaka of Hawaii.

[The prepared statement of Senator Akaka appears on page 66.]

Chairman ROCKEFELLER. Neil Tetzlaff, if you are ready, sir, we would like to proceed to your testimony.

## STATEMENT OF NEIL R. TETZLAFF, PERSIAN GULF WAR VETERAN, REED CITY, MI

Mr. TETZLAFF. Good morning, sir. In August 1990 I was a Lieutenant Colonel with the United States Air Force, serving as Assistant Deputy Commander for Resource Management for the 48 Tactical Fighter Wing, RAF Lakenheath, United Kingdom. On August 20, with 6 hours notice, I was deployed with 11 others as an advance party pursuant to the deployment of the 48th's F–111's to Saudi Arabia.

While being mobilized, I was issued a 7-day supply of pyridostigmine bromide pills and was told to start taking them on an 8-hour schedule, which I did. The package contained no warnings. For me, this was a chronic overdose of pyridostigmine. Both my immediate physical and mental symptoms corroborate this fact.

On the plane ride to Saudi, and during my first day in-country, I was nauseated and vomited. I attributed the sickness to the plane ride and the tension of the situation. On my second day there I vomited again and felt different. I attributed the sickness to something I had eaten. On the third day there I was extremely nauseated and vomited many times. I sought out the doctor and discussed my illness with him. We dismissed it as something I had eaten at the Saudi canteen. On my fourth day there I vomited violently, the worst ever of my life, and was acting a bit off center and muddled. On the fifth day I didn't vomit but was sore, lost much of my bounce, acted strangely silly and was totally out of character. On the sixth day I was incoherent, extremely tired, and at times irrational. On the morning of the seventh day I vomited about a quart of blood.

I knew then that I was in deep trouble and headed straight for the doctor. Shortly thereafter, I began to lose consciousness. The doctor started an IV. After examining me at the Taif Clinic, the doctor commandeered a C–130 and air-evacuated me to the Royal Saudi Hospital in Riyadh.

At the hospital, I was given a general anesthetic to knock me out. The doctors looked in my stomach and found a tear of approximately one and three-quarters inches caused by retching near the entryway from my esophagus. They fed me intravenously for 2 days, put me on a special diet, and then released me to USAF medical personnel after a total of 4 days in the hospital.

An article entitled "Interactions between Nerve Agent Pretreatment and Drugs Commonly Used in Combat Anesthesia" from "Military Medicine" hypothesizes about the damage caused by the interaction of pyridostigmine and anesthetics at the postsynaptic neuromuscular junction. Could this event have exacerbated damage

to my nervous system and been the cause of my resultant sustained pain? To date, no scientific research has been done in this area.

Under ideal conditions, by day 3 my attending physician, who was also taking pyridostigmine, would have recognized my symptoms as an overdose of pyridostigmine and taken the following steps: Immediately stop me from taking pyridostigmine, started detoxification procedures by introducing saunas and baths with deionized water, put me on an antitoxic diet, have me air-evacuated to a detoxification center, put me in a hyperoxygenated clean air chamber on a special diet. The therapy for chemical decontamination has been known for over 40 years.

From July 9 to September 6, 1990, no entries were made in my medical record. Therefore, none of the events concerning pyridostigmine bromide are in my medical records.

The disabling effects of pyridostigmine are not known and are not being investigated by DOD or VA, even though the drug was used during Desert Storm on an experimental basis. For over 2 years I have researched the drug pyridostigmine. Military and VA doctors have consistently held that in the dose that was given to me, it was a completely harmless drug. However, the written materials on the drug, as well as civilian doctors and pharmacologists, tell a different story. Pyridostigmine is chemically similar to carbamate pesticides, just as the nerve gases GD and GX are to organophosphorus pesticides. Both of these classes of pesticides belong to the group acetylcholinesterase inhibiter pesticides. Pyridostigmine in any dose can do harm.

The side effects of pyridostigmine bromide most commonly associated with overdose can be found in the "Physicians' Desk Reference" and in the "Handbook of Poisoning." Overdosage can cause cardiac arrest. The "Handbook of Poisoning" puts the estimated fatal dose of pyridostigmine at 300 mg for an adult.

Military doctors routinely returned soldiers taking pyridostigmine and suffering from overdose symptoms such as vomiting, increased urinary frequency, and headaches to duty, without telling the soldiers to stop taking pyridostigmine. I find it interesting that many Gulf War veterans are reporting mysterious illnesses of pain, chronic fatigue, and other nerve disorders, and neither the VA nor the DOD has asked any of them if they took pyridostigmine. Because no records were kept, no one knows who did or who didn't take pyridostigmine.

During Desert Storm, soldiers reported to aid stations with extremely high blood pressure caused by taking pyridostigmine bromide. While I was in the VA hospitals, several Gulf War veterans related that they were astonished by the healthy young people who died of heart attacks. They were amazed that no investigation was accomplished; rather, these soldiers were simply stuffed into body bags and sent home. Every one of these veterans when questioned confirmed that in every case, the deceased were taking pyridostigmine bromide. A final indication of an overdose of pyridostigmine bromide is a heart attack and death. I have since found evidence that an unusual number of soldiers who had heart attacks in the Gulf War are being discharged.

The use of investigational new drugs on the general population will cause both unwonted and unwanted results.

Prior to going to Saudi Arabia, I considered myself in excellent physical condition, as I enjoyed running 3 to 5 miles a day, worked out at the gym three times a week, and participated in a number of sports.

Now I suffer from shooting pains throughout, joint and muscular pain, testicular pain, headaches, fatigue, diarrhea, sleep disorder, short-term memory problems, speech disorder, palsy, and dry cough, to name a few symptoms. In short, I am multiply chemically sensitive with a nerve disorder manifested by pain and have damage to the speech and short-term memory areas of my brain. Thank you.

[The prepared statement of Mr. Tetzlaff appears on page 87.]

Chairman ROCKEFELLER. Thank you, Mr. Tetzlaff, very much for your testimony.

Rev. Walker, when you are ready, sir, we would welcome your testimony.

## STATEMENT OF THE REV. DR. BARRY M. WALKER, PERSIAN GULF WAR VETERAN, EAST PALESTINE, OH

Reverend WALKER. Thank you, sir. Good morning. My name is the Rev. Dr. Barry M. Walker, Chaplain, Lieutenant Colonel, United States Army. I want to thank you for the opportunity today to testify for the veterans of Desert Shield and Desert Storm.

I first entered the Army in January 1964, and spent time on active duty from 1966 through 1970, the era of Vietnam. I was mobilized with my Reserve Units in September 1990 with the 475 Quartermaster Group Petroleum. We were responsible for theater fuel and bulk water for all the services. As a Chaplain, I supervised four Chaplain Unit ministry teams in Saudi Arabia, and ultimately in Iraq and Kuwait. We had some 4,700 under our command, which was made up of active duty Army units, now activated Army units from the Army Reserves, and National Guard.

I was very healthy except for a slight blood pressure problem when I went to the Persian Gulf, and had no health problems during the first few months there.

On January 16, I received the first of two shots of a vaccine, but we were not told exactly what they were. I did have them recorded and I have a record of that here. We were later told that the purpose of these shots was to protect us, and rumor was that they were anthrax. Also in January, after the first SCUD was launched, we were ordered to start taking the pyridostigmine pills, although we were not told exactly what they were either. All we were told was that the pills would protect us against chemical and biological weapons. We were told to take the pills, and not given a choice, though some soldiers did not take them at first. I later learned that the pills were pyridostigmine.

My knowledge is that none of the 4,700 troops, except maybe the command headquarters, was given any real information about the risks of these drugs or vaccines. We were not shown anything in writing or told anything other than that these were given to protect us. My chemical officer was asked to find out more about the pills, and she shared some of the information with the group commander

and a few of the staff officers. She said there were no problems with the pills.

The fact that we were given the vaccine or drugs is not recorded in my medical record nor anybody else's within our group, to my knowledge. Many soldiers did not carry a vaccine record; most wouldn't have even thought to have it recorded. I did. I do not recall any list being made of who was given the vaccine.

A few people seemed to get diarrhea after the vaccines, but there were no major problems. After the pills were distributed, more people got diarrhea, and so they stopped taking the pills. Even people who were not sick stopped taking the pills because they saw the effect that it had and wanted to avoid getting sick. The commanders directed everyone to take the pills. Since the pills were taken in privacy, it was thus possible not to take them. The fact that people got sick was not included in their medical records.

I do not remember thinking that the vaccine or the pills that I took were causing me any problems, although I stopped taking the pills when I saw that they seemed to have a great effect in making other people sick. However, around the same time I was having major problems with what seemed like allergies. I didn't pay much attention because I didn't have time to get sick. I was an officer, I had a job to do, and I kept going.

I started having problems with my back after the February 25, 1991, SCUD attack on my unit. It was probably from moving bodies, lifting debris, and so on, after the 475th Quartermaster Groups headquarters and barracks were hit. The attack was horrible; soldiers were killed, lost limbs, one soldier's head was half blown off. Afterwards, my back hurt considerably. I went to the 85 Med Hospital for treatment. Since I told them I have been moving bodies on cots, the cause was written down as moving cots.

We left the Persian Gulf at the end of May. I was discharged on June 19, 1991. I was so happy to get home that I didn't worry that anything was wrong with me. I did go as a walk-in to the VA hospital in Pittsburgh on June 18, 1991, for treatment of back pain.

It wasn't until that summer, when I went to the Pittsburgh Oakland VA for further back treatment, that I realized something else was wrong. The VA doctor arranged for an EMG, CAT Scan, MRI, and so on, to try and find out what was wrong. With the EMG, they found that the nerves from my waist down were not as they should be, and that my right leg was worse than my left leg, which I hadn't noticed.

Because of my symptoms, I was also checked for alcohol abuse, diabetes, and other possible causes, such as lead poisoning, but they found nothing.

Now my symptoms include headaches, rashes, fatigue, loss of memory, sweating, and occasional blood in my urine. I am unable to concentrate, and I have definite trouble sleeping, with bed sweats at times.

For the past 3 years, I have been spending much of my time with other Gulf War veterans and their families. I have taken over 150 veterans personally in my car to hospitals for treatment, or helped them in many other ways. Many of them have symptoms similar to mine. Some don't know where they are or get lost for periods of time

and do not know how they got where they are. Some have trouble walking. Some pass out and don't remember it. Their wives are having trouble dealing with them because of their anger and their quick tempers and their pains.

I would like to just quote from a statement I am going to put in the record, just an opening and closing, from Sgt. David L. McGee, a Marine sergeant who is seated in the back there, if he would stand up. "Where do we turn now? Who will help us after we have helped so many? At a point in our lives, we stepped forward, we took an oath to defend this country, its people, and its ideas. We were unquestionably to go places most would never go. We did things that most could not imagine. We survived through the extremes and the pressures, and are not told by the Government or media when we came back what we did." And his closing comment: "What could have caused this to happen to me? Chemicals. Biological agents. Parasites. Burning oil fields. Or could it have been the series of shots and pills administered countlessly and never recorded in our medical records? We want to be cured; we don't want to be paid."

Again, thank you for this opportunity to speak. I would be more than willing to answer any questions that you may have.

[The prepared statement of Rev. Walker appears on page 94.]

Chairman ROCKEFELLER. Thank you, Rev. Walker, very much. I appreciate your forthright testimony.

I would like to turn to you, Mr. Mills—and is it OK if I call you Rudy?

Mr. MILLS. Yes, Senator.

Chairman ROCKEFELLER. I cannot tell you how angered I am by what you have told us. That a 17-year-old young man would be asked to go into a gas chamber under the circumstances that you have described is beyond belief. Did you ever receive any medical information or treatment from the Department of Defense after you participated in the gas chamber experiments?

Mr. MILLS. No, sir.

Chairman ROCKEFELLER. How did losing your voice affect your career, which had been as a traffic manager?

Mr. MILLS. That's what killed it, sir. Once you have cancer and you enter that into any application you go to, you are dead meat.

Chairman ROCKEFELLER. They just tell you "no."

Mr. MILLS. They will not hire you, no sir.

Chairman ROCKEFELLER. It is interesting, you and your twin brother entered the service at exactly the same time.

Mr. MILLS. Yes. We had to go.

Chairman ROCKEFELLER. But you participated in the gas chamber experiments and he did not.

Mr. MILLS. No, sir.

Chairman ROCKEFELLER. You both smoked when you were young.

Mr. MILLS. Yes, sir.

Chairman ROCKEFELLER. But you were a light smoker and you stopped smoking, in fact, more than 20 years ago.

Mr. MILLS. Yes. Better than 20 years ago.

Chairman ROCKEFELLER. And your brother is still smoking a pack and a half a day. Is that right?

Mr. MILLS. At least, and plays 18 holes of golf.

Chairman ROCKEFELLER. And in your testimony you mention that he is very healthy.

Mr. MILLS. Very. Yes, sir.

Chairman ROCKEFELLER. Mr. Davenport, I understand that you received numerous vaccinations while working at Dugway. Do you know what they were?

Mr. DAVENPORT. No, sir. All we knew were just symbols. We were working with tularemia, anthrax, Q fever, and VEE. But one day we had a doctor, it wasn't a Dugway doctor, and he was standing in the doorway when we took our shots. He told each person that this shot may cause flu symptoms, but we went ahead and took it.

Chairman ROCKEFELLER. Are any of these things recorded in any medical record that you have?

Mr. DAVENPORT. Sir, all I have in my medical record is that in 1984 they gave me a booster. But up in the corner here it says—I worked there from 1962 till 1966 and I took Baker shots— "Record is no longer available." I don't know where the records are.

["Baker shots" are referenced in Mr. Davenport's prepared statment, in Appendix 2, on page 79.]

Chairman ROCKEFELLER. Earl, what can you tell us about other people that you worked with at Dugway? Do they have any illnesses like you have or any illnesses that seem to be related to the work that they had been doing at Dugway?

Mr. DAVENPORT. Yes, sir. There were 4 or 5 of my coworkers who came over to my house last week and we went through a list of people. There were 51 of them sick, 19 are dead. They have heart attacks, arthritis, cancer, MS, and Q fever. I'll put this in the record also.

Chairman ROCKEFELLER. I want to cease my own questioning at this point and turn to the other Senators. I will start with Senator Tom Daschle.

Senator DASCHLE. Colonel Tetzlaff, how would you describe the experiences you have had with the VA since all of these symptoms have been apparent to you?

Mr. TETZLAFF. One word—atrocious.

Senator DASCHLE. You would call them atrocious?

Mr. TETZLAFF. Yes, sir.

Senator DASCHLE. Dr. Walker, would you use a similar term?

Reverend WALKER. I wouldn't say good at all, sir.

Senator DASCHLE. What is it that has brought you to that conclusion? Could you share with us some of the experiences you have had in getting the kind of cooperation from VA that one would have the right to expect under these circumstances?

Mr. TETZLAFF. Well, sir, I have told the story of pyridostigmine bromide to every doctor that I have been seen by since I started going to VA; I did not miss a one. I told them exactly what I took and for how long I took it. They dismissed it as something that didn't happen. They have also said that all my problems I made up myself. In other words, I wanted to make my life this way.

Secondly, as I have been in the hospital, I have been with a lot of other soldiers who are not receiving any economic help from the VA. Though the VA may not know exactly what happened to us, they could give us economic help. If a person suffers from severe cases of

diarrhea, or if he suffers from memory loss, he can get rehabilitation. I think that every veteran is due that today, not tomorrow or not next year. I think if the VA had any sense of justice, they would get in motion and issue a check to every one of those veterans on the Gulf War registry who is having problems keeping his job. VA would say this first check is for your last month's pay. Tomorrow, we will give you one for this month. And then we will get somebody to take care of you from here on. Then the economic problems that these young soldiers are having would not exist.

I learned from a person who specializes in rehabilitation. I could have been helped a long time ago with my speech problem. I could have been helped to learn how to speak again. Maybe I wouldn't be just sitting around all the time now. But VA has denied this categorically because there is nothing wrong with me as far as VA is concerned, except that I have a mental disorder.

Senator DASCHLE. So the burden of proof is entirely on your shoulders.

Mr. TETZLAFF. Yes, sir. 100 percent.

Senator DASCHLE. Not only that, but there appears to be a degree of humiliation.

Mr. TETZLAFF. Yes, sir.

Senator DASCHLE. Every time you have sought some assistance—

Mr. TETZLAFF. If I could play a tape that I got when I called one of the senior VA people in Washington about my case. I figure if they are treating me this way, and being the type of person I am—which is bullheaded, hard to get along with sometimes, and come at you straight up—if they are treating me this way, what about somebody like the young Marine I met that feels he is doing a disservice to his country by filing a claim. That young Marine should be taken by the hand and led through the whole process. He should not be ignored.

Senator DASCHLE. Rev. Walker, could you shed any light on this? I was very impressed not only by your own personal story, as with Col. Tetzlaff's, but the fact that you have assisted approximately 150 veterans who have had similar experiences. Is Col. Tetzlaff's experience similar to that which has been experienced by others?

Reverend WALKER. Yes. First, we have mental problems. That is our problem. Second, the aches and pains in the joints is arthritis. There is a gentleman over here in a uniform, Sgt. Bob Blackwell, who was told just 2 days ago in the VA hospital that it is hereditary in your family; you have arthritis, even though it just appeared since he came back from the Persian Gulf. The Marine in the back, David McGee—David went in for treatment and they have disregarded that there is anything wrong with him except that he is having problems mentally and he can't handle it. At times, he does not know where he is. He cannot work. Maj. Mike Bricelin, in the back, is presently out of work because of the problems that he has. VA has said he has PTSD. Gina Brown—she is here with us today—her husband has missed work for 3 days this week because he can't work because of the headaches and the pains. This is being passed on to the wives and spouses. I have many fellows and some of them will let me use their name and some of them won't. I have a shot record of somebody else who was my assistant—I told everybody to bring their shot cards and

those that did and were with me got it recorded—but he has not been able to keep a full-time job since he has been back from Saudi Arabia.

The treatment that we are getting is that it is all in the head. Appointments take forever to get because the VA is overtaxed; they don't have the time to fit us in. The cursory investigation that I was given by Desert Storm would not give evaluation for anything. I have been through all the tests, and 2 days ago I handed the preliminary draft report from the National Institutes of Health to the doctor who has been treating me for what was thought to be a heart attack last summer, for which I had catheterization and had stress tests given to me afterwards. You are trying to get appointments. Even dealing with the mental health department, appointments are a month to 2 months apart sometimes, they are so overloaded. They will not admit that it might be something else. As I said, I have been through all the tests—lead poisoning, diabetes, alcohol, and so on—and there is nothing wrong with you; it is in your head.

Senator DASCHLE. I want to thank both of you for your candor and for the eloquence with which you have presented your experiences today. As the Chairman indicated, I have had a fight of incredible length, more than 12 years, in trying to address very similar concerns experienced by veterans exposed to Agent Orange during the 1960's and 1970's. It is so remarkable, the similarity between their experiences then and your experiences today. The same fights we had in the 1970's and 1980's, we are having exactly today—the disparity, the mistruths, the distortion, the incredible humiliation and ridicule that you were subjected to when you come into the VA. It was just as evident back then as it is now.

You would think we would have learned from our experiences. You would think that after all of this, we would have a much different attitude, given the number of experiences that you personally have had with other veterans. It is outrageous; the disparity is just outrageous. I can't thank you enough for again sensitizing us to how serious this problem is and giving us the additional incentive to go and try to correct this problem. You have provided a real service this morning. Thank you for being here.

Chairman ROCKEFELLER. Thank you, Senator Daschle.

Senator Jeffords.

Senator JEFFORDS. I want to continue expressing the same outrage that Senator Daschle has. He and I worked together in the House. It wasn't until 1988 and then after court decisions and legislation that it was finally recognized that there must be some connection between the dioxin in Agent Orange and the illnesses that were suffered. I just can't tell you how outraged I feel about the treatment you're getting. We can't just let this attitude go on.

It is my understanding that neither of you, Rev. Walker or Col. Tetzlaff, are considered to have service-connected problems. Is that correct?

Reverend WALKER. No. I am considered to have service-connected PTSD—mental problems.

Senator JEFFORDS. OK.

Reverend WALKER. Also, because of the SCUD attack, I lost some hearing.

Senator JEFFORDS. They have given you a little break on that.

Reverend WALKER. They gave me a little break on that.

Senator JEFFORDS. What about you?

Mr. TETZLAFF. I have a 20 percent disability due to the fact that I shake and I have ringing in my ears. They say that is all that is service-connected for any disabilities. They have given me about six or seven other diagnoses which have 0 percent. But I have asked them to adjudicate the pyridostigmine bromide and the effect of the shot given me while I was on pyridostigmine bromide, and they have refused to do that for 2 years, since I submitted my claim in 1992.

Senator JEFFORDS. Yes?

Reverend WALKER. I have an appeal which has been pending now for 17 months, and nothing further can go forward with VA until that appeal comes out of Washington. That was 17 months ago that it was first put in.

Senator JEFFORDS. You know, we passed legislation that says you should be given priority treatment. Do you think you are receiving priority treatment?

Reverend WALKER. No.

Mr. TETZLAFF. Did you see me jump? No, Senator, we are not receiving priority treatment. Just 2 days ago I was at the hospital, I arrived for my 1:30 appointment and I was not seen by a doctor until a little after 4, and I got out of the hospital at approximately 4:25. That's priority treatment. In all the time I was sitting there, because of the toxins that are in a hospital, I had to wear a mask to keep those types of toxins from getting into me; otherwise, sitting there I start vomiting and have problems with diarrhea. When I go in for an appointment, I can wait 6 months to a year for a simple appointment. That's my priority treatment, Senator.

Reverend WALKER. I had to wait 4 months for my back appointment. And I will probably get a resident this time rather than a neurologist.

Senator JEFFORDS. Well, Mr. Chairman, I just can't express how disturbed I am to listen to this. I appreciate your calling these hearings. This is incredible. I hope that something will result from these hearings. Thank you.

Chairman ROCKEFELLER. I want to continue with more questions. I would just say to either Senator Daschle or Senator Jeffords, just interrupt when you have something you want to say.

Neil, did anybody from the Department of Defense contact you to ask about your adverse reaction to pyridostigmine?

Mr. TETZLAFF. No, sir. Nobody from the Department of Defense has contacted me on that. I have contacted the Department of Defense several times, and written to the Secretary of Defense's office. Every doctor that I was seeing between August 1990 and June/July 1992 were military doctors. I told every one of them about pyridostigmine bromide, but in every case it was dismissed.

Chairman ROCKEFELLER. While you were in the Gulf, did your doctor know what drug you were taking when you got sick?

Mr. TETZLAFF. Yes, sir. On the plane ride down, we had discussed this and the doctor was in the discussion as to exactly what our timetable should be for taking the drug, and when we should take it so we would stay on a constant 8-hour schedule. We checked with each other to see that we had taken the drug.

Chairman ROCKEFELLER. And did he tell you that it was perfectly safe and that you could go right ahead and keep taking it?

Mr. TETZLAFF. No, sir. He made no indication whatsoever one way or the other. He was just in on the conversation that we should take it, not what the effects of the drug would be.

Chairman ROCKEFELLER. So it sounds like the doctors did not realize that you were having an adverse reaction to the drug?

Mr. TETZLAFF. I would say that he thought it was like giving me a cough drop, sir. There is no adverse reaction to a standard cough drop. That is how safe I think that gentlemen thought it was. I discussed it with him several months later and at that time he didn't even pick up on it.

Chairman ROCKEFELLER. You were in the Persian Gulf for a very short time, and yet you have the same kind of symptoms that many soldiers have who were there for a much longer period of time. From your testimony, Neil, it sounds like your problems could not possibly have been caused by the stress of being in the Gulf at that time, isn't that right?

Mr. TETZLAFF. Well, sir, I was in the Gulf for exactly 11 days and the only thing that I took was pyridostigmine bromide. I never saw a fire. I never saw any missiles. I never saw or fired any nuclear rounds. I didn't do any of that stuff. The symptoms that I have are just from taking that drug. I firmly believe that.

Chairman ROCKEFELLER. Thank you, Neil.

Mr. TETZLAFF. And I just forgot the last portion of your question. I had it in my mind and it just went through, so I couldn't answer it.

Chairman ROCKEFELLER. You did well. Rev. Walker, from your testimony, it appears that the investigational drug and vaccines were never recorded in each servicemember's medical record; is that correct?

Reverend WALKER. Correct. Unless he carried his own shot record, and only the group that was there when I was being insistent got them recorded. I have a copy here of my own personal record taken out of my file 3 days ago.

Chairman ROCKEFELLER. The Committee staff that I mentioned at the beginning of the hearing have read all the studies that the Department of Defense has done to evaluate the safety of pyridostigmine bromide on healthy men. The doctors conducting the studies excluded men with a long list of health problems, including blood pressure problems, kidney problems, asthma, that sort of thing. They did that because they were concerned about the danger of pyridostigmine bromide for patients that had those conditions. Now, you mentioned that you had blood pressure problems when you went to the Gulf. Did anybody ever warn you that there might be problems from taking pyridostigmine?

Reverend WALKER. Not one bit. They did not, and they reissued me after 6 months my Vasotec so I could continue taking them.

Chairman ROCKEFELLER. Of all the doctors that you've seen since you came back from the Gulf, have any of them mentioned that possibility to you?

Reverend WALKER. No.

Chairman ROCKEFELLER. I understand that you have brought several Persian Gulf War veterans with you from Ohio and Robert

Blackwell who works in West Virginia. He works in Wheeling. I would like to thank you and to acknowledge them and have them stand up, if that's all right.

Reverend WALKER. And two of them are Vietnam veterans as well.

Chairman ROCKEFELLER. Is Henry Lee in the audience? Let me say something about Henry Lee, who is from Romney, WV, I'm proud to say. Our Committee staff did a survey of 146 Gulf War veterans. Most of those who have seen their medical records said they were missing or that they were incomplete. However, several veterans from West Virginia told us that their medical records were complete because of your extraordinary personal efforts. I understand that you personally updated the records of military personnel in your unit to make sure their records were accurate. That being the case, I hope you will understand that this Committee respects your perseverance and dedication. Thank you, sir, very much.

Do either Senator Daschle or Senator Jeffords have other questions?

Senator DASCHLE. Mr. Chairman, I have a couple of points that I want to reiterate. First of all, this issue is not just one of legal dimension; it is attitudinal. What concerns me from the testimony we have received this morning is, first, that from a legal point of view, these men are being denied treatment and compensation. Pure and simple. The authorization to provide compensation has generated approximately 3,500 claims. I am sorry to report to the Committee this morning that according to the information we have, out of those 3,500 claims, merely 278 veterans have actually received compensation. So going to VA to obtain the compensation that Colonel Tetzlaff said is so necessary, you have less than a 1 in 10 chance of getting compensation today. That is outrageous.

Not only that, but the authority for providing you care, if it is provided at all, expires this December. We have to extend the authority to provide VA the ability to give you any kind of medical care after December 31 of this year. It seems to me that we ought to use that as an opportunity to tie down VA's inaction and unwillingness to confront this issue more directly. It seems to me that we have got to be much more specific. It says in the law today that if the Secretary determines the condition may be related to your service in the Gulf, only then are you eligible for medical care. Well, it appears that only in a very small number of cases does the Secretary determine that your conditions are related to your experience.

But it is not only that legal issue, it is the attitudinal problem that you have described that concerns me the most. This humiliation, this sense of apology that you have to somehow subject yourself to every time you come into a hospital is just inexcusable, and frankly, inexplicable. These people are good people. Frankly, I am surprised that given the direction Secretary Brown has given VA over the last year, that this issue has not been rectified. But clearly it has not been. And that humiliation to me is the most reprehensible of all of the things that you have told us this morning. You should never have to apologize for walking in the front door of a VA hospital. Never should you have to wait 4 hours to get care if you are told you are given priority care.

So those are the kinds of things that I think we have got to address. Again, it sensitizes all of us to hear these remarks and to hear these personal stories. It takes courage to come before a congressional hearing and in that personal way reflect the experiences you have had and the tragedy that you have had now for some years. Again, let me just thank you very much for your willingness to do so.

Chairman ROCKEFELLER. Thank you, Senator Daschle.

Senator Jeffords.

Senator JEFFORDS. Just a parting comment. Yesterday, we had hearings on how we could allow the VA to participate more fully in health care with a new health care plan. I have been pushing to try to improve and expand the ability of the Department of Veterans Affairs to participate in a health care plan. But you listen to the evidence today and you wonder whether your judgment is correct to say that, gee, we ought to allow more veterans to be able to participate in a system which reacts the way it has to this. So, I am very discouraged. I hope that VA will take note of that, and I am sure you feel the same way. If we get this same kind of attitude in other directions, you wonder whether we should allow them to expand their care. Thank you, Mr. Chairman.

Chairman ROCKEFELLER. Senator Jeffords, that's an important point. It's one VA will have a chance to respond to when they are witnesses later today.

Gentlemen, I want to thank you. As I look at the four of you totally different people—in some degree different ages, different experiences, different backgrounds—what I'm looking at is not just four Americans who served their country and are paying a terrible price for that, but I'm really looking at what may be hundreds of thousands of veterans. And you know we conduct our business in the Senate and in the House and we go from crisis to crisis. We're trying to reform the health care system and worry about crime on the streets, and things of that sort; and it often works out that we forget, and don't have brought to our attention, some incredible injustices that are being perpetrated by our own government on people whom we are sworn not just to honor for their service, but to protect in terms of health care. So, your statements are very powerful, your answers to the questions are very powerful, and your personal presence is very powerful. And I think that you can take with you, from this hearing, a sense of certainty that you will have started in motion an investigation and a sense of scrutiny and the beginnings of a real sense of accountability on the part of the United States Government. So, you've served your country very well in the last hour, all four of you. I want to thank you very much for your courage, and we hope for your treatment and recovery. Thank you all very much.

I would like now to welcome the second panel. The second panel includes scientists, ethicists, and doctors. Let me also thank all of you for testifying and helping us to understand all of this. Our panel is composed of Dr. Leonard Cole, author and professor of political science, Rutgers University; Dr. Thomas Callender, a physician who has treated numerous Persian Gulf veterans; Dr. James Moss, a scientist with the Department of Agriculture; and Dr. Arthur Caplan, director of the Center for Biomedical Ethics, University of Minnesota.

The statements that you have submitted are already included in the hearing record. In order for us to complete our questions, please try to keep your oral testimony brief, as best you can. Please forgive me for that.

Before we begin, once again, because this is a very serious hearing, I would ask all of you to rise and raise your right hand. Do you swear that your testimony will be the truth, the whole truth, and nothing but the truth?

[All witnesses responding in the affirmative.]

Chairman ROCKEFELLER. Let the record reflect that each of the witnesses replied in the affirmative.

Dr. Cole, we will begin with you.

## STATEMENT OF LEONARD COLE, PH.D., PROFESSOR, RUTGERS UNIVERSITY, RIDGEWOOD, NJ

Dr. COLE. Thank you. My name is Leonard Cole and I teach at Rutgers University in Newark, NJ. I have written a good deal about testing done in the U.S. Army's biological defense program.

I appreciate your invitation, Senator Rockefeller, to testify about experiments involving simulated biological and chemical warfare agents. These are agents that are intended to mimic more lethal bacteria and chemicals that might be used in an actual warfare attack.

As described in my book, "Clouds of Secrecy," the Army began a program in 1949 to assess the Nation's vulnerability to attack with biological weapons. During the next 20 years, simulant agents were released over hundreds of populated areas around the country, including many of our major cities—New York, San Francisco, portions of Hawaii, Alaska, and some areas of Washington, DC. The entire country in effect was being used as an experimental laboratory and millions of people had become unsuspecting guinea pigs.

Vulnerability testing continues at Dugway Proving Ground, 70 miles from Salt Lake City. The stated purpose of those tests is to evaluate biological detector systems and protective gear. A July 1993 news release by the Dugway public affairs office indicates that no specific safety controls are required for testing with simulants. The statement implies erroneously that the simulants are harmless.

In fact, during the past 45 years of open air testing, from time to time the Army has stopped using certain simulants for reasons of safety. This was true in the 1950's with a fungus named Aspergillus fumigatus, and later on in the 1960's with a chemical containing cadmium, a known carcinogen. In the 1970's, a bacterium called Serratia marcescens was taken out of service after almost 30 years of use as a simulant because it was known to cause infection and sometimes death. In the 1980's, as you heard from Earl Davenport who was exposed to dimethyl methylphosphonate, this chemical was removed because it also was suspected of being a possible cancer cause, as well as having other toxic effects.

The truth is that any microorganism that seems harmless under some circumstances may cause illness under others. Exposure to high concentrations of any microorganism can be critically dangerous to people in weakened conditions in particular. The elderly, the very

young, people with AIDS, and others who have weakened immune systems are more susceptible to life-threatening infections.

In addition to people who are unwittingly exposed to the Army's bacteria and chemicals, human research subjects may not be receiving appropriate information. A test at Dugway this past November raises important questions in this regard. The test was intended to assess the ability of chemical agents to penetrate protective clothing. Yet, the consent form that the subjects—

Chairman ROCKEFELLER. Dr. Cole, it might be useful for the audience if you could explain the Dugway operation and what it is meant to be doing.

Dr. COLE. Yes. There is open air testing at Dugway that involves the spraying of chemicals and biological agents outdoors. Some individuals will be dressed in protective clothing to see whether there can be penetration of this clothing or other shelter-type materials. The object, of course, would be to see whether these would be effective against simulants, which are less lethal bacteria or chemicals, so that in a real warfare situation we could have some confidence that the people wearing this clothing would be protected.

Chairman ROCKEFELLER. Thank you.

Dr. COLE. The consent form that these individuals signed in November, however, was signed in advance of the test and nothing had been said about any of the chemicals on that consent form.

In addition, several physicians at the University of Utah Medical School in Salt Lake City said they do not feel they have sufficient information that would enable them optimally to handle infections and complications that might be caused by the tests.

Finally, I will just summarize what I think would be appropriate policy suggestions in this regard.

The first would be to inform people in an area before each test that they may be exposed to the Army's biological and chemical agents. For a substantial period after each test, these people should be monitored for their health. In fact, the entire population that might be exposed should be monitored for health. Comprehensive information should be provided in understandable language to human subjects before they participate in any test. Fully inform the neighboring medical community about the nature of each test and its possible medical complications. Finally, and above all, strive for safety, candor, and openness. Thank you.

[The prepared statement of Dr. Cole appears on page 96.]

Chairman ROCKEFELLER. Thank you, Dr. Cole, very much.

Dr. Callender.

## STATEMENT OF THOMAS CALLENDER, M.D., LAFAYETTE, LA

Dr. CALLENDER. Thank you, Mr. Chairman, for the opportunity of being here today. I am an internal medicine specialist in civilian practice. I have worked with a lot of Desert Storm victims and I believe that I see a lot of unusual serious physical impairments that are typical of what you would expect to see in a person who has been exposed to some type of nerve poison. It also appears to me that the military, in general, has disowned these soldiers and basically rates them as being neurotic.

By my evaluation and the testing that I have done, the soldiers are not getting the state-of-the-art evaluation that really exists in this day and time. Pyridostigmine bromide is one of the possibilities that has come up in my discussions with these soldiers. Analysis of some of the research related to pyridostigmine bromide that I have done leads me to believe that there really is not enough information nor adequate research to expose hundreds of thousands of people to this particular agent.

Some of the issues that really need to be considered are the synergistic effects that pyridostigmine bromide could have with many other medicines, foods, pesticides, and other agents. One of the things that I was very alarmed about during the course of my research is that the animal research shows adverse effects, yet this has seemingly been ignored. Testing that has shown adverse effects in humans has really been discounted. And very often the experience with myasthenia gravis patients has been used as proof of safety. However, it is well known that the physiology of such myasthenia gravis patients is very different than a normal individual's. You could make an analogy to a patient treated with insulin who has diabetes; that doesn't mean that you can give insulin to everybody and expect to have a good outcome.

I have been impressed with the sincerity of the Desert Storm soldiers. I see that many of them are very ill, they are having financial problems, they feel very humiliated with their treatment. They are not getting any kind of medical treatments and very often their private medical insurance will not cover treatment, even if they do have such, because the problems are defined to be combat-related, but the military does not agree, and so they end up in a Catch-22 situation with no medical care. And many of them are in a very bad state of affairs.

One of the observations that I have made in interviewing these patients is there seems to be a very high incidence of complaints of side effects in the actual combat veterans, as opposed to what is estimated from the tests that have been done on humans in controlled situations. It has been interesting to note that the individuals who might be susceptible, i.e., who are biochemically susceptible based on lab tests, are excluded from the studies. There were no women, as mentioned earlier, and they excluded people that might have any kind of medical problems. I think it is very dangerous to take that kind of information and try to extrapolate it to a large population in a combat situation. They would really have to do acetylcholinesterase levels on the soldiers during combat and try to monitor their adverse effects, and should also try to adapt the dosage for the differences in body weight in different individuals.

All the research that I have read indicates that people that had adverse effects were taken out of the studies right away. But the soldiers indicated that if they had adverse effects, they were told they had to continue the medication. Therefore, you have a totally different situation in research versus application. Again, I think this makes it very difficult to extrapolate some of the research data to that actual environment.

One of the things that has been apparent to me is that many of the soldiers also told me that they had to seek help very often through

their own family or friends paying for their care. They would go to civilian physicians and have tests done and those tests would very often show some significant abnormalities. When that information was presented to military physicians, it was basically ignored and some degree of hostility was sometimes apparent. I think that situation really needs to be changed; there needs to be cooperation between the military and any physicians that notice adverse effects or that suggest testing that needs to be done. That information really should be integrated into the overall database that is used to evaluate these soldiers. Thank you.

[The prepared statement of Dr. Callender appears on page 99.]

Chairman ROCKEFELLER. Thank you, Dr. Callender, very much. We will come back with questions to all of you.

Dr. Moss, I understand that we didn't request a written statement from you, but that you do have some preliminary research findings that might be relevant to the Persian Gulf health experience. I also understand that you tried to present these findings of yours to your superiors and to researchers at the Department of Defense, but without success to this point. Could you just tell us a little bit about your research on pyridostigmine bromide and pesticides. Try to summarize some of that for us.

Dr. MOSS. Yes. I haven't really been ignored by the Department of Defense. I have submitted a pre-proposal and that is still in process. So I wouldn't say that has been turned down.

Chairman ROCKEFELLER. They have accepted your proposal?

Dr. MOSS. They have not answered yet, so that is still pending.

Chairman ROCKEFELLER. But they do have it?

Dr. MOSS. They have it. They have had it for several months now.

I began looking at pyridostigmine as an offshoot from some mode-of-action research I have been doing on insecticides. Anything I say here is insects; I have not been working on vertebrates. Essentially what I did is I began looking at the mode of action of boric acid, which I don't think has relevance to this Committee, but that led me into looking at interactions of several compounds.

I have found that the synergistic interactions between a formalindene insecticide and several other compounds paralleled very much the interaction between the repellent DEET and some other compounds. I began to look at the interactions of DEET and theophylline; DEF, which is a cotton defoliant; lambda-cyhalothrin, which is a pyrethroid insecticide; permethrine, which is a pyrethroid insecticide; chlordimeform, which is a formamidine pesticide; PMS, which is phenylmethylsulphonal fluoride and it is known to inhibit a number of hydrolytic enzymes, enzymes the nerve gases might also inhibit; pyridostigmine, which has been discussed here; amatraz, which is another type of insecticide; and eserine, which is chemically similar to pyridostigmine. And I have found that all of the compounds that I have listed here increased the toxicity of the repellant DEET to some degree; the range is anywhere from 2-fold to 2,500-fold, depending on which compound you are talking about.

In addition, I have looked at the reverse order and taken DEET and used it as a synergist for other compounds, and found that DEET synergizes eserine toxicity, increases it. It also increases pyridostigmine toxicity. It does not increase another carbamate

insecticide toxicity. So this is not all carbamates.

Chairman ROCKEFELLER. You have used the word DEET quite a bit. Just for explanation purposes, is that a common pesticide?

Dr. MOSS. DEET is a repellent that was developed I believe towards the end of World War II, with the cooperation of DOD and the Agriculture Department. Essentially, it is the same compound as found in commercial repellents you buy in the store and I believe it is also a military issue.

Chairman ROCKEFELLER. Thank you.

Dr. MOSS. That is pretty much the list of compounds that interact.

Chairman ROCKEFELLER. All right, Dr. Moss. I thank you. We will have questions for you later.

Dr. Caplan.

## STATEMENT OF ARTHUR CAPLAN, PH.D., DIRECTOR, CENTER FOR BIOETHICS, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA

Dr. CAPLAN. Thank you, Senator. Some would argue that the entire discussion of research in the context of war, when the threat to the Nation's security is immediate and real, doesn't permit any discussion of the niceties of ethics. The rules of experimentation go out the window; they are for times of peace, not for times of war. But, I think it is important that the Committee understand that the rules and regulations, and the core assumptions of law and morality in human experimentation, come from a time of war. They come from the Nuremberg Code, which was written in response to wartime circumstances.

What I would like to do is just cover two points with you in my testimony. First, with special reference to the Gulf, is the use of agents, vaccines, drugs that were used for purposes other than those for which they had been approved or which were unlicensed research. Does that constitute research? I think some would say it does not if the point is to try and provide protection to the troops to allow them to survive attack by hostile forces trying to use biological or chemical weapons. But I think that the argument that this is not research because the intent or the goal is to provide protection just doesn't hold up.

It seems to me that even though one might do a careful risk-benefit analysis and decide that, other things being equal, it is worth trying to take the gamble to see if you could protect someone against an attack, the fact that you have done a risk-benefit analysis doesn't transform the use of experimental, innovative, investigational agents into therapies. These agents were used, as we have heard, in large populations for purposes other than those for which they were originally designed, in some cases, and circumstances under which they had never before been tried out in the desert. This seems to me to cinch the case that what took place fell into the category of experimental, innovative, and investigational, and that makes them research.

The other point I would like to make to this Committee is that, if it is research, then another question arises. If the decision is made to try these agents out to see if they would provide some protection, then what do we owe to people who don't get the expected protections

ethically and legally required of informed consent, and Committee review and so forth, that we would normally have in place in medical research in peacetime and civilian life?

I think what we owe them, quite simply, is careful followup, quick therapy for those harmed, and compensation. It seems to me those who are put at risk for purposes of trying to help them achieve their military mission are exposed to substances/agents that may do them harm, but the decision is made to take the gamble. They at least are owed, for the waiving of those protections, careful and close followup, and for those who are harmed or hurt, as the case may be, treatment and compensation. That I have not seen much in evidence in the statements that we heard in the previous panel. It seems to me that we are not doing our ethical duty to those that we chose to expose to substances that carried unknown risks, and that is where, to date, I think our Nation has failed those who were exposed.

Chairman ROCKEFELLER. Dr. Caplan, thank you very much.

[The prepared statement of Dr. Caplan appears on page 117.]

Chairman ROCKEFELLER. I would like to start the questioning with you, Dr. Cole. The Department of Defense claims that the biological agents that they use are perfectly safe. Some of them are found, in fact, they say, in common garden soil. Yet, in your testimony, you say that the Department of Defense officials have sometimes claimed that a biological agent might be safe, but later admit that might not be the case. What evidence is there that they are wrong about the safety of some of the biological simulants that they are using and we are discussing today?

Dr. COLE. Clearly, by removing some of the biological simulants from service, which I alluded to in my testimony, the Army implicitly recognizes that they were not safe. Every one of the microorganisms that the Army has used and removed from service had long been known, years and years before they were removed from service, to be capable of causing disease. This was in the medical literature. There are articles written about it. Even now, one of the simulants that the Army is using called Bacillus subtilis, which is fairly harmless in many natural conditions, is recognized as a potential source of infection and can cause serious illness in some people when they are exposed to it in large numbers and they inhale large numbers of those microorganisms. This is in the medical literature.

Chairman ROCKEFELLER. The Department of Defense needs to classify some information for national security reasons. But we also need public disclosure in order to help individuals who are ill and, as you indicated, to protect society as a whole. How do both of these needs get met?

Dr. COLE. Well, Senator, I think the answer is fairly simple in terms of large-scale spraying of bacteria or chemicals. Since the Army suggests that these are not very, very harmful materials, it should have no compunction about letting a community know when individuals in that community, including at Dugway, might be exposed. So I don't see there would be a conflict between those two important items that you suggest.

I think the average citizen who might be wandering 10 or 20 or 30 miles from the border of Dugway should have the right to know that

he or she might be exposed to some of these so-called harmless simulants, which in fact are not harmless.

Chairman ROCKEFELLER. Dr. Caplan, in your testimony you talked about the fact that using an investigational drug under an IND is research; you made that very clear, even if the goal is to provide treatment. I will say that I agree with you. So I have a question which is related to that. What is your view of the ethics of the Department of Defense not collecting information about the safety of pyridostigmine for the hundreds of thousands of soldiers who took it? It seems to me this was a great opportunity to learn about what is safe and what is not; yet, the Department of Defense did not do any kind of objective evaluation.

Dr. CAPLAN. Well, Senator, there's really two issues there. One is, if you waive the standard protections of disclosure and ability to consent, ability to refuse, because you are in circumstances and conditions where those may not be practical, then I think, if anything, you turn up the heat on the need to follow up carefully and to understand exactly what happens in terms of outcomes when you try these unproven, untested, innovative approaches to trying to do something to prevent harm to troops.

I would add that when people say it isn't research, one of the things that you must do as well, I would argue very strongly, is take advantage of the fact that you have got this large-scale experiment going on where we are exposing people. We owe it to people who have had these exposures to say that we learned whether it worked or not. Oddly enough, post this experience, I am not sure we're in a better position to say today what the side effects are of these agents and whether they would have proven more harmful than beneficial, because we haven't followed up. That is a failure of responsibility.

Chairman ROCKEFELLER. Let me back off questioning for a bit and turn to Senator Daschle.

Senator DASCHLE. Thank you, Mr. Chairman. Let me commend our panel. It was an excellent presentation by each of you. I appreciate very much your guidance as we address some of these questions.

I really would like to address just one question to Dr. Caplan and anyone else who may wish to respond. Currently, the law requires that Gulf veterans be eligible for inpatient or outpatient care at VA if the Secretary determines that the condition may be related to their service in the Gulf. In your view, would we better serve our veterans if the legislation stated that, "Gulf veterans are eligible for care unless the Secretary determines that the condition is not related to their service in the Gulf"? Could you respond to that, Dr. Caplan?

Mr. CAPLAN. Senator, that's a little bit off the issue of human experimentation ethics and into the question of what we owe somebody who gives service. It would seem to me that someone who is asked to make sacrifices and undertake the threat of the ultimate risk of death should not carry the burden of proof in seeking out care. It should be the other way around. Those seeking care, I believe, are owed ready access to diagnosis and treatment.

Senator DASCHLE. That is the issue, isn't it, burden of proof. Who should shoulder the responsibility for bearing the proof of these problems. In past wars, going all the way back through civilized history, I guess, and uncivilized as the case may be with war, the

wounds were always more evident. Obviously, wounds of the traditional nature are clearly ones that we have built our whole system of compensation and care upon. Wounds today are not as visible, not as tangible, not as evident, and, as a result, our system is not as capable of addressing these new wounds. And then comes the question of burden of proof.

Would anybody else care to address this question of burden of proof? Is it more the responsibility of VA or the veteran to establish a burden of proof?

Dr. Cole.

Dr. COLE. I might suggest that in much of science, and certainly in this case, we probably would never be able to establish a matter of proof without doubt. There will be uncertainties. But I think there should be not only a preponderance of evidence, but, as Dr. Caplan suggested, a recognition of why these people were exposed, and I think that there is surely a balance in their favor.

Senator DASCHLE. So, do I take from your answer that you would favor, not as a scientist necessarily, but as one who has studied this issue extensively and looked at the ramifications of your study, that there ought to be more of an opportunity for veterans to address their problems without having to demonstrate this burden of proof?

Dr. COLE. Yes.

Senator DASCHLE. Yes, Dr. Callender.

Dr. CALLENDER. I have a comment. No matter on which side you decide to put the burden of proof, there has to be a mechanism where the truth is really going to be looked for in an honest, straightforward fashion. Regardless of which direction you are proceeding from, you can have problems with objectivity. The biggest complaint I have had from veterans is that even when they had proof, it was thrown in their faces and they were told to leave.

Senator DASCHLE. That's the attitudinal question.

Chairman ROCKEFELLER. Could you say the end of that again?

Dr. CALLENDER. That even when they had objective proof that they had significant health problems, it was basically just thrown in their face. They were told that we are going to ignore these data; you can't possibly be sick. So even if they do go to a doctor on their own and get positive medical information, the prevalent military attitude is that, "We're not going to help you, and the level of proof we ask for is an obstacle. And if you get over that obstacle, we will find another one."

Senator DASCHLE. You have answered my question well. Thank you. Thank you, Mr. Chairman.

Chairman ROCKEFELLER. Senator Jeffords.

Senator JEFFORDS. Dr. Caplan, I would like to follow up on this line of questioning. It is my understanding from your observations—and let us put us in the situation as it existed at the time—there was information in our possession that the threat of the utilization of nerve gas was a possibility which should be dealt with. So I suppose you have to give some leeway to the reaction to that in the way things were handled. But also in taking that into consideration, you also have to lean over, I think, a little further to support those who may have been adversely affected.

What I am trying to get at is, assuming you did that in sort of an emergency situation, would you agree that still there is no excuse for

not keeping track of what each individual received and how many individuals received it, and whether or not it was across-the-board application rather than a more experimental, "Well, let's have a control group and we will give half to it." So we don't know any of those answers, do we?

Dr. CAPLAN. Senator, it seems to me we have to be realistic. If someone is shooting at your head, it probably gives you less reason to be concerned about what they are shooting in your arm in terms of trying to prevent danger from biological or chemical weapons. So I am not here to be naive about the circumstances under which we are going to make choices, and people and commanders have to make policy about trying to come up with the best defense. But it does seem to me what you then owe those to whom you are saying we have to take a gamble, and we're not going to be able to get the usual consent from you to say I do/I don't want to take it, and so on, is careful followup. They are owed that simply because they are asked to take more risk than ordinarily would be expected. I think we have to try as hard as we can to figure out what happened to them, was the risk as we thought, or was it worse, or was it minimal.

Moreover, we don't want to be in a situation where we don't learn from what took place in terms of getting the answer to the question of how risky is it relative to trying to secure these benefits. It bothers me a great deal that we've been through this experience and, as I said, I am not sure we're in a better position to answer the questions of are the agents safe, harmful, or dangerous than we were before the enterprise started, because the recordkeeping and the followup hasn't been what it should be.

Senator JEFFORDS. I would also guess that you would also conclude that in the question of the burden of proof or who has the responsibility, if someone has an opportunity to keep the evidence or to make available the evidence, and whether it is through the exigencies of the time or whatever, fails to do so, and maybe it is even defensible that they didn't; but if they did not do that, then it again would seem to cast a greater burden, would it not, on the Government to have the proof to show that what had occurred to the individuals who were exposed was not caused by that. Would you agree that would be a logical conclusion?

Dr. CAPLAN. Yes, I would. And I would only add that we did hear testimony today that when individuals, such as the gentleman from West Virginia, wanted to keep records and tried hard to insist that be done, he got them. So I am not sure it was impossible. It may have been understandable it didn't happen, but I am not sure it was impossible to do it. Some of it happened when it was initiated by people out in the field. Certainly, the case that the burden, when you are asking people to waive the usual protections and undergo risks that they ordinarily would not, without the usual options of saying yes or no to taking those risks, is there to then go out and aggressively pursue what happened to these people and then treat and compensate them.

Senator JEFFORDS. This is probably a better question for the next panel, but are any of you aware of any orders or any papers or documents that were sent out by someone to tell how these drugs were to be applied and to whom? In other words, we know the

individual records did not include it, but are you aware of any documents which indicated how this was to be done and how it was reported? Is anybody aware of anything on that?

[No response.]

Senator JEFFORDS. I take it from the lack of any nodding of heads that the answer is you do not know.

Dr. CAPLAN. Well, there was some discussion, Senator, in some of the published literature, about the vaccines having to be taken in a particular sequence of shots in the Gulf War, pentavalent toxoid vaccine antibotulinum and the pills having to be taken in certain ways. We have heard that compliance in both of these areas with at least those recommendations was not necessarily what it should have been.

Senator JEFFORDS. Thank you. Thank you, Mr. Chairman.

Chairman ROCKEFELLER. Thank you, Senator Jeffords, very much.

Dr. Caplan, it is also true that the Department of Defense did no research regarding the safety of pyridostigmine bromide on women. One of the phenomena that is no longer new is that there are a lot of women soldiers and now a lot of women veterans. Women by the thousands were given this pill in the Persian Gulf. And then there is the further point that Dr. Callender made that women would tend to be lighter than men, and yet the dosage was identical for all men and women, which would imply that the effect on women could be much worse. What ethical response do you have to that?

Dr. CAPLAN. On the one hand, it might be said that we didn't do research because we simply gave out these various agents in the hope of providing some protection in a very serious situation. On the other hand, if you are giving out agents to women, to people with conditions—diabetes, high blood pressure—in a mass way, if you are doing it under conditions of high heat and desert environments and so on, with tough environmental circumstances, it seems to me then at minimum you want to study and understand what happened after the fact. It seems to me, again, the obligation to figure out was there harm, were people injured, did people who normally might not have been exposed to this in standard trials but had contrary medical conditions suffer more, run into problems. We can't answer that question because of the failure to follow up. And that seems to me ethically wrong.

Chairman ROCKEFELLER. I thank you for that.

We have a chart here which I think is very disturbing, and it shows some of the symptoms that have been reported for patients suffering from pyridostigmine sensitivity. Next to that is a list of the symptoms reported by veterans with so-called mysterious symptoms that are often spoken of in terms of the Persian Gulf War. If you look at it, the similarities are very real and very ominous. You can just go right down the list, they are made parallel to each other. You have "profuse perspiration" on the pyridostigmine side effects, and then across from that under the so-called mystery illnesses is "night sweats." Well, that's not a big difference perhaps. There is just an enormous parallel right down those two lists of effects.

**Chart Comparing Pyridostigmine Side Effects and Symptoms of Persian Gulf War "Mystery Illnesses"**

| Pyridostigmine Side Effects* Reported by DOD Prior to 1990 | Symptoms of Persian Gulf War "Mystery Illnesses" |
|---|---|
| skin rash | skin rash |
| fatigue | fatigue |
| decreased short-term memory | short-term memory loss |
| diarrhea | diarrhea |
| vomiting | vomiting |
| nausea | nausea |
| profuse perspiration | night sweats |
| abdominal cramps | stomach cramps |
| increased salivation | increased nasal secretions |
| loss of bladder/bowel control | loss of bladder control |
| muscle spasms | muscle, joint pain |
| muscle cramps, twitching | twitching |
| increased bronchial secretions | chest pain |
| heavy eyelids | vision problems |
| seizures | headaches |
| respiratory arrest | shortness of breath |
| | sleep disturbances |
| | personality changes |
| | bleeding gums |
| | sinus problems |

*Side effects are from overdosage and reportedly stop after therapy is discontinued.

Dr. Callender, what does this say to you?

Dr. CALLENDER. As I said, I am an internal medicine physician and I do neurotoxicity work with patients. The problems that I have seen in the Desert Storm veterans parallel what you have there, and those are typical of neurotoxic effects. It suggests that there is a similarity and possibly a similar cause in the complaints of the veterans by something such as pyridostigmine. However, those symptoms are also associated with other nerve toxins. So it is not proof that there is a 1-to-1 relationship there, but it is very suggestive and it needs to be looked at seriously.

Chairman ROCKEFELLER. So, in other words, it does not prove anything but suggests enough that further investigation is warranted?

Dr. CALLENDER. That's correct. Several of the comments have been made about long-term followup. I would like to second that as being very necessary. Some of the effects from nerve agents have been shown, such as with some of the pesticides, e.g., organophosphates, to have caused delayed nerve damage. It took many weeks or months to really reach their peak. Some of the research that was done on the pyridostigmine bromide was done only for a very few days or weeks. So it would be very likely that they would miss the development of these types of effects. One thing I would like to see is that not only in the Desert Storm individuals, but in the subjects of any research done in the past with pyridostigmine bromide, that those individuals be found and long-term followup done on them also.

Chairman ROCKEFELLER. Dr. Callender, this is something I want to ask just for the record. Last week, the Federal Government conducted a workshop to examine possible causes of Gulf War illnesses. There was a neurologist there by the name of Dr. Shaumberg, and he was apparently not persuaded that pyridostigmine was a likely cause. However, it has come to my attention that Dr. Shaumberg also believes that Agent Orange is not a cause of serious illness. That sounds like a prejudicial statement and I don't mean it to be. But I would like to get your comment about that.

Dr. CALLENDER. I am sorry?

Chairman ROCKEFELLER. Here is a neurologist, in other words, who is saying to the Federal Government that pyridostigmine is not a likely cause of either mysterious illnesses or Gulf War illnesses. I would just like to have your response to what he has said.

Dr. CALLENDER. Well, I really don't know the analysis that he is applying to the situation. I certainly don't agree. I think it is a very good possibility that it has a relationship and I think it should be investigated. I am not sure if he meant that it couldn't be a possibility or exactly the details of that comment, since I wasn't there. But I do believe that pyridostigmine bromide has not been tested adequately to rule it out at this point. And I think it is very suspicious and it needs to be investigated.

But like any issue of this nature, there are going to be differences of opinion. We need to apply the perspectives of many different individuals while looking at these subjects to cover all the bases. Dr. Shaumberg might have certain issues he is thinking of, he may have certain experiences he has had with medications that he is thinking of, yet another doctor may have a different experience. When you put all that together and you pool that information, you can find out a lot of interesting things about toxicities that you will not find if you are only looking at one individual and what his experience is. So I think that everyone should have some input into this matter, i.e., that everyone really should take the experiences of patients and the victims of these exposures into account. But as far as categorically saying that pyridostigmine bromide is not involved, I would not agree.

Chairman ROCKEFELLER. The reason that I brought up the Agent Orange factor is because I wanted to get on the record that he had said that Agent Orange really wasn't a problem either. In fact, he has testified on behalf of chemical companies to that effect. Since what he has said may be used in further panels, I wanted to simply put that on the record.

[See deposition of Dr. Schaumburg regarding Agent Orange and Gulf War illnesses, and related documents, beginning on page 470.]

Dr. Moss, I asked you to summarize your research and you did so too technically for me to understand. So I want to say what I think it was that you said. You did research on cockroaches. And you used DEET and pyridostigmine at levels that would not normally kill cockroaches, is that correct?

Dr. MOSS. That's correct.

Chairman ROCKEFELLER. In combination, that is, when it was used with pyridostigmine, the DEET was 10 times as lethal as when it was used alone.

Dr. MOSS. In the case of pyridostigmine, that is correct.

Chairman ROCKEFELLER. Therefore, according to your research, what would be the effect of giving pyridostigmine to persons also being exposed to large doses of DEET?

Dr. MOSS. It would depend on if they responded the same way as cockroaches. The LD–50 of DEET on rats is approximately 3 to 5 grams per kilogram. The LD–50 is the amount it takes to kill half of them; that is just a common toxicological term. The LD–50 for German cockroaches from my data is about 6 grams per kilogram. Statistically, they would probably be about the same, though I haven't really looked at the overlap of these numbers.

[Data from Dr. Moss' study appears in Appendix 10, page 407.]

Chairman ROCKEFELLER. Obviously, research on cockroaches, as you have indicated, may not be relevant to humans. But it certainly indicates that there could be a serious problem, and you have indicated that. Now, it is my understanding that you tried to notify the Department of Defense of your research findings. Were you able to talk with the folks there about that?

Dr. MOSS. I have submitted a proposal to Fort Detrick. They have what is called a Broad Agency Announcement. Unfortunately, it is difficult to bring grant money when you are working at an institution that isn't supportive of that research. The research I am proposing is work on vertebrates because of my findings on cockroaches. So, there are some conflicts here that may prevent me from getting funding that have nothing to do with the merits of the research.

Chairman ROCKEFELLER. Is it fair to say that your superior at the Agricultural Research Service did not think that your work was sufficiently important to submit to the Department of Defense?

Dr. MOSS. I am not sure what his opinion was about the Department of Defense submission. They are aware that I submitted it. I don't think it was considered important enough for ARS to support as an institution, though.

Chairman ROCKEFELLER. OK. I don't have further questions at this point. I want to say for the record that the Department of Agriculture was not very happy about your coming here today to testify. I want to say that to immunize you, so to speak. I really appreciate your coming to share your information with us.

Let me say that more broadly to all four of you. In what is an incredibly complex, mostly neglected area as far as American public information is concerned, hopefully a little less so as we proceed with hearings of this sort, you have all lent very important and valuable expertise. I want to thank each of you very genuinely on behalf of Senator Daschle and Senator Jeffords and myself. Thank you very, very much.

Our third panel consists of officials from the Department of Defense, the Department of Veterans Affairs, and also the Food and Drug Administration. I would like to thank each of these folks for testifying, because this is a very important hearing. From the Food and Drug Administration, we have Dr. Robert J. Temple, who is Director, Office of Drug Evaluation, Center for Drug Evaluation and Research, accompanied by Dr. Russell Katz, Deputy Director, Division of Neuropharmacological Drug Products; Dr. Karen Goldenthal, Director, Division of Vaccines and Related Product Applications,

Center for Biologics Evaluation and Research; and Catherine Lorraine, general counsel.

I also want to identify, from the Department of Defense, Dr. Edward Martin, who is the Acting Principal Assistant Secretary of Defense for Health Affairs. You are accompanied by Jeanne Fites, who is Deputy Assistant Secretary of Defense for Personnel and Readiness. And from the Department of Veterans Affairs, we have R. J. Vogel, who is Under Secretary for Benefits, accompanied by Susan Mather, M.D., Assistant Chief Medical Director for Environmental Medicine and Public Health.

Inasmuch as we have many questions we'd like to ask, we had requested that you not give your prepared statements today. All of your prepared statements are in the record in their entirety. If any of you object to that and want to give a part of your oral statement, you are entirely welcome to do so. This is not an attempt in any way to not allow you to do that. To provide balance, you ought to be able to if you want to. But this is something that we discussed with you before and it seemed to be acceptable.

If that is the case, then I want to ask all of you to rise and to raise your right hands. Do you swear that your testimony will be the truth, the whole truth, and nothing but the truth?

[All witnesses responding in the affirmative.]

Chairman ROCKEFELLER. Let the record show that all witnesses answered in the affirmative.

## PANEL OF ADMINISTRATION WITNESSES

**EDWARD MARTIN, M.D., ACTING PRINCIPAL ASSISTANT SECRETARY OF DEFENSE, HEALTH AFFAIRS, ACCOMPANIED BY JEANNE B. FITES, DEPUTY ASSISTANT SECRETARY OF DEFENSE, PERSONNEL AND READINESS**

**R. J. VOGEL, UNDER SECRETARY FOR BENEFITS, DEPARTMENT OF VETERANS AFFAIRS, ACCOMPANIED BY SUSAN H. MATHER, M.D., ASSISTANT CHIEF MEDICAL DIRECTOR FOR ENVIRONMENTAL MEDICINE AND PUBLIC HEALTH**

**ROBERT J. TEMPLE, M.D., DIRECTOR, OFFICE OF DRUG EVALUATION, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY RUSSELL G. KATZ, M.D., DEPUTY DIRECTOR, DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS; KAREN L. GOLDENTHAL, M.D., DIRECTOR, DIVISION OF VACCINES AND RELATED PRODUCT APPLICATIONS, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH; AND CATHERINE C. LORRAINE, GENERAL COUNSEL**

[The prepared statement of Dr. Martin appears on page 124; the prepared statement of Mr. Vogel, on page 129; and the prepared statement of Dr. Temple, on page 134.]

Chairman ROCKEFELLER. Let me start with the Department of Defense, which would be you, Dr. Martin. Let me start out by saying that I understand that the Department of Defense was absolutely committed to trying to protect soldiers from the deadly effects of

biological and chemical weapons. I say that clearly. I respect those motives and efforts. I also understand that a battlefield is not a research lab. There are lots of things going on, and collecting data is clearly not necessarily seen as a priority. So let's start by talking about the research that DOD conducted on pyridostigmine bromide before the Gulf War.

DOD conducted many studies of healthy men, but excluded men with sensitivity to pyridostigmine bromide and those taking various medications. Why didn't DOD study the effects of these at-risk populations before giving it to 400,000 U.S. troops, many of whom were on medications or had those illnesses or were sensitive to pyridostigmine?

Dr. MARTIN. The original evaluations by DOD would have been carried out as it was researched within a series of rules associated with protection of human subjects. And indeed, it was the judgement at that time to focus the research on what elements of safety and efficacy could be evaluated. It is important to point out that part of the reason that it continues to be an investigational drug is that research did not allow, ethically, for us to look at pyridostigmine in the context of its efficacy against exposure to organophosphate nerve gases. That would be, in itself, unethical. There were limitations in the evaluation that we made as part of that research.

The second point which is important is this: We depended very substantially on the overwhelming bulk of research which had already been done on the safety and efficacy of pyridostigmine by other agencies in the Federal Government, like NIH grantees and the pharmaceutical industry, through the auspices of the Food and Drug Administration.

Chairman ROCKEFELLER. But DOD did say that they tested safety, am I right?

Dr. MARTIN. Yes, sir.

Chairman ROCKEFELLER. I recognize the Majority Leader is here, and that puts constraints upon any of the rest of us. [Laughter.] But I want to just finish this particular line of questioning.

Again, Dr. Martin—and Senator Mitchell, if you will forgive me just for these two questions—why were all men and women given the same dose of pyridostigmine regardless of their weight?

Dr. MARTIN. I think two points need to be quickly made. You recollect that this particular set of decisions about these interventions was being made in the fall of 1990. We were facing an enemy who had used nerve gas before, and we had every reason to believe that they had integrated the use of nerve gas and biologic weapons into their combat arms. There was a very strong feeling that we had hundreds of thousands of troops who most likely would face chemical and possible biologic weapons.

The Department, in making the determination, went to very substantial and appropriate efforts to consult with our best scientists, with those in the Public Health Service, NIH, and especially, in FDA. This process where the judgment of the best scientists supported the particular approach DOD proposed, resulting in the dosages that were made available in the kits. To completely repackage and to create, for the hundreds of thousands of troops being deployed into

the desert, new dosages or modifications, in the press of war, was not considered a viable option.

So essentially, the answer to your question is that in the face of those circumstances, we made the best scientific/medical judgment that could be made, consistent with the safety of those troops in the situation it appeared they were facing.

Chairman ROCKEFELLER. So, the fact that you used the same dosage for women as for men, even though women would usually be much lighter and smaller, and therefore the effect of the dosage stronger, is reflected within your answer.

Dr. MARTIN. Yes, sir. The dosage we were using was about 15 percent of the dosage normally used in myasthenia gravis. Those considerations were looked at in that particular scientific review. You have got to remember that this particular agent is to be administered by the soldiers or marines themselves. It was prepackaged in kits and issued as the soldiers, marines, sailors, and airmen were being deployed into the Gulf. It was not logistically possible to redo the PAM, hydrochloride, atropine, and pyridostigmine kits that were integral components of the chemical defense capability, which also included gear. There were such discussions, but the ultimate scientific and clinical judgement was to use that which was prepackaged and then available to all the soldiers in the field.

Chairman ROCKEFELLER. Again, just for the record—you brought up myasthenia gravis. That is a neurological disorder, is it not?

Dr. MARTIN. Yes, sir.

Chairman ROCKEFELLER. And therefore has nothing to do with what we're talking about.

Dr. MARTIN. I defer to Dr. Temple in discussing the degree to which the use of pyridostigmine as an effective pharmacologic agent has to do with work on myasthenia gravis, and the judgments, scientifically, that were made in the context of that determination. My expertise is not the pharmacology of pyridostigmine or the basis of the scientific determination. So I defer to Dr. Temple on that matter.

Chairman ROCKEFELLER. OK. We will defer to Dr. Temple. Go ahead, Dr. Temple.

Dr. TEMPLE. We thought that the extensive experience in myasthenia gravis was relevant to the safety of pyridostigmine. Myasthenia gravis is a neuromuscular disorder in which the body makes antibodies to a critical component of muscle reaction. We certainly anticipated that the response of the muscles of a person with myasthenia gravis and the response of the muscles of a normal person might be different; we expected that normals would be more likely to get muscle cramps and twitching. But with respect to other responses, we thought that a myasthenic patient would be a reasonable surrogate for an ordinary, normal person.

The ordinary dose of pyridostigmine in myasthenics is about 600 milligrams per day, but dosage recommendations go all the way up to 1,500 per day. So the dose being administered for nerve agent protection to normals was somewhere between less than 10 percent to 15 percent of the myasthenic, a very large safety margin.

Either now or later, I would like to comment more on the male/female question.

Chairman ROCKEFELLER. That's my final question before I turn to the Majority Leader. Again and again on these studies, DOD did them on men, but did not do them on women. Now, I can either say that women just did not happen to be included or I can say that women were excluded from these tests of pyridostigmine. I would like to have your response.

Dr. MARTIN. Mr. Chairman, it is very clear that the attitude about the use of women in combat has changed fairly dramatically in the last decade. When pyridostigmine was developed, fielded, and the training manuals developed in the late 1970's and early 1980's by NATO and the United States, there was a very clear policy that women were not in combat or direct combat support units. By the time we were in Southwest Asia, and even more so now, that policy has changed.

So, if the question to DOD is, now with the very substantial number of women potentially exposed to these kinds of threats, will DOD, working with FDA, begin to look at different populations, the answer is distinctly yes.

Chairman ROCKEFELLER. Diana Zuckerman, who sits at my right and who is responsible for this investigation, says that the DOD studies were done in the late 1980's, not in the 1970's.

Dr. MARTIN. The most recent studies were done in the late 1980's. Again, the policy was still extant. The troops in combat—we were looking at World War III in Europe—were the troops that we were going to need to protect. In the scenarios that we were looking at in 1986, 1987, and 1988, those troops were largely healthy males. In fact, in forward-deployed combat units, there was no anticipation that women would be serving. Now, given what happened in 1991, if we did that study again today, we would very clearly not exclude women.

Chairman ROCKEFELLER. But then I can understand from what your statement implies that women were intentionally excluded from the DOD studies.

Dr. MARTIN. By design, the original DOD studies did not include, intentionally, women. Yes, sir.

Chairman ROCKEFELLER. The Majority Leader, Senator Mitchell.

## OPENING STATEMENT OF SENATOR MITCHELL

Senator MITCHELL. Thank you very much, Mr. Chairman. I appreciate your courtesy and that of the other Committee members. I am involved at the moment in managing legislation on the Senate floor and will have to return there. But I wanted to come to convey, first, my sense of gratitude to you and the members of the Committee for this inquiry and this hearing, and also my own sense of the great importance of the subject that is being discussed here, and to impress upon those Government officials present the very heavy obligation that we all have in this matter. The American people want to know, and will insist, that the Defense Department, the Department of Veterans Affairs, and all Federal agencies are responding promptly and adequately to the medical and compensation needs of affected veterans and their families.

Last week the statement following the National Institutes of Health's assessment workshop on the Persian Gulf experience and health again could not pinpoint any specific cause of the health

problems affecting Persian Gulf War veterans, but did express belief in the reality of the health problems being suffered by those veterans. The conference called for continued research into several areas, and it was critical of the Government's response so far.

What is clear and should be without doubt is that this Nation has an unshakable obligation to pursue vigorously and with diligence answers to the question of what caused these illnesses. This Nation has an obligation to provide the best medical care possible to every veteran whose life has been altered by virtue of his or her service. A democratic Nation can ask no greater sacrifice of its citizens than that some should risk their health and lives for the sake of the rest of us who risk nothing. Our Nation owes to those individuals the very highest standard of leadership, and the first requisite is total honesty and forthrightness.

Americans have been shocked to learn in recent years that United States citizens were intentionally exposed to mustard gas and radiation without their knowledge or consent during federally sponsored research programs in the 1940's and 1950's. This Committee, under Senator Rockefeller's distinguished leadership, is concerned that military personnel may still be exposed to dangerous consequences without adequate opportunity for informed consent or any systematic attention to the individual's long-term health.

It is, of course, in some respects unfortunate that much of man's scientific and technical knowledge has been directed toward the construction of weapons of destruction. But it is a reality. Clearly, there is a distinction between exposure to environmental hazards on the battlefield and deliberate exposure in Government-sponsored research. But in all cases, it remains unacceptable that any American soldier or sailor or marine or coast guardsman or any other person that our Government has knowingly exposed to dangerous substances would be unable to receive compensation because their medical records were missing, difficult to obtain, or incomplete. It is unacceptable that medications with unproven efficacy and safety are administered to our troops without adequate monitoring, followup research, and medical care. That seems to be the case with many individuals who were participants in the mustard gas experiments.

I think we must all remember that if our Nation fails to meet its obligation to those who have served in times of crisis in the past, it will be unable to summon those needed to serve in times of crisis in the future. If our military forces are seen as willing to subject their members to the worst of hazards without accepting the full responsibility for the consequences, it cannot hope to attract the men and women it needs and our Nation needs to defend us in the future.

Mr. Chairman, I ask unanimous consent that the full text of my statement and some written questions that I have for members of the panel be placed in the record. And I again thank you for your courtesy in permitting me to make this statement.

[The prepared statement of Senator Mitchell appears on page 64.]

[Written questions from Senator Mitchell to the Department of Veterans Affairs and the responses appear on page 184.]

Chairman ROCKEFELLER. Senator Mitchell, I thank you very much. And I thank you for taking the time to come to this Committee hearing. You always do because of your deep concern for veterans, not

only in Maine, but across the rest of the Nation. We all understand that you are in the middle of a tangle on the floor.

Senator Daschle.

Senator DASCHLE. Thank you, Mr. Chairman. Let me commend the Majority Leader for a very strong statement and for his contribution over the years to this particular issue. He made a point of noting that the American people expect the highest standard of leadership measured in honesty and forthrightness when it comes to these issues. I only wish he would have had the opportunity to be here earlier, because I think the testimony was unanimous in that we are failing to meet that standard today. It was unanimously critical not only of the legal interpretation of veterans' current position, but unfortunately, the attitudinal response that they get when they seek assistance.

I would begin by asking Mr. Vogel if he would have some response to the testimony that he heard this morning.

Mr. VOGEL. I would be delighted to, Senator Daschle. Dr. Mather is with me from the Veterans Health Administration. I would defer to her with respect to medical treatment. She is far more expert on that than I.

If we haven't learned anything else in the history of this country, I think we know that actions taken with good intentions are not always without adverse consequences. We have learned in retrospect that veterans who have endured the hazards of combat and service to their country, and have been able to escape what would traditionally be considered a war wound, in fact can leave the service with other wounds, psychological as well physiological.

We know about the health consequences of mustard gas and lewisite. We have in place mechanisms to provide compensation for those individuals and, in addition to that, medical care and rehabilitation services.

When we first began to look at claims from veterans of the Persian Gulf claiming exposure to environmental hazards, the first thought that came to our mind was the exposure to pollutants from the large oil fires. As time went on, it became fairly obvious that some of the health problems were likely attributable to some other environmental agents or causes. We broadened our own investigations about what those causes might be.

Almost 700,000 individuals served in the Persian Gulf during Operation Desert Shield/Desert Storm. About a little less than half of them have been discharged from the military; 300,000 have been discharged. About 10,000 receive VA disability compensation from us for a number of conditions, a lot of which are directly service-connected. In other words, an event happened—shell fragment wounds, vehicular accidents, or such things. So we have dealt, we think, forthrightly with those individuals.

VA, I might point out, has assumed, and Jesse Brown wanted to assume, the position of coordinator of all federally funded research into the possible health effects of veterans who served in the Persian Gulf War. There are over 20 Persian Gulf-related research activities being undertaken now by the Federal Government. We're collecting data to identify patterns of disability claims sharing common environmental factors that may help us to point to the potential cause

of the health hazards that they are experiencing.

Senator DASCHLE. Mr. Vogel, let me just stop you there. You are giving me, with all due respect, a very bureaucratic answer to what I think was an outpouring of emotion and personal experience this morning that I think deserves better than that. Obviously, VA has a responsibility to provide the best possible research in order to make the best possible decisions with regard to both care and compensation. We understand that and we applaud VA for the work that they have done in research.

In the meantime, much as we saw with Agent Orange, there is an equal obligation to give the veteran the benefit of the doubt both for care and compensation. And in that regard, I think VA has failed miserably. I think it is very important for us to listen to what we heard again this morning with more empathy, with more understanding of the consequences of that failure, than your answer would have indicated for the last couple of minutes.

What I would like you to do, if you could, is to address those specific concerns. Were you as concerned as I was about the attitudinal problems that these people confront every time they walk into a hospital? Are you as concerned as I am by the fact that hundreds of people are out there daily seeking care, and not one of them apparently is getting the kind of responsiveness that we would expect from VA? Does that concern you?

Mr. VOGEL. Senator Daschle, I have good ears and I have a good heart. I heard them. I think VA is doing what we can to respond. An operation run by human individuals sometimes fails. We let ourselves down; we let our veterans down.

The gentleman from Virginia, Mr. Mills—while we spoke, a member of my staff called the Roanoke Regional Office, and I was briefed on exactly what Mr. Mills' concerns are. We know we have a bottom line answer to his compensation needs. We have a rule in place that allows us to service connect laryngitis and soon will have a rule to service connect laryngeal cancer.

Senator DASCHLE. Have those answers been provided?

Mr. VOGEL. No.

Senator DASCHLE. Well, if you have the answer, what is keeping you from giving it to these people directly affected?

Mr. VOGEL. I heard Mr. Mills this morning, Mr. Daschle.

Senator DASCHLE. Why does it have to take John Vogel to respond to Mr. Mills? That's my point. He shouldn't have to come to a hearing in the United States Senate to get redress of the problems that he has had for years.

Mr. VOGEL. You are absolutely right.

Senator DASCHLE. That is the problem we're talking about here. And as I said, you and all of the people that work with you are good people, well-intentioned. And I am sure, as you said, you are motivated by the right reasons. But there is something seriously wrong here. When good people, well-intentioned, in there for the right reasons, listen to the testimony that we had this morning and fail to respond, then there is something wrong with the system. And working with you, we have got to find a better way to address it.

How many more lessons do we have to learn? We have gone through this decade after decade. I personally have gone through it,

and the Senators at the dais today have experienced similar situations. Yet, here we are again, 1994, a different set of lists, a different set of veterans, but exactly the same kind of bureaucratic irresponsibility when it comes to solving the problems that they have presented.

Mr. VOGEL. Senator Daschle, I applaud you. Your leadership is legend on the Agent Orange issue. You will not see, Americans will not see, anything less than a vigorous response to Persian Gulf veterans' health and compensation issues.

Senator DASCHLE. Mr. Vogel, I wish I could believe that. You can't sit there this morning and say that with any legitimacy. I honestly wish that you could come and prove that to me. The only way I can be shown that that is actually the case is if the next time we have a hearing, veterans like we have heard this morning come and say, you know what, I want to stand up and I am here to tell you VA is doing everything possible beyond my expectations in responding to the problems I have, because they understand. I haven't heard that yet. That is the problem we have.

We can talk about research, but frankly that doesn't cut it. What I want to know is how we are going to give these people the benefit of the doubt until these problems are resolved, either through research or through compensation. But nonetheless, we simply can't allow the constant parade of veterans with the humiliation that they have had to face and the inadequacy of care and responsiveness that they have had from VA, and then have somebody come and say, well, we're doing the best we can.

I have said enough. Mr. Chairman, I know there are a lot of other questions, but obviously I think we have got a lot of work to do.

[Applause.]

Chairman ROCKEFELLER. Well, Tom Daschle, you are a Vietnam veteran and you know whereof you speak. So I appreciate your line of questioning.

I turn now to Senator Jeffords from the State of Vermont.

Senator JEFFORDS. Thank you, Mr. Chairman. I appreciate the comments of my colleague, Tom Daschle. We worked together on Vietnam problems with Agent Orange, and I respect your leadership now.

My question goes to Dr. Martin. You heard Dr. Caplan testify earlier about the difficulties he perceives in trying to go back and determine what happened, especially with the anti-nerve gas pills. What can you tell the Committee as to what the policies were, any information that researchers could definitely discern as to who was given the pills and when they were given the pills, whether everyone was required to participate, and those kinds of things, which Dr. Caplan at least seemed to indicate were not available. I would first like you to comment on if there are such records where we can be assured what was done—especially since I believe the Committee staff here was briefed before the Gulf on what might be done—and whether there were changes in that, so that we get a better idea as to whether or not there are available data to give us information that is important to discern the ethics as to how things were conducted.

Dr. MARTIN. I think you raise three questions. In regards to the ethical and legal issues, this was a much debated topic in 1990. There

were people who felt very strongly that it was unethical for us to provide pyridostigmine, or, in fact, many of the protections that we did provide in the Gulf. The purpose of the medical/scientific/ethical evaluations with FDA and NIH were specifically to deal with those concerns. Subsequently, a decision was reached based on the circumstances those troops faced. The basic ethical question was framed: What is the ethical alternative? Given that there was a very distinct possibility of substantial nerve gas exposure by troops, the most ethical decision was to provide the protections that we did. That decision was tested, as I think the Committee is aware, in the judicial system, both in district court and the circuit court. That sort of complex ethical/legal issue will continue to occur.

The points made about whether or not we met our obligation, given what we did, particularly with Dr. Caplan's and Dr. Callender's testimony, were raised also at the NIH conference. The assumptions about pyridostigmine, which the FDA representatives can discuss better than I, deal with what we attempted to do. In fact, there were a whole series of after-action evaluation surveys, including over 40,000 troops, dozens of questionnaires, and evaluations of individuals who got the "bot tox" (botulinum toxoid). The point that Dr. Callender was making, and it is a point also raised at NIH by other people, is there may have been a series of interactive considerations that we didn't know then, and don't know now. It is very clear that the Public Health Service, VA, and DOD included, among the things that are being looked at now, and will be looked at more deeply, both the more comprehensive evaluations that Dr. Callender was suggesting in multiple chemical sensitivity, and, possibly pyridostigmine, as well as the kind of research that was mentioned today.

The veterans here have said, and hundreds more are saying, that we don't have good scientific or medical responses for the concerns that they have raised. I think that is a de facto determination. In retrospect, what we did, in regards to the evaluation, certainly is not adequate, given the test that Senator Daschle laid out. There has been substantial commitment by the Secretaries of the three Departments to be far more aggressive in finding answers, yet still be open and sensitive to the needs of the patients.

We are now "after the fact," in a very different environment, and we're not facing the Iraqi Army; we are in 1994. The important ethical question is: Are we doing those things which would be appropriate and proper even if we had used those drugs for treatment, that is, effective followup and better determined processes to find the answers. I would have to suggest that until, as was suggested, there are no longer veterans coming here to say they are not getting answers to their concerns, corporately we are not doing what you should expect of us. Indeed, DOD, VA, and the Public Health Service feel very strongly that we need to do a great deal more.

We are struggling within the limits of our knowledge and capabilities to try to find what those answers are. I think we heard some very good suggestions this morning, particularly from Dr. Callender. Indeed, they are very consistent with a discussion we had yesterday among representatives of all the Departments. We

discussed how we are going to proceed in evaluating the new evidence that is coming out on things like pyridostigmine.

Senator JEFFORDS. I am not sure you answered my question as to who received it, who didn't. The problem we are going to be worried about, as the people testified this morning, is proof of claims. They are being told that there is no evidence that there is anything to do with it being service connected, basically. Then we hear the experts say we really don't know because nobody knows who took what, when, and what percentages, is there a control group out there, people that didn't get it, are these things normally that occur in life anyway and they just happened to be coincidentally in the circumstances. None of those questions can be answered.

So our Committee has to wonder as to what we have to do, if there is that kind of a mess out there, to make sure that the burden is shifted to the Government to prove that it is not service connected, rather than the other way around. I am not at all convinced right now that there is any way that the facts are out there, available, wherein there is a defense of the VA that they can say we know because of statistical evidence and so forth that it is totally unlikely this is service connected.

Dr. MARTIN. I can try to answer the first part of your question again, Senator. My apologies. In regards to pyridostigmine, it was not intended, nor is there a record of the hundreds of thousands of troops that got pyridostigmine. This is so for the simple reason that it was almost always self-administered, and administered in the environment. So there was no intention nor was there a record of pyridostigmine administration by individual soldiers.

There were a series of studies and evaluations of who got it and what they thought their responses were, which were collected. We provided to the Committee some that we have provided to the FDA.

Senator JEFFORDS. Was it just generally that everybody should take it? Was it distributed and said that everybody should take it, regardless of where they are in the war zone?

Dr. MARTIN. No, sir. Basically, it was a part of a chemical protection system that each soldier, sailor, airman, or marine had with them. The final determination of whether they should actually take pyridostigmine was made by the responsible unit commander at whatever level. So, for example, it could be a company or a battalion or even a squad commander who directed the soldiers to take pyridostigmine.

Senator JEFFORDS. Is there any record of who gave orders?

Dr. MARTIN. Essentially, General Schwarzkopf gave authority to the commanders at the senior levels, and they delegated down very low in their respective commands to the actual combat leaders in the field. They left the decision up to commanders at levels as low as a company or a squad. Certainly at the Wing level and higher, the decisions were made by those commanders. Some units, particularly those close to the Kuwaiti or Iraqi borders, pretty consistently used pyridostigmine, and certainly those units under regular or possible SCUD attack did. But those were military decisions left up to military commanders in the field.

Senator JEFFORDS. I am not trying to be critical, I am just trying to get information. Was there any requirement to report when it was ordered to be given?

Dr. MARTIN. No, sir.

Senator JEFFORDS. Let me turn to Mr. Vogel. I am concerned about the treatment now of the individuals who testified today, as well as others more generally. Has VA yet given the symptoms associated with Gulf War service a name or diagnostic code?

Mr. VOGEL. Senator Jeffords, on the environmental front, we have a number of individuals who claim disabilities caused by environmental agents. One of the raging debates is whether or not there is a condition that can be recognized and evaluated called multiple chemical sensitivity. The scientific community has not agreed that that can be utilized across the board as a discrete diagnostic entity for which we can provide compensation. We do have guidance out and we have recognized—

Senator JEFFORDS. The answer then is "no" at this point.

Mr. VOGEL. Not to that. Chronic fatigue syndrome is something that we have seen in Persian Gulf veterans. There is guidance out on that. We are able to evaluate that condition. A number of individuals who we think have environmentally induced ailments can, in fact, be service connected based on the chronic nature of their condition, the most common one being a respiratory ailment. We can provide compensation for respiratory ailments. Skin disorders and such things are the kinds of things that we're seeing in the environmental hazard cases for which veterans make claims for disability compensation. About 3,500 such claims, Senator Jeffords, have been made based purely on environmental hazards.

Senator JEFFORDS. How many have resulted in compensation being awarded?

Mr. VOGEL. Only about half of that number have actually been decided. And of that, about 300 have received service connection for disabilities related to service. A common reason for the nonreceipt, if you will, of compensation is when we examine the veterans—they specify no disabilities in some cases. In all cases we examine the veteran, but don't find a residual disability in a large number of them.

Senator JEFFORDS. Thank you, Mr. Chairman.

Chairman ROCKEFELLER. Senator Jeffords, thank you very, very much.

Dr. Temple, I want to follow up on a point that Senator Jeffords was questioning Dr. Martin on. As part of the IND [Investigational New Drug process], the Department of Defense promised to gather information about the safety and the efficacy of the investigational products, both pyridostigmine bromide and also Botulism vaccine. But they conducted surveys instead of obtaining more objective data about safety. Is that appropriate for an IND?

Dr. TEMPLE. Just to be clear on one point, there was no possibility of assessing the effectiveness of pyridostigmine under the circumstances because there was no nerve agent distribution. Let me turn to the safety assessment carried out. We saw the Department of Defense's plans for followup and evaluation by survey and considered it, and we accepted that as the best that could be done under the

circumstances, where there was no one-to-one, patient-to-doctor relationship leading to drug use. I think it could perhaps be argued that there might be some better way of identifying each specific person who took the drug, e.g., with a card to be filled out at the time use is started, but we accepted the idea that under battlefield circumstances, where whole companies would be asked to take the drug, that was not realistic. You are supposed to learn from experience, however, and we might think differently another time.

It is notable, to me anyway, that the survey results described in JAMA [the Journal of the American Medical Association] by DOD people actually reported a somewhat higher than expected rate of adverse reactions, despite the limitations of their survey methodology, and raised a couple of issues worth pursuing, including the possibility that some people have hypertensive reactions to pyridostigmine.

Chairman ROCKEFELLER. Was that at about a 50 percent rate?

Dr. TEMPLE. The 50 percent rate refers to gastrointestinal distress. We expected that there would be gastrointestinal reactions to pyridostigmine. That is one of the predicted reactions. The rate of them surprised me a little bit. I would have thought at these doses the rate would be somewhat lower.

One of their principal ways of determining what important events happened was to see how many people came to medical attention with some associated reaction. It was a very small number. And only 28 people had to have the drug stopped because of an adverse reaction. The theory of the analysis was that people who get into trouble or have significant discomfort will come to medical attention, and you can assume anyone who doesn't was doing reasonably well. The optimal way to discover what the adverse reactions to a drug is, is to interview every person exposed and to have a control group. There was no control group in this setting, and, of course, each person exposed was not specifically interviewed.

Chairman ROCKEFELLER. In preparing for this hearing, this number of 28 has boggled my mind just a little bit. No women, exclusion of people who would have bad reactions to this vaccine, only 28 men in some of the studies, and based upon what came from that, the distribution of pyridostigmine to 400,000 soldiers. I am really curious, and maybe this is more for Dr. Martin, as to why 28 people constitute enough people for a study.

Dr. TEMPLE. No, that is not what I am describing. The report in JAMA by Keeler and coworkers described exposures of about 40,000 people and then observed, I think, 28 people had to stop therapy because of an adverse reaction. That is what that refers to.

Chairman ROCKEFELLER. OK.

Dr. TEMPLE. You have raised a number of issues. Let me describe how we saw the situation at the time we were asked whether widespread distribution seemed appropriate. We did not think of pyridostigmine as an untested drug. It had been used for many years in the treatment of patients with myasthenia gravis at, as I said before, very large doses in both men and women.

Chairman ROCKEFELLER. And not mixed with anything else.

Dr. TEMPLE. Well, no. I think people with myasthenia have whatever conditions other people have, so concomitant use would occur.

Chairman ROCKEFELLER. I mean, there was no other drug that was co-used with that.

Dr. TEMPLE. Not in any specific way, certainly. Widespread use of the kind that occurred with myasthenia isn't the same as observations taken in clinical trials, but the drugs had been around for decades and adverse reactions were known and predictable. There is also a mountain of animal data on pyridostigmine and its close relative, neostigmine. Anyway, I am just saying that the drugs were not thought to be mysterious or unknown. They were thought to have reversible, predictable effects that were entirely expected from their known pharmacology and from their effects on the enzymes they were known to inhibit, so we did not have a high index of worry there.

Since the dose being given was very low compared to the dose that had been given before, we did not have major worry about differences between men and women, because the dose being used seemed to be way below the doses that are toxic.

Sometimes, of course, you learn things when you expose several hundred thousand people that you didn't know from exposure of several thousand, so you do have to be prepared to learn something you didn't know when you expand use of a drug. Nonetheless, as I describe, as well as I can, our state of mind about pyridostigmine, we were not highly worried about this drug because there was a very long history of use and, as I said, mountains of animal data.

The antidiolinesterases are interesting compounds and they have been extensively studied for decades. Their pharmacologic effects are thought to be well understood. For example, you know you are going to get stimulatory gastrointestinal effects with nausea, vomiting, cramps, diarrhea, things like that, and blurry vision. Those are expected. What would be not expected would be for those effects to persist because they are thought to be reversible. So, finding these effects in the acute setting is not news. If somehow the drug led to a prolonged effect of the same kind, I would have to say that I would be surprised; that would be news.

Chairman ROCKEFELLER. OK. I am going to pursue very systematically and methodically a line of questioning to the Departments of Defense, VA, and FDA.

Before I continue, I want to say that this Committee would not be able to operate in any way, shape, or form with any effectiveness without the services of Senator Frank Murkowski of Alaska. He obviously would be here but for the fact that he, like Senator Mitchell, is responsible for some legislation which is taking place on the floor right now. So I want John Moseman, who is senior staff for the Republican side and for Senator Murkowski in particular, to feel free to ask any questions that he wants to as we go along. Do you want to ask one now?

Mr. MOSEMAN. Just a brief question.

Chairman ROCKEFELLER. Please go ahead.

Mr. MOSEMAN. Thank you very much, Mr. Chairman. I just have one factual question that arose from Dr. Martin's testimony. I thought I heard you say that the decision to use the drug would be a field decision once the troops arrived in the Persian Gulf. Yet, we heard testimony this morning from Colonel Tetzlaff that he actually

took the drug on the airplane over or somehow ingested it prior to arriving in the Gulf. How does that square?

Dr. MARTIN. The basic decision was a Central Command decision; it was left up to commanders. I can't comment on the specific case. My recollection of the testimony is that he was in an advance unit going into an area that might very well have been under attack, and a commander made the decision. Presumably it was his Wing Commander or someone in his chain of command. My point was that it was a military decision. And, appropriately, those decisions are left up to the military personnel in charge of troops, who base their decisions on their current assessment of potential risk.

Mr. MOSEMAN. The decision that the commander would make would have nothing to do with the medical notions about these drugs, but rather the expected exposure to incoming weaponry from Iraq?

Dr. MARTIN. Yes, sir.

Mr. MOSEMAN. Was there any training provided to the military commanders in terms of the potential effects of these drugs, in terms of troop readiness issues?

Dr. MARTIN. The official training manuals, which we assumed had been provided as a basis for training—not only of the commanders but also of the troops—include, for chemical warfare, training in the indications and the side effects of specifically pyridostigmine and other things. So that if you look at the training manuals, which we provided the Committee, the expectation is that not only the commanders, but also the troops know the indications and effects. What is clear is that in a number of cases, either commanders were not fully aware or they missed the training course. Certainly some number of troops didn't know about the implications or effects. But as a point of doctrine, there are specific training manuals and there is specific training, particularly on chemical weapons protection, because for two decades we had concern about the possibility of a chemical warfare attack in Europe as a part of a combined arms Soviet Union attack.

So my answer is that training was supposed to take place. I will point out that in a number of cases, commanders had not been aware of the specifics or the side effects of these protective agents. And certainly, a number of troops were not aware it. That is recognition that less than full application of training is what occurred.

Mr. MOSEMAN. If I may, just one more, Mr. Chairman.

Chairman ROCKEFELLER. Certainly.

Mr. MOSEMAN. Other troops were in the Gulf, including those from Great Britain, France, and other countries. Do we have any knowledge about their use of this drug or any other drugs?

Dr. MARTIN. The other nations did use the drug. There have been a couple of published studies, one a study of troops that was published by an Israeli group. In fact, pyridostigmine is widely used within NATO forces. There is apparently not, as far as we've seen, as much information or concern relative to the particular kinds of things that we're talking about here. I think this is because, in largest part, the numbers of participants were smaller. We are talking about hundreds of thousands of United States troops that used pyridostigmine. There was no comparable number from the other countries.

We have heard only anecdotally that in other countries, such as England, there are concerns about symptoms analogous to the ones that we are looking at. We are not the only country that is experiencing at least some degree of difficulty. We are obviously the largest and we have certainly had the most public discussion of it.

Mr. MOSEMAN. In terms of this particular drug, though, is there any attempt being made now by DOD to coordinate potential research projects with those other countries?

Dr. MARTIN. As a part of our membership in NATO, the whole process of lessons learned is a subject of discussion with those countries.

Chairman ROCKEFELLER. John Moseman, as questions arise in your mind, just feel free to let me know and interrupt and go ahead and ask them.

I am going to continue, Dr. Martin, and I am going to ask all of you. The questions have been fairly short; the answers have been fairly long. I understand that the ratio is necessarily that way, but some of the answers could be shorter. We have a lot of questions to go. I want to go through them systematically because I want to build a record on this. And to the extent that you can make your answers succinct, I would like to have them made succinct.

Again to you, Dr. Martin. Has DOD conducted any studies to see if pyridostigmine can make soldiers more susceptible to pesticides?

Dr. MARTIN. Not to my knowledge, but I will have to submit a more detailed answer for the record.

[The information to be provided appears on page 147, response to question 8.]

Chairman ROCKEFELLER. Are you aware of Dr. Moss' study of the possible dangers of combining exposures to pesticides and pyridostigmine?

Dr. MARTIN. No, sir.

Chairman ROCKEFELLER. But you will become so.

Dr. MARTIN. Yes, sir.

Chairman ROCKEFELLER. I was handed an interesting document which is based on FDA documents, and it regards pyridostigmine bromide studies conducted by DOD. What is interesting about it is that it shows, in virtually all cases, that very few people were actually studied in these individual investigational studies. It ranges from the highest of 133, but that is by far the highest; 39 is the next largest, and then it is 12, 12, 24, 5, 4, 4, 2. So that the studies that were done used only a very few human subjects. That is a point I think that needs to be made.

[Information about DOD studies of pyridostigmine bromide are presented in Appendix 6, beginning on page 245.]

Back to you, Dr. Martin. I really can't understand why so few military personnel seemed to have any information about the side effects of the investigational drugs that were intended to protect them. Medical personnel seemed to know nothing of the established adverse reactions. Can you tell us how that happened?

Dr. MARTIN. The proportion of troops that were not aware of the side effects, as I indicated before, is really unknown. We do know that there are significant numbers of people who were unaware of what the Department expected to be provided through the normal training.

This is particularly true of troops that are going to be exposed to chemical weapons. In regards to medical personnel, a number of very specific programs of education developed by us and FDA were provided to our practitioners in the field. In fact, we sent over a number of specialists in chemical warfare who trained several thousand of our providers over there. So, actually during preparation, there was a great effort to train our medical personnel. The proportion of people who were not aware of pyridostigmine side effects is unknown but, obviously, from what we have heard, it is not insignificant.

Chairman ROCKEFELLER. Some soldiers took the pyridostigmine bromide for 2 days and some for 2 months. There are no studies of the safety of this drug for healthy people for more than a week or two. Why didn't DOD conduct any studies evaluating the longer term safety of that drug?

Dr. MARTIN. There are two parts to the question. First, the expectation is that the troops would take it for 3 days unless another decision was made by the command. Each soldier is carefully provided with only 21 tablets, which is enough under the protocol to last for a week. If soldiers were on pyridostigmine for extended periods of time, that meant that the individuals responsible were getting new kits and providing them.

Very frankly, we had not anticipated a potential chemical attack for an extended period of time. The development of this particular set of protective approaches to chemical warfare anticipated a massive confrontation with the Soviet Union for a short period of time. It is fair to say that no one anticipated that we would have troops in imminent danger of a potential chemical warfare attack for months at a time. In retrospect, it obviously is planning that should be rectified.

Chairman ROCKEFELLER. You mentioned, in answering a previous question, that various levels of military commanders from squad level up were made aware of all of this. Were any of the health care workers in the Gulf War informed of the risks of pyridostigmine?

Dr. MARTIN. Yes, sir. We provided very extensive information to our medical staff. In fact, as I indicated, we sent over specialists to teach them about chemical warfare and treatment of chemical casualties. Whether or not there was a substantial problem associated with long-term usage of it was not a factor we had anticipated, and I have to defer to Dr. Temple relative to the science of whether that would even be a problem. We thought it was a fairly short-lived effect. Except for people who developed symptomology where, if it was significant, we should have stopped the pyridostigmine, I was unaware of any major concerns raised scientifically about the effect of taking pyridostigmine for extended periods of time. In fact, myasthenics do take it for extended periods of time. But I defer to Dr. Temple on the science of that.

Chairman ROCKEFELLER. I will also when I come to him. If we find out that pyridostigmine or some other of these investigational drugs turns out to be the cause of some Persian Gulf diseases, how on earth are you going to know who received them?

Dr. MARTIN. For pyridostigmine, there would be no record. For the other agents, specifically the botulinum toxoid vaccination, we gave

explicit instructions that records were to be developed and maintained. General Schwarzkopf went further and required that records be kept. So, theoretically, the Department should be expected to provide to the Department of Veterans Affairs verifications of those individuals and units where those vaccinations were undertaken. But, as you have heard, and I am sure you are aware, there will undoubtedly be some failures in that particular record system.

Chairman ROCKEFELLER. That answer was in complete sentences and everything. But it is my understanding that the Department of Defense has told us that records were simply not kept.

Dr. MARTIN. I don't know which part of the Department of Defense told you that records were not kept. I can't respond to who said that.

Chairman ROCKEFELLER. You have no knowledge of that?

Dr. MARTIN. I can say that, specifically, for the second IND substance, the vaccine, it is our clear understanding that, in the theater, General Schwarzkopf and the Central Command directed that records be kept, with Social Security numbers, and that, in fact, informed consent papers be signed. That was our understanding of General Schwarzkopf's instructions.

[See Appendix 11, page 442, for document regarding General Schwarzkopf's decision.]

Chairman ROCKEFELLER. I am informed that DOD officials who briefed Committee staff told them that some of the lists of names were lost.

Dr. MARTIN. I am unaware of that, Senator.

[DOD later notified the Committee that these lists are missing. See Appendix 3, page 148.]

Chairman ROCKEFELLER. A moment ago you mentioned the botulism vaccine. Again, that is intended as a protection against other kinds of biological warfare. But you had available only 8,000 doses of that vaccine. Now, if you were concerned that Iraq was going to use that kind of a biological weapon, what in heaven's name were you doing with only 8,000 doses?

Dr. MARTIN. One of the two or three top lessons learned that General Powell articulated in hearings subsequent to the Gulf War was the very substantial concern he had about our level of preparedness, and vaccine availability, for biological warfare threats. The simple answer to your question is that that situation should not have occurred, particularly for a known or possible threat. And we have been working very aggressively in the last 3 years to substantially improve the availability of those particular vaccines, including the investigational ones. We also have conducted more research and development in areas where we don't have effective bio defense capabilities, but we know certain biological warfare capabilities exist.

Chairman ROCKEFELLER. I believe the botulism vaccine needs to be given in three separate doses in order to become effective.

Dr. MARTIN. It is my understanding that a certain level of protection is provided with two doses, but the optimal is with three doses. I defer again to Dr. Temple on the science of that.

Chairman ROCKEFELLER. Dr. Temple?

Dr. TEMPLE. Well, I will defer to Dr. Goldenthal.

Dr. GOLDENTHAL. Most of the available data would be with three doses. The antibody response which would provide the protection has been extensively evaluated after three doses. With regard to two doses, I think it would be speculation to say how much actual protection would be provided. It is possible that there is some, but I couldn't give you anything quantitative on that.

Chairman ROCKEFELLER. The reason that I ask that is that most soldiers received only one or two doses. And the first one was not even given until late January 1991. So that, in effect, these soldiers would not have been protected when the war started and they were still not protected when the war ended because of this delay, not only the shortage, but then not being given the proper number of doses. Do you have an explanation of that? Incidentally, CDC [the Centers for Disease Control and Prevention] indicates that one or two doses just doesn't cut it; there has got to be three.

[The CDC document with this information appears on pp. 257-259.]

Dr. MARTIN. First of all, there were additional doses. The decision particularly on—

Chairman ROCKEFELLER. Excuse me, Dr. Martin. Reading from an FDA document, it appears that three injections are needed for detectable antibody titers.

Dr. MARTIN. The failure was in not having the "bot tox" early on in November or December, when it more likely would have been needed. By late January through February, the need to complete the inoculations, for this particular set of vaccinations, was determined within Central Command to be unnecessary. That would have been a decision by the theatre commander.

Medically, what we knew about the need to have three doses was communicated to General Schwarzkopf and the medical people within the theater, because it was an FDA IND drug. So it is supposition, but we can attempt to get more specific information for the Committee. It is my understanding that a determination was made not to complete the immunizations because of a modification in the risk.

Chairman ROCKEFELLER. I think, as my question indicated, they were started too late. You would certainly have to admit that.

Dr. MARTIN. Yes, sir.

Chairman ROCKEFELLER. I want to turn to Dugway for just one moment. We really haven't gone into that in detail even though we had witnesses on our first two panels involved with Dugway. The kinds of mistakes that we have revealed pertaining to investigational drugs in the Persian Gulf are apparently similar to the problems at Dugway. What research has DOD actually done to make sure that the simulants and investigational vaccines and drugs used there are in fact safe?

Dr. MARTIN. I became aware of those sets of concerns this morning. I am not an expert witness on that, but I can assure you that the Department will answer those questions for the record, since the questions that have been raised require answers.

[The following information was subsequently provided: The following vaccines are at Dugway Proving Ground under IND status: Q fever vaccine, Tularemia vaccine, Venezuelan Equine Encephalomyelitis vaccine, Clostridium botulinum toxoid, and one

antitoxin: Botulism Immune Globulin (F(ab)2), heptavalent, equine. All vaccines have completed Phase 1 Safety Trials under the requirements of the Food and Drug Administration. Anthrax vaccine is a licensed product and is also at Dugway Proving Ground. Botulism Immune Globulin (F(ab)2), heptavalent, equine is kept at Dugway Proving Ground as an emergency treatment but has never been used. Only two simulates, Bacillus subtilia var. niger (a bacterial simulant) and MS2 coliphage (a viral simulant), are now used in open air biological defense tests at Dugway Proving Ground. Bacillus subtilia var. niger is commonly found in soil samples throughout the world, and it is frequently aerosolized by winds and dust storms. It is identified in the CDC/NIH biosafety guidelines as a non-pathogen. MS2 is a picorna (small virus) bacteriophage. A bacteriophage is a virus that grows only in bacteria. MS2 is further classified as a coliphage, being a virus that will only grow in certain strains of Excherichia coli such as F+ strain. MS2 is found throughout the environment. It has been isolated in untreated sewage and in wastewater treatment facilities, where its host bacteria can also be isolated. Bacillus subtilia var. niger and MS2 have been handled in laboratories observing Biosafety Level 1 and 2 containment guidelines and released outdoors at Dugway Proving Ground. There have been no ill effects. All tests are conducted in full compliance with the National Environmental Policy Act.]

Chairman ROCKEFELLER. Thank you, Dr. Martin.

John Vogel, this morning Rudy Mills told an incredible story. I think it is just extraordinary. He basically said he would do it all over again. He doesn't want any money; he just doesn't understand why his country couldn't take care of him. In any event, it is a story that should never have happened. He was exposed to mustard gas 50 years ago. He has been paying the price for 50 years. He talked about it really in very humble terms, very muted terms. I think there was a lot of rage inside of him, but he was rather gentle even in the way he presented it. These tests were secret until 3 years ago. But for approximately 3 years, he has been trying to get the VA to admit that he has a service-connected disability.

You testified that the rule regarding cancer of the larynx is not yet final. When will it be final, and what can be done to help Rudy Mills and men like him in the meantime?

Mr. VOGEL. I agree with you, Senator Rockefeller, that Mr. Mills' testimony was very touching, very persuasive. It is people like him that make America the land that it is, his willingness to do what he did and willingness to do it again if he was called upon to do it.

The regulation that recognizes laryngeal cancer secondary to mustard gas exposure should be in effect by this summer. What happened was the National Academy of Sciences did a survey of literature and expanded a previously recognized list to allow that that be recognized. Laryngitis and some other such conditions are currently recognized; laryngeal cancer is being added on. So, by the end of the summer we should have the answer to his specific compensation issue, although I think, perhaps, we can do something on the laryngitis front in the short-term for him.

Chairman ROCKEFELLER. I think you have answered the question. I sure as heck hope that you will do something to help him in the meantime. I don't know what the end of the summer is, whether that is August or—

Mr. VOGEL. August I think. The final rule is out for comment and I think there is a 60-day mandatory period for final comment.

[Followup documents regarding this issue are presented in Appendix 11, pp. 443-447.]

Chairman ROCKEFELLER. Our Committee staff looked at the Defense Department studies of pyridostigmine bromide on healthy men. There were very serious adverse reactions reported even with studies of only 20 to 30 people, I have already mentioned that. Did anyone at VA ever read those DOD studies? If they did, they might have noticed that some men in these studies stopped breathing. Wouldn't that have caused some concern?

[DOD descriptions of these adverse reactions are presented in Appendix 11, pp. 448-452.]

Mr. VOGEL. Senator Rockefeller, I don't know about the review of the scientific literature. Perhaps Dr. Mather can respond.

Chairman ROCKEFELLER. Do you know, Dr. Mather?

Dr. MATHER. Yes. There has been review of some of those articles and we are aware of the serious side effects. I think the question that we have to ask is do these side effects persist after the drug is stopped. And that is a question that I simply don't know the answer to.

Chairman ROCKEFELLER. All right. In a survey of 146 Persian Gulf War soldiers conducted by our Committee staff, several reported that they knew of soldiers who had heart attacks after taking pyridostigmine in the Gulf War. How many Gulf War soldiers died from heart attacks during or after the war?

Mr. VOGEL. I don't know that, Mr. Chairman.

Chairman ROCKEFELLER. Do you know, Dr. Martin?

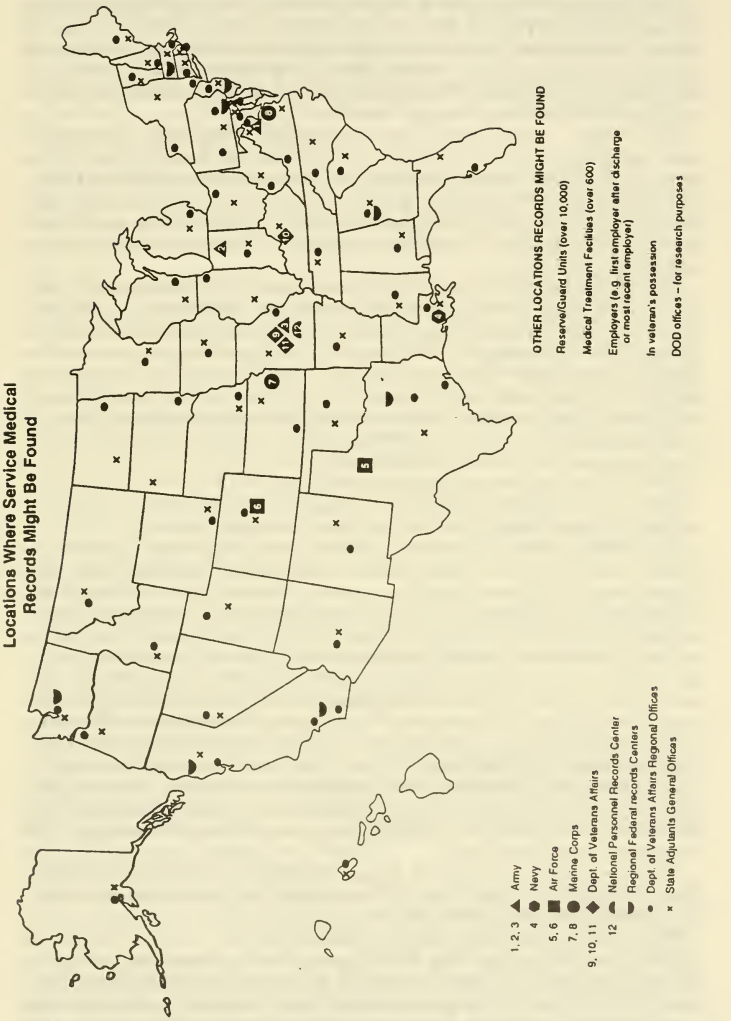
Dr. MARTIN. No, sir. We will have to submit that for the record.

[The following information was subsequently provided: Data from DD Form 1300, "Report of Casualty" indicates that during the Persian Gulf War there were 23 cardiac related deaths. The Department is currently conducting an Epidemiologic analysis of the mortality experience (all causes of death) of active duty and reserve veterans of the Persian Gulf War. The analysis will include calculation of Standardized Mortality Ratios comparing Persian Gulf War veterans to civilian populations and military populations that did not deploy to the Persian Gulf.]

Chairman ROCKEFELLER. One of the many frustrations faced by Persian Gulf War veterans who are sick is finding their medical records, and here we enter an interesting issue. There is a chart on the right hand side over there which takes the different branches of the services and it shows that the places where service medical records might be found are all over the country. It says 10,000 other locations exist where medical records might be found. Now, if there is ever a prescription for chaos and disaster, that is it. All over the country, as it is, for various groups, and then 10,000 more locations.

Secretary Brown informed the Committee that all Persian Gulf claims based on exposure to environmental hazards are sent to the Louisville Regional Office for processing. So a staff member called the Louisville VA Regional Office on behalf of a veteran who was looking for his records. However, our staff member was told that "the record could be almost anywhere in the world." After she mentioned that she worked for me, that is me as a Senator, she was told that perhaps they could narrow that down just a bit. [Laughter.] I don't find that funny. I assume this Regional Office processes these claims in addition to all other claims that are filed there. Is that correct?

[The chart displaying locations for medical records appears below.]



Mr. VOGEL. That is correct, Mr. Chairman.

Chairman ROCKEFELLER. I understand that 37 percent of all claims at the Louisville VA Regional Office have been pending for more than 1 year. I realize that is due in large part to the enormous growing claims' backlog that exists in regional offices generally, and John, you and I have discussed that before. How many of the pending claims at the Louisville Regional Office are claims for service connection based on exposure to environmental hazards?

Mr. VOGEL. I don't know the answer, Mr. Chairman. But when that number grows and outstrips our ability to handle them on a more timely basis than all the rest, we move other work from there. In other words, we have a priority for processing environmental hazard exposure cases. We adjudicate them in a manner quicker than the run of the mill—if I could use the term—disability compensation and pension claims.

Chairman ROCKEFELLER. GAO did a chart illustrating—and that is to the far right of me and to the left of you—20 examples whereby the Louisville Regional Office requested a medical record from the Army Reserve Personnel Center and is still waiting to receive the record months later. The chart indicates that these requests are not getting the attention they deserve. In fact, our staffer was informed that getting one's medical records could take months unless there is a congressional request, something which I find obnoxious, which then hastens the process considerably.

[GAO chart appears in Appendix 5, page 243.]

Why do we need congressional requests or chairmen of Senate veterans committees to find all of these missing records?

Mr. VOGEL. Mr. Chairman, it has been a long-term problem of getting records in a timely fashion. However, working with the Department of Defense, I think we are on the road to solving that. As of the beginning of this month, all recently separated servicemembers' medical records come directly to the VA; they don't go off into record centers that are run by the Department of Defense, they are given to us. We now have about 140,000 service medical records in our possession, primarily those discharged in the comparatively recent past. We still deal with records that are in archive centers. We do in fact have difficulty from time to time in getting records out of reserve units because they don't send them down to where they belong. To have to get the intervention of a United States Senator, not the least of whom is the Chairman of our Committee, is, I find, distasteful. We also know that squeaky wheels get the grease and sometimes you will do things to get the record.

Chairman ROCKEFELLER. I guess the objective is that the Rudy Mills' of this world ought to be the squeaky wheels as much as the Jay Rockefeller's of this world.

Mr. VOGEL. Absolutely. Before, I would say.

Chairman ROCKEFELLER. The chart refers to how you get your records. It is kind of a Rube Goldberg thing. On the left is the way it used to work. And if you are a veteran, that is what you would have to go through. And then it was modernized, and on the right is the way it works now. And that is simply to make a point, that for a veteran to get records in order to get compensation or to receive justice, it is unbelievably difficult. You would not disagree with that.

[The charts appear in Appendix 5, pages 227, 230, 233, and 236.]

Mr. VOGEL. No, I wouldn't, Mr. Chairman. Although I think it bears saying that the direct receipt of service medical records for currently separated members goes a long way towards alleviating an historic problem that that flow chart so graphically illustrates.

Chairman ROCKEFELLER. John Moseman.

Mr. MOSEMAN. Thank you. Mr. Vogel, are those records that you just referred to being computerized or are those still being maintained in a manual fashion?

Mr. VOGEL. They are still paper records.

Mr. MOSEMAN. Are you moving towards computerization?

Mr. VOGEL. We will, but we won't be able to image documents and have them retrievable until the completion of our modernization, which is probably 1997. We just are not ready technologically to do that.

Mr. MOSEMAN. On another set of records, the Congress, as I recall, mandated that the VA maintain a Persian Gulf registry and I am told that between 10,000 and 12,000 veterans—that is a wide range—have now received medical examinations at VA medical centers, I assume on a voluntary basis. When the veteran presents for a medical examination, are any questions asked as to whether that veteran took the kinds of drugs that we've been talking about at today's hearing?

Dr. MATHER. Yes. There are questions about the various exposures, medical exposures and environmental exposures.

Mr. MOSEMAN. But my question is, is there a question asked as to whether the veteran consumed the anti-nerve gas drug?

Dr. MATHER. In the first iteration of the registry examination process, we did not specifically ask how many. In the revised, we are going to. This has come up again and again and we are going to ask that question.

Mr. MOSEMAN. So you are going to be in the process of capturing some data about those veterans presenting with illnesses I presume.

Dr. MATHER. Yes, and about those who present who are well.

Mr. MOSEMAN. Or healthy veterans.

Dr. MATHER. It is a self-selected population.

Mr. MOSEMAN. Thank you.

Chairman ROCKEFELLER. Thank you, John.

Turning now to Dr. Temple. In their prepared statement, the Department of Defense claimed that their use of investigational drugs and vaccines in the Persian Gulf War was therapy, not research. But under the IND, the DOD was responsible for collecting data on safety and effectiveness. Is that not correct?

Dr. TEMPLE. That is correct.

Chairman ROCKEFELLER. Before the Gulf War, the Department of Defense was very careful in their research studies of pyridostigmine to eliminate all risks by excluding men with various medical conditions, and we've been through this before, or those who were taking medication of some sort. Then, as I indicated in my opening statement, they threw caution to the winds and gave 400,000 people the same drug without warning them about any possible dangers.

Do you have an opinion on this from the point of view of FDA's expectations for an IND?

Dr. TEMPLE. Let me start a little bit from the beginning. The question we were asked by the Department of Defense was whether we would grant permission for widespread distribution of a drug we consider investigational, specifically in the Desert Storm theater. And we needed to determine whether we thought, on balance, that such distribution was likely to do more harm than good in an attempt to protect soldiers from nerve agents.

What we had, with respect to whether it would be safe to do this, was a long history of apparently benign use of pyridostigmine in people with myasthenia gravis, both men and women, for long-term use and at very large doses. In addition, we had the modest amount of information that was gained from studies of the drug at much lower doses in soldiers. The principal purpose of those studies, as I understand it, was to see whether soldiers would be affected in ways that made them unable to function as soldiers; the studies also assessed the extent of cholinesterase inhibition that would occur.

So our conclusion that it was safe to distribute pyridostigmine in this way was based very much more on the long history of use and the extensive animal data than on any of the trials that were carried out. And as I said, that history reflected use in women, people of various sizes, young and old, that is, anybody who would have myasthenia gravis. We also accepted the idea that it would be difficult to obtain, for reasons Dr. Martin gave, individual exposure data in the war theater, and accepted as fulfilling the spirit of the regulations the attempts to do this by surveys and after-the-fact examinations. So we certainly agreed that those were reasonable measures to take.

Now, with respect to effectiveness, we do not believe that effectiveness against nerve agents in humans has been demonstrated. But, we believe that the evidence from rodents and larger animals makes it appear promising in this use, and we concluded that it was the best available treatment. That is, if you really believe that nerve agent exposure is a potential problem, and certainly DOD did, pyridostigmine was the only thing you could do in addition to giving out 2 PAM and atropine, which is part of the treatment of nerve agent exposure once it occurs.

Chairman ROCKEFELLER. Dr. Temple, in that we have already established that people with blood pressure problems, asthma, etc., were excluded from these studies, is there any other explanation for the reason of their exclusion than the fact that there was a very substantial reason for concern about their safety in the use of this drug?

Dr. TEMPLE. Actually, I can't answer that. It is possible Dr. Katz can.

[Documents describing safety precautions for DOD studies of pyridostigmine appear in Appendix 6, page 245.]

Chairman ROCKEFELLER. Why else would somebody exclude people who already had problems?

Dr. TEMPLE. It is perhaps regrettably typical in early studies of drugs that there are attempts to keep things very simple, that is, to try to pick people who don't have any other complications. We actually have been trying to discourage that approach, because if you don't study potential interactions, you will never learn about them.

I don't know whether they were particularly concerned about use in these people or not. The labeling for pyridostigmine does not suggest a particular concern, again for much larger dose, about most of those conditions. So I don't think the alarm would have been great. Perhaps Dr. Katz has something to add.

Chairman ROCKEFELLER. Before he does that, you referred just a moment ago to early studies. My understanding is that this is 10 years' worth of studies.

Dr. TEMPLE. Yes, but they are still early studies. We did not perceive DOD as trying de novo to establish the safety of pyridostigmine. We considered that largely established, again within the limitations that use experience can give you. We considered that established by the long marketing history of pyridostigmine in treating myasthenia. We were not expecting DOD to establish safety de novo. Now, it may be that enough questions have arisen that it would be worth thinking about how one could look at possible adverse reactions better. And if you want me to take the time, I have some thoughts on that.

Chairman ROCKEFELLER. I won't take the time now, but I do want your thoughts and I would like to have them in writing. I would very much like to have your thoughts about that.

Dr. TEMPLE. OK.

Chairman ROCKEFELLER. Who at FDA actually read the studies of pyridostigmine that DOD provided for the IND?

Dr. TEMPLE. This is before Desert Storm, you mean?

Chairman ROCKEFELLER. Yes.

Dr. TEMPLE. People in the Division of Neuropharmacological Drug Products. We would have different people reviewing animal studies and other people reviewing the human studies. Dr. Katz is deputy director of that division and can perhaps tell you more.

Chairman ROCKEFELLER. In that there were serious adverse reactions reported even in the small studies where many men were excluded, weren't these cause for concern?

Dr. TEMPLE. Let me ask Dr. Katz. I don't believe we thought there were serious reactions.

Dr. KATZ. Yes. There were certainly reactions seen. As you have mentioned, the population exposed in those studies was relatively small. I don't recall that there were terribly many reactions. We got progress reports on these studies as they were being conducted. I recall one reaction of a loss of consciousness in a normal subject who had gotten an infusion, that is to say, pyridostigmine intravenously. That occurred about 18 hours after the infusion was stopped, as far as I recall.

Chairman ROCKEFELLER. Are you referring to the 28-person study where one person stopped breathing altogether?

Dr. KATZ. I am referring to a patient who lost consciousness. There was one study in which a patient was rebreathing carbon dioxide before he even got pyridostigmine and had something that looked like a seizure and perhaps stopped breathing. But I don't recall that specific patient that you are referring to, unless it was that one.

Chairman ROCKEFELLER. Well, it is a different person and it is in the record.

[This study is presented in Appendix 11, pp. 448-452.]

FDA's list of adverse reaction reports for pyridostigmine is a very small one, just a handful of reports. Yet, even DOD reports that half of the Persian Gulf War soldiers who took pyridostigmine were ill. That is half—50 percent—were ill. What efforts did FDA make to ensure that adverse reaction reports are accurate?

Dr. TEMPLE. I missed the very first part of your question. Are you saying that our adverse reaction reporting system has very few reports?

Chairman ROCKEFELLER. In essence, yes.

Dr. TEMPLE. This is a spontaneous reporting system. People report to it events that they think are interesting and important. For a long-marketed drug, such events as nausea, vomiting, diarrhea would rarely be reported by a physician because it wouldn't be interesting. Those are already in the labeling.

We don't have control over that system, but, in general, we want physicians to report occurrences that are entirely new, or worse than previously seen and important. It is not a system that is designed to help you get the percentage of people who will develop an adverse reaction. You need very different kinds of studies for that.

Chairman ROCKEFELLER. Is it true that FDA is on the "honor system"? And if so, what does that mean?

Dr. TEMPLE. I am not sure what it refers to. I believe what the term is being used to refer to are what attempts we make to be sure that people operating under an IND actually do all the things they say they are going to do. And the answer is, we don't do very much under the IND. We carry out on-site inspections when data are submitted to us to market a drug, but while investigations are going on, we reach agreements with sponsors on what kind of monitoring they will do, and what kind of reporting to do, and then expect them to do it. Violations of those agreements are serious infractions and some would involve criminal penalties. But, we have nothing like the capacity to monitor the many thousands of IND's that we have or to actually do on-site inspections and see that reports are being made. There is no way to do it.

We do make sure that people submit the annual reports they are supposed to under the regulations. And if we were to hear that someone wasn't carrying out steps they had promised to take, we would certainly look into that. We also review IRB [Institutional Review Board] performance periodically. But the basic relationship between the investigator and the patient is just not accessible to us for the most part. It is in large part a resource issue. We have enough trouble looking at the data submitted to market drugs.

Chairman ROCKEFELLER. OK. And John, again, any questions you have, please interrupt.

As part of the IND, the Department of Defense promised to gather information about the safety and efficacy of the investigational products, both pyridostigmine and botulism vaccine. But they conducted surveys instead of obtaining more objective data about safety. Is that appropriate for an IND?

Dr. TEMPLE. Well, we agreed to those plans.

[Documents describing the agreements between FDA and DOD are presented in Appendix 9, page 347.]

So we did think it was the best that could be done under the circumstances. As I said, I can think of other kinds of studies to do if you thought you had a problem. You asked for them in writing, but let me describe my suggestion briefly. We spend a lot of time trying to persuade sponsors of drugs that more rigorous approaches to things will, even though they are more difficult and expensive, get the answer better in the long run. In this case, if after reviewing the available cases, including the possible long-term toxicity, DOD still believes that pyridostigmine is probably not responsible for those reactions and is safe for a 7-day course at 90 mg per day in normal people, there are ways to show that convincingly. DOD could randomize large numbers of people to either pyridostigmine or placebo, and assess the adverse reactions, blood pressure response, etc.

I would be the last person to disparage epidemiologic methods, but they are limited. There are certain things they will not tell you as well as a clinical study. And the kind of large, simple trial I suggested, so long as people were ethically comfortable with it, could pin down a definitive answer in short order and without too much expense. We didn't think such a study was necessary, given what we knew about pyridostigmine, but if that point of view is seriously challenged, there are ways of getting an unequivocal answer, an answer that epidemiologic approaches will have trouble providing.

Chairman ROCKEFELLER. OK. Now, you indicated that you let them go ahead with this, and that was your answer.

Dr. TEMPLE. Yes.

Chairman ROCKEFELLER. That being the answer, did you evaluate whether or not the Department of Defense kept their promises about informing people of the side effects of the investigational drugs?

Dr. TEMPLE. No, I can't say we evaluated their performance. We agreed with them on the distribution of the data sheet. We had some discussion about the field manual; we thought it was somewhat overpromising. We did not try to check about the distribution of the data sheet.

Chairman ROCKEFELLER. Was that again because of the honor system?

Dr. TEMPLE. I guess you would have to call it that. We have no real way to monitor that process. We can, of course—I don't want to overstate our helplessness here—we can ask people for evidence that they have done something, that is, records of distribution. We did not in this case.

Chairman ROCKEFELLER. Do you know whether there were increases, for example, in birth defects among veterans who took these drugs?

Dr. TEMPLE. No, I don't know. That would be very hard to discern, too, from available data.

Chairman ROCKEFELLER. CDC is looking into that. Do you know if there are increases in heart disease among veterans who took these drugs?

Dr. TEMPLE. No. I am not aware of any documented, long-term consequences. I realize that is a subject that is under discussion. Again, those are hard things to discern from the kind of data that is available.

Chairman ROCKEFELLER. I understand that the Department of Defense now wants the interim rule for waiving informed consent, which is a very large subject here, to be made permanent. If they failed to uphold their promises—and you have indicated you are not sure whether they did or not—to warn soldiers of the risks of the investigational drugs and to collect data on safety with the interim ruling, do you think they will uphold their promises with a permanent rule?

Dr. TEMPLE. That is a fair question, and I think we need to consider it in considering the permanent rule. But I don't think we have reached a conclusion as to whether they did or did not uphold their promises.

Chairman ROCKEFELLER. What is the status of the Department of Defense's new drug approval application, so-called NDA, for approval of pyridostigmine bromide for use to enhance antidotes against chemical weapons?

Dr. TEMPLE. It has been received and we recently sent out a letter with the unpleasant title called "Refusal to File." We considered the manufacturing and controls section of that application incomplete and have asked for more data. We actually are reviewing the other parts of the application, however.

Chairman ROCKEFELLER. That, for the moment, concludes the questions that I have. The questions have been very deliberate and very methodical, and there will be more of them addressed to each of you.

You may think it was appropriate to give pyridostigmine to Persian Gulf War veterans, but evidence today suggests that this was a crap shoot and that the veterans were the losers. You may think that it was OK to use Agent Orange in Vietnam, but the evidence grows that this, too, was a crap shoot and that the veterans were the losers. And so, it appears, it goes. Be it mustard gas or lewisite, radiation exposure and research, atomic veterans, Agent Orange, pyridostigmine, experiments at Dugway even today, it is very hard to figure out what to tell veterans.

I am a rather even-tempered person, and I suspect that by observing me, you would draw the same conclusion. My mind at this point goes back to a number of years ago, 5 or 6 or 7, perhaps 8 years ago, in my first year in the Senate, when there was an atomic war victim veteran who had made himself available for atomic testing, and he was sitting in a wheelchair in the process of dying. He described what it was like to die—to feel and to know that he was dying—in very soft and eloquent terms to the Veterans' Committee, which was then chaired by Alan Cranston. I will never forget the emotion that I felt at that time. His voice was very much like Rudy Mills', rather calm, quiet. You did not even feel the anger inside of him, because I think at that point that he had gone beyond that to the point of resignation and was, in fact, probably dealing with his own very imminent death.

Tom Daschle was angry when he was describing in his summation statement his feelings about the way veterans have been treated in this particular series of cases. We have talked about the Persian Gulf War for the most part this morning, but in fact we are talking World War II, that's Rudy, and we're talking about every single incidence of

war. Actually, at this point we don't know of examples from the Korean War, but certainly all others, and we have been talking about some other non-war activities as well during the last 50 years.

I just want you all to know that I have a very cold sense of anger, a very cold rage in me and it has not essentially changed a whole lot since I saw that veteran—of course, he's long dead—many years ago. To see a United States veteran describe to a veterans' committee representing the people of the United States what it felt like to die, and somebody who knew that he had offered himself experimentally in atomic radiation testing and then had been told systematically by his Government for 40 years that his illness was not a result of what he had done and that they bore no responsibility. It took legislation, which was in fact passed, to redeem that. It was not helped or brought forward by the Department of Defense, by the Veterans Administration, or by anybody else in the United States Government. It was people like Tom Daschle and John Kerry and others who did that.

I understand the way large bureaucracies work and I know that it is very easy for a Congressperson or a Senator to come to a hearing with a panel of people who work for Government and work very hard and long hours, and for that Congressperson or Senator to be angry at what they have done or what the agencies they work for have done. But it would seem that is the only way one gets things done. And so I just want to put all of you on notice that this new Chairman of the Senate Committee on Veterans' Affairs is capable of longly held, sustained rage, and that I don't quit. I may not show my emotions in ways that other people do, but I have them. I will not yield and I will not step aside and I will not back off until the kinds of problems we have been discussing this morning are settled in favor of the veterans. It does not mean that all cases that are put forward by veterans will be proved to be justified; life doesn't necessarily work like that. But one has the feeling of an overwhelming sense of neglect of people, as George Mitchell said, who have volunteered or been drafted in the service of their Nation, who are then literally cast aside almost as if chattel by the Government that they fought to protect.

So, this hearing will conclude now. But I hope that over this weekend and for many months to come, we will work together to resolve this problem—and we will work together. I recognize that you are people of good faith, and I said that in my opening remarks. But resolve this problem we will. That is the conclusion of this hearing.

This hearing is adjourned.

[Whereupon, at 1:47 p.m., the Committee adjourned, to reconvene at the call of the Chair.]

# APPENDIX 1.—PREPARED STATEMENTS OF COMMITTEE MEMBERS

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## PREPARED STATEMENT OF CHAIRMAN JOHN D. ROCKEFELLER IV

A few months ago, Americans were shocked to learn that our government had intentionally exposed thousands of U.S. citizens to radiation without their knowledge or consent. Although many of us expressed horror at the apparently unethical behavior of our government, we all were relieved to hear that such experiments had been stopped long ago.

We'd like to think that these kinds of abuses are a thing of the past, but the legacy continues. During the Persian Gulf War, hundreds of thousands of soldiers were given experimental vaccines and drugs, and today we will hear evidence that these medical products could be causing many of the "mysterious illnesses" those veterans are now experiencing. And for several decades, and continuing today, the testing of chemical and biological agents at U.S. military facilities has put soldiers and civilians at risk.

Today's hearing will examine the results of an intensive 6-month investigation conducted by Committee staff. The investigation focuses on Persian Gulf War veterans, but extends from World War II-era veterans to the present.

The results of our investigation showed a reckless disregard that shocked me, and I think they will shock all Americans. The use of investigational drugs in the Persian Gulf is especially troublesome. The Pentagon did studies of one of these drugs, pyridostigmine, in a cautious way before the war, excluding anyone who might be harmed by the drug. But, after protecting a few hundred men who volunteered for these studies, they threw caution to the winds, ignoring all warnings of potential harm, and gave these drugs to hundreds of thousands of soldiers with virtually no warnings and no safeguards.

If that wasn't bad enough, they administered these drugs and vaccines in such a way that there is a very good chance they wouldn't have even worked for the intended purpose. They would not have protected most soldiers from chemical or biological warfare.

These are strong statements and I don't make them lightly.

The situation is unfair from start to finish. It begins with soldiers who are asked to participate in research, or to take experimental drugs, but are not told what the risks are before, during, or after.

Then, information about the exposures is not included in soldiers' medical records, putting them at even greater risk. And, when these soldiers leave the service and become veterans, the VA lacks information about the exposures, and about any resulting illnesses, making it more difficult to help them.

Finally, when these veterans become ill, they are unable to get the medical records and other information they need in order to prove that their illnesses are related to military service.

This situation is unacceptable.

Our witnesses today include nationally respected experts and four veterans with very compelling stories of illnesses that seem to have resulted from intentional exposures they experienced while in the military or working for the military. Our witnesses also include scientists and officials from four federal agencies: the VA, DOD, FDA, and the Department of Agriculture.

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## PREPARED STATEMENT OF SENATOR GEORGE J. MITCHELL

Today this committee will continue consideration of the mysterious illnesses that plague many veterans of the Persian Gulf War. We will attempt to ascertain the adequacy of the Federal Government's efforts to determine the causes of those illnesses and to respond to the very real needs of veterans and their families.

The Persian Gulf syndrome will be one of the areas we will be examining while exploring the risks to veterans from their unwilling or unknowing participation in military experiments or exposures to potentially toxic substances or harmful medications, both in the past and currently.

Witnesses will include WW II and PGW veterans; scientists; and Defense Department, Department of Veterans Affairs, and Food and Drug Administration officials.

On the specific point of the health of Persian Gulf veterans, I commend the Chairman for scheduling this hearing and for his determination to provide a record upon which this committee may act on a very important subject. I note that the committee staff has been diligent and persistent in its pursuit of answers to the many outstanding questions about what is causing Persian Gulf War veterans so many health problems.

The American public wants to know that the Defense Department and the Department of Veterans Affairs and all Federal agencies are adequately responding to the medical and compensation needs of affected veterans and their families.

A number of causes have been suggested: disease agents, viruses and pests specific to the region; exposure to deplete uranium munitions; adverse reactions to the various vaccines and medicines given to military personnel in the Gulf by our own medical personnel; exposure to microwaves; air pollution; oil well fires and other petrochemical exposure; pesticides; and most ominously, exposure to chemical weapons—from Iraqi forces or from emissions from

destroyed Iraqi facilities or caches. Some theorize veterans may suffer from multiple chemical sensitivity syndrome from the combined exposure that make those affected highly sensitive to all sorts of allergens.

Last week, the statement following the National Institutes Technology Assessment Workshop on the Persian Gulf Experience and Health of Health again could not pinpoint any specific cause for the health problems affecting PGW veterans but expressed belief in the reality of the health problems being suffered by veterans. The conference called for continued research into several areas and was critical of the government's response so far.

As I've said before, Mr. Chairman, what is clear and without doubt is that this Nation has an obligation to pursue with vigor and with diligence, answers to the question of what caused these illnesses. The Nation also has an obligation to provide the best medical care possible to every veteran whose life has been altered by virtue of his or her service. We're here today to find out the progress that is being made on both fronts.

On the broader question of the possible exposure to military personnel from toxic agents, unsafe substances or environmental dangers, today's hearing is important. A democratic Nation can ask no greater sacrifice of its citizens than that some should risk their health, their limbs, and their very lives for the sake of all the rest, who risk nothing. Our Nation owes those individuals the highest standard of leadership—honesty—forthrightness.

Americans were rightly shocked over the past several years to learn U.S. citizens were intentionally exposed to mustard gas and radiation without their knowledge or consent during federally sponsored research in the 1940's and 1950's. This committee is concerned that military personnel may still be exposed to dangerous substances without adequate opportunity for informed consent or any systematic attention to any individual's long term health.

It is unfortunate that much of man's scientific and technological advancements has been directed into weapons of destruction. But it is a reality. And clearly there is a distinction between exposure to environmental hazards on the battlefield or inadvertently and deliberate exposure in government-sponsored research.

However, in all cases, it remains unacceptable that any soldiers and sailors that our government knowingly exposed to dangerous substances would be unable to receive compensation because their medical records were missing, difficult to obtain or incomplete. It is unacceptable that medications with unproven efficacy and safety can be administered to our troops without adequate monitoring, follow up research and medical care. That however, seems to me to be the case with many individuals who participated in the mustard gas experiments and in the Persian Gulf.

If our Nation fails to meet its obligation to those who have served it will be unable to summon those needed to serve in times of crisis in the future. If our military is seen as willing to subject its members to the worst of hazards without accepting the full responsibility for the consequences, it cannot hope to attract the men and women it—and we—need to defend this Nation.

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## PREPARED STATEMENT OF SENATOR DANIEL K. AKAKA

Thank you, Mr. Chairman. I commend you for holding this hearing today on the health risks of classified military research. I join you in welcoming the many distinguished witnesses who are testifying this morning on this important subject.

Mr. Chairman, revelations concerning the participation of service members in past medical experiments, often without informed consent, have persuaded many veterans to question whether in fact their illnesses may be related to the drugs or chemicals they were subjected to as soldiers. For example, World War II veterans who took part in secret mustard gas experiments, wittingly or unwittingly, long wondered whether those exposures could be related to conditions they later developed. It was only recently, however, after the existence of the experiments was acknowledged by the government, that VA issued regulations affirming service connection for certain disabilities based on poison gas exposure.

More recently, we have learned that hundreds of thousands of Gulf War veterans were provided investigational drugs to counteract the effects of biological and chemical weapons that we feared would be unleased by Saddam Hussein. Given this fact, many have considered whether there might be a causal connection between these drugs and the mysterious illnesses reported by Gulf War veterans.

For my part, revelations about the manner in which military experiments have historically been carried out, often without the full knowledge of the soldier-participant, and usually without adequate record-keeping or appropriate health monitoring, are additional reasons to assume that the mysterious ailments reported by Gulf War veterans are not the product of imagination or malingering, as some would have us believe.

As with the mustard gas victims of the Second World War, or more recently, those exposed to Agent Orange during the Vietnam conflict, the needs of our Gulf War veterans should no longer be questioned. It is time to rid ourselves of the self-serving doubts about the cause or even existence of Gulf War-related disorders. To achieve progress on this issue, we must assume that the problems are real, and marshall our concern and resources accordingly. In short, we should now focus our energies on providing quality care for these unfortunate victims of modern warfare, while continuing the search for the scientific basis upon which to build appropriate treatment.

Thank you, Mr. Chairman. Let me again commend you for your leadership on this issue. You have my pledge to work with you in ensuring that the Nation fulfills its obligation to those who served in uniform.

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## PREPARED STATEMENT OF SENATOR BEN NIGHTHORSE CAMPBELL

I very much appreciate the Committee holding this hearing. Today we will examine the Department of Defense's less-than-laudable record in experimentation on military personnel and how the government responded—or didn't respond—to the needs of veterans.

Even though the Gulf War is over, the pain and suffering of our veterans is not. I regularly hear from Persian Gulf veterans who are afflicted by strange and unexplained illnesses, ailments and complaints. The war is not over for them, and won't be for this Committee or for me until we get to the bottom of the Gulf War Syndrome and bring some relief to these veterans.

We don't need to wait for studies to know that these veterans are sick. Departments of Veterans Affairs and Defense seem to be saying: "It's all in your head. Go away." I want that to stop.

The question shouldn't be: "Are these veterans sick?" It should be: "How can we take care of these veterans quickly and equitably?" I insist that VA and DOD health care providers listen to our veterans so we can provide them the best health care even as we study what caused their illnesses and how we can make them better.

Last year Congress passed authority for the VA to provide health care for all Persian Gulf veterans on a priority basis. I thought this would mean veterans would be taken care of, but today we find out that care is meted out stingily, with suspicion and reservation.

The government should work with the same vigor to meet the health care needs of these veterans that the veterans showed in the Gulf War. Eligibility for benefits, access to health care and compensation have to be provided sooner, with less red tape.

I want to again thank the Committee for its interest in this issue and hope that the health and well-being of our veterans is now on the fasttrack to a resolution.

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## PREPARED STATEMENT OF SENATOR FRANK H. MURKOWSKI

I thought, Mr. Chairman, that we had learned a few lessons from Vietnam. I thought, for example, that we had learned that substances—like Agent Orange—thought to be harmless might later be found to be harmful. And I thought we had learned that the possibility of injury from so-called "harmless" agents compels that we be very careful to keep records on exposures to all but the most innocuous of substances.

Unfortunately, Mr. Chairman, I'm told that we will learn today that we did not learn the lessons of the Agent Orange debacle. I'm told we are going to hear today that soldiers were given an anti-nerve gas drug that everyone believes is harmless—but that the Department of Defense kept no records on who was given the drug.

All I can say, Mr. Chairman, is this: God help us if we later learn that that drug is harmful. We will never be able to tell who took it—and we will, therefore, probably have to presume that all 600,000+ servicemembers who served in the Persian Gulf did.

Finally, Mr. Chairman, let me just say that I hope that Persian Gulf veterans were not harmed by the medicines they were given to protect them from harm. But let them be sure that if they were, they will be cared for.

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## PREPARED STATEMENT OF SENATOR STROM THURMOND

It is a pleasure to be here today to receive testimony concerning possible effects on veterans health resulting from military research and the use of investigational medical products. I extend a welcome to our distinguished witnesses. This committee appreciates your work on this issue on behalf of al veterans, and we value your knowledge and expertise.

Mr. Chairman, earlier human research experiments involving biological and chemical agents are of concern. While that research was conducted in a different era, when there were no policies or regulations regarding human research subjects, we cannot ignore the consequences of that research. I am pleased that he Department of Veterans Affairs and the Department of Defense are taking measures to identify those consequences.

With regard to the use of investigational medical products in the Persian Gulf, I can say that the Department of Defense has been cooperative and responsive to the Senate Armed Services Committee. The Department has shown a great deal of concern with the health and well-being of Persian Gulf veterans.

Mr. Chairman, this hearing will help us better understand the consequences of military research and how DOD and VA are responding. I look forward to reviewing the testimony.

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## PREPARED STATEMENT OF SENATOR JAMES M. JEFFORDS

Mr. Chairman, almost 6 months ago the Committee first opened discussions relating to Persian Gulf War veterans and the illnesses they have encountered since they returned from the Gulf War. It is disturbing that we gather here again today with little new information on the causes of these illnesses.

While this issue has been widely discussed and researched in the last 6 months, there are still no concrete answers; in fact, there are probably more questions. But one thing is clear, some of our Persian Gulf War veterans are suffering because of unknown illnesses. I want to be sure that this Government does all that it can and is able to do to determine why it is happening and how we can help.

We ask our veterans to risk the ultimate sacrifice for our country, and they accept. Now it is our turn to make sure that those suffering because of their service are given the best treatment and our full attention.

I was a Member of the House of Representatives when the Government was trying to determine service connection for men and women exposed to Agent Orange in the Vietnam War. I saw these veterans and their families suffer because of the red tape and bureaucracy in our Government, with many veterans dying in the time it took for the compensation to be awarded to them. This cannot happen again.

I have long believed that veterans should be able to be given the benefit of doubt when they are obviously sick and need health assistance, and service connection cannot be proven. This is proving to be one of those times. I was a sponsor of a bill in the House of Representatives back in October of 1988 which would have established interim compensation to those veterans exposed to Agent Orange for non-Hodgkin's lymphoma and soft-tissue sarcoma. Former

Secretary Derwinski of the Department of Veterans Affairs acted on a court's decision to include these health problems on a list of Agent Orange symptoms and they were later made service connected.

We cannot take long in determining which illnesses are or are not service connected to the Gulf War. I am pleased that a bill was signed into law by President Clinton which gives Gulf veterans priority care at VA facilities, and that recent DOD authorization funds research projects related to this issue. However, the wheels of government move slowly. For example, it is disturbing to note that back in January, VA solicited its medical centers across the country to establish environmental hazard research centers for basic and clinical science studies of environmental hazards. To this date there has been no selection as to which facilities will host these centers. It is my understanding that 19 VA medical facilities expressed an interest in the research, however, VA can only say that three will be chosen in this fiscal year. I would expect that VA would have a fairly good idea of which facilities are best suited to be a host of a center and that it would not take a long time to deliberate. I understand it is beneficial for a VA medical center to be awarded the funds to establish a center of this sort, and therefore it is competitive, but isn't the bottom line that we have to get these centers up and running as quickly as possible so that we may possibly get answers back to these Persian Gulf War vets who need assistance?

I am particularly disturbed to keep hearing over and over how past records from DOD and VA, which should be readily available, are either missing, classified, or mismanaged which makes it even more difficult to establish service connection for veterans with health problems. VA and DOD will be the first to admit that because of a lack of organized personnel and health records in their departments it is hard to prove service connection in some cases. This as particularly true of WWII veterans who were exposed to mustard gas and lewisite. Obviously, DOD and VA need to take drastic measures to make sure that proper records are obtained and that DOD and VA coincide and streamline their records so that they can improve access and information from service records. Poor records should not be used as an excuse in this day and age of technology.

Finally, there has been much discussion as to what may be causing the illnesses which are plaguing our veterans. They range from stress, oil vapor inhalation, chemical pollution, parasites, and drugs given to servicemen and women in the Gulf to act as an anti-nerve gas agent.

I have testimony here which I would like to submit for the record from a constituent of mine, Mr. Craig Stead. Mr. Stead's domestic water system was contaminated with petroleum oil for three years, in which time Mr. Stead and his family experienced many of the same symptoms reported by Desert Strom veterans. The similarities in illnesses are amazing. Testimony like this would lead one to believe that the burning of Kuwaiti oil wells were the cause of the illnesses that servicemen and women are experiencing. However, I understand that there are many other presumed causes of these illnesses. Therefore, it is important that we not exclude any of the possibilities, and that we keep an open mind in realizing that possibly there could be more than one cause of these illnesses.

An independent committee of experts was recently organized by the National Institute of Health and a report was issued last Friday by this panel

that stated that the so-called Gulf War syndrome involves symptoms that could be attributed to one cause or to a combination of causes including: stress, chemical pollution or parasites. I found it interesting that they mentioned stress as a cause of some of these illnesses. Many people may feel stress is too easy of an answer to the problem, however, in a letter to General Ron Blank at Walter Reed Army Medical Center on January 26, 1994, I informed him of research being done by Dr. Matt Friedman, who is the Executive Director of VA's National Center for Post Traumatic Stress Disorder, located at Vermont's White River Junction VAMC. Dr. Friedman sits on the Blue Ribbon Panel which has been studying Gulf War illnesses, and has been publicly concerned about the adverse health effects of Persian Gulf War veterans with PTSD and whether veterans with PTSD are more vulnerable to developing multiple chemical sensitivity. So again, there may be many causes to the problems we are facing here today.

It is important that DOD and VA commit to working together to solve the problems that face our Persian Gulf vets, not to mention our WWII veterans and the veterans who may have been exposed to radiation and other chemical experiments by our government. I hope to hear of progress that has been made regarding this issue today. We must act cautiously and quickly in getting the compensation and care to all veterans in need.

# APPENDIX 2.—PREPARED STATEMENTS OF WITNESSES

## PREPARED STATEMENT OF RUDOLPH R. MILLS, WORLD WAR II VETERAN, FREDERICKSBURG, VA

Mr. Chairman and Senators: My name is Rudolph Mills and I live in Fredericksburg, Virginia. I am here today to relate to you my problems with the Department of Veterans Affairs.

Fifty years ago, in December 1944, my twin brother and I quit high school to join the U.S. Navy. World War II was still going on and we wanted to serve our country. Once we were inducted we went our separate ways. I was at Recruit Training in Bainbridge, Maryland, when a call came for volunteers to participate in gas mask experiments. I stepped forward. I was seventeen years old, just out of boot camp and willing to do anything to help my country. And it wasn't just me, there were thousands of patriotic young Americans who felt the same.

In April of 1945 I participated in gas chamber experiments with the same gas mask approximately a dozen times for an hour each time. I had on an experimental mask and the Navy was trying to determine if people wearing these masks could communicate with each other.

I was enticed to sing over the intercom. At the time I could sing quite well. I remember the corpsman conducting the tests seemed serious about "taking me uptown" for tryouts. When I sang, the air pressure of my voice caused the sides of the mask to open up and I suffered burns on my cheeks and chin. No one ever told me that the mask became less effective against the gas with each use.

We were sworn to secrecy and it wasn't until 45 years later that I learned I had been part of around 4,000 or more servicemen who were human guinea pigs in gas experiments conducted from 1942 through 1945 by the Chemical Warfare Service. I was among those who received high doses of mustard gas.

Even before my discharge in July, 1946, my health started to deteriorate. I started to lose my teeth and I had a chronic sore throat. Within three years of my discharge my tonsils and all teeth had to be removed. I developed a hacking cough when I was in my twenties which culminated in a diagnosis of cancer of the larynx in 1970. At the age of 43 I underwent a long series of radiation treatments and later surgery to remove part of my voice box and larynx. This left me with difficulty breathing, and the voice you hear today.

It didn't occur to me that my exposure to mustard gas was responsible for my physical problems until June, 1991, when I read an article in my hometown paper. This article said the Department of Veterans Affairs was urging veterans exposed to mustard gas in chemical warfare experiments during World War II to come forward for compensation. Given that my cancer had effected not only my health, but my career and family, with its associated financial burdens, I came forward. Just as I believed in my country when it asked me to volunteer for those experiments, I took the VA at their word when they said they would compensate suffering veterans. In that regard I was very naive because my experience with this agency has been a bureaucratic nightmare.

I cannot take the time today to tell you the details of my story which have left me depressed and disheartened, but I can tell you that for the past three years I have gotten a royal runaround from the Department of Veterans Affairs. I filed a claim which was eventually denied because the particular type of cancer (laryngeal) I had was not recognized as being related to mustard gas exposure. After a study, conducted by the National Academy of Sciences, found a causal relationship between exposure to mustard gas and the subsequent development of laryngeal and other cancers I was notified these additional diseases would be recognized by the VA. My spirits were lifted when I read another article which quoted Acting Secretary of Veterans Affairs, Anthony J. Principi, as saying, and I quote, "The years of silent suffering have ended for these World War II veterans who participated in secret testing during their military service. I am pleased that we are able to continue the process toward compensating those veterans who have health problems that may be related to significant mustard gas exposure." I was told that once the VA promulgated a new regulation my case would be reevaluated. It has now been a year and a half and this regulation has still not gone into effect. My Congressman, Herbert Bateman, makes inquiries on my behalf and each time his representative is told the new regulation should be finalized in the near future.

At the time the new regulation was first proposed, VA officials were quoted as saying those veterans who received significant exposure to mustard gas would be given the benefit of the doubt as to other causative conditions. The NAS report found that delayed effects of mustard gas exposure may appear even though no acute effects were noted at the time of exposure. I feel very strongly that my laryngeal cancer fits within the guidelines of the NAS's 1993 report. Yet the VA's proposed ruling states, and I quote, "we have determined it is reasonable to consider evidence of intervening cause which may exist. . .". This loophole could conceivably deny benefits to those whose problems the VA decides could have been caused by another source. As it is, I have a twin brother who has lived a very similar lifestyle as myself (with the exception of mustard gas exposure) and has, throughout the years, enjoyed much better health than I do.

Finally, let me say that I almost wish I had never read the article asking those who participated in these experiments to step forward. It has resulted in my disillusionment with the way the government of my country treats its own citizens and the veterans who wanted nothing more than to serve their country. I have absolutely no regret joining the Navy as a very young man and doing what was asked of me for I loved my country and I love it just as much or more today. And in spite of all the agony the VA has put me through, I would step into a gas chamber again today if it would help preserve this great country

for my grandchildren. I'd step forward and do it again. Even so, I can't help but feel that my government hasn't played fair with me. I was asked to come forward and file a claim-I did so. I was told the silent suffering was over-It is not. I was told I would be given the benefit of the doubt-that has not happened. The VA has sat back and engaged in their endless bureaucratic games while many of us died off before our cases could be considered. In my opinion, they have acted callously and have not been truthful. If I never get a penny's compensation for the fact that I repeatedly breathed poisonous gas into my lungs that will be all right. But I will never be able to forget that my government has given such shabby treatment to me and so many others like me. That hurts more than my exposure to mustard gas.

## Notes on the VA's Proposed Rule

The VA's current rule applies only to those veterans exposed to mustard gas while participating in secret tests of "protective equipment" during WWII. This terminology implies awareness and acceptance on the part of the test subjects. It is a well known fact that some servicemen were asked, or in many cases summarily "volunteered" to test "summer clothing", *not* "protective equipment".

The VA now proposes to expand the current rule to include veterans exposed to mustard gas under battlefield conditions in both World Wars and those engaged in manufacturing and handling of vesicant agents. They further propose to add a requirement that service connection will not be established if there is affirmative evidence that establishes a nonservice-related supervening condition or event as the cause of the claimed condition.

Expanding the rule to include the additional diseases is long overdue. Expanding the rule to include veterans exposed to mustard gas under battlefield conditions is also necessary and long overdue. However, it clouds the issue. Those veterans who were locked in gas chambers and given no warning or clear understanding of what risks they would be facing were assured by the VA that *they would be given the benefit of the doubt* concerning any possible intervening cause of presumptive service connected conditions. The proposed ruling, however, states that the VA believes, and I quote, "it is reasonable to consider evidence of intervening cause which may exist, just as we do for other presumptive conditions."

This verbiage would have one believe that the VA equates a battlefield injury with being locked in a gas chamber under very questionable circumstances. This is an equation I simply cannot support. Subparagraph 2(b) under Subpart A, Part 3-Adjudication, should not apply to those veterans who served as test subjects in gas chambers as they have been promised to receive the benefit of the doubt as to any other cause of the claimed condition.

# PREPARED STATEMENT OF EARL P. DAVENPORT, VETERAN AND FORMER EMPLOYEE, DUGWAY PROVING GROUND, TOOELE, UT

Earl P. Davenport
379 So. Main Street
Tooele, Ut. 84074

## INTRODUCTION

My name is Earl P. Davenport. I was employed by the United States Government for twenty-three years before retiring in 1993.

The nature of my career was testing chemical and biological agents for both the Army and the Navy.

| | | |
|---|---|---|
| 1958-1960 | *Army* | Dugway Proving Ground |
| 1962-1966 | Civ. | Dugway Proving Ground |
| 1966-1973 | Civ. | Dahlgren, Virginia |
| 1983-1993 | Civ. | Dugway Proving Ground |

I entered the Army in 1958. I was stationed at Dugway in December of 1958 through June of 1960 where I worked as a clerk who delivered supplies to support toxic field test areas.

In 1960, I was discharged from active duty. In 1962, I went to work at Dugway as a civilian in the position of a decontamination equipment operator.

I worked with a variety of agents; VX, GD, GB, BZ, Mustard gas, Tear gas, and Nerve gas simulants. I also worked with a variety of biological agents; U, X, UL, etc.

Both biological and chemical tests were conducted in the open air by many delivery systems. This required military and civilian personnel to wear protective clothing and also take biological shots. We were told they were to built up our immunity to the agents we were testing. We were never told the names of these shots, we were only given the symbols. When I questioned taking these shots I was told I was receiving hazard pay and it was part of my job. At this time hazard pay was six cents an hour.

Like many workers at Dugway, I never doubted the assurances and judgments of my superiors, who briefed me on the hazards of my job. But, I assumed, that if they were wrong, the government would take responsibility for it and protect its workers. Now I am wondering if I was wrong.

On July 13, of 1984, I was involved in a test the Army was conducting to test a laser system that would detect nerve agents. I was operating a sprayer, blowing a fog of nerve agent simulant called DMMP (Dimethyl Methylphosphonate) into the path of a laser beam. During the test I noticed a sudden shift in the wind direction and quickly cut off the sprayer. But, before I could don my protective mask, a cloud of the chemical covered me. I could feel it on my skin and taste it; it was oily. I tried to wipe it off as best I could and put my mask on. I secured my area

then left the test site to shower. At that time I was checked out by a medic and seemed to be OK. I then reported to my supervisor to fill out an accident report. I was told at that time if I became ill to report to the base hospital.

I wasn't too concerned about getting hit with a simulant. I trusted the Army's assurance that DMMP was" practicly non-toxic" according to the material safety data sheets [MSDS] that were available to the employees at the time of the test. It also stated that DMMP may irritate mucous membranes and respiratory tract, and that prolonged skin contact may cause irritation, blisters and burns. Dugway's Safety Office recommend workers wear a military protective mask, rubber gloves and apron.

The day after the accident I felt different. I was wheezing and coughing up phlegm, after two weeks my condition had not improved so I went to the Dugway Army Hospital. I was given cough syrup and antibiotics for what they diagnosed as bronchitis, but after several weeks There was still no improvement in my condition so I was sent to the University of Utah for further evaluation. There I was diagnosed as having a mild exacerbation of chronic obstructive pulmonary disease by irritant effect of DMMP.

Over the years my condition worsened. I seemed to get colds and bronchitis more frequently and was short of breath, especially at high altitudes. In 1988, I suffered a heart attack and by 1992, I missed an average of six days of work a month due to illness. Twice I left work in an ambulance because of heart and breathing problems. The days I seemed to feel the worst where when outdoor simulant tests conducted. At this time, because of medications I needed to take for my heart and lung problems,I was considered a safety risk and was eventually removed from chemical and bio-agent work. In 1993, at the urging of my doctors, I took an early retirement.

I was very concerned about my health and the connection to the DMMP exposure, especially with my past history of working with chemical and biological agents and the possibility of unknown and low-level exposures, also there where the shots I had been given.

I did some research and found the Government had underestimated the health hazards of DMMP.

- An Army memo issued three months before the laser test said a study was under way on the cancer-causing potential of DMMP. "a positive finding in this study would eliminate the material for consideration as a simulant," the memo said.

- A 1986 memo saying the studies confirmed DMMP as a mild carcinogen and harmful to the male reproductive. The memo recommended developing an alternative simulant; meanwhile, those handling DMMP should continue to wear a mask and protective clothing.

- A 1988 "disposition form" from Dugway Safety Office Chief Larry K. Whisenant: "DMMP has been determined to be a mild carcinogen and potent renal toxin. Because of these hazards, there is a grave concern over the release of DMMP into the environment and the exposure of personnel to liquid and vapors," he wrote. "A safer simulant should be substituted for outdoor

testing."

Whisenant also said a standard respirator mask is not sufficient for protection against DMMP. He recommended that the chemical be used only in a test chamber, and even then personnel handling DMMP should wear a mask hooked up to separate oxygen supply.

Dugway safety officials confirmed that DMMP was used extensively as a simulant for chemical agents until 1988, when the Army surgeon general reviewed studies identifying it as a "suspect carcinogen".

"Since 1988, the use of DMMP has been reduced significantly because the recommended exposure limit required protective clothing criteria and engineering controls that were so astringent that DMMP lost most of its value as a simulant," Dugway's public affairs office said in a written response to Deseret News' queries about DMMP.

Although the Army clearly miscalculated the health hazards of DMMP for several years, the government concluded my health problems were caused because I smoked and not because of my exposure to DMMP.

While talking to other Dugway employees, I discovered that many of them were also having health problems similar to mine. We decided to have a meeting to discuss our individual health problems. While we were talking, we discovered that at least twenty-nine of the people, including ourselves, who had worked with chemical and bio testing at Dugway and who had received the shots had also had heart attacks, and twelve of them had died. Another thirteen had other serious problems such as cancer, MS, and Q fever.

Many of us had found we could not depend on Dugway for much help. Many of the records requested could not be found or were unavailable. The shots we had all taken during the sixties were of special interest but we were unable to get records of just what they were.

We all have grave concerns about our health and what we may have been exposed to while working at Dugway. We cannot get answers to our questions and we do not know what to tell our doctors to help them in our treatment, but we all feel that our chemical exposures and the bio-shots are playing a role in our current health problems.

I am here today to ask for help for myself and all those like me who worked for the government either in the military or in civil service who have become sick or injured by unknown circumstances and are not able get documents, records, or even follow-up care from the places they were injured.

THANK YOU

Earl P. Davenport
379 So. Main Street
Tooele, Ut. 84074

PERSONAL HISTORY 1984-1993

To whom it may concern:

This is a brief history of my job service and health over past nine years.

In 1984 I was working in the Weapons Branch at Dugway Proving Ground and was in reasonably good health.

On July 13, 1984, I was involved in a test using the agent DMMP (Dimethyl Methylphosphonate). During this test there was a shift in wind direction and I was saturated with DMMP. An accident report was filed and within a few days I became ill. I was treated at Dugway for bronchitis, but, after several weeks, my condition had not improved and I was sent to a pulmonary specialist at the University of Utah. At that time, I was said to have chronic obstructive pulmonary disease (COPD) and, because of lack of symptoms prior to the accident, chemically induced asthma. I was treated by Dr. Renzetti and, after a few weeks, released to return to work.

By December of that year, my health seemed to improve and I transferred to the Test Conduct Branch. Although my health was not at a critical level, I was constantly plagued with colds, bronchitis, pneumonia and various other respiratory disorders.

I enjoyed my job and was well trained in my field; I had been working in the chemical field since the 1960's testing different chemicals and agents. Although it was becoming more difficult, I tried to do my job well and participate in all testing asked of me.

Then, in December of 1987, I was sent on a high-altitude test in Colorado. I found that I had a difficult time working at this high altitude and, by the time I returned home in late December, I was feeling quite ill.

A few weeks later, on January 17, 1988, I had a heart attack and was hospitalized for several weeks. My doctor, Lee J. Burke, had me stay off of work for a couple of months. With rest and medication my health began to improve, though never to the state it had been prior to the 1984 accident, and I returned to work at a light duty status for a time, then began to be involved in field testing once more.

From that time on, my health started to become a real problem. I was missing more and more work and, even while working, I never felt well. My job performance was beginning to suffer.

By July of 1992, I was having a very difficult time on the job. Twice I was taken off the job and sent to the Dugway Hospital. The first time, I was transferred to the LDS Hospital in Salt Lake, treated for atrial fibrillation, tested and released. The second time, I was sent home and back to the

University of Utah hospital for evaluation of my lung con[illegible] and this time I saw Dr. Holly Carveth. I was suffering from severe breathing problems and asthma. She agreed with Dr. Renzetti's diagnosis, put me on medication and, in two weeks, I returned to work. Then again I was taken to Dugway Hospital, transferred to LDS Hospital and treated for atrial fibrillation. After a two day stay, I returned to work, although I was still having a extremely difficult time breathing.

In August of 1992, I had another attack at home and went to the Tooele Valley Hospital Emergency Room. I was treated for asthma. After a few days recovery, I returned to work as my leave was at a low level. At this time, I filed a recurrence of the 1984 DMMP accident with Workman's Compensation. Within weeks, my case was accepted.

I was seeing Dr. Carveth every few weeks and using the medication she prescribed, but, instead of getting better, I was getting worse. By November of 1992, I was too ill to work. This is when I decided to seek the help of Dr. Robert Farney as I was already being treated by him for sleep apnea.

On November 19, 1992, I had my first visit with Dr. Farney. He started a very aggressive treatment for my asthma and COPD and advised that I not return to work for a few weeks.

On December 4, 1992, I had a return visit with Dr. Carveth as she was the doctor of record with Workman's Compenstation. She looked at me briefly and told me to return in four weeks. Five hours later, I was in the Tooele Valley Hospital Emergancy Room with severe breathing problems and atrial fibrillation with a heart rate of 240. From there, I was transferred to the LDS Hospital Emergency Room in Salt Lake where I was given medication to get my heart rate under control, which took approximately nine hours. When I was stable, I was transferred to Cardiac Care, where I remained for three days. I was treated for COPD and told my lung condition was most likely the factor that caused the atrial fibrillation. I was given more lung treatments and a new drug for my heart arrythmia. I was also advised by my doctors that my present job could be harmful to my health and not to return. In fact, it was questionable for me to return to any kind of work.

By January 21, 1993, all leave, both personal and borrowed, had been used. Having received the letter of acceptance from Workman's Compensation, I filed for wage compensation.

I was seeing my doctor every few weeks and taking the medications prescribed to me. Although I began to feel somewhat better, I knew I would not be able to return to work.

By April of 1993, I still had not received neither wage compensation nor word on why the payment delay. Then, in May of 1993, I was told they would need a second doctor's opinion and was sent to see Dr. Nathan C. Dean. Three weeks later, I was contacted by Workman's Compensation. I was told that my illness was not in dispute, nor the fact that I was to ill to work, but that I was a smoker and, because my lung disease was symptomatic of smoking, my compensation claim was now being denied.

I was told I would receive a check that would cover my wages from January 22, 1992 to June 12, 1992 and that medical treatment in that time frame would be paid, but anything after the denial date of June 12, 1992 would not be compensated.

So, at fifty-four, with twenty-three years government service, and a disease that makes it impossible for me to return to work, I find my only option to be an early retirement and to try to appeal Workman's Compensation's decision.

THINGS I REMEMBER AT DUGWAY OVER THE YEARS
(PERSONAL DOCUMENTATION)

1. Shots for Baker Lab (1958-1966)

For each series of tests, I was given shots to build up immunity to the agent they were testing. I didn't know what they were, I just knew them as symbols. Example; U, X, UL, etc... No records can be obtained from Dugway on these shots. They are not in my medical files. Rumors are they may have been burned in a fire in St. Louis, though I do not know for sure.

I can remember one time we were told to get our shots updated by our supervisors. An Army doctor was waiting at the doorway to the dispensary. He explained to us that this shot may cause flu symptoms. We received the shot and everyone that took it became ill. This consisted of possibly two hundred military and civilian personnel. The sickness lasted for approximately forty-eight hours. If you were at home, you were given leave, if you were at work, you did not have to do anything. We never knew what these shots were. We were told that we had to take them; it was part of our job. We also received hazard pay and could not refuse.

2. Hazard Pay (1962-1966)

We received six cents per hour for hazardous duty performed; a total of forty-eight cents per day. We received this hazard pay daily.

3. Formaldehyde (1962-1966)

I can remember when biological tests were always ran at night. The next day, we would get into rubber suits, M9A1 masks with M14 canisters and decontaminate twenty to thirty, three-quarter ton army vehicles. They were run up on a ramp and all residue was removed by a high-pressure hose. They were then placed in a building, five or six at a time. A container of formaldehyde was placed on a rack directly above an activated steam line. The formaldehyde slowly dripped into the exhaust of the steam, consisting of approximately five gallons of formaldehyde. After a time, personnel would open the doors, enter the building, and turn the steam off. I became sick many times due to this procedure because the formaldehyde would pass through the M14 canister on the mask. I complained many times about this problem. I was told to adapt the M11 canister to the M14 canister on the mask. This helped some, but did not totally protect me from the fumes. This procedure involved civilians and military personnel and continued until I left Dugway in 1966. We did not remove the trucks from the building. They were then sprayed down with a "so-called" rocal. They were then ready to be used by unprotected personnel. I have since discovered that

formaldehyde in a carcinogenic material.

4. The M9A1 Gas Mask (1958-1966)

I can remember, in my early use of the mask with the M11 filter, a problem with loose charcoal when a new can was first opened. If the filter was tapped on a surface, bits of charcoal would fall out of it. I have heard reports of people getting bits of charcoal in their eyes while wearing the mask. I am concerned about the amount of charcoal that I inhaled while I was wearing the mask in question. The mask was worn for several hours a day continuously over a period of many years while testing and as far as I know, the mask and filter has not been NOSHA/approved.

I can remember a test I was asked to do in 1964. I was asked to suit up in Level-A protection fitted with a new M11 canister with true weight. A chamber was charged with a high concentration of, I believe, GB agent. I was asked to enter the chamber and remain for thirty minutes. I then left the chamber. The M11 filter was removed, swabbed with alcohol, and reweighed. The canister had increased in weight by either 13 mg or 13 g, I am not sure. My concern; did any past through this filter and into my lungs. I would like restate that, although I believe the agent to be GB, I am not sure.

6. Military voluntary exposure to BZ (1961-1966)

I can remember, when I was employed as a decontamination equipment operator, I supported tests with military volunteer personnel to BZ (a hallucinogen). The personnel were placed on or around the grid and the test was initiated. I was told concentration varied from individual to individual and that their masks would allow a certain amount to enter and then would be converted and filtered. After the tests were completed, they were flown to a field hospital adjacent to the base, by helicopter, for observation.

7. The M8 chemical detector

I can remember in the late 1950's and early 1960's, the M8 chemical detector was being developed. We used the M8 with rabbits, pigeons, and guinea pigs as a means to determine when to mask up. We were never sure the M8 was giving a true reading and we had to rely on the symptoms that appeared in the test animals. The concentration involved to activate the M8 detector was approximately five times the acceptable level of 1993.

8. Duties as a Supply Clerk (1958-1960)

I can remember hauling radioactive waste, in barrels filled with concrete, from the lab to a shipping point to be disposed of.

## ORIGINAL 1984 ACCIDENT REPORTS

U.S. DEPARTMENT OF LABOR
Employment Standards Administration
Office of Workers' Compensation Programs (OWCP)

REQUEST FOR EXAMINATION AND/OR TREATMENT

PART A – AUTHORIZATION

1. NAME AND ADDRESS OF THE MEDICAL FACILITY OR PHYSICIAN AUTHORIZED TO PROVIDE THE MEDICAL SERVICE

US ARMY HEALTH CLINIC
DUGWAY, UT 84022

| 2. EMPLOYEE'S NAME (Last, first, middle) | 3. DATE OF INJURY (mo., day, year) | 4. OCCUPATION |
|---|---|---|
| DAVENPORT, EARL. P | 07/13/84 | Explosive Test Operator |

5. DESCRIPTION OF INJURY OR DISEASE

Fluid in Lungs

6. YOU ARE AUTHORIZED TO PROVIDE MEDICAL CARE FOR THE EMPLOYEE SUBJECT TO THE FOLLOWING CONDITIONS

☐ A - FURNISH OFFICE AND/OR HOSPITAL TREATMENT AS NECESSARY FOR THE EFFECTS OF THIS INJURY. ANY SURGERY, OTHER THAN EMERGENCY, MUST HAVE PRIOR OWCP APPROVAL.

☒ B - THERE IS DOUBT WHETHER THE EMPLOYEE'S CONDITION IS CAUSED BY AN INJURY SUSTAINED IN THE PERFORMANCE OF DUTY OR IS OTHERWISE RELATED TO HIS EMPLOYMENT. YOU ARE AUTHORIZED TO EXAMINE THE EMPLOYEE, USING INDICATED NON-SURGICAL DIAGNOSTIC STUDIES, AND PROMPTLY ADVISE THE UNDERSIGNED WHETHER YOU BELIEVE THE CONDITION IS DUE TO THE ALLEGED INJURY OR TO ANY CIRCUMSTANCE OF THE EMPLOYMENT. PENDING FURTHER ADVICE, YOU MAY PROVIDE NECESSARY CONSERVATIVE TREATMENT IF YOU BELIEVE THE CONDITION MAY BE DUE TO THE INJURY OR TO THE EMPLOYMENT.

7. IF A DISEASE OR ILLNESS IS INVOLVED, OWCP APPROVAL FOR ISSUING AUTHORIZATION UNDER ITEM 6B ABOVE, WAS OBTAINED FROM

(Name of OWCP official)

| 8. SIGNATURE OF AUTHORIZING OFFICIAL (Sign all copies) | 9. TITLE |
|---|---|
| G. NEIL MAGANN | Chief, Weapons Systems Branch |
| **10. LOCAL EMPLOYING AGENCY TELEPHONE NUMBER** | **11. DATE (mo., day, year)** |
| 5331 | |
| **12. SEND ONE COPY OF YOUR REPORT TO (Fill in address)** | **13. NAME AND ADDRESS OF EMPLOYEE'S PLACE OF EMPLOYMENT.** |
| U. S. DEPARTMENT OF LABOR<br>Employment Standards Administration<br>Office of Workers' Compensation Programs | Dept. or Agency<br>Bureau or Office<br>Local Address (Including Zip Code) |

FORM CA-16
(REV. DEC. 1974)

U.S. DEPARTMENT OF LABOR
EMPLOYMENT STANDARDS ADMINISTRATION
OFFICE OF WORKERS' COMPENSATION PROGRAMS

FEDERAL EMPLOYEE'S NOTICE OF TRAUMATIC INJURY AND CLAIM FOR CONTINUATION OF PAY/COMPENSATION

| 1. Name of Injured Employee (Last, first, middle) | 2. Date of Birth | 3. ☒ Male ☐ Female | 4. Social Security Number |
|---|---|---|---|
| DAVENPORT, EARL P. | 10/27/39 | | 258-56-5955 |

5. Employee's Home Mailing Address (No., street, city, state, zip code)
259 So. Main, Tooele, UT

6. Home Telephone Area Code Number N/A

| 7. Name and Address of Employing Agency | 8. Place Where Injury Occurred (e.g., 2nd floor, Main Post Office Bldg., 12th & Pine) |
|---|---|
| US Army<br>Dugway Proving Ground<br>Dugway, UT 84022 | APG<br>Dugway, UT |

| 9. Date and Hour of Injury (mo., day, year) | 10. Date of This Notice (mo., day, year) | 11. Dependents | 12. Employee's Occupation |
|---|---|---|---|
| 7/13/84 ☒ AM ☐ PM | | Wife/Husband ☐<br>Children Under 18 Years Old ☒ | Expl Test Oper |

13. Cause of Injury (Describe how and why the injury occurred)
Experienced a wind shift during dissimination of DMMP at the All Purpose Grid.

14. Nature of Injury (Identify the part of the body injured, e.g., fractured left leg, etc.)
Lungs

15. If This Notice and Claim Was Not Filed With The Employing Agency Within Two Working Days After The Injury, Explain The Reason For The Delay.
Under Doctors care.

16. I certify, under penalty of law, that the injury described above was sustained in performance of duty as an employee of the United States Government and that it was not caused by my willful misconduct, intent to injure myself or another person, nor by my intoxication. I hereby claim medical treatment, if needed, and the following, as checked below, while disabled for work:

☐ a. Sick and/or annual leave

☒ b. Continuation of regular pay not to exceed 45 days and compensation for wage loss if disability for work continues beyond 45 days (If my claim is denied, I understand that the continuation of my regular pay shall be charged to sick or annual leave, or be deemed an overpayment within the meaning of 5 USC 5584).

Earl P Davenport
Signature of Employee or Person Acting on His/Her Behalf

17. Statement of Witness (Describe what you saw, heard or know about this injury)

| 18. Witness' Signature | 19. Witness' Address | 20. Date Signed (mo., day, year) |
|---|---|---|
| | | |

Form CA-1
Rev. Sept. 1975

## OFFICIAL SUPERIOR'S REPORT OF TRAUMATIC INJURY

| 21. Department or Agency | 22. Bureau or Office |
|---|---|
| US ARMY | Dugway Proving Grounds |

23. Name and Address of Reporting Office *(No., street, city, state, Zip Code)*
Weapons Systems Branch
Dugway, UT 84022

30 OCT 1984 10 22
DUGWAY PROVING GROUND

| 24. Regular Work Day | 25. Number of Hours Worked Per Day | 26. Circle Days Paid Per Week |
|---|---|---|
| Begins 0700. ☒ AM ☐ PM  Ends 1730 ☐ AM ☒ PM | 10 | S M T W T F S |

| 27. Date and Hour of Injury *(mo., day, year)* | 28. Date Reporting Office Received Notice of Injury *(mo., day, year)* | 29. Date and Hour Stopped Work *(mo., day, year)* | 30. If Pay Has Been Terminated, Give Date *(mo., day, year)* |
|---|---|---|---|
| 07/13/84 ☒ AM ☐ PM | 07/13/84 | N/A | N/A |

| 31. 45 Day Period Begins *(mo., day, year)* | 32. Pay Rate When Employee Stopped Work | 33. Date and Hour Employee Returned to Work *(mo., day, year)* | 34. Name of Supervisor at Time of Injury |
|---|---|---|---|
| N/A | $ N/A per _____ | N/A ☐ AM ☐ PM | G. Neil Magann |

35. Was Employee in Performance of Duty At The Time of Injury? ☒ Yes. ☐ No. If No, furnish a detailed explanation or attach copy of Employing Agency's Investigation Report.

36. Was Injury Caused By Willful Misconduct, Intoxication or Intent To Injure Self or Another?

☐ Yes ☒ No. If Yes, Furnish Detailed Report.

37. Was Injury Caused By Third Party? ☐ Yes ☒ No. If Yes, Furnish Name and Address of Party Responsible.

| 38. Date Employee First Obtained Medical Care for the Injury *(mo., day, year)* | 39. Name and Address of Physician First Providing Medical Care | 40. Do Medical Reports Show Employee is Disabled For Work? |
|---|---|---|
| 07/25/84 | US ARMY HEALTH CLINIC<br>DUGWAY, UT 84022 | ☐ Yes ☒ No |

41. Does Your Knowledge of The Facts About This Injury Agree With The Statements of The Employee And/Or Witness?
☒ Yes ☐ No. If No, Furnish A Detailed Explanation.

42. Does The Employing Agency Controvert Continuation of Pay? ☐ Yes ☒ No. If Yes, Give Full Explanation for Basis of Controversion (See Item 6 of Instruction Sheet), and, if applicable, the date pay was terminated. Attach Additional Sheets If More Space Is Needed.

43. Filing Instructions

☐ No Lost Time and No Medical Expense, Place this Form in Employee's Official Personnel Folder
☐ Medical Expense Incurred or Expected, Forward this Form to OWCP
☐ Lost Time Covered by Leave, LWOP, or COP, Forward this Form to OWCP

44. All Information requested on this Form has been furnished. If Not, it will be submitted by _____ *(Fill in Date)*

| 45. Signature of Supervisor | 46. Title and Office Telephone Number | 47. Date *(mo., day, year)* |
|---|---|---|
| G. NEIL MAGANN | Chief, Weapons Systems Branch | |

## PART B – ATTENDING PHYSICIAN'S REPORT

1a. EMPLOYEE'S NAME (Last, first, middle)
DIFFENDORF EARL

15. WHAT HISTORY OF INJURY OR DISEASE DID EMPLOYEE GIVE YOU?
exposed to Dimmp Silicone oil & fog oil over 25 pak yrs smoking

16. IS THERE ANY HISTORY OR EVIDENCE OF PRE EXISTING INJURY, DISEASE, OR PHYSICAL IMPAIRMENT?
(If yes, please describe) 25 yrs of smoking
☑ Yes ☐ No

17. WHAT ARE YOUR FINDINGS (Include results of xrays, laboratory tests, etc.)? Diffuse wheezing

18. WHAT IS YOUR DIAGNOSIS?
Bronchitic Vs Asthma

19. DO YOU BELIEVE THE CONDITION FOUND WAS CAUSED OR AGGRAVATED BY THE EMPLOYMENT ACTIVITY DESCRIBED?
(Please explain your answer if there is doubt.) The Emphysema may have caused acute episode but COPD from smoking maybe chronic
☐ Yes ☐ No ?

20. DID INJURY REQUIRE HOSPITALIZATION? ☐ Yes ☐ No
If yes, date of admission (mo., day, year)
Date of discharge (mo., day, year)

21. IS ADDITIONAL HOSPITALIZATION REQUIRED?
☐ Yes ☐ No

22. SURGERY (If any, describe type)

23. DATE SURGERY PERFORMED (mo., day, year)

24. WHAT (Other) TYPE OF TREATMENT DID YOU PROVIDE?
Symptomatic meds
Referred to pulmonary MD

25. WHAT PERMANENT EFFECTS, IF ANY, DO YOU ANTICIPATE?

26. DATE OF FIRST EXAMINATION (mo., day, year)
9-25-84

27. DATE(S) OF TREATMENT (mo., day, year)
7-30-84
9-6-84
9-15-84

28. DATE OF DISCHARGE FROM TREATMENT (mo., day, year)

29. PERIOD OF DISABILITY (If termination date unknown, so indicate) (mo., day, year)
TOTAL DISABILITY: FROM TO
PARTIAL DISABILITY: FROM TO

30. DATE EMPLOYEE ABLE TO RESUME WORK (mo., day, year)
LIGHT WORK
REGULAR WORK

31. IF EMPLOYEE IS ABLE TO RESUME WORK, HAS HE/SHE BEEN ADVISED? ☐ YES ☐ NO IF YES, FURNISH DATE ADVISED (month, day, year)

32. IF EMPLOYEE IS ABLE TO RESUME ONLY LIGHT WORK, INDICATE THE EXTENT OF PHYSICAL LIMITATIONS AND THE TYPE OF WORK, THAT COULD REASONABLY BE PERFORMED WITH THESE LIMITATIONS.

33. GENERAL REMARKS AND RECOMMENDATION FOR FUTURE CARE, IF INDICATED.
AS FAR AS I KNOW HE is still under care of Pulmonary Dr. STEVEN B. KUPITZKE, MD

34. DO YOU SPECIALIZE? ☐ OPT. MD ☐ (If yes, state specialty)

35. SIGNATURE OF PHYSICIAN 307-60-6223
Richard [illegible] MD

36. ADDRESS (Number, street, city, state, zip code)
USA Health Clinic
Dugway Proving Ground
Dugway, UT 84022-1093

37. PHYSICIAN'S SOCIAL SECURITY NUMBER

38. DATE OF REPORT (mo., day, year)
11-15-84

39. MEDICAL BILL. Charges for your services may be presented in the space below or on your billhead stationery.

| Code or period of treatment | Service or supplies must be itemized | Quantity or number | Unit price Cost | Per | Amount $ | ¢ |
|---|---|---|---|---|---|---|
| | | | | | | |
| | TOTAL | | | | | |

Standard Form 600
General Services Administration and
Treasury Committee on Medical Records
FPMR 101-11.806-6
October 1975
Exception Approved by NARS
1 Aug 78

**HEALTH RECORD** — **CHRONOLOGICAL RECORD OF MEDICAL CARE**

| DATE | SYMPTOMS, DIAGNOSIS, TREATMENT, TREATING ORGANIZATION (Sign each entry) |
|---|---|
| 13 JAN 1983 | USA Health Clinic<br>Dugway Proving Ground<br>Dugway, UT 84022 -1093<br>Pre employ PE<br>TIME 10:00<br>BP<br>TEMP<br>PULSE<br>RESP<br>ALLERGIE<br>[redacted] MD<br>CPT, MC<br>307-60-6112 |
| 29 JUN [illegible] | [redacted] |
| 18 APR [illegible] | USA Health Clinic<br>Eye Clinic<br>Dugway, UT 84022<br>pt. Scan for SA & insert Rx<br>SPS [redacted] 91U20 |
| JUL 1984 | USA Health Clinic<br>Dugway Proving Ground 4540 WM 25 PK yrs<br>Dugway, UT 84022 -1093<br>TIME 0745<br>BP 132/88<br>TEMP 97.6 (oral)<br>PULSE 80<br>RESP 22<br>ALLERGIES NKA<br>S: C/O SOB at rest, has frequent coughs, states he works at [illegible] facility and has been spraying DMMP (simulant for nerve agents), silicone oil, and fog oil past 2 wks, onset of SOB/cough 2 wks ago. J. Kittel, 2Lt, ANC<br>DMMP is a local irritant<br>Diffuse bilat wheezes and [illegible]<br>Remarks |

PATIENT'S IDENTIFICATION (Use this Space for Mechanical imprint)

| PATIENT'S NAME (Last, First, Middle initial) | | | SEX |
|---|---|---|---|
| DAVENPORT EARL P | | | M |
| YEAR OF BIRTH | RELATIONSHIP TO SPONSOR | COMPONENT/STATUS | DEPART/SERVICE |
| 39 | | | DAC |
| SPONSOR'S NAME | | | RANK/GRADE |
| Self | | | GS-4 |
| SSAN OR IDENTIFICATION NO | | ORGANIZATION | |
| 458-56-5955 | | SO-G | |

CHRONOLOGICAL RECORD OF MEDICAL CARE
Standard Form 600
600-106-01

| DATE | SYMPTOMS, DIAGNOSIS, TREATMENT, TREATING ORGANIZATION Sign each entry |
|---|---|
| | CXR = 7.1 MG infiltrate |
| | Dx: bronchitis & pneumonia |
| | Rx: Keflex 500 qid x 7d |
| | Robitussin DM |
| | Ammophyllin 200 qd x 10d |
| | D/C smoking |
| | Bed x 48h |
| | ↓ mandy |
| | Celeste |
| | MICHAEL W. GILCHRIST |
| | CW2, PA, 557-58-9668 |
| 30 JUL 1984 | USA Health Clinic |
| | Dugway Proving Ground |
| | Dugway, UT 84022-1093 |
| TIME 0715 | S: Has persistent cough. States he feels better than a... |
| BP 114/78 | but continues to have SOB. I. Keith, 2Lt, MSC |
| TEMP 98.3 (po) | Dx: Diffuse Bilat Ronchi and wheeze |
| PULSE 60 | 0830 0.4cc 1:1000 IM SQ |
| RESP 20 | Tx: same unchanged X-ray Read AS WNL |
| ALLERGIES NKA | Dx: Acute Bronchitis |
| | Ph: Cont meds |
| | NO strenuous physical |
| | activity - no exposure to chem vapor or fumes |
| | √ in 1 WK - |
| | MICHAEL W. GILCHRIST |
| | CW2, PA, 557-58-9668 |

## PREPARED STATEMENT OF NEIL R. TETZLAFF, LT COL, USAF (RET), PERSIAN GULF WAR VETERAN, REED, MI

In August of 1990 I was a Lieutenant Colonel in the USAF serving as the Assistant Deputy Commander for Resource Management for the 48th Tactical Fighter Wing, RAF Lakenheath, United Kingdom. On the 20th of August, with six hours notice, I was deployed with 11 others as the advance party pursuant to the deployment of the 48th's F–111's to Saudi Arabia.

While being mobilized I was issued a 7-day supply of pyridostigmine bromide pills and was told to start taking them on an eight-hour schedule, which I did. The package contained no warnings. For me this was a chronic overdose of pyridostigmine. Both my immediate physical and mental symptoms corroborate this fact.

On the plane ride to Saudi, and during my first day in-country, I was nauseated and vomited. I attributed the sickness to the plane ride and tenseness of the situation. On my second day there I vomited again and felt "different"; I attributed the sickness to something I'd eaten. On the third day I was extremely nauseated and vomited many times. I sought out the doctor and discussed my illness with him. We dismissed it as something I had eaten at the Saudi canteen. On my fourth day there I vomited violently, the worst ever of my life, and was acting a bit off center and muddled. On the fifth day I didn't vomit but was sore, lost much of my bounce, acted strangely silly and was totally out of character. On the sixth day I was incoherent, extremely tired, and at times irrational. On the morning of the seventh day I vomited about a quart of blood.

I knew then I was in deep trouble and I headed straight for the doctor. Shortly thereafter, I began to lose consciousness, and the doctor started an I.V. After examining me in the Tiaf clinic, the doctor commandeered a C–130 and air-evacuated me to the Royal Saudi Hospital in Riyadh.

The plane ride to Riyadh was extremely painful, every bump sent pain throughout my body. Though the worst of the pain was in my abdomen, my back, neck, head, arms, and legs were also in pain.

At the hospital, I was given a general anesthetic to knock me out. Doctors looked in my stomach and found a tear of approximately one and three quarters inches caused by retching near the entryway from my esophagus. They fed me intravenously for two days, put me on a special diet, and then released me to USAF medical personnel after a total of four days in the hospital.

Since taking pyridostigmine while deployed for Desert Shield, I have been suffering moderate, severe, and intolerable pain, fatigue easily and lately have developed one heck of a palsy. I've lost my ability to speak because I can't recall words, have extreme problems with my short term memory, and I had a dramatic change in my olfactory system. The last three and a half years have been extremely difficult on my family and me. This brief description by no means enumerates the mental and physical disabilities I've had to overcome.

As the situation stands now the disabling effects of pyridostigmine are not known and are not being investigated (by the DOD or VA), even though the drug was used during Desert Storm on an experimental basis. I am caught in the same dilemma as the victims of Crossroads and Agent Orange. During the nuclear tests in the 40's, radiation wasn't considered hazardous; and during

Vietnam, agent orange wasn't considered harmful. Pyridostigmine, taken at the dose of 30mg every eight hours, is considered to be noninjurious to humans by the DOD.

For over two years I have researched the drug pyridostigmine. Military and VA doctors have consistently held that at the dose it was given to me it was a completely harmless drug. However, the written material on the drug, as well as civilian doctors and pharmacologists tell a different story. Pyridostigmine is chemically similar to the carbamate pesticides just as the nerve gases GD and GX are to organophosphorus pesticides. Both of those classes of pesticides belong to the group acetylcholinesterase inhibiter pesticides. Pyridostigmine in any dose can do harm.

An article from *Military Medicine* entitled "Interactions between Nerve Agent Pretreatment and Drugs Commonly Used in Combat Anesthesia" made me question the significance of my receiving a general anesthetic at the Royal Saudi Hospital on or about 26 August 1990. This article hypothesizes about the damage caused by the interaction of pyridostigmine and anesthetics at the neuromuscular junction. Could this event have exacerbated damage to my nervous system and been the cause of my resultant sustained pain? To date no scientific research has been done in this area.

The side effects of pyridostigmine bromide most commonly associated with overdose can be found in the *Physicians Desk Reference*. And in the *Handbook of Poisoning*, I find that it can also cause cardiac arrest. The *Handbook of Poisoning* also puts the estimated fatal dose of pyridostigmine at 300mg for an adult.

Military medical doctors routinely returned soldiers taking pyridostigmine to duty, even though they were suffering overdose symptoms such as vomiting, increased urinary frequency, and headaches, without telling the soldiers to stop taking pyridostigmine.

Some pharmacists deployed to the Gulf refused to issue pyridostigmine bromide pills to soldiers in November of 1990 without getting advise and consent forms from the soldiers. They raised a number of moral, ethical and legal issues. Such as, was the United states guilty of doing exactly same thing the Nazis did in World War II? This forced DOD to get FDA's approval to issue the experimental medicine to soldiers without individual consent. Even with FDA's approval there is still a great deal of discussion in medical and pharmaceutical literature as to whether DOD violated the Geneva Accords.

FDA's approval for DOD use of pyridostigmine bromide in the Gulf War without getting informed consent from the soldiers rests on DOD's claim that pyridostigmine bromide had been used in the treatment of myasthenia gravis and therefore was completely safe. There was no scientific laboratory research accomplished to test the safety of the drug. Myasthenia gravis is a rare disease caused by an autoimmune attack on the acetycholine receptor of the postsynaptic neuromuscular junction. The mechanism of an overdose of pyridostigmine accomplishes about the same thing as the disease. DOD is relying upon a drug industry mechanism where doctors report their problems to the company. Use your knowledge of the world and try to come up with a doctor who is going to claim overdosing a patient. If you have one in mind, you probably know the lawyer's best friend. Now try to think of a doctor who would write on a death certificate that a patient either died from myasthenia

gravis or from an overdose of pyridostigmine bromide. The foundation of DOD's logic and subsequent claims rest on the assumption that such did happen without fail.

In 1992 the United States Army Medical Research and Development Command, Fort Detrick, Frederick, Maryland, substantiated the safety of pyridostigmine bromide with studies conducted on "over 100 volunteers under environmental stress conditions that measured the effect of PB on numerous physiological and performance criteria." Actually their studies are a conglomeration of 13 tests conducted over a period of eight years on 111 people, 63 of which took 60mg or less of pyridostigmine bromide in less than a 48hr period. The prescribed pyridostigmine dose during Desert Storm was 90mg per day. In other words, the USAMRDC study does not meet criteria required to test pyridostigmine for safety.

In my case, under ideal conditions, on day three if the doctor attending me would have recognized my symptoms as a severe overdose of pyridostigmine and taken the following steps: immediately stopped me taking pyridostigmine; started detoxification procedures by introducing saunas and baths with deionized water; put me on a antitoxic diet; have me air evacuated to a detoxification center; put me in a hyperoxygenated clean air chamber on a special diet. The therapy of chemical decontamination has been known for over forty years.

I find it interesting that many Gulf War vets are reporting mysterious illnesses of pain, chronic fatigue, and other nerve disorders, and neither the VA nor DOD has asked them if they took pyridostigmine, an experimental drug that was never before given to such a large number of healthy human beings. Nor, is anyone doing a followup investigation of the damage it did do. Unless DOD and VA do the followup study, the symptoms of an overdose of acetylcholinesterase inhibitors will continue to baffle doctors.

While I was in VA hospitals a number of Gulf War vets related they were astonished when apparently healthy young people died of heart attacks. They were amazed that no investigation was accomplished; rather, these soldiers were simply stuffed in body bags and sent home. Every one of these Vets when questioned confirmed that in every case the deceased were taking pyridostigmine bromide. One of the final indications of an overdose of pyridostigmine bromide was a heart attack and death. I have since found evidence that an unusual number of soldiers who had heart attacks in the Gulf War are being discharged.

Yet, the US government doesn't have in its employ a single medical doctor whose specialty and job it is to recognize, diagnose and treat chemical casualties. Heretofore, the DOD, though it has in its stockpile tons of nerve agents, has done no research on the long term effects of acetylcholinesterase inhibitors.

There have been several rays of light in my treatment. The first of these occurred at Landstuhl Army Medical Center. While I was an inpatient there I happened to corner the top neurologist in his office for several hours. I think he was interested in my case. After intense questioning on my part the neurologist opened up. He said he was only a chemist, treating the body as a chemical factory. When he had to correct symptoms he used drugs. He would use the favored drug first and increase its dosage to get results. If that drug

didn't work he would switch to the next drug in line. He couldn't tell me why the drug would work in ten cases and fail in the eleventh. He did not even know for certain the mechanism by which the drug worked in the nervous system, he could only monitor the results by observing the patient.

He then slid open the drawer he was resting his foot on and pulled out a cardboard with white pills enclosed in plastic. He said these were pyridostigmine pills just like the ones I was issued. Because pyridostigmine hadn't been tested to the extent it should have he couldn't tell me whether or not pyridostigmine could cause permanent damage to the nervous system. He couldn't even guarantee it would do the job it was meant to. He ended by saying that maybe in 15 to 20 years medical science would come up with the answers. Until then I would have to live with what he, with some degree of certainty, could tell me.

The second incident occurred over the three-month interval I spent with a psychiatrist at Wilford Hall Medical Center. As our time was drawing to a close he confided that I didn't fit the profile of a person with a psychiatric disorder. My whole life history and symptoms were inconsistent with such a diagnosis. He also confirmed that medical science was long a time away from having the answers to my problem.

A third ray of light occurred while at Houston Veterans Medical Center. The chief of neurology told me there were (I don't recall the exact number) either 16 or 18 different chemicals in the nervous system that medical science didn't know anything about. They didn't know exactly what they did nor in what concentration they should occur. This substantiated what Dr. Anderson had told me. It told me that when it comes to the nervous system medical science doesn't have all the answers. Pyridostigmine bromide could have altered my nervous system, thus I continuously feel pain and have a host of neural associated problems.

And then the sun started to shine when I met Dr. Claudia Miller, M.D., M.S., Environmental and Occupational Medicine, Department of Family Practice of the University of Texas Health and Science Center at San Antonio at the Houston Veterans Medical Center. She is the only doctor who of her own accord spent four hours with me. She questioned, she listened, and she advised. Though she did not cure my illness she made my life much more tolerable by explaining multiple chemical sensitivities and how to avoid exacerbating my situation.

From the text *Chemical Exposures*, by Nicholas Ashford and Dr. Claudia Miller, I quote, "Compensation for the chemically sensitive worker is vigorously resisted, and in some cases patients have to be labeled with a psychiatric disorder such as post traumatic stress disorder in order to receive compensation for their illness." This is exactly what was done to me.

In December of 1991, before I could be accepted into the Wilford Hall Medical Center pain management program, I had to prove through psychiatric exams that my pain was not due to mental causes. However, four months later I was recommended for separation from the USAF for psychological factors.

On 11 January 1994 I was able to get the USAF physical evaluation board to change the characterization of my separation from the USAF from being due to psychological factors to being due to a severe reaction to pyridostigmine

bromide. This was achieved by letting Dr. Miller explain multiple chemical sensitivities in relationship to my medical history.

I would like to talk to you about pain. In order for us to have discourse about pain I should tell you about my ability to withstand it. I lived by the following: When playing contact sports if one is injured, one doesn't quit, but rather refocuses oneself and gets backs in the game. A player can't achieve reciprocity if he is not in the game. When flight testing chemical warfare gear, the Aircraft Commander doesn't remove his or her gear because of the pain, but rather he or she keeps it on so he or she can debrief the flight surgeon and personal equipment people what it was like throughout the total mission. After a while one's head no longer hurts from the straps; the area concerned just goes numb.

When interpreting pain, a negative pain is a good situation, you feel good and you enjoy it. A rating of zero means you are feeling no physical pain. At a rating of three you are feeling discomfort and are making adjustments for it, such as the aches and pain of a severe flu. A level five pain is a pain which you will do a great deal to avoid. It's like having a raw nerve in your tooth exposed, or deep breathing against several broken ribs. At a level seven pain you find it almost impossible to maintain your composure. It stops you dead in your tracks. You have trouble talking. If you are driving a car, you immediately pull to the side of the road and sit. You are almost going into shock. At a level eight and nine pain you are headed for the emergency room by fastest means available and beg some doctor to put something you violently abhor into you, namely drugs. At level ten pain the world becomes pain free because you pass out.

In my first year after taking pyridostigmine bromide I lived continuously at level seven pain and above. I slept only when alcohol and fatigue, or just fatigue alone, overcame the pain. I got to the pass out level a number of times. I didn't use the emergency room much because I was still thinking of having a shot at full colonel. I did pass out a number of times though and learned to recognize the symptoms which occur just prior to passing out. As I said, passing out is a way of being pain free. Over three fourths of the time, when I was in a present for duty status, I was up nights doing slow walk meditation trying to control pain or convince myself to pass out. During a thirty day leave period I got to level three pain with over the counter drugs, just lying still, sleeping, and being in motion only to take care of necessities. But most of my leave time was still spent at level five pain and above.

In October 1991, I began taking prescription drugs for pain. Since going on drugs I live constantly at level three pain with pain spikes which are level five, and I also receive several level seven and eight spikes a day. About half of my nights are interrupted with level seven spikes of pain. I get four to six hours a day of good time approximately four days a week.

Besides the pain problem, I have a chemical sensitivity problem which knocks me out of action for three or four days at a time. I endure a whole host of symptoms, some of which I've covered.

I have been hospitalized twice in the past year for one-week periods, been in the Emergency room once, and got pain relief from my private doctor once.

Prior to going to Saudi Arabia, I considered myself in good physical condition, as I enjoyed running three to five miles a day, worked out at the

gym three times a week, and participated in a number of sports. Since then, my running has halted because of pain and it takes an exorbitant amount of drugs for me to tolerate participation in a simple game of golf.

Early in 1992 I finally realized total body pain, fatigue, weakness, headaches, rashes, nausea, vomiting and the like were here to stay. But, most saddened and disheartened am I by what has happened to other faithful, honest, and dedicated soldiers who served this country. I've met them in the veterans' hospitals, where in addition to being chemically sensitive, they suffer with swollen extremities, memories that don't recall, and nervous systems that are disabled in ways doctors don't understand. Like me they to went on behalf the United States to the Gulf War, yet receive no VA economic or rehabilitative assistance because they can't prove in what ways and how badly they are injured.

I firmly believe the DOD and VA medical communities are being pressed far beyond their capabilities with having to diagnose and treat just a few thousand soldiers who were smitten by very low levels of acetylcholinesterase inhibitors, biological substances and radiation. Their illness result from exposure to a combination of NBC agents as a result their using DOD weapons, receiving biological and chemical prophylactics, and bombing of Iraq's chemical and biological munitions upwind from their positions. Imagine what the situation would have been like had Iraq used NBC weapons and we retaliated with same.

[The articles listed below were attached to the original testimony of Mr. Tetzlaff, but because of space constraints, are not reprinted here.]

LIST OF ATTACHMENTS TO WRITTEN TESTIMONY OF NEIL R. TETZLAFF BEFORE THE SENATE COMMITTEE ON VETERANS' AFFAIRS

Attch 1: Dunn and Sidell. "Progress in Medical Defense Against Nerve Agents." JAMA. August 4, 1989 - Vol 262. No.5. pp 649-652

Attch 2: PHARMACY ETHICS. "Waivers for military use of investigational agents." Am J Hosp Pharm. July 1991 - Vol 48. pp 1525-9

Attch 3: Excerpt from Memorandum to Commissioner of Food and Drugs. "IND 23,509 - Pyridostigmine Bromide 30 mg Tablets - Action." DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM. January 8, 1991. one page

Attch 4: Keeler, Hunt and Dunn. "Pyridostigmine Used as a Nerve Agent Pretreatment Under Wartime Conditions." JAMA. August 7, 1991 - Vol 266. No. 5. pp 693-5

Attch 5: DISORDERS OF NEUROMUSCULAR TRANSMISSION. Myasthenia Gravis." Merek Manual. 1991. p 1449

Attch 6: Keeler. "Interactions between Nerve Agent Pretreatment and Drugs Commonly Used in Combat Anesthesia." Military Medicine. November 1990 - Vol 155. pp 527-33

Attch 7: United States Army Medical Research Command research paper excerpt. Safety Summary. 1992. pp 71-4

Attch 8: SUPPLEMENTAL WRITTEN TESTIMONY ON CHEMICAL SENSITIVITY AND THE PERSIAN GULF VETERANS OF DR. CLAUDIA S. MILLER, M.D., M.S. BEFORE HOUSE COMMITTEE ON VETERANS AFFAIRS 1993. pp 1-9

INFORMAL / X FORMAL

# FINDINGS AND RECOMMENDED DISPOSITION OF USAF PHYSICAL EVALUATION BOARD

DATE: 11 JAN 94

1. THE BOARD CONVENED AT LACKLAND AFB TEXAS 78236-5607 PER ATTACHED ORDERS (Exhibit A)

2. A QUORUM WAS PRESENT AS INDICATED ON EXHIBIT A | 3. EXHIBITS ATTACHED: A, B, E, G, H-R

| 4. MEMBER'S NAME (Last, First, Middle initial) | 5. GRADE | 6. SOCIAL SECURITY NO. | 7. YEARS OF SERVICE UNDER 10 USC 1555 | 8. COMPONENT |
|---|---|---|---|---|
| TETZLAFF, NEIL R. | LT COL | 384-42-4728 | 26 | X REG AF / USAFR / ARS |

9. FINDINGS CONCERNING INDIVIDUAL DEFECTS OR CONDITIONS

Column A - Include degree of severity.

Column C - Enter "YES" for in line of duty, "M" for intentional misconduct, "N" for willful neglect, "A" for incurred during a period of unauthorized absence, or "NA".

Columns B and D - Enter "YES", "NO", or "NA".

Columns E and F - Self-explanatory.

| A. DIAGNOSIS | B. INCURRED WHILE ENTITLED TO BASIC PAY | C. LINE OF DUTY (Applies only if answer to B is YES) | D. DIRECTLY RESULTED FROM PRESCRIBED MILITARY DUTY (Applies only if answer to C is YES) | E. DISABILITY RATING (Percent) | F. VA DIAGNOSTIC CODE |
|---|---|---|---|---|---|
| History of severe reaction to pyridostigmine bromide, with resultant onset of nauseau, vomiting, fatigue, chronic pain syndrome, multiple system symptoms, and residual increased sensitivity. Mallory-Weiss tear resolved. | YES | YES | NA | 80 | 6399-6350 |

| 10. ADDITIONAL FINDINGS | YES | NO | NA |
|---|---|---|---|
| A. MEMBER IS UNFIT BECAUSE OF PHYSICAL DISABILITY | X | | |
| B. DISABILITY WAS INCURRED IN LINE OF DUTY IN TIME OF WAR OR NATIONAL EMERGENCY OR AFTER 14 SEPTEMBER 1978 | X | | |
| C. DISABILITY WAS THE DIRECT RESULT OF ARMED CONFLICT OR WAS CAUSED BY AN INSTRUMENTALITY OF WAR AND INCURRED IN LINE OF DUTY DURING A PERIOD OF WAR | | X | |
| D. DISABILITY WAS THE DIRECT RESULT OF A COMBAT RELATED INJURY (Applies only if member entered military service on or after 23 September 1975) | | | X |

11. DEGREE OF IMPAIRMENT ☐ IS ☒ MAY BE PERMANENT

12. COMPENSABLE PERCENTAGE: 80

13. RECOMMENDED DISPOSITION: RETAIN ON TDRL

14. SUMMARY STATEMENT ATTACHED ☐ YES ☒ NO

15. SIGNATURE OF PEB PRESIDENT OR PEB REPRESENTATIVE: Andrew M. Stanley Jr.
ANDREW M. STANLEY, JR., COLONEL, USAF

16. REMARKS

At this point, the available data indicates that the clinical condition is due to organic rather than psychological factors. Testimony provided by Dr. Claudia S. Miller, University of Texas Health Science Center, was extremely important in the overall evaluation of this case. The correlation between the onset of symptoms and exposure to pyridostigmine bromide was discussed in detail. The onset of nauses, vomiting, fatigue, diffuse pain syndrome, and persistence of symptoms is important in this case. (cont'd)

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# PREPARED STATEMENT OF REV. DR. BARRY M. WALKER, PERSIAN GULF WAR VETERAN, EAST PALESTINE, OH

TESTIMONY OF CHAPLAIN BARRY WALKER
May 6, 1994

Good morning. My name is the Rev. Dr. Barry Walker, and I want to thank you for the opportunity to testify today for the veterans of Desert Shield and Desert Storm.

I first entered the Army in January of 1964, and spent time in active duty from 1966 through 1970, the era of Vietnam. I was mobilized in September, 1990, with the Quartermasters Group (POL). We were responsible for theater fuel and bulk water for all the services. As a Chaplain, I supervised four Chaplain Unit ministry teams in Saudi Arabia, and ultimately in Iraq and Kuwait. We had some 4700 troops in the command, which was made up of Army Active Units and now activated Army Units from the Army Reserves and National Guard.

I was very healthy except for a slight blood pressure problem when I went to the Persian Gulf, and had no health problems during the first few months there.

On January 16, 1991, I received the first of 2 shots of a vaccine, but we were not told exactly what it was. We were later told that the purpose of the vaccines was to protect us; rumor was that it was for protection against anthrax. Also in January, after the first SCUD was launched, we were ordered to start taking some pills, although we were not told exactly what they were, either. All we were told was that the pills would protect us against chemical and biological weapons. We were told to take the pills, and not given a choice, though some soldiers did not take them. I was expected to be an example to others, so I took them at first. I later learned that these pills were pyridostigmine.

To my knowledge, none of the 4700 troops, except maybe the command Headquarters, was given any real information about the risks of these drugs or vaccines. We were not shown <u>anything</u> in writing, or told anything other than that these would protect us. My chemical officer was asked to find out more about the pills, and she shared some of that information with the Group Commander and a few staff officers. She said there were no problems with the pills.

The fact that we were given the vaccine or drugs was <u>not</u> recorded in our medical records, although I insisted that the vaccine be recorded in my personal record. Many soldiers did not carry a vaccine record, and most wouldn't have thought to ask that it be recorded. I don't recall any list being made of who was given the vaccine.

A few people seemed to get the runs after the vaccines, but there were no major problems. After the pills were distributed, more people got the runs and so they stopped taking the pills. Even people who were not sick stopped taking the pills because

they wanted to avoid getting sick. The commanders directed everyone that they should take the pills, but since the pills were taken in privacy, it was thus possible not to take them. The fact that people got sick was not included in their medical records.

I do not remember thinking that the vaccine or the pills that I took were causing me any problems, although I stopped taking the pills when I saw that they seemed to make people sick. However, around the same time I was having major problems with what seemed like allergies. I didn't pay much attention because I didn't have time to get sick -- I was an officer and I had a job to do. I kept going.

I started having problems with my back after the February 25, 1991, SCUD attack. It was probably from moving bodies, lifting debris, and so on, after Quartermaster Groups headquarters and barracks were hit. The attack was horrible; soldiers were killed, others lost limbs, one soldier's head was half blown off. Afterwards, when my back hurt, I went to the Med Hospital for treatment. Since I told them I had been moving bodies on cots, the cause was reported as being from moving cots.

We left the Persian Gulf at the end of May, and I was discharged on June 19, 1991. I was so happy to get home that I didn't worry that anything was wrong with me. I did go as a walk-in to the Pittsburgh Oakland VA on June 18, 1991, for treatment of back pain.

It wasn't until the summer, when I went to the Pittsburgh Oakland VA for further back treatment, that I realized something else was wrong. The VA doctor arranged for an EMG, CAT Scan, MRI, etc., to try and find out what was wrong. With the EMG, they did find that the nerves from my waist down were not as they should be, and that my right leg was worse than my left, which I had not noticed.

Because of my symptoms, I was also checked for suspected alcohol abuse, diabetes, and other possible causes, but they found nothing.

Now my symptoms include headaches, rashes, fatigue, loss of memory, sweating, and I sometimes have blood in my urine. I am unable to concentrate, and I have trouble sleeping.

For the past three years, I have been spending much of my time helping other Gulf War veterans and their families. I have taken over 150 veterans to the hospitals for treatment, or helped them in other ways. Many of them have symptoms similar to mine. Some are much more serious. Some just plain get lost for periods of time and do not know how they got where they are, some have blood in their urine. Some have trouble walking, some will pass out and not remember it. Their wives are having trouble dealing with them because of their anger and quick tempers.

Again, thank you very much for this opportunity to speak and I will be more than willing to answer any questions that you may have.

# PREPARED STATEMENT OF LEONARD COLE, PH.D., PROFESSOR, RUTGERS UNIVERSITY, RIDGEWOOD, NJ

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Testimony before the Committee on Veterans' Affairs
United States Senate, May 6, 1994

Open Air Testing with Simulated Biological and Chemical Warfare Agents

Leonard A. Cole, Ph.D.

My name is Leonard A. Cole, and I teach science and public policy at Rutgers University in Newark. My research interests include biological and chemical warfare policies, and I have written in particular about testing done in the U.S. Army's biological defense program.

I appreciate your invitation, Senator Rockefeller, to testify about experiments involving simulated biological and chemical warfare agents. These agents, which the army calls simulants, are intended to mimic more lethal bacteria and chemicals that might be used in actual warfare.

As described in my book, Clouds of Secrecy, the army began a program in 1949 to assess the nation's vulnerability to attack with biological weapons. During the next 20 years, the army released simulant agents over hundreds of populated areas around the country. Targets included portions of Hawaii and Alaska, San Francisco, St. Louis, Minneapolis, New York City, Washington, D.C., Key West, and many other cities. The purpose was to see how the bacteria spread and survived as people went about their normal activities.

Evidence suggested that the tests may have been causing illness to exposed citizens. Nevertheless, as army spokesmen subsequently testified, the health of the millions of people exposed was never monitored because the army assumed that the bacteria and chemicals were harmless.

Vulnerability testing continues at Dugway Proving Ground, 70 miles from Salt Lake City. Several smaller communities are

closer to the base, and Dugway itself is home to hundreds of civilians and military personnel and their families. The stated purpose of the tests is to evaluate biological detector systems and protective gear.

Since tests involve spraying simulants outdoors, it is important to understand how much risk they pose to humans who are exposed. Official statements have not always been clear on this matter. A July 1993 news release by the Dugway Public Affairs Office indicates that "no specific safety controls or protection are required for testing with simulants." The statement implies, erroneously, that the simulants are harmless.

In fact, during 45 years of open air testing, from time to time the army has stopped using certain simulants for reasons of safety. In each instance the army belatedly recognized they could be causing disease and death, although such information had long been available in the medical literature. This was the case in the 1950s when it ceased using the fungus Aspergillus fumigatus as a simulant. The fungus had long been known to cause aspergillosis, a disease that can be fatal. Similarly, in the 1960s the army stopped using zinc cadmium sulfide, a chemical that had been known for years to cause cancer.

In the 1970s, the bacterium Serratia marcescens, a source of infections that can lead to death, was taken out of service as a simulant. And in the 1980s, dimethyl methylphosphonate, a chemical known as DMMP, was removed from use as a simulant because of its carcinogenic and other toxic potential. I understand that one of today's witnesses, Earl Davenport, was exposed to DMMP at Dugway in 1984 and may still be suffering health problems as a result.

Indeed, simulants now used at Dugway continue to pose risks. The chemical ethylene oxide, which is present in some of the mixtures used in outdoor spraying, is a known carcinogen. The bacterium Bacillus subtilis, while not generally seen as dangerous, is cited in medical textbooks as able to cause serious infections. In truth, any microorganism that seems harmless under some circumstances may cause illness under others.

Exposure to high concentrations of any microorganism can be critically dangerous to people in weakened conditions. The elderly, the very young, people with AIDS and others who have weakened immune systems are more susceptible to lifethreatening infections. Nevertheless, the army has not monitored the health of citizens who may have been exposed during its tests, while maintaining that its bacterial agents cause no harm.

In addition to people who are unwittingly exposed to the army's bacteria and chemicals, human research subjects may not be receiving appropriate information. A test at Dugway in November

1993, for example, raises important questions in this regard. The test was intended to assess the ability of chemical agents to penetrate protective clothing.

Test subjects wore special outergarments and were then sprayed with chemicals in simulated battle conditions. An army Environmental Assessment before the test indicated that some of the chemicals could be toxic. Yet the consent form that the subjects signed in advance of the test said nothing about any of the chemicals.

Subsequently, two of the test subjects said they were asked to sign another consent form sometime after the test had been completed. The second form described the chemicals. But having the subjects sign a consent form after an experiment, rather than before, makes little ethical sense. The procedure renders meaningless the notion of informed consent.

Finally, several physicians at the University of Utah Medical School in Salt Lake City continue to express concern about the tests at Dugway. They do not feel they have information that would enable them optimally to handle infections and complications that might be caused by the tests. Dugway officials have thus far not satisfied their concerns either about field tests involving simulants or indoor tests with highly pathogenic agents.

These are a few of the disconcerting issues associated with testing at Dugway. If such tests must continue, several policy suggestions seem appropriate:

--Inform people in the area before each test that they may be exposed to the army's biological and chemical agents.

--For a substantial period after each test, monitor the health of the exposed population.

--Provide comprehensive information in understandable language to human subjects before they participate in any test.

--Fully inform the neighboring medical community about the nature of each test and its possible medical complications.

--Above all, strive for safety, candor, and openness.

## PREPARED STATEMENT OF THOMAS J. CALLENDER, M.D., LAFAYETTE, LA

Mr. Chairman and members of the Committee: My name is Dr. Thomas J. Callender, M.D. I am pleased to have an opportunity to address this committee. I am a physician in private practice who specializes in Internal Medicine as well as Environmental and Occupational toxicology. During the course of my medical practice, I have had the opportunity to evaluate thousands of individuals who have had illnesses that developed as a result of medications or exposures to chemical agents. As a result of this experience, I have been involved in many publications concerning the toxic effects of chemicals and heat stress.

I have interviewed about forty Desert Storm veterans, performed extensive medical evaluations on three and have reviewed medical records on several more. I have also evaluated many patients who have been taking medications or been exposed to chemicals similar to those at issue with the Desert Storm soldiers. Based upon my evaluation of the soldiers and my experience, I would like to make several observations.

First, as a result of their activies in Iraq-Kuwait-Saudi Arabia, the physical health of many of the Desert Storm veterans has been seriously impaired and many more are having significant problems. My second observation is that the military has abandoned the soldiers and behaves as if it does not want to know what happened. Many of the soldiers I talked to are heroes in the classic American sense of the word and this country should be proud of them. One particular soldier stands out in my mind, Carol Picou. It is people like her and the thousands of other American soldiers that makes America worth figthing for. They are not disposable objects to do a job and then be discarded when they are no longer needed.

There are many possibilities regarding the potential etiologies of their complaints; however, the use of experimental drugs was of major concern to the soldiers and to myself. For these possibilities to be properly explored, an honest and frank evaluation must be made of the facts; however, the military is very recalcitrant to explore this possibility.

The military has erroneously, superficially and often deliberately chosen to conclude that the Desert Storm veterans are either over stressed, neurotic or simply seeking secondary gain. In cases where physical impairment is undeniable, the military has simply turned its back on the soldiers and denies that the soldiers' problems could be related to Desert Storm.

Many of the military health professionals do not have the proper training to deal with complex toxicological subjects. Those that do have the basic knowledge take an antagonistic posture before thay have seen the facts. The military health professionals that do need information are reluctant to seek information outside their fields. It has been my experience that military health professionals who do ask for assistance of knowledgeable physicians outside the military, avoid doing so officially as if they are afraid of their superior's awareness of such a contact. In fact, civilian physicians are frequently ignored or verbally attacked by the military personnel who have not even researched the subjects at issue. Whenever asked to explain their behavior, I have been told that they state that they are following orders.

Although I am positive that the vast majority of the Desert Storm veterans who are complaining about their health do indeed have significant health problems, I do not know, as of yet, what actually caused their problems. The interviews that I have had with many veterans have suggested several possible etiologies for their complaints. I believe that the main possibilities would be as follows: Toxic effects of the pyridostigmine bromide (given as an anti-nerve gas agent), adverse reactions to the immunizations given for biological agents (e.g. anthrax and botulinum toxin vaccinations), chemically adulterated pesticides used in the camps, chemically contaminated food or water due to the poorly controlled methods used to obtain and to transport food and water, exposure to organic solvents and other chemicals used for maintenance of equipment, exposure to chemicals such as volatile organics, organic tin and organic lead that are used as fuel additives, exposure to unknown chemicals from the smoke produced when Iraqi munitions bunkers and military equipment were destroyed by explosives and fire.

I also believe that the involvement of an unknown biological agent, natural or man made, needs to be ruled out. Legionnaire's disease and the AIDS virus have been around for a long time, however, it took serendipitous circumstances for us to realize that these microorganisms even existed, much less a cause for public concern.

To reach a definitive conclusion as to the etiology of the Desert Storm Syndrome would require a combination of epidemiological studies, interviews of veterans by specially trained physicians, comprehensive medical evaluations and site evaluations for possible biological or chemical agents.

I am particularly concerned about the military medical personnel and their apparent lack of knowledge or lack of willingness to use the state-of-the-art medical testing that could be applied to these problems. As a nation we have spent fortunes developing and using smart weapons, however when it comes to our servicemen, the military is using routine medical techniques as if looking for a common cold.

I would like to address one item on the list of possibilities above, i.e. pyridostigmine bromide (PYB). It is my medical opinion that PYB has not been adequately tested to be safely given to hundreds of thousands of people as a prophylaxis for chemical warfare.

1) Pyridostigmine's biochemical mechanisms are not well enough understood to be safely used in such a large scale manner as seen in Desert Storm. PBY is a compound that is well known to act as an inhibitor of the enzyme acetylcholinesterase (AChE). This class of agent is essentially a pesticide or nerve poison and works in a fashion similar to other nerve poisons used as chemical warfare agents. Its intended purpose is to utilize the fact that PBY is believed to not bind permanently to the acetylcholinesterase enzyme as the more potent chemical warfare agents. It is very important to realize that other acetylcholinesterase inhibitor agents have been discovered to have mechanisms of action other than AChE, e.g. Neurotarget esterase (NTE). NTE effects result in permanent damage to the nervous system whereas AChE effects are believed to be temporary. Other biochemical pathways could be involved in the toxicity of these chemicals, e.g. cyclic AMP, however, little research has been done in this area. What research has been done indicates that additive or multiplitive effects are possible between PBY and many pesticide agents, caffiene and medications used in the Desert Storm War. New

biochemical mechanisms of action of PYB are still being discovered in in-vitro reasearch. How this exactly applies to human safety is still unknown but, the implication is that we should proceed with caution because all is not known about this drug. (1,2,3,4,5,6)

The bottom line is that AChE (temporary effects) have been studied with PBY, but not the many other known or possible biochemical pathways, despite the likelihood of their existence and importance, especially in producing permanent nervous system damage. These theoretical considerations are important in light of the fact that I have found significant and permanent nervous system damage in the Desert Storm soldiers I have evaluated. It is also important to note that the symptoms and findings reported by the Desert Storm soldiers as a whole are typical of what you would expect to see in victims of a neurotoxic poisoning. (7,8,9,10)

Most testing, to date, done or reported to have been done, on PBY has not used the state-of-the-art methods for looking for long term human neurological and psychological effects because of the assumption that this was not necessary. Neuropsychological testing, neuroimaging such as PET/SPECT, MRI, neuroelectrophysiological testing and other state-of-the-art modalities should have been used in animal and human studies. Anything less than these technologies are not adequate to define toxicity to the nervous system. (11,12)

In a 1992 article in Military Magazine, we can see good examples of how inadequately PYB has been tested(13). This article attempts to show that PYB is safe under desert conditions. It fails to consider that if long term effects occur then a cross over design after seven days will not allow distinguishing between the two groups. They take all symptoms and lump the severity into two groups instead of allowing for a wider response range. They used an inadequate number of subjects for an inadequate length of time, i.e., they started off with seven very healthy males, but not all finished the test series. No subject had any health problems or was on any medications. The physical examination, biochemical testing and all parameters measured were all based upon the assumption that only immediate and short term AChE effects could occur. There is no long term follow up of the subjects to monitor the kind of problems they may be have having weeks or months later. It is well known that the AChE inhibiting agents that cause permanent nerve damage typically take several weeks to months for the nerve damage to become evident; however, this article mentions studying the subjects only during the two test periods, therefore, the subjects had zero to one week followup after exposure. They say that very few symptoms occured, but they do not explain why so many Desert Storm soldiers did have acute symptoms. Were they comparing the same drug, same bioavailability, same dose? Were blood tests done in combat to verify the proper dose was being absorbed as was done in the tests? These authors note that the greatest effects were seen in people who took the PYB the longest, however, they failed to extend any testing past seven days. They do talk about how the PYB affects the parasympathetic nervous system. I have seen Desert Storm soldiers that I believed had degeneration of the parasympathetic nervous system. It is hard to evaluate symptoms of AChE inhibition in a group of men doing strenuous physical exertion in a heat stress chamber because many of the symptoms will be confused with those due to the physical environment, therefore, many of the parameters they intended to measure, e.g. fatigue, salivation, shortness of breath, weakness amd nausea, will be difficult to evaluate.

Research done by the Department of Defense excluded people with a susceptibility to PYB, however, such screenings for susceptibility were not done in combat personnel. Additionally, women were never included in the studies despite the fact that they would obviously be in combat areas. These facts make the entire concept of the safety of PYB as being promoted by the military untenable. If only a few percent of the soldiers are susceptible, then many tens of thousands of individuals are at risk for serious side effects. I believe that it is deplorable that there is pertinent U.S. government research done regarding PYB safety issues that has not been released to the public. I believe that it is imperative that this information be made available for independent analysis.

Note that in a paper by J.R. Keeler, a conclusion is reached that since they estimated that 0.1 to 1 percent of soldiers had adverse symptoms to PYB severe enough to require that they stop the PYB and that in general the soldiers performed their duties well. The soldiers I spoke with reported that if they had bad symptoms they were told to take the PYB anyway and that some did have problems performing their duties, for periods of time, after taking PYB. This paper uses information supplied by the medical officers and not the combat soldiers, and does not use any independent means to gather unbiased information nor does it use any physiological or neuropsychological means to objectively measure long term health effects in these soldiers. Judging from the number of soldiers that I belive to be ill, I think it would be impossible interview 41,650 soldiers and to find only 1 % of the soldiers with significant, immediate symptoms (14).

Note that research has clearly indicated that there are sexual differences in response to PYB, therefore safety research that excludes gender considerations poses an unwarranted risk to women in combat zones (15).

Much of the research done on PYB as described above typically has several reoccuring flaws: a) They only used used short term exposures of several days. b) Only immediate effects and not long term effects were measured, c) the mechanisms of toxicity were assumed to be only, reversible AChE inhibition and d) The end points tested for, were not comprehensive enough. The paper by Glikson on human neuromuscular function is a good example(18).

Most PYB literature seems to indicate that PYB does not affect the central nervous system. It is important to note, however, that even such a basic issue is not clear because contradictory literature exists that indicates that PYB human central nervous system effects apparently do occur, e.g. inhibition of somatostatin secretion from the hypothalamus. (17)

2) PYB has not been adequately tested in regards to synergistic or additive effects with other chemicals, pesticides or medications.

Synergism means that when a victim is exposed to combinations of chemicals or medications, the outcome is much worse than what you would expect the toxicities of the agents by themselves. Additive effects occur when the toxicity of combination can be predicted by adding up the toxicity of each component of the combination.

The importance of synergism is obvious when you consider the Malathion as an example. This pesticide is considered one of the less toxic pesticides on the market. When a human is exposed to Malathion, their natural body chemistry begins to break the pesticide down, i.e. to detoxify it. However,

impurities in the Malathion, other pesticides, chemicals or medications can amplify the toxicity of the Malathion by many times because the presence of these other compounds block the ability of the victim to detoxify the Malathion. Malathion breaks down spontaneously with heat and time to form potent synergistic contaminants and can be synergistic with many other common pesticides and chemicals. In other words, consider that medications such as PYB likely interact with other medications and many pesticides and that combinations of pesticides such as Malathion and others were frequently used in Desert Storm. Also consider that many of these agents have the likelihood of amplifying each other. Apparently, testing to determine synergistic effects between PYB and medications, pesticides and chemicals commonly found in a battlefield has not been done.

3) PYB has not been adequately tested in regards to how it will affect individuals with different genetic make up despite the fact that there is a tremendous variability between individual humans. Testing on lab animals is often not as informative regarding such issues because the animals are deliberately chosen for experimental reasons to ensure a similar genetic make up. Repeating these experiments to take into account genetic variations is usually not done, therefore, such constrained data is hard to extrapolate to predict what will happen when a large, heterogeneous human population is exposed. Some of the patients that I interviewed that had the worst side effects from PYB also had personal histories and familial histories of an intolerance to many medications, therefore, suggesting a genetic, biochemical susceptibility. This history was ignored, as well as complaints of adverse reactions following each time the PYB was taken. It is also important to note that the research done by the Army used very healthy males and did not use females or anyone with any medical problems or that was on any medications.

4) There exists animal testing that shows that PYB can be severely toxic and cause degeneration of the muscles and nerves associated with muscles within days of exposure. (18,19,20,21,22) I have seen muscle and nerve degeneration in Desert Storm soldiers that is similar to the changes described in animal studies.

Some past animal studies were inadequately designed and are not adequate to define long term health effects at doses and lengths of exposures comparable to combat useage with variablility of genetics, simultaneous medications and comparable human health problems. These studies usually do not measure end points or effects that have adequate clinical relevance. The pubication by Kerenyi et al is an example of research that could be misleading concerning PYB safety if you do not understand the studies limitations(23).

This paper is in direct contrast to the one quoted in 4) above and other articles that indicate definite behavioral changes due to PYB in rats at doses comparable to those given to soldiers(24).

5) Adverse reactions do occur in humans. (25,26,27)

The exact incidence of adverse reactions to pyridostigmine is not clear and what information does exists shows a great variation in incidence between studies. This is partly due to differences in definitions of adverse reactions, dose, length of time exposed, small numbers of subjects in the studies, methods of data collecton, methods of measurement of adverse reactions, ect. In a study done by the U.S. Army, three out of six persons had to be taken off PYB (25).

In other study the incidence of adverse reactions was 1 percent(14).

The true incidence of a wide spectrum of adverse human reactions and variable severities to PYB has not been precisely determined and in fact may be related to several variables.

It is clear that individuals participating in tests with PYB had the opportunity to be taken off PYB when they became symptomatic, however, the soldiers in Desert Storm had to continue past that point.

This army study also does not indicate what became of the three persons who got ill or if long term follow up was even done (25). If the adverse responders are all removed from the study before they become severely ill, but combat soldiers are requried to take PYB irregardless of the symptoms, then we can not compare the incidences and severity of adverse reactions in monitored tests to those in combat.

6) Much of the human data comes from giving pryidostigmine to patients as a treatment for myasthenia gravis. These patients already have a neurological disease with neurological impairments and symptoms.

The development of medical problems from the use of PBY in MG patients will, therefore, be likely overlooked due to MG as a confounder. I have used PBY and similar medications of myasthenia gravis patients and noted that these drugs can easily cause adverse effects, the dose is critical and varies greatly between individuals and in the same individual on different days. Myasthenic patients also receive other medications such as prednisone that could be protective of some of the side effects of PYB. Additionally, myasthenia gravis patients have an abnormal physiology that allows them to benifit from PYB analogous to a diabetic benefiting from insulin. Diabetics can take hundreds of units of insulin without harm, however 5 units given to a normal, i.e. non-diabetic person, can cause serious harm. You could consider that the diabetes mellitus "protects" against the ill effects of the insulin. In a similar fashion, a normal, i.e. non-myasthenia gravis person, could have adverse effects from PYB that is tolerated by a MG patient. Also note that MG patients can get side effects such as diarrhea, blurry vision, salivation, etc however we normally do not expect those symptoms at lower doses. Why did the Desert Storm soldiers have so many side effects at supposedly lower doses?

7) Despite their adverse symptoms to PYB and warnings in military training manuals, many of the Desert Storm Veterans that I interviewed were required to continue taking PYB. The symptoms that they reported were of the type that indicated adverse effects of an acetylcholinesterase inhibitor. Some units also took PYB longer than recommended.

8) My experience interviewing the Desert Storm soldiers indicates that there is significnat a discrepancy between the incidence and severity of symptoms expected from public literature and the actual incidence.

Besides possible differences in personnel with regards to age, sex, race, genetic phenotype as well as synergistic effect, we should consider the possibility that there were differences between the PYB preparations used in research and those used in actual combat. There are several possiblities, e.g. differences in bioavailabilty, possible errors in strength made during preparation, lengths of time the drugs were used, aging or deterioration effects secondary to storing the drug for extended lengths of time or new and the use

of enhanced formulations that could have contained components intended to increase the protective capacity of the medication (28,29). It has been long established that certain anti acetylcholinesterase inhibitors will deteriorate with time or heat and will form much more toxic chemicals.

Such theoretical possibilities need to be considered in evaluating the Desert Storm Syndrome.

9) Whenever evaluating issues such as the effects of chemicals on the human nervous system, we must consider the biases of the parties involved in the evaluation process. Some agencies in the Government of the United States have done outstanding work in regards to defining toxicities and informing the public as to the health hazards from chemical exposures and pharmaceutical agents. There are components of the same government, however, that have an adversarial position in regards to the proposition that chemicals or medications can cause long term adverse health effects. A good example is that on many military bases, civilian workers are often exposed to hazardous chemicals. The federal worker's compensation system bitterly fights the workers attempts to receive their basic workers compensation rights. I have seen examples were the same military that spends billions of dollars on its military objectives, has spent millions of dollars on useless safety equipment and payments for sick leave and medical costs, yet it will fight against providing basic safety equipment to civilian workers, protecting the environment around military installations or giving medical assistance to the injured.

I believe that the possibility exists that an act, of omission or commission by the military, has caused or contributed to the development of these illnesses. We must then assure ourselves that an objective evaluation of these matters is possible. Based upon the reports I have received by soldiers regarding their harassment by the military for reporting medical complaints, I must conclude that a serious attitude and communications problem exists and would likely interfere with investigations of the soldier's complaints. Note that several soldiers told me that their medical records had not be properly updated with what they had been exposed to nor the obvious adverse reactions they reported.

When those records had been accurately updated in the field, that information had been removed before returning to the United States.

I do not know for certain the specific causes of the Desert Storm Syndrome, however, I believe that there are definable causes that can and need to be found and that the soldiers need to quickly receive adequate medical care and support. In this testimony I have only tried to outline some issues that need to be taken into account. The potential etiologies of the Desert Storm syndrome need to receive an objective, unbiased and comprehensive evaluation that is long overdue. Based upon my medical training and experience with this matter, I recommend the following as part of the evaluations needed by the Desert Storm personnel.

They need a complete, basic medical evaluation to look for and to rule out garden variety illnesses.

They need to have a standardized, structured interview that contains the proper questions concerning the type and severity and chronological development of symptoms and a description of the soldier's activities, including geographical position and dates and times, wind direction, etc while in the Middle East, as well as estimations regarding types and degrees of exposures.

The soldiers need to be triaged based upon the results of their symptom profiles and they need to be divided into categories based upon severity and type of symptoms, i.e, neurological, pulmonary, dermatological, etc.

All of the most significantly effected soldiers, a selected number of the less affected soldiers and some controls, e.g. combat veterans from Granada, Somalia and Panama, need evaluations by state-of-the-art testing methods that are appropriate for the problems observed in that individual or group.

These tests would include state-of-the-art testing such as Positron Emission Tomography and/or 3 headed Single Photon Emission Computerized Tomography of the brain. PET is available at the VA hospital in Los Angeles via Dr. Ali Khonsary, M.D.). SPECT is available at most major hospitals.

Other tests would include visual, cognitive, somatosensory and auditory brain stem evoked potentials, quantitative and standard electroencephalograms, rotational chair and dynamic Posturography, electromyography, electro-nystagmography nerve conduction velocity and quantitative sensory testing.

Note that such tests are available at the best medical institutions, and most major hospitals, including VA and active duty hospitals, and are used by NASA and the Department of Defense. It is interesting to note that when such common medical tests have been used to diagnose the Desert Storm soldiers, the military states that such tests are experimental or not valid, however, they use the same tests themselves when it suits their objectives.

Proper medical studies and comprehensive toxicological studies need to be done to properly explore the toxicity of pyridostigmine bromide and the experimental immunizations as well as to study the potential synergistic interactions between those agents and other factors such as chemicals, medications, and genetic make up of the soldiers.

In the Desert Storm troops of which I have personal knowledge, I can not emphasize enough, their sincerity and honesty, nor can I adequately describe the seriousness of their condition, the amount of suffering caused by their medical problems and the humiliation of being abandoned by the government that they fought for. Once again we are witnessing a historical tragedy where many dedicated Americans put their lives on the line in the service of their country and their country is letting them down. We should put the same energy and resources into protecting and helping our American soldiers as we put into protecting our strategic interests and as in helping other countries and their citizens.

We should not let politics, saving face or hidden agendas deter us from our sacred duty to our soldiers.

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**APPENDIX**

**Neurotoxins:At Home and The Workplace: Report to the Committee On Science and Technology U.S. House of Representatives 99th Congress**

WHAT DOES NEUROTOXICITY MEAN? A poison to the nerves
Pg 3: "A. THE NERVOUS SYSTEM
The nervous system performs the important biological task of directing and maintaining normal bodily function, as well as processing, storing and releasing information that allows the human being to be unique among mammals. However, this intricate and crucial system is often affected by chemical substances present in the environment. Some of these effects are short-term and reversible, e.g. dizziness and nausea; other effects- such as loss of memory and motor coordination-are long-lasting, permanent and even progressive."

"A neurotoxin is a substance that can damage the nervous system permanently or temporarily interfere with nervous system function so as to produce significant harm to the exposed person."

"Neurotoxins affect parts of the nervous system to different degrees. Often, they affect peripheral nerves found in the extremities, thereby causing weakness in the hands and feet, motor coordination problems, and loss of sensation."

"Some neurotoxins can damage the fatty coating (the myelin sheath) that surrounds the nerve fibers of the central and peripheral nervous system and irreversibly diminish or destroy motor ability and organ function. Most importantly, neurotoxins can cause prolonged imbalance of critical chemical systems (called neurotransmitters) used by the brain to transmit information. Chronic chemical imbalance in the brain can lead to debilitating neurological dysfunction, as seen in the involuntary movements of the drug-treated schizophrenic or the patient afflicted with Parkinson's Disease. Thus, exposure to neurotoxins may result in devastating neurological or psychiatric disorders that impair the quality of life, cripple and potentially reduce the highest intellect to a vegetative state.

Pg 1 " People who have experienced acute exposure to neurotoxins show the readily recognizable symptoms of dizziness, nausea, muscle weakness and blurred vision. But, symptoms of chronic exposure-such as increased irritability, loss of memory, inability to concentrate, and sexual dysfunction-may go unnoticed, or be ascribed to social pressures rather than to neurological damage.

**Singer- Neurotoxicology pg 8** In 1976 estimated that 40,000

chemicals and 2,000,000 mixtures in common industrial use and 1,000 new compounds were being developed each year.

**Neurotoxins:At Home and The Workplace: Report to the Committee On Science and Technology U.S. House of Representatives 99th Congress**

"Most commercial substances have not even been examined for neurotoxicity. As of 1989, thorough neurotoxicity testing of commercial products is not practiced."

Pg 2 para 2: "... recent studies suggest that neurological damage from environmental factors can cause diseases virtually indistinguishable from Parkinson's and Lou Gehrig's disease."

CASE EXAMPLE #1:
pg 2 para 3: "..., the hearing testimony of Frank Carsner, a former painter from Portland, Oregon, illustrates the importances of regulating exposure to neurotoxins in the workplace. Mr. Carsner was a master painter at a large truck manufacturing plant for eight years. As a result of inadequate protection from paints and solvents he now suffers from brain and nervous system damage in addition to the other organs and muscle dysfunction and, according to his testimony, he reacts violently to solvents, acetones, glues, nail polishers and similar substances.

Case #2: pg 2, 8-9 "In 1979, a substance called BHMH was introduced into a factory in Lancaster, Texas as a catalyst in the manufacture of reinforced bathtubs. After only a few weeks, it started causing serious problems, first among one operator, who was then replaced, then among the second operator when came up the line. It was almost like a battle line. (One pers fell down and the next one came up and held the pipe, * * * and so and so on. It was a mini-epidemic. Years later, some of the affected workers still show signs of muscle weakness and sensory loss."

The incident in Texas demonstrates several of the health effects of neurotoxins discussed at the hearings. The rapid incapacitation of the workers brought on by the gross over-exposure to BHMH, followed by the long-term effects evidencing poorly reversible and probably permanent, nervous system damage, show the susceptibility of the nervous system to be attacked from environmental substances."

**NEUROTOXICITY TESTING:**
"Presently, there are two general types of tests used to determine whether a substance is neurotoxic. **Neurological tests**, consisting of pathological and electrophysical examination, can detect the pathophysiological effects in animals of both acute

and chronic exposures to specified chemicals. However, some neurotoxic effects produce subtle behavioral changes that may not be detected through pathological examination of the nervous system. Thus, **behavioral tests** are often employed to measure changes in the learning, response times, movement and motor abilities. It has been suggested that behavioral test may be especially useful as test screens that may show the need for further in-depth neurological examination of suspect chemicals."

Lesions of specific areas of the brain result in specific signs and symptoms. These areas of the brain are associated with such functions as:

Frontal lobes:pain perception, intellect, concentration, autonomic function, respiration and blood pressure.
Temporal lobes: odor, auditory function.
Limbic System: restlessness, emotions, odor, motion, sensory function, autonomic nervous system, hyperactivity, biorhythms.
Hypothalamus; endocrine system, obesity, libido, temperature contro
Thalamus; muscle tone, perception of sensation, central pain syndro
Basal Ganglia; muscle tone spacitity, tremors, movement disorders.

BRAIN SCANS:

**Image Processing for the Study of Brain Structure and Function: Problems and Programs-Nancy Andreasen, Gregg Cohen, et al Journal of Neuropsychiatry 1992;4:125-133**

Medical imaging with devices such as SPECT allows clinicians the capacity to see brain structure in a high level of detail and to observe metabolic and neurochemical processes in the brain such as cerebral blood flow, glucose utilization, and neuroreceptor occupancy and blockade.

...these techniques are clinical tools to permit physicians and render judgment as to whether a structure or function is normal or abnormal.

**Regional Cerebral blood flow at the time of diagnosis of chronic toxic encephalopathy induced by organic-solvent exposure and after the cessation of exposure.**
Scan J Work Environ Health 1989: 15:130-5 Stefan Hagstadius, BA, Palle Orbaek, Jarl Risberg, May Lindgren Regional cerebral blood flow was abnormal in patients with chronic toxic encephalopathy induced by organic solvent exposure.

**PET and Neurobehavioural Evidence of Tetrabromoethane Encephalopathy** Lisa Morrow, Tom Callender, Journal of Neuropsychiatry, Volume 2 Number 4, Fall 1990

**Three Dimensional Brain Metabolic Imaging in Patient with Toxic Encephalopathy** Tom Callender, M.D. Lisa Morrow, et al World Health Organization meeting on Neurotoxicology in Japan July 1991

**A Case of Organic Solvent Exposure and Temporal Lobe Demyelination:** M.S. Gatley, G.A. Kelly, I.W. Turnbull Department of Occupational Health and Diagnostic Radiology North Manchester General Hospital Manchester, U.K.
Organic exposure resulted in left temporal lobe on CT with chronic exposure.

**A Proposed National Strategy For the Prevention of Neurotoxic Disorders,** The Association of Schools for Public Health, 1988 pg 2 "Many more workers may be exposed for short periods to high concentrations of substances that may lead to neurotoxic health effects."

**Encephalopathy and Vestibulopathy Following Short-Term Hydrocarbon Exposure:** Michael J. Hodgson, Joseph Furman, et al Journal of Occupational Medicine Volume 31/January 1989 pg 51-53

**Acute tolulene poisoning. Electroneurophysiological and vestibular investigations.** G.P. Biscaldi, M. Mingardi, G. Pollini, A. Moglia and M.C. Bossi, Toxicological European Research Volume III no 6, November 1981 **chronic changes after acute exposure.**

**PHYSICIANS TRAINED IN NEUROTOXICOLOGY:**
Neurotoxins:At Home and The Workplace: Report to the Committee On Science and Technology U.S. House of Representatives 99 Congress
"Dr. Spencer. There are remarkably few individuals who have toxicology training in medicine and who are sensitized to the possible problem of neurological effects, behavioral effects, psychiatric effects resulting from occupational exposure. "

**SYMPTOMS OF NEUROTOXICITY:**

The book **"Neurotoxicity: Identifying and Controlling Poisons of the Nervous System"** published by the Congress of the United States, Office of Technology Assessment, 1986, pg 46 gives a list of typical symptoms that occur with exposures to toxic substances.

It is interesting how many unusual types of symptoms can result from toxic exposures that are not typical of many other illnesses, e.g. that symptom of intolerance to smells and low level chemical vapors that many Desert Storm soldiers have reported. This type of symptom is characteristic of a certain medications or industrial chemicals.

> **Disturbances of smell: Cacosmia and Neurobehavioural Dysfunction Associated With Occupational Exposure to Mixtures of Organic Solvents.** Chris M. Ryan, Lisa Morrow, Michael Hodgson, American Journal of Psychiatry, 1989.
>
> Abnormal reactions to environmental chemicals, such as odor intolerance, results from exposure to organic solvents and is associated with neuropsychological test abnormalities.

Other books, medical or scientific articles relating symptoms of chemical toxicity are listed below. Note that each of these sources lists many symptoms that the Desert Storm soldiers have and yet our Vets have been often dismissed as being emotionally weak, neurotic or seeking secondary gain.

> **Neurotoxicity Guidebook:** Raymond Singer Van Nostrand Reinhold New York, 1990 Pg 3-8
>
> **Effects of Vapor Phase Pollutants on Nervous System and Sensory Function-Robert I. Henkin, M.D.** pg 210
> "With repeated and prolonged exposure to carbon monoxide and other substances of this type, neural and sensory changes occur that can alter various aspects of sensory perception including visual acuity, temporal perception and higher mental function. These effects may be long lasting if exposure is protracted.
>
> Sensory changes may be early and useful diagnostic signs of the toxic tissue levels of these substances in man. Dysgeusia, usually phantogeusia (a phantom, usually metallic, taste present in the oral cavity without the presence of food) may occur after toxic exposure to lead or mercury.

**THE RECOGNIZED LIST OF SYMPTOMS AND REFERENCES INCLUDE:**

> nausea, loss of appetite, vomiting, diarrhea
> persistent taste of gasoline
> headache, weakness, mylagia, ataxia, feeling of drunkenness, light- headedness, fainting,

narcotic effects accompanied by exhilaration, dizziness, neuropsychological: behavioral, cognitive, and emotional dysfunction; dizziness, fatigue, paresthesia, pain, weakness; subjective complaints of memory disturbances; impairment of memory lack of concentration, general intellect, problem solving, speed and initiative; emotional symptoms: increased fatigue, depression, anxiety, emotional liability, irritability, loss of intellectual ability of sufficient severity to interfere with social or occupational function; chronic prolonged solvent exposure can result in dementia.

Neurophysiological: EEG: loss of neurons or neuronal function, ENG: peripheral neuropathy, dynamic posturography- vestibular dysfunction
SPECT (cerebral blood flow)- significantly lowered regional cerebral blood flow, mainly in temporal parietal lobes, basal ganglia, hypothalamus
chronic prolonged solvent exposure can result in current perception threshold damage: slowed sensory nerve conduction velocity - polyneuropathies.
electroneurography: slowed motor sensory nerve conduction velocity - mono and polyneuropathies.

References: **Neuropsychological Toxicology**, Hartman, D.A., Pergamon Press, 1988 Pa 115-120

**"Three Dimensional Brain Metabolic Imaging in Patients with Toxic Encephalopathy"**,Callender, T.J., Morrow, L.A., Subramanian, K., Duhon, D., Ristovv, M.E. presented at the 4th International Symposium on Neurobehavioural Methods in Occupational and Environmental Health, Tokyo, Japan, 1991

**Singer, 1990 pg 11, Table 1-2**

**HAMILTON, A., HARDY, H.**
**PSG PUBLISHING CO., 1985 PP 269**

**Neurotoxins:At Home and The Workplace: Report to the Committee On Science and Technology U.S. House of Representatives 99 Congress pg 2**
**(2-t-butylazo-2-hydroxy-5-methyl hexane (BHMH)**

**"Changes in Psychological Performance of Solvent-Poisoned and Solvent Exposed Workers."** Linstrom,K. American Journal of Industrial, Medicine vol 1, 1980, p.69-84;

**"Psychological Function Changes Among Maintenance House Painters Exposed to Low Levels of Organic Solvent Mixtures."** Linstrom, K. Wickstrom, G.

**Acta Psychiatrica Scandinavia, Supplement 303, 67, p. 81-91** industrial toxicology.... sleepiness, fatigue, "drunkenness," slurred speech, disequilibrium, disorientation, depression, loss of consciousness.

**Effects of Vapor Phase Pollutants on Nervous System and Sensory Function-** Robert I. Henkin, M.D. pg 201 "...CNS depression, headaches, anorexia, fatigue muscular weakness, neuromuscular drowsiness, and loss of consciousness."

Tremors of extremities, eyelids, tongue, the facial muscl and the remainder of the extremities. Muscle excitabilit weakness and personality changes - "mad as a hatter" and peripheral neuropathy. REFERENCE; **OCCUPATIONAL MEDICI JOSEPH LADOU APPLETON & LANCE PUBLISHERS 1990 PP 271**

**A Proposed National Strategy For the Prevention of Neurotoxic Disorders, The Association of Schools for Public Health, 1988 PG 2-3** "The effects of neurotoxic agents on the central nervous system are less readily recognized. They occur with a wider range of chemicals and present more varied forms of disturbances. Perhaps the most striking CNS disturbances noted in Appendix 3 are those related to personality and cognitive functions. Psychoses and suicidal tendencies, for example, have resulted from high exposures of manganese and carbon disulfide. High concentrations of methylene chloride produce delusions and hallucinations. Cognitive dysfunction manifested as shortened attention span, lack of alertness, or loss of memory have obvious implications for safety; these are prominent neurotoxic effects that occur following exposure to many chemicals, such as carbon monoxide and a wide range of solvents.

**A Proposed National Strategy For the Prevention of Neurotoxic Disorders, The Association of Schools for Public Health, 1988 pg 6,** "Control of occupational exposures in specific workplace settings may involve a variety of approaches, including education, engineering controls, personal protective equipment and improved work practices.

pg 7 Ventilation is widely used to control neurotoxic substances, as illustrated by the use of local exhaust ventilation to control solvent exposures in tire manufacturing.

Throughout history there have been mass toxic chemical incidents, some of which are well known such as Bophal India. However, there are many other incidents such as the BHMH epidemic in **Lancaster Texas**, contaminated food from methyl mercury poisoining in Iraq and pesticide contaminated food incident in **Saudi Arabia**. These and many other epidemics involving

neurotoxic chemicals illustrate the concern we should have for a situation like the one that has developed in the aftermath of Desert Storm. The methyl mercury poisonings in **Iraq** in the 1970's that severely affected thousands of people because the Iraqi's mistakenly used grain for food that was intended for planting only and was coated with an antifungal agent, methyl mercury. In **Pakistan**, hundreds of people where poisoned with malathion that contained a toxic degradation product from malathion or its manufacture. Since this toxic ingredient is produced in malathion when it is heated and since the Desert Storm troopers were reported to have used a lot of Malathion in a hot environment, then we must consider such an event as that occurred in Pakistan to be very possible in the Desert Storm operation. Mass poisonings due to food that was contaiminated with pesticides has previosly occured in Saudi Arabia. The book **"Neurotoxicity: Identifying and Controlling Poisons of the Nervous System" published by the Congress of the United States, Office of Technology Assessment, 1986, pg 47** gives a list of various neurotoxic epidemics that have occurred in the past.

## PREPARED STATEMENT OF ARTHUR L. CAPLAN, PH.D., CENTER FOR BIOETHICS, UNIVERSITY OF PENNSYLVANIA

### I. Introduction

I would like to begin my testimony by thanking you Mr. Chairman and the other members of this committee for the opportunity to offer testimony on a subject that is of great concern to those currently serving in our military, to veterans and to the American people. The issues of what our has nation done and what ought be done in the future to protect the interests and welfare of military personnel who serve as test subjects in war-related research is vexing, complex, controversial and of the highest ethical importance.

I have been working in the field of medical ethics for more than fifteen years. I have held faculty appointments at Columbia University, the Hastings Center, the University of Pittsburgh, and the University of Minnesota. This month, I am assuming a new position as the Trustee Professor of Bioethics and the Director of the Center for Bioethics at the University of Pennsylvania. In the course of my academic career I have taught and written extensively on the ethics of human research. I have had the privilege of working with numerous Federal and state agencies and committees charged by law with protecting the interests of human subjects.

In my work in the area of the ethics of human experimentation, I have come to understand what I think is a crucial point which ought to guide this committee's inquiries into activities involving new, innovative or experimental drugs, vaccines or protective measures in situations where military personnel are the subjects of intervention such as the Gulf War and in earlier conflicts. Ethical problems in research involving human beings often arise, not from the desire to cross over a moral boundary, or to cut ethical corners but, from a desire to pursue a goal that is thought by those doing the research to be an indisputable good.

Even the most horrendous forms of human experimentation were justified by those who did the research on moral grounds. The outrageous experimentation conducted in the horrors that were the concentration camps of Hitler's Germany as well as the research undertaken in this country on the clinical course of syphilis during the forty year run of the ethical travesty that was the Tuskegee Study are all examples of immoral research carried out by persons convinced of the propriety of their actions.

Even outright fraud in research can occur from moral motives. While hardly credible, the explanation given by the physician/researcher in Montreal who is alleged to have falsified his research data in a crucial National Cancer Institute study aimed at determining the best way to treat breast cancer was his desire to help women gain access to the latest treatment.

It should not come as a surprise that those undertaking even the most heinous of research inquiries or who knowingly commit fraud usually have persuaded themselves that their actions are right. Most people want to do what is right. In research involving human subjects there are often many valuable and important goals that can come into conflict. It is difficult to protect the interests of human subjects not because researchers set out to hurt or harm them but because they so often set out to zealously pursue knowledge and to find beneficial treatments. This is a pursuit which may make it difficult to see

when the interests of subjects are being compromised in the pursuit of ethically laudable ends.

The problem of mediating among valuable goals and worthwhile purposes is very much in evidence in the area of research related to the prevention or treatment of war-related injuries and diseases using military personnel as subjects. Those involved in undertaking research or unapproved uses of vaccines or drugs with American military personnel do so in the earnest desire to provide them with protection against hostile action by an adversary with few if any moral scruples as to what weapons they are willing to employ. Those who seek to understand the risks of biological or chemical weapons and how best to treat those subjected to them want to insure our troops can perform the missions given to them. These are morally worthy goals. The moral challenge facing those conducting this hearing and those who are responsible for protecting the interests of human subjects who are also military personnel when asked to participate in new, innovative or unproven medical interventions is whether the pursuit of these goals has or might in the future come at a cost that is dubious or patently too high.

## II. Conflicts Among Morally Desirable Goals

Those who serve our nation in the armed forces understand that they may be called upon to sacrifice their lives in the course of that service. Those who serve and those who command them understand that they have military objectives to accomplish which can and do require the sacrifice of lives. Military leaders know that they could become involved in conflicts in which adversaries may use not only conventional weapons but, various treaties and international covenants notwithstanding, biological or chemical means of attack. Those in the military and those in government have a duty to our troops to provide them with the best possible forms of defense and prophylaxis against such weapons. We have a duty to provide the best available treatments against any and all manner of weapons that there is reasonable reason to suppose may appear in combat.

The clash of important values and goals—the importance of achieving the mission set for the military for our nation's well being and the need to protect our troops in order to allow them to accomplish their mission with minimal loss of life and morbidity must be weighed against the need to respect the rights of our fellow citizens who serve in the military. Every American must take responsibility for those who have been injured or made ill as a result of that service. And our government must be vigilant in its efforts in insure that the a proper and accountable balance is achieved among these various moral goods.

## III. Research in the Context of War: Hot and Cold

The most difficult context for conducting research upon military personnel is when the nation is threatened with the prospect of war or is actually engaged in an armed conflict. The pressure to do something to prevent harm from weapons whose possible effects are poorly understood can be enormous. During the past year we have begun to learn how the desire to learn more about the impact of radiation upon the human body in the context of the cold war led researchers to conduct experiments on unconsenting or uncomprehending subjects, both in the military and among civilians. The fear

of nuclear weapons led to the exposure of thousands of unconsenting military personnel to radiation during atomic bomb testing in the Pacific just after the end of the Second World War. The fear of biological weapons and agents such as nerve gas apparently led to ethically suspect experimentation on military personnel involved in conflicts as far apart in time as World War II and the Gulf War. Fear of mind control and the use of psychoactive agents led to the conduct of dubious experiments involving the use of LSD and other agents on uninformed subjects during the 1960s.

Some would argue that the entire category of ethically suspect research makes no sense in the context of war, hot or cold. When the threat to the nation's security is immediate, real and serious then the prevailing rules of human experimentation requiring the informed consent of subjects and prior review by research review committees must, of necessity, go out the window. The niceties of ethics regarding how to conduct human experimentation are for times of peace, not for the exigencies imposed by the threat or reality of war. But this argument is wrong.

The prevailing standards for human experimentation were set down as a direct response to experiments conducting under conditions of war. The Nuremberg trials at the end of the Second World War promulgated a code of research ethics that has been absorbed into both professional ethics and law by many bodies and governments in the years since that war. The Nuremberg Code makes no exception for research conducted in the context of war. The enormously important goal of protecting the nation's security is not held to be a value that is so overriding as to obliterate the individual subjects rights. The Code states clearly and unambiguously that everyone involved in research is to be so informed and that they are to have the right to give or withhold their consent to that research.

The need for informed consent and peer review of proposed research as essential prerequisites to justify experimentation is not modulated by the existence of a state of war. Moral standards have not shifted concerning the requirement for informed consent at any time during the past fifty years. Our own current law governing the use of human subjects where funding for research comes from the Department of Defense is not ambiguous: "Funds ... may not be used for research...unless the informed consent of the subject is obtained in advance..." (P.L. 98-525, 1401 (c), October 19, 1984, 98 Stat. 2615.)

What can be debated and what is more appropriate to debate is whether every untested and unproven medical intervention undertaken in the context of impending conflict or war constitutes research. What can and should be debated is the degree to which circumstances and conditions conspire to make the application of standing moral principles governing research practical or impractical at times when war is imminent or has actually been declared. What can and should be debated is what steps should be taken when circumstances make it impossible to conform to standing moral tenets governing research and what responsibilities are owed to those individuals who are not afforded the same protections and options that would routinely be given to civilians.

## IV. What Is Research?

One topic of much dispute when the subject of research arises with respect to military personnel is what counts as research. The standing definition of research in American law looks to intent to define research. If a goal of undertaking an intervention with a human being is to generate new knowledge then that activity counts as research.

Some forms of intervention carried out by our military or security agencies indisputably fall into the category of research. When persons are subjected to high doses of radiation, when they are given LSD or other agents, when persons are asked to subject themselves to exposure to toxic agents in order to understand the impact of these agents on the human body the intent of such actions is clearly research.

But, the label of research does not always clearly apply to actions taken in war. For example, during the War in the Gulf a number of actions were considered and taken to try and protect military personnel against the perceived risk of biological or chemical weapons attack.

Pyridostigmine bromide tables were given to more than two thirds of the troops in the field, about four hundred thousand soldiers. These tablets were given in the hope that they might provide protection against the use of nerve-gas. The tablets have never been approved for use for this purpose.

Consideration was also given during Operation Desert Shield to the mass administration of Botulinum Pentavalent Toxoid via vaccination. This vaccine, while used by more than 3,000 persons during the 1970s who worked in laboratories where exposure to botulism bacteria was possible, had also not been approved for licensure. No systematic data on safety and efficacy for this vaccine has ever been collected. Still, when the request was made for approval to waive informed consent for the use of this vaccine to the Food and Drug Administration and the Department of Defense 'informed consent waiver group' it was granted. Ultimately, it appears that as many as 8,000 troops were given one or two shots of Botulinum Pentavalent Toxoid.

It may well be argued that the use of these agents to protect those involved in military operations against attack from chemical or biological weapons is not research. Indeed, that seems to have been the thinking of many of those involved in the decision to grant a waiver from standing informed consent requirements for the use of Botulinum Pentavalent Toxoid and anti-nerve gas tablets. There had been previous use of these agents in human beings. There were some reports in the medical literature about these agents. And, most importantly, the reason and intent behind administering these agents was to protect troops in order to minimize casualties and permit the performance of the military mission assigned to these forces by the President.

But, these arguments against the appropriateness of applying the label 'research' to the use of these agents during Desert Shield are not persuasive. The use of unapproved, unlicensed agents clearly was understood by FDA and DOD to be research in as much as both agencies recognized the need to seek waivers from prevailing informed consent requirements. And regulatory and military officials understood that the very reasons why practical circumstances made it difficult to obtain consent for the use of untested, unproven agents in large populations deployed in trying environments under battlefield conditions meant that the use of these agents had to be seen as experimental.

It can be argued that those who sought to use agents that might confer a prophylactic benefit on American military personnel did so by weighing carefully the cost, risk and potential benefits to be obtained. But, the fact that a careful weighing of risk and benefit comes out in favor of using untested, unproven and unlicensed agents in the hope of securing a benefit does not transform an experimental intervention into a therapy. Nor does the fact that those who use unproven, untested or unlicensed agents do so with the intent to benefit, treat or prevent harm transform what is experimental, innovative or research into therapy. If that were so then those who do research would merely have to change their intentions and they could succeed in making the most innovative and experimental medical interventions into therapies merely by a change of mind.

The regulatory definition of research, intent to create generalizable knowledge, is sound as far as it goes. But, it does not go far enough. For what is needed is a term that can capture activities that are manifestly experimental but are not conducted with the intent of generating new knowledge.

This is obviously what took place in the Gulf with anti-bot toxoid and Pyridostigmine. These agents were used in large populations for purposes other than those for which they were originally designed in circumstances under which they had never before been tried. Moreover, in the case of both agents it was not clear exactly what chemical or biological agents might have put into the field by our adversary. This meant that the agents used may have had no efficacy or might actually have had an adverse effect in the case of the utilization of certain nerve gas agents. The circumstances which prevailed in the combat environment of the Gulf also meant that these agents were administered in a manner that deviated a great deal from the previous use of these agents such as when troops were given only one or two shots of anti-bot toxoid when three shots were believed to be essential in order to achieve efficacy.

The case for considering the use of unapproved and unlicensed agents in dire circumstances as manifestly falling into the research end of the research to therapy spectrum is further cemented by the obvious uncertainty that accompanied the utilization of these agents as to the efficacy they would have in the field. In reviewing the documents that led to the decision to grant waivers of informed consent for the utilization of these anti-biological and anti-chemical warfare agents it seems plain that the most accurate description that can be given for the decision to grant the waiver is that there was a chance the agents would do more good than harm but that the efficacy of these agents to prevent harm was seen as far from certain.

## V. Balancing Practicality Against Our Moral Ideals

It seems correct to say that the agents employed in the Gulf as anti-biological and anti-chemical weapons were used in a way that is most accurately described as experimental, innovative and investigational. This makes their use fall squarely into the category of research. But, the issue still remains as to how these agents should have been administered.

Is it ever appropriate in conditions of impending war or actual combat to waive informed consent? And, if consent is waived, then what are the

responsibilities generated to those who are not afforded the standing protections expected for those in medical research?

One crucial distinction that has application to situations where informed consent is not possible is the distinction that is made in bioethics between informed *consent* and *assent*. When research is done in situations where, for a variety of reasons, full informed consent is not possible, researchers will at least strive to let individuals know that they are involved in an investigational, innovative or research activity. These would appear to be a requirement even in conditions of impending or actual war.

If troops are to be subjected to unproven, unlicensed, or innovative interventions they should at least know that this is so. Assent is important for a number of reasons. It may result in greater compliance with the regimen that is being tried. It may also allow troops to report side-effects or problems that may arise either in the combat theater or subsequently. And even if refusal is not permitted or even practical, obtaining assent through disclosure demonstrates a respect for the individual which is not present when persons are merely given agents without any information as to why or what is being done to them.

Those exposed to unproven and untested agents also have a right to expect that their administration will follow as closely as possible the best available information about the use of unproven agents. This does not appear to have been the case in the Gulf War in that the administration of vaccines and tablets was not always done in accordance with the best available knowledge at the time. Attention to compliance by those taking the agents was apparently not always as careful as it should have been.

The use of innovative, experimental and investigational medical interventions may be warranted in a military theater. If so, it is important to understand that when circumstances make informed consent impossible or difficult there is a strong responsibility generated to carefully follow-up those to whom agents of unknown and unproven efficacy and safety are administered. If conditions in combat make it impossible to follow all the requirements usually associated with research and investigation they do not excuse the failure to provide careful and comprehensive follow-up to those who do not receive them.

Apparently, this did not occur in the context of the Persian Gulf war. Medical follow-up for those exposed to anti-biological and anti-chemical warfare agents seems to have been at most, minimal. Not only is this duty owed to those exposed in terms of establishing whether harm or injury has occurred but it is also morally incumbent upon those who waive standing ethical protections for research to compile as much information as possible about the benefits and risks associated with the use of new agents so that this information can then be brought to bear in future situations where military personnel are facing the prospect of chemical or biological warfare.

## VI. Recommendations

The experience with the use of unproven and untested agents in Operation Desert Storm as well as earlier instances of experimentation for military or national security purposes involving human subjects points out a number of

areas in public policy and regulation where improvements can and should be made.

1. All persons involved in experimental, innovative, investigational or other forms of research activity should be notified and their consent obtained. If this is not possible then assent ought to be obtained. When deemed practical, the right to refuse participation ought to be respected.

2. Medical follow-up of all subjects is obligatory both to protect subject interests and in order to obtain new information about untested, unproven agents.

3. Systematic attempts to acquire information about safety and efficacy should be made following standard requirements for the ethics of human research prior to the involvement of the military in combat or war.

4. Approval for waivers must always be sought on a case by case basis.

5. Policies for the conduct of research in conditions of war and combat or for the purposes of national security should receive greater public debate. No existing regulations governing military personnel should be finalized without such public dialogue.

6. Exemptions to prevailing standards for human experimentation, research and innovation should be seen as exactly that—exemptions. There should not be a two tiered system of morality for human experimentation, one for civilians and one for soldiers.

Those engaged in decisions to use unproven, untested, unlicensed or otherwise experimental or research agents in the context of biological and chemical warfare or other battlefield circumstances must understand that conditions of war may lead to decisions which, while undertaken with the best of motives, may not serve to protect the welfare of military personnel or permit the completion of the assigned military mission. Americans when faced with a challenge often feel that it is better to try something rather than to do nothing. The history of human experimentation in this century shows that often, when faced with a crisis, doing nothing in the face of uncertainty can be the most prudent course of action to follow.

# PREPARED STATEMENT OF EDWARD MARTIN, M.D., ACTING PRINCIPAL ASSISTANT SECRETARY OF DEFENSE, HEALTH AFFAIRS

## MILITARY USE OF INVESTIGATIONAL MEDICAL PRODUCTS

Mr. Chairman, distinguished Members of the Committee, I appreciate the opportunity to represent the Department of Defense before your Committee. Today, I would like to discuss the use of investigational drugs and biologics and the procedures we have in place which protect the health and welfare of our military personnel when such investigational products are used, both in peacetime and during military combat exigencies. Before I address that issue, however, I would like to draw a very clear distinction between the use of such products during the Persian Gulf War, and the human experiments involving mustard agents or Lewisite which were conducted almost half a century ago.

Human experiments involving mustard agents or Lewisite were conducted during World War II to ascertain the physiological effects of these compounds, to explore potential treatments, and to develop new measures of protection. The intention of these experiments was clearly research; to gain scientific information which was lacking on the effects of exposure to these chemical warfare agents. In addition, this research was conducted prior to any federal policy or regulation for protecting human research subjects.

On the other hand, investigational products were employed during the Persian Gulf War as prophylactic **treatments against biological and chemical warfare agents. This was not research but direct prevention and treatment.**

Referring to these products as "investigational" is in accordance with Food and Drug Administration (FDA) regulations and not a definitive statement regarding the scientific information available about the products. In the vernacular of the FDA, a drug is

"investigational" if it has not been approved by FDA for general commercial marketing for a particularly stated medical purpose. In the Persian Gulf War, DoD used two drugs that, although not approved by FDA for general commercial marketing for the particular medical purposes involved, were specifically allowed by FDA for the special military uses proposed by DoD. FDA allowed these uses because there was evidence they would be effective and no recognized alternative existed, and because FDA thought the use would be safe. The FDA also specifically allowed the use of these drugs in the military combat circumstances involved without the usual informed consent requirements required for investigational products. Withholding the use of these products would have been contrary to the best interests and possibly the lives of our military personnel.

I would now like to discuss the procedures which protect the health and welfare of our military personnel when investigational products are used, either in peacetime or during military combat exigencies.

Studies of new drug or vaccine products are conducted in animals to define dosages that may be safe and effective in humans. The findings from these studies are subsequently reviewed by the FDA as part of an Investigational New Drug (IND) application. Acceptance of the IND by the FDA then permits investigational products to be studied in humans. Under an IND, Phase I trials are conducted in humans to determine the safety of dosage and frequency of administration. Phase II trials are then conducted on a small "at-risk" population to demonstrate the efficacy of the drug or vaccine before application is made to the FDA to begin large scale Phase III trials, which would lead to approval or licensure. Approval or licensure by the FDA is based upon the results of well designed studies in humans which demonstrate efficacy and safety of the product.



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For products designed to protect against biological or chemical warfare agents, a clear demonstration of efficacy would require deliberate exposure of humans to these highly lethal agents in order to determine effectiveness, such a protocol is clearly unethical in most cases and inappropriate. Thus, in the case of new products designed to protect or treat our troops against lethal biological or chemical warfare agents, the "normal" process of new drug approval is not feasible.

Under the Federal Food, Drug and Cosmetic Act, any use of an IND, whether for research purposes or for treatment purposes, must be preceded by obtaining informed consent from the subject or patient, unless it is "not feasible.". In all peacetime military applications, we believe strongly in informed consent and its ethical foundations. Furthermore, in peacetime, we readily agree to inform military personnel, as provided in FDA's regulations, that research is involved, that there may be risks or discomforts, that participation is voluntary and that one may refuse to participate without prejudice. However, during the existence of military combat exigencies, military personnel may be exposed to endemic diseases as well as chemical and biological warfare agents in a specified theater of operations. For some of these risks, the best preventive or therapeutic treatment calls for the use of products under IND protocols of the FDA. In situations of this kind, which the FDA interim regulations refer to as "a military combat exigency," informed consent procedures do not in our view apply. However, military personnel are to be given information concerning potential benefits or risks in taking the drugs. Under those regulations, a military combat exigency is one in which, in order to facilitate accomplishment of the military mission, preservation of the health of the individual and the safety of the other personnel, that a particular treatment must be provided to a specified group of military personnel, without regard to what might be any individuals' personal preference for no treatment or some alternative treatment. In such special circumstances,

the FDA Commissioner may approve a DoD request to waive normal informed consent procedures.

During the Persian Gulf War, two IND products, Botulinum toxoid and Pyridostigmine, were used to protect U.S. personnel against the potential use of biological and chemical warfare agents suspected to be in the Iraqi arsenal.

Pyridostigmine is a drug approved by the FDA since 1955 for use in the treatment of myasthenia gravis (MG), a neuromuscular disease. Pyridostigmine has been used safely in the treatment of MG at average daily doses of 600 mg. Pyridostigmine is also regarded as the product of choice by the Armies of NATO for the pre-treatment of organophosphate nerve agent intoxication and has been held in reserve by the DoD for that use since 1986. The dose used as a pretreatment in our military personnel during the Persian Gulf War was 15 percent of the average daily dose for MG (30 mg every 8 hrs - i.e. 90 mg daily).

Prior to its use in the Persian Gulf War, Botulinum toxoid had been used for more than 20 years in over 3000 individuals with over 10,000 vaccinations to prevent Botulism. The use of Botulinum toxoid is sponsored by the Center for Disease Control (CDC) in an IND to make this product available for medical use in persons at risk for occupational exposure to Botulism. The FDA has reviewed the annual reports of the administration of Botulinum toxoid to at-risk laboratory personnel and it continues to be used safely to protect laboratory workers.

Following the Persian Gulf War, the Assistant Secretary of Defense (Health Affairs) issued a policy memorandum which directed the Military Departments to document in the individual Service member's immunization record and health record

information regarding the receipt of Anthrax vaccine (a licensed vaccine) or Botulinum toxoid. The memorandum also required the Services to retain records regarding distribution of Pyridostigmine issued to various combat units. This information was considered classified due to order of battle and deployment of selected force units. The actual use of Pyridostigmine was accomplished by individual Service members themselves, and entry into medical records was not possible, since date, time frequency of use and dosage could not be clearly established.

In summary, Pyridostigmine and Botulinum toxoid were not used for experimental purposes in the Persian Gulf War and the military personnel who received these products were not experimental subjects. These products were used only after careful review both by a duly constituted human use review committee and the FDA. These products were used under the auspices of a treatment protocol, not an experimental protocol. With respect to both drugs, Dr. David Kessler, Commissioner of Food and Drugs, specifically found that in view of the risks associated with the potential use of biological or chemical warfare agents by Iraq and the lack of any alternative therapy, withhold these drugs "would be contrary to the best interests of military personnel".

The Department of Defense is committed to providing our military personnel with safe and efficacious medical products in peacetime and in combat. Regardless of the scenario, we will continue to furnish medical products to our Service men and women that will meet and respond to the world's evolving military requirements and biomedical technologies.

I want to thank you, Mr. Chairman, and the Members of this Committee for your interest in these issues, but more importantly for your concern for the health of Service members and Veterans.

## PREPARED STATEMENT OF R. J. VOGEL, UNDER SECRETARY FOR BENEFITS, DEPARTMENT OF VETERANS AFFAIRS

Mr. Chairman and members of the committee: I am pleased to be here today to discuss what the Department of Veterans Affairs (VA) has done and is doing to assist veterans who were exposed to hazardous substances while in the military.

Accompanying me is Dr. Susan Mather from VA's Veterans Health Administration.

If history has taught us nothing else, it has taught us that certain actions, even if considered necessary at the time they are taken, are not always without consequences. Some veterans, we have learned in retrospect, have suffered even more than the traditional hardships of combat; they were exposed to substances which many years after the fact have had devastating effects on their health. The long term effects of exposure to chemicals or environmental agents are as much a consequence of their military duty as a gunshot wound.

Mr. Chairman, we in VA are well aware of the hardships these veterans have endured. We have taken, and continue to take, measures to identify those hardships and to provide medical care and disability benefits. To describe some of these measures, let me begin by discussing action VA has taken to help world war ii veterans experimentally exposed to mustard and lewisite agents during secret testing of clothing and equipment.

As you know, mr. Chairman, VA provides disability benefits if the medical evidence of record relates the veteran's disability to his or her military service. In the case of veterans who were exposed to mustard gas and lewisite, VA has found it a difficult challenge to make decisions on the validity of some claims because the evidence of possible exposure of an individual is usually not available in the veteran's service medical records.

In spite of this difficulty, VA established a framework to establish presumptive service connection for chronic forms of certain conditions based on full-body exposure to mustard gas in the field or chamber experiments conducted during world war ii. Our current regulations allows presumptive service connection for chronic forms of laryngitis, bronchitis, emphysema, asthma, conjunctivitis, keratitis, or corneal opacities.

In initially establishing presumptive service connection for disabilities related to mustard gas exposure, VA was influenced by the long history of secrecy surrounding the world war ii mustard gas experiments. We determined that, through no fault of the veterans involved, there was inadequate documentation of their participation in the tests, which were classified. Further, due to the secrecy of the tests, some participants may have been deterred from filing claims for resulting disabilities or from seeking medical care.

VA responded to this unprecedented situation in many ways, one of which was to contract with the national academy of sciences to conduct a review of the world wide medical and scientific literature to determine the long-term health effects of exposure to mustard agents. Earlier this year, VA acted on the findings of the NAS report by publishing proposed amendments to our current regulations to extend the opportunities for veterans to seek service connection based on exposure to mustard gas and lewisite. Of significant importance, our proposed amendment would expand the current list of conditions we presently

associate with mustard gas exposure to allow service connection under certain conditions for chronic obstructive pulmonary disease, scar formation, acute nonlymphocytic leukemia, nasopharyngeal cancer, laryngeal cancer, squamous cell carcinoma of the skin or lung cancer except mesothelioma.

As of march 7, 1994, 1,145 veterans have filed compensation claims for disabilities they believe are associated with exposure to mustard gas and we have approved service connection for 154 of them.

The executive branch of government fully understands the importance that documentation of certain events in military service has in VA's decision making process. Thus, VA and DOD are working diligently to understand the nature of the information that is available and to determine how VA may use it to make fair and equitable decisions on entitlement to VA benefits.

VA has obtained a list of over 2,400 navy personnel who participated in mustard gas tests at the naval research laboratory (NRL) in Washington DC between August 1943 and October 1945. Until recently, this list, which represents virtually all NRL test participants, consisted of the participant's last name only. VA has just received additional information concerning the individuals who participated in testing at NRL which includes the first names of the participants. This, we feel, is a major breakthrough and is the type of information we need to make fair decisions on veteran's claims.

We also know that perhaps as many as 6,000 to 20,000 persons participated in tests at the university of Chicago at great lakes. However, VA has not been as fortunate in obtaining records on the army's tests because prior to the early 1950's, information about a person's participation in any kind of testing by the army was placed only in the individual's service medical records. Since the 1950's, the records on army testing have been stored in a number of locations. Compounding the difficulty is the fact that personnel records for some of the testing were never kept or no longer exist. However, DOD has assured us they will continue their efforts to identify records concerning personnel exposed to mustard agents and provide these data as they becomes available.

Mr. Chairman, in the case of the Persian Gulf war veteran, VA became faced with complex issues relating to exposures to environmental hazards. VA's initial concern was the possible health effects of exposure to pollutants from the oil well fires. As time went on, it became obvious that a number of health problems may be attributable to various other environmental agents and VA broadened its investigation.

Of the nearly 697,000 active duty military service members and activated national guard and reserve unit members who served in the Persian Gulf theater of operations, approximately 300,500 are veterans who have been discharged from the military. At this time, VA is providing disability payments to almost 10,000 of these veterans.

Of the total number of veterans of the Persian Gulf war, approximately 3,500 have filed claims for disabilities they believe to be the result of exposure to an environmental hazard. We have made decisions in 1,600 claims and service connection has been approved for 278 veterans. We are in various stages of developing evidence in response to nearly 1,900 claims and about 160 more claims are ready to be decided.

The most common ailments claimed by Persian Gulf war veterans as a result of exposure environmental hazards are respiratory complaints and skin conditions. They often relate their disabilities to exposure to oil well fires or smoke, shots or medications, chemicals and paints, insect bites or parasites, contaminated water, radiation and chemical or biological warfare weapons. We find that many claims based on exposure to environmental hazards while in the Gulf are made based on exposure only, without further specification of a disability. Exposure alone does not provide a basis to grant service connection to a veteran. Also, many veterans do not receive service connection because the claimed disability is not shown by the evidence of record or an acute condition was shown without residual disability.

Some feel VA is not aggressively pursuing answers to the health concerns of the Persian Gulf war veteran. Therefore, I would like to give some examples of the proactive efforts we are taking to meet the needs of these veterans.

VA is the overall coordinator of all federally funded research into the possible health effects of service in the Persian Gulf war. currently, there are over 20 different Persian Gulf-related research activities being undertaken by the federal government.

VA is collecting information to identify patterns of disability claims sharing common environmental factors that may point to potential health hazards. We have in place guidance for evaluating conditions such as chronic fatigue syndrome and leishmaniasis. And, we continue to review our data and share as well as compare them with DOD to ensure we are thorough and consistent in determining disabilities and benefits.

Additionally, VA has awarded a contract to the national academy of sciences to evaluate (1) VA and DOD actions to maintain useful information on the health consequences of military service, and (2) the scientific advisability of epidemiological studies.

VA is establishing one to three environmental hazards research centers. These centers will focus on toxic environmental hazards and will take full advantage of both government and non-government resources. activation of these centers is planned for the fourth quarter of FY 1994 following appropriate peer review.

Further, VA, DOD, and health and human services have merged expertise and capabilities to form the Persian Gulf veterans coordinating board. The mission of this interagency board is to coordinate efforts to find the cause of and treat Persian Gulf veterans' health problems and develop guidelines for compensation and benefits.

Although VA must rely on DOD for information about what occurred during the war, our first and foremost responsibility is to remain sensitive to the concerns of veterans. I believe VA is seriously attempting to understand and find answers to the causes of health problems some Persian Gulf war veterans are experiencing. We continue to review our policies to expedite claims processing and are providing medical services to veterans suffering from various health problems that may have been incurred in the Gulf. The proactive approaches presently being taken by VA and DOD exemplify our mutual commitment to serving those who participated in military operations.

Mr. Chairman, I would now like to discuss what VA is doing both to provide medical services to Persian Gulf veterans exposed to hazardous substances, and to help to find answers to their concerns.

Even before the fighting in the Gulf ended, we began designing programs to focus on the anticipated needs of this group of veterans. Our role in determining the health consequences for veterans who participated in the Persian Gulf war has been multifaceted. VA developed a registry program modeled on the existing agent orange and ionizing radiation registries and under the authority of section 702 of public law 102-585. The registry is designed to provide veterans who have health problems or concerns, access to a comprehensive physical examination, baseline laboratory testing, and further diagnostic evaluation of identified medical problems when indicated. to date, more than 19,000 veterans have had health examinations as part of the registry. The data obtained from these examinations are entered into a computerized database. Our environmental epidemiology service closely monitors this information to track discernible symptom patterns among Persian Gulf veterans. The analysis of a part of this information has revealed a wide variety of reported symptoms; however, neither a clear trend in diagnosis nor clues to a cause or causes has yet emerged.

In addition to the registry program, VA has established several specialized programs to serve Gulf war veterans. First, three clinical referral centers were established at the VA medical centers in Houston, Los Angeles, and Washington, DC. These centers perform tertiary specialized evaluations for veterans whose condition has evaded diagnosis at their local VA facility. As of April 15, 1994, there have been 89 admissions to these centers. Diagnoses in this highly selected group of veterans suggest a diverse array of disease processes and etiologies.

Second, in response to concerns raised by some members of reserve units who served in the Persian Gulf theater that they are now suffering from the long-term effects of exposure to chemical agents and because their findings of memory loss may be consistent with such exposure, we established a special focus pilot program at the Birmingham VA medical center. A specialized neurological examination protocol was developed, to determine what, if any, neurobehavioral effects these veterans are experiencing. In the absence of biomarkers for exposure to chemical agents, detection of disabilities that could result from such exposure is the only available clue to diagnosis.

Finally, VA established a surveillance program at the Baltimore VAMC for individuals with retained fragments of depleted uranium shrapnel. This five-year program provides health surveillance for these veterans and screens for elevated levels of depleted uranium that could potentially result in kidney damage.

While some of these VA programs have a narrowly defined primary role, each in addition looks more broadly for evidence of any possible health consequence of Persian Gulf service, including the possible effects of the treatments and vaccinations that are the focus of your hearing today. To date we have been unable definitively to identify large numbers of veterans who are suffering from chronic illness that our physicians attribute to these agents.

You have requested that we comment on VA's role in determining the health consequences for veterans who were exposed to agents such as mustard

gas and lewisite. The military's experiments of mustard gas and lewisite began in a wartime climate of urgency and secrecy. Because of the secret nature of the testing, VA has found it a challenge to provide medical care to affected individuals because it has been difficult to validate their claims for service-connected disability due to a lack of verifiable exposure records. However, VHA researched the available literature and developed a list of long-term health effects that could result the exposure to mustard gas. These were chronic laryngitis, bronchitis, emphysema, asthma, conjunctivitis, keratitis and corneal opacities. VA's final regulation permitting service connection for these conditions, which was published in July 1992, has helped some veterans.

Also, in 1991, VA contracted with the national academy of sciences institute of medicine (IOM) to evaluate more thoroughly the long-term health effects of mustard gas and lewisite through a survey of the scientific literature. The IOM's review was designed to assess the strength of association between exposure to these agents and development of specific diseases, and to identify gaps in knowledge on the subject. In January 1993, the IOM committee to survey the health effects of mustard gas and lewisite published their report which concluded that the lack of follow-up health evaluations diminished the quality and amount of scientifically-relevant information. In addition, because few veterans could prove participation in these tests disability determinations were negatively impacted. As a result of the IOM findings, VA has initiated rulemaking to permit presumption of service-connection for disabilities resulting from exposure to mustard gas and lewisite for scar formation and the following cancers: nasopharyngeal, laryngeal, lung (except mesothelioma) or squamous cell carcinoma of the skin in addition to the original seven conditions.

It is important to stress that the VA has received no direct or indirect reports of similar human experimentation on Gulf war military forces. The analogy between mustard gas studies and Persian Gulf issues is relevant only in relation to lack of individual documentation of the presence and magnitude of exposure to certain agents. Veterans have however, expressed their concern about the use of pyridostigmine bromide and vaccinations for anthrax and botulism. Pyridostigmine is an active cholinesterase inhibitor that the military used for prophylactic treatment of possible nerve agent exposure. Pyridostigmine has been used extensively as a food and drug administration (FDA) approved therapy for myasthenia gravis, a neuromuscular disease. Doses recommended for use by military troops did not differ from the common clinical dosage. Acute side effects of this compound have been well described and include nausea, vomiting, diarrhea, abdominal cramps, urinary retention, increased salivation, constriction of the pupils, and sweating. Side effects resolve when the oral intake is discontinued. Some veterans report experiencing one or more of these side effects upon taking the pills, and a small number appear to have had an acute toxic reaction. Since service members were issued packets containing 21 tablets of pyridostigmine bromide for self-administration, no record of total individual dosage or administration exists.

In addition, the department of defense (DOD) has reported that front-line troops were vaccinated for anthrax (150,000 individuals) and botulism (8,000 individuals). These agents were known to be part of the biological warfare arsenal of Iraq and protection of troops was deemed a priority by the department of defense. We understand that safety and efficacy records

regarding these vaccines have been provided to this committee by the FDA, which should aid in assessment of potential effects on service members.

In most cases, for both pyridostigmine use and vaccinations we have been unable to identify medical records that record their administration, although we have been told that anthrax immunization and botulism toxoid are recorded as code "a" and "b" respectively.

VA has provided a prompt response to the concerns of Gulf war veterans. We have not allowed the potential for lack of adequate follow-up medical information to occur and thereby impair future studies of the health consequences of Persian Gulf service. The early establishment of the Persian Gulf registry, other focused VA clinical evaluation programs, and the passage of public law 103-210, which authorizes priority care for Persian Gulf veterans, have all served to establish a database upon which further study can be built. We would welcome the release of any other sources of information which could aid us in illuminating the important health issues in Persian Gulf veterans.

Finally, I note the three-day workshop on the Persian Gulf experience and health that was held last week. This conference, conducted under the aegis of the national institutes of health, was jointly sponsored by VA, DOD, the department of health and human services, and the environmental protection agency. a panel of scientific experts was convened to examine the available information relating to possible adverse exposures of troops serving in the Persian Gulf and the reported illnesses; to attempt to develop a working case definition; and to explore biological explanations for illnesses experienced by some Persian Gulf veterans. The workshop helped to sharpen our joint focus on the issues of diagnosis, treatment, and future research into the health of Gulf war veterans. the expert panel found "it is impossible at this time to establish a single case definition" and that "a premature attempt to establish a case definition for this illness may be misleading and inaccurate". the panel did make recommendations for further research that VA, along with DOD and HHS, is considering very carefully.

In all our clinical and research efforts, VA will continue to pursue explanations for the illnesses identified by Persian Gulf veterans and endeavor to return them to good health. We are fully committed to investigate all plausible causes and exposures.

Mr. Chairman, I would like to thank you for the opportunity to discuss VA's efforts to assist veterans who were exposed to hazardous substances while serving their country.

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## STATEMENT OF ROBERT J. TEMPLE, M.D., DIRECTOR, OFFICE OF DRUG EVALUATION, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION

The following statement is provided for the hearing of the Committee on Veterans' Affairs, United States Senate, May 6, 1994, on the subject of the use of investigational drugs without obtaining informed consent during Operation Desert Storm/Shield.

As the Committee knows, following a request from the Department of Defense (DoD), the Food and Drug Administration (FDA) granted waivers

from current informed consent regulations for the use of two products in specific protocols: pyridostigmine and botulinum toxoid vaccine.

## Pyridostigmine

Pyridostigmine has been approved by FDA since 1955 for the treatment of myasthenia gravis, a chronic disorder characterized by muscle weakness. As a result, there is considerable human experience on its long-term use. Further, the DoD has been investigating the effects of pyridostigmine pre-treatment on healthy soldiers under an Investigational New Drug (IND) application on file with FDA since 1984. No serious adverse reactions were reported in this population from this experience.

The determination that pyridostigmine could be administered safely to healthy soldiers during Operation Desert Storm under the IND was based primarily on the long experience with pyridostigmine at doses considerably greater than those proposed as pre-treatment for organophosphate nerve agent exposure, (30 mg three times a day for a maximum of 7 days). Patients with myasthenia typically are treated with pyridostigmine doses of up to 1500 mg a day for many years. While myasthenic patients are not, of course, entirely healthy, we believed their experience was pertinent to the effects of pyridostigmine in completely healthy individuals. Patients with myasthenia gravis have antibodies directed at skeletal muscle structures. They would be expected to differ from healthy persons with respect to effects of pyridostigmine on skeletal muscle, and be less likely to develop muscle twitching and muscle cramps. But in other respects, their response should be similar. We knew from past experience with the use of this drug that side effects (e.g., abdominal cramps, nausea, diarrhea, rash, muscle weakness, dimmed vision) were possible, and these were described in the DoD's Field Manual, which was included in the IND submission.

In addition, broad acceptance of the safety of the proposed dosing regimen can be found in the medical literature (an article in the Medical Letter of November 16, 1990, and an article by Dunn and Sidel in the Journal of the American Medical Association on August 4, 1989). (Copies of these are provided for the record).

The effectiveness of pyridostigmine, given as pre-treatment in conjunction with the acute use of atropine and 2-PAM (the regimen being used in this instance), in decreasing toxicity of nerve agents in humans, has not been demonstrated. In monkeys however, the regimen greatly increases the lethal dose of nerve agent compared to the lethal doses in untreated monkeys. Despite the lack of human data on protection (it would be unethical to administer toxic agents to subjects for such research), pyridostigmine, in conjunction with the acute use of atropine and 2-PAM appears to be the best available means of decreasing organophosphate nerve agent intoxication. It has been available to NATO armies and has been held in reserve by DoD for that use since 1986.

The Agency has reviewed Chemistry and Manufacturing Controls data for pyridostigmine bromide on a continuing basis. Additionally, under a long-standing agreement with the DoD, Agency chemists periodically reviewed stability study data from studies conducted on pyridostigmine bromide tablets stockpiled by DoD at various locations to be available in time of war for

distribution and use by military personnel. The Agency has concluded that the two primary suppliers of the drug provide acceptable products.

### Botulinum Toxoid Vaccine

With regard to the botulinum toxoid vaccine, there is no satisfactory alterative product to prevent botulism. This vaccine has been provided for over 20 years to laboratory workers and public health professionals at risk of infection. This has been accomplished under an IND sponsored by the Centers for Disease Control and Prevention (CDC). FDA has reviewed data and information on this use in annual reports to the IND submitted by the CDC. The 1990 annual report provided the cumulative safety experience with this vaccine since 1970 for 10,414 doses administered. (This includes 2,203 doses of the vaccine that were administered during the 5 years prior to operation Desert Shield). Available information indicated that individuals could experience side effects associated with vaccination, predominately at the injection site. Such local effects included pain, tenderness, swelling, redness and itching. Systemic reactions such as fever, tiredness, headache, and/or muscle pain could also occur. Rarely an individual could be unable to perform duties for a day or two. Sometimes a lump developed at the injection site which resolved, generally within several weeks. These reactions were described in the information sheet prepared for vaccines in the Desert Storm/Shield protocol.

The experience under this IND provided adequate safety information for the use proposed by DoD. Military clinical investigators had considerable experience with the use of this vaccine under the IND sponsored by the CDC and were familiar with it's reactogenicity profile. The vaccine dose, route of administration, and schedule in the Desert Storm protocol was identical to that used in the CDC protocol.

This vaccine continues to be used under the CDC's IND. The 1993 annual report to the IND summarizes the cumulative experience of 12,499 doses administered.

The botulinum toxoid vaccine used in the Desert Storm/Shield protocol was manufactured at the Michigan Department of Public Health (MDPH). For this vaccine, the animal testing results for immunogenicity (antibody as determined by a toxin neutralization assay), safety, purity, identity, and sterility for all lots to be used in Desert Storm had been previously reviewed by the Agency and were considered satisfactory for human use. This lot testing is typical for a biological investigational product and could be considered "required" testing prior to the first use of a lot in humans. In addition, results from standardized studies that evaluated animal protection from toxin challenge were available for most of the final lots. Vaccine manufactured at MDPH had been previously tested in humans and was demonstrated to be immunogenic. Some sera from the vaccinated humans in ongoing studies was assessed for ability to neutralize toxin.

The immunogenicity/neutralization and challenge/protection data in animals and the immunogenicity/neutralization data from human studies give evidence of probable effectiveness in humans and have been provided to the Committee. These animal and human data also provide evidence of product safety.

## FDA Process

To provide a context for the decision-making process on the use of these two products under these circumstances, the following information is provided.

The Food and Drug Administration (FDA) regulates the use of investigational drugs under provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act). In FDA terms, any drug not approved for marketing and any drug used for treatment other than that identified in the approved labeling, is investigational. In order for clinical testing to proceed with unapproved products (or, in some cases, for testing approved products for unapproved uses), an investigational new drug (IND) application is filed with FDA. The IND must contain information sufficient to demonstrate that it is reasonably safe to study the drug in humans, including drug composition, manufacturing and control data, the results of animal and, if available, prior human testing, and the protocol for the planned study. The investigator must agree to obtain approval of an institutional review board before proceeding, must obtain written informed consent from patients, and must report adverse effects that occur.

The FD&C Act specifically requires that investigators inform subjects receiving drugs under an IND that the drugs are investigational and "obtain the consent of such human beings or their representatives, except where they deem it not feasible, or in their professional judgment, contrary to the best interests of such human beings." There have been few instances in which obtaining informed consent has not been considered feasible or contrary to patients' interests.

During the months preceding the Persian Gulf War, DoD had discussions with FDA regarding the potential use of specific investigational products in military personnel serving in the Persian Gulf. We also had extensive internal discussions involving technical and policy-level staff, as well as experts from other Federal agencies and academia. It was thought that the products discussed represented the best preventive or therapeutic treatment for diseases endemic to the area 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." It should be appreciated that FDA appropriately gave considerable deference to the Department of Defense's judgment and expertise regarding the feasibility of obtaining informed consent under battlefield conditions.

In response to this request, on December 21, 1990, FDA published an interim regulation amending its current informed consent regulations. This regulation allowed the Commissioner of FDA to determine, upon receipt of an appropriate application from DoD, that obtaining informed consent from military personnel for use of a specific investigational drug or biologic would not be feasible in certain circumstances, and to grant a waiver from the requirement for obtaining such consent.

The exception extended, on a case-by-case basis, only to investigational drugs (including antibiotic and biological products) for use in a specific military operation involving combat or the immediate threat of combat. The application was to include the justification for the conclusion (made by physicians responsible for the medical care of the military personnel involved)

that: 1) the use was required to facilitate the accomplishment of the military mission, 2) the use would preserve the health of the individuals and the safety of other personnel, without regard for any individual's preference for alternate treatment or no treatment; and 3) the application contained documentation to indicate that the protocol had been reviewed and approved by a duly constituted institutional review board for the use of the investigational drug without informed consent.

Each application for waiver from the informed consent requirements was assessed by the appropriate FDA review division, and by the agency's Informed Consent Waiver Review Group (ICWRG). The ICWRG included senior management of the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Office of General Counsel, the Office of Health Affairs, and NIH's Office of Protection from Research Risks. This ICWRG core was supplemented by technical experts as appropriate for the particular investigational drug being considered for exception. The ICWRG considered DoD's justification supporting the request for the waiver and the reviewing division's evaluation of the available safety and efficacy data. The ICWRG requested additional supporting information in some cases, and required changes in the information to be provided to the troops in several rounds of iterative exchanges with DoD. The ICWRG then made a recommendation to the Commissioner regarding whether or not to grant the waiver. The Commissioner made a decision on the application, and informed DoD in writing.

## IND Requirements

The IND regulations set forth certain regulatory responsibilities for sponsors of INDs, many of which apply to DoD's use of pyridostigmine and botulinum toxoid vaccine. FDA expects IND sponsors to fulfill commitments that are made regarding the conduct of studies. The Agency does not routinely follow up each agreement made with sponsors with respect to drugs being used under an IND. We would, of course, pursue such information if we had reason to believe agreed-upon procedures were not being followed.

The IND requirements include the selection of qualified investigators to conduct and monitor the study, maintenance and retention of records by individual investigators, and submission of progress reports by the investigators. In addition, the sponsor is required to submit safety reports identifying any adverse experience associated with the use of the drug, provide investigators with a brochure containing information on the drug under study, maintain records with regard to the disposition of unused supplies of the drug, and submit annual reports to the IND.

FDA recognized the limitations of these requirements for data collection and recordkeeping under the special circumstances encountered in battlefield conditions. Accordingly, FDA waived the regulations that apply to the performance and responsibilities of individual investigators because "individual investigators" were not identified in this instance. Certain information was nonetheless required. With regard to the botulinum toxoid vaccine, each vaccination was to be recorded on the individual's permanent immunization record. In addition, a roster was to be maintained with the name, social security number, date and military unit of all individuals receiving each vaccine dose. Adverse reactions were to be reported to the principal investigator.

Individuals were specifically advised in the information to be given them to report to sick call if they were worried about a reaction following vaccination. In addition, the sponsor was obligated to perform a post-card survey of at least 100 individuals following vaccination. Under the IND for pyridostigmine, DoD specifically proposed to collect, and summarize, adverse reaction data from medical personnel caring for casualties by the use of a form designed for this purpose, which the Agency found to be acceptable.

Ordinarily, sponsors of INDs are required, among other responsibilities, to report adverse reactions to the FDA in the form of safety reports. The regulations impose different reporting requirements depending upon the seriousness of the reactions. Because of the exigencies of battlefield conditions, the Agency agreed to waive the requirements for the reporting of unexpected fatal or life-threatening experiences by telephone within 3 days of the receipt of this information by DoD, as well as the requirement for submission, in writing, of reports of reactions that are both serious and unexpected within 10 days of the receipt of this information by DoD. DoD was asked, however, to collect, review, and make reports of all adverse clinical consequences attributed to the treatment in as timely a manner as conditions permitted. In addition, annual reports of experience gained under the IND also were required.

Although it had been concluded that informed consent was not feasible, FDA did obtain DoD's agreement to provide accurate, fair, and balanced information to those who would receive the investigational products. To do this, information leaflets on both products were developed and approved by FDA.

## Conclusion

As mentioned above, waivers were granted for two products during Operation Desert Storm/Shield. The regulation allowing informed consent to be waived during this operation was developed to allow what was believed to be the best available medical treatment or preventive therapy to be utilized under combat conditions. FDA granted these waivers because there was reason to believe the products would be effective, because there was no available satisfactory alternative therapy, and because the products appeared safe for the intended use.

# APPENDIX 3.—WRITTEN QUESTIONS AND THE RESPONSES

## DEPARTMENT OF DEFENSE

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United States Senate
COMMITTEE ON VETERANS' AFFAIRS
WASHINGTON, DC 20510-6375

May 16, 1994

Dr. Edward Martin
Acting Principal
Assistant Secretary of Defense
Health Affairs
Department of Defense
The Pentagon
Washington, DC 20301

Dear Dr. Martin:

Thank you very much for your participation at the Committee's May 6 oversight hearing on military research, focusing on investigation compounds administered to Persian Gulf veterans.

Unfortunately, we had very limited time at the hearing to ask questions of the witnesses. Therefore, I am submitting the enclosed questions, and ask that you provide responses to these questions by June 1.

I look forward to working with you to solve the problems facing our Persian Gulf War veterans. If you have any questions, please contact Dr. Diana Zuckerman of the Committee Staff at (202) 224-9126.

Sincerely,

John D. Rockefeller IV
Chairman

**Posthearing Questions**
**for Dr. Edward Martin**
**Acting Principal Assistant Secretary of Defense**
**Department of Defense**

**from Senator John D. Rockefeller IV**
**Chair, Senate Committee on Veterans' Affairs**

Question: Please provide information on long-term medical follow-up for those health military men who participated as research subjects in DoD experiments designed to determine the side effects of pyridostigmine.

Answer: In human protocols in which pyridostigmine was used in healthy Army volunteers, there was no long term medical follow-up, nor was there any need or requirement to perform such follow-up. The Army, as DoD Executive Agent for the DoD Chemical and Biological Defense Program, is currently determining what follow-up was conducted in Air Force studies not included under the Army's IND or NDA submissions on pyridostigmine. This information will be forwarded to your office as soon as it is available. Enclosed please find copies of adverse reaction forms provided to the FDA under IND 23,509.

Q.2 Please provide a list of 1992 and 1993 research projects whereby military personnel, acting as human subjects, received living biological agents (natural, genetically engineered, virulent, or avirulent) as part of a research protocol.

A.2. Military personnel, acting as human subjects, would have received living biological agents as part of infectious diseases or biological warfare defense research protocols only. The Army is the DoD lead agency for both infectious diseases and biological warfare defense research; the Navy and Air Force do not fund studies in these areas. It is possible that military clinical research centers may have performed studies using living biological agents in military personnel; these studies would have been very limited in scope but, in the interest of thoroughness, their records currently are being reviewed.

The Army has provided the attached list of 1992 and 1993 research projects in which human subjects received living biological agents either as a vaccine or a challenge. The human subjects used in these projects may have been military or civilian, as available Army records do not detail the types of human subjects used.

| LOG NO. | 1992 TITLES |
|---|---|
| A-5167 | Outpatient Studies on the Safety and Immunogenicity of the Auxotrophic E. coli/Shigella flexneri Hybrid Vaccine Candidate, ECSF-2a-2. |
| A-5651 | Clinical Evaluation of a Coxiella Burnetii Inactivated Whole Cell Vaccine. |
| A-5668 | Immunization with a Live, Attenuated Junin Virus Vaccine Study 9: Dose Study of Candid #1, Lot 2, IND 2257. |
| A-5669 | A Study Correlating Infection by Falciparum Malaria Sporozoites with Host Genetic Factors and T Cell Reactivity to the Circumsporozoite Protein. |
| A-5688 | Development of a Live, Attenuated Prototype Cholera Vaccine Part I. Safety and Colonization of Toxin Deleted Mutants of Wild Type Vibrio cholerae Strains. Part II. Safety and Immunogenicity of a B Subunit of Cholera Toxin Positive Prototype Vaccine Strain and Efficacy in Preventing Cholera in an Experimental Challenge Model. |
| A-5688 | Modification to Development of a Live, Attenuated Prototype Cholera Vaccine, Part I. Safety and Colonization of Toxin Deleted Mutants of Wild Type Vibrio cholerae Strains, Part II. Safety and Immunogenicity of a B Subunit of Cholera Toxin Positive Prototype Vaccine Strain and Efficacy in Preventing Cholera in an Experimental Challenge Model. |
| A-5283 | Argentine Hemorrhagic Fever Project (IND #2257). |
| A-5696 | Safety, Immunogenicity and Efficacy of Escherichia coli K-12/Shigella flexneri Hybrid Vaccines Using a Four Dose Regimen. |
| A-5702 | Evaluation of the Safety and Immunogenicity of a Modified Vaccinia-Recombinant Rabies Vaccine in Healthy Adult Volunteers. |
| A-5716 | Safety and Immunogenicity of a Candidate Cell Cultured Vaccinia Virus Vaccine (TSI-GSD-214) Administered by the Subcutaneous Route. |
| A-5644 | Male Gonococcal Urethritis: A Human Infection Study II. |
| A-5820 | The Effect of Parenteral Immunization with the Shigella flexneri 2a r-EPA Vaccine in Priming the Immune Response with Orally Administered Shigella Vaccine, Escherichia coli/Shigella flexneri 2a-2 (ECSF2a2). |

| LOG NO. | 1993 TITLES |
|---|---|
| A-5718 | Safety and Immunogenicity of a Candidate Cell Cultured Vaccinia Virus Vaccine. |
| A-5718 | Safety and Immunogenicity of a Candidate Cell Cultured Vaccinia Virus Vaccine (TSI-GSD-241) Administered by the Subcutaneous Route. |
| A-5590 | Safety, Immunogenicity and Protective Efficacy of a Malaria Vaccine, Non-repeating Vaccine Antigen in Healthy Adult Volunteers. |
| A-5846 | Randomized Placebo Controlled Efficacy Trial of the Orally Administered Attenuated Strain of Auxotrophic Escherichia coli/Shigella flexneri 2a (ECSF2a-2) and the Parenterally Administered Shigella sonnei/ Pseudomonas aeruginosa Exoprotein A Vaccine. |
| A-5865 | Evaluation of Chikungunya Vaccine TSI-GSD-218, Protocol F: Effect of Simultaneous Inoculation of Venezuelan Equine Encephalitis Vaccine TC-9R 102 upon Immunogenicity and Reactogenicity of Chikungunya Vaccine TG-83 (NDPR 102). |
| A-5866 | Safety and Immunogenicity of a Hantaan M-S (Vaccinia Virus Vectored) Recombinant Vaccine (TSI-GSD-264) Administered Subcutaneously. |
| A-5846 | Randomized Placebo Controlled, Efficacy Trial of the Orally Administered Attenuated Strain of Auxotrophic Escherichia coli/Shigella flexneri Type 2a Hybrid (ECSF2a-s) and Exoprotein A. |
| A-5580 | Development of a Live, Attenuated Prototype Cholera Vaccine, Study 3. Safety and Immunogenicity of the Attenuated Motility Deficient Prototype Vaccine Strain Peru-14 Containing the B Subunit of Cholera Toxin. |
| A-5618 | Phase I Testing of Live-Attenuated Dengue Vaccine Candidates Produced by Mahidol University. |
| A-5937 | Phase I Safety and Immunogenicity of a Live, Attenuated Shigella flexneri 2a Vaccine Prototype (SC 602). |
| A-5990 | Safety and Immunogenicity of a Candidate Live-Attenuated Cholera Vaccine, Peru-14 Vaccine. |

| LOG NO. | 1993 TITLES |
|---|---|
| A-5948 | Initial Clinical Evaluation of Safety and Immunogenicity of Rift Valley Fever Vaccine, Live Attenuated, Mutagenized ZH548 MP-12, TSI GSD-223, Lot -2-88. Study 2: A Dose Escalation Study in Human Volunteers. |
| A-6001 | Pilot Study of the Safety and Immunogenicity of Live, Attenuated Vibrio cholerae 0139 Vaccine Prototypes (Bengal-3, Bengal-15, and VRI-16). |
| A-4707 | Evaluation of a Tularemia Vaccine Protocol B Conformative Assessment of Francisella tularensis Vaccine, Live, TSI-GSD-213. |
| A-6028 | Comparative Safety and Immunogenicity of a Cell Cultured Vaccinia Virus Vaccine (TSI-GSD-241) Administered by the Intradermal and Intramuscular Routes. |
| A-6029 | Phase I Testing of NIVAC-JEV and ALVAC-JEV vaccines; Evaluation of Safety and Immunogenicity of a Highly Attenuated Recombinant Vaccinia - Japanese Encephalitis Virus (NIVAC-JEV) Vaccine and a Recombinant Canarypoe-Japanese Encephalitis Virus Vaccine in Humans. |

Question: Please provide a description of any DoD plans for research to determine if the investigational drugs used in the Persian Gulf War (PGW), alone or in combination with other drugs and/or chemicals, may be contributing to the undiagnosed illnesses reported by many PGW veterans.

Answer: We currently have no plans to initiate intramural research which would examine the interaction of pyridostigmine or botulinum toxoid alone or in combination with other drugs or chemicals. However, the Department is in receipt of one preproposal to examine these issues, and has been approached by another group of investigators with a request to provide technical support to their independently funded efforts to address these same issues.

Q.4. Dr. Herbert H. Schaumburg, Professor and Chairman, Department of Neurology, Albert Einstein College of Medicine, was a panel member at the NIH Technology Assessment Workshop on the Persian Gulf Experience and Health, April 27-28, 1994. Please list any consultation or research that has involved Dr. Schaumburg on behalf of, or funded by, the Department of Defense, or by companies that make pesticides or pyridostigmine.

A.4. The Army is the DoD lead agency for medical chemical defense and has reported finding no evidence that Dr. Schaumburg served either as a consultant or a researcher on behalf of, or funded by, the Department of Defense during Fiscal Year 1990 through the present.

#5

Question: There is evidence that the pyridostigmine and botulinum toxoid used in the Persian Gulf War may not have been efficacious. According to DoD's own data, pyridostigmine bromide may have reduced the efficacy for treating sarin toxicity. In addition, the atropine dose in the Mark I kit was questioned by the FDA as inadequate (IND Amendment, Reference to IND# 28480, March 28, 1988). Please provide data which supports the dosage of atropine in the Mark I kit for enhancing the kit's efficacy for soman toxicity by pyridostigmine pretreatment.

Answer: The dose of atropine in the Mark I kit was established based exclusively on safety, rather than on efficacy, considerations. The relevant references follow.

(1) Robinson, S., Buckingham, R.E., Pearcy, M., Smith, J.H., Daly, W. Maletich, R., Miller, D., and Robinson, D. (1953). 1952 Field Test of Atropine. In The Physiological Effects of Atropine and Potential Atropine Substitutes. (S. Robinson, ed.), pp. 83-98. Medical Laboratory Contract Report 15, AD 019988. Aberdeen Proving Ground, MD.

(2) Cullumbine, H., McKee, W.H.E., and Creasy, N.H. (1955). The effects of atropine sulfate upon healthy male subjects. Quarterly Journal of Experimental Physiology, 40, pp. 309-319.

Atropine is the quintessential nerve agent antidote. The atropine and 2-PAM contained in the Mark I kit are approved by the FDA to treat nerve agent poisoning. Atropine, which is used to treat muscarinic symptoms of nerve agent poisoning, is administered in doses which depend on the dose of nerve agent received by the casualty. There is , therefore, no relationship between pyridostigmine dosage, which is a constant, and atropine dosage, although atropine is administered in 2 mg. increments. Atropine must be administered whether or not pyridostigmine has been taken, if the casualty chances of surviving an otherwise lethal nerve agent exposure are to be maximized. Furthermore, current doctrine states that a casualty will continue to receive additional doses of atropine sufficient to overcome the muscarinic effects of the nerve agent. Toward this end, medics are supplied with additional autoinjectors of atropine which are to be used to treat nerve agent casualties. A new product which incorporates atropine in a bronchial inhaler is also now available for maintenance of nerve agent casualties. More recent articles describing the effects of the atropine dose contained in the Mark I kit are listed below.

(1) Friedl, K.E., Hannan, C.J., Schadler, P.W., Patience, T.H., Mader, T.H., Jones, R.E., Weir, T.E., and Smallridge, R.C. (1987). Atropine Absorption After Administration with 2-Pralidoxime Chloride by Automatic Injector: A Comparison Between Injection of the Drugs into Same and Separate Sites. MAMC 87-1. Madigan Army Medical Center, Tacoma, WA.

(2) Friedl, K.E., Hannan, C.J., Mader, T.H., Patience, T.H., and Schadler, P.W. (1989). Effect of eye color on heart rate response to intramuscular administration of atropine. Journal of the Autonomic Nervous System, 24, pp. 51-56.

(3) Friedl, K.E., Hannan, C.J., Schadler, P.W., and Jacob, W.H. (1989). Atropine absorption after intramuscular administration with 2-pralidoxime chloride by two automatic injector devices. Journal of Pharmaceutical Sciences, 78, 728-731.

#6

Question: Please provide copies of all studies indicating safety of pyridostigmine for healthy women, including separately all studies of women taking birth control pills and pregnant women.

Answer: There are no studies of this type included in the pyridostigmine NDA recently submitted to the FDA.

#7

Question: Please provide a list of all medical conditions that did not preclude service in the Persian Gulf War. In addition, provide copies of all studies indicating safety for men and women with medical conditions which were permitted for military service in Desert Shield/Storm, but were excluded from most DoD studies, such as asthma.

Answer: DoD Directive 1332.18, Separation from the Military Service by Reason of Physical Disability, February 25, 1986, Enclosure 4 provides a list of all medical conditions which require processing by the disability systems of the Military Departments. The Department did not waive the disability process for Operation Desert Shield/Storm. If the service member did not have an assignment restriction imposed by medical personnel during processing for overseas replacement (POR) for example, pregnancy or being HIV positive, then that individual was considered medically qualified for deployment assignment. The safety net used by the Medical Services is similar among the three Military Departments. The Army profile, the Navy limited duty status (LIMDU), and the Air Force Code C and/or profile, are the mechanisms by which the military medical services recommend to the line commanders duty/assignment limitations their service members have due to their specific medical conditions. Since the safety of service members is of prime importance to the Department, and those policies are already part of the medical/disability system, this office is not aware of any specific safety studies mentioned in the question.

#8

Question: Please provide copies of all studies of men or women indicating the safety of pyridostigmine bromide in combination with pesticides or other chemical exposures, and in combination with multiple vaccines (such as those administered to military personnel serving in the Persian Gulf).

Answer: No studies of this type can be identified.

#9

Question: What percentage of volunteers for DoD studies of pyridostigmine were excluded because they were sensitive to pyridostigmine? For these individuals who were deemed sensitive to the drug, or who had substantial adverse reaction in the studies, please provide all information on the medical follow-up of these individuals.

Answer: No volunteers for Army studies of pyridostigmine were excluded because of known sensitivity to pyridostigmine.

#10

Question: Please provide copies of all adverse reaction forms filed for pyridostigmine by DoD and provided to FDA.

Answer: Enclosed please find copies of adverse reaction forms provided to the FDA under IND 23,509.

Senate Committee on Veterans' Affairs
May 6, 1994
#11

Please provide copies of all informed consent forms signed by military personnel in the Persian Gulf who received an investigation drug.

Answer: In the Persian Gulf War, DoD used two IND status drugs that, although not approved by FDA for general commercial marketing for the particular medical purposes involved, were specifically allowed by FDA for the special military uses proposed by DoD. FDA allowed these uses because there was evidence they would be effective and no recognized alternative existed, and because FDA thought the use would be safe. The FDA also specifically allowed the use of these drugs in the military combat circumstances involved without the usual informed consent requirements required for investigational products. Although there was no informed consent required, there was a decision made by the command structure in the theater of operations to use informed consent for the botulinum vaccine. Attached is the information about the botulinum vaccine presented to individuals and a sample of the informed consent form used. Unfortunately, to date, we have not been able to obtain the original informed consent forms used in the theater of operations, however, our efforts will continue until all avenues have been exhausted.

# INFORMATIONAL BROCHURE
# PENTAVALENT (ABCDE) BOTULINUM TOXOID

## COMPOSITION

PENTAVALENT (ABCDE) BOTULINUM TOXOID ALUM(NUM PHOSPHATE ADSORBED is a combination of aluminum Phosphate-adsorbed toxoid derived from formalin-inactivated, Partially Purified types A,B,C, D, and E botulinum toxins. Each vial contains 0.022% formaldehyde and 1:10,000 thimerosol as a preservative. The currently distributed toxoid is manufactured by the Michigan Department of Public Health.

## Administration and Dosage

SHAKE WELL before withdrawing each dose. Administer 0.5 ml of vaccine via deep subcutaneous injection; do not inject intracutaneously or into superficial structures. Vaccinees will remain in the area where the vaccine is administered for no less than 30 minutes after receiving each dose to monitor immediate adverse effects. A 48 hour post vaccine arm examination is desirable following each inoculation. Vaccinees should be informed that they are to report any adverse local and/or systemic reaction that occurs within one week subsequent to the administration of the vaccine. The first injection is represented by week 0. There is a 2 week interval between the first and second injection and a 12 week interval between the first and third injection.

Initial Vaccination Series: 0.5 ml. deep subcutaneously at 0-2-12 weeks.

First Booster: 0.5 ml. deep subcutaneously 12 months after the first injection of the initial series.

Receipt of each vaccine dose will be recorded in the individuals permanent vaccine file. Additionally, a subset of sporoi, 100 vaccinees receiving each vaccine ~~trial~~ will be prospectively identified for monitoring by a postcard-based questionaire.

## PRECAUTIONS

1. Botulinum toxoid is not a licensed product and is distributed as an investigational New Drug (IND) in accordance with the requirements of the U.S. Food and Drug Administration (FDA). It must be administered under the supervision of qualified medical personnel.

2. The toxoid should be administered only to healthy men and women between the ages of 18 and 65 years, since investigations have been conducted exclusively in that population.

3. PREGNANCY. The effects of administration of the toxoid during pregnancy have not been established. Data are not available on the safety of pentavalent botulinum toxoid for the developing fetus. There should be no risk to the fetus from the product itself because the toxoid contains only inactivated protein. However, a theoretical risk from severe allergic reaction or anaphylaxis does exist. The incidence of severe systemic reactions has been extremely low (< 1%) in previous recipients (male and female) of this vaccine. In contrast, the risk to the developing fetus of botulism is probably considerable. The toxoid should be given only to those persons deemed at risks to exposure of botulinum toxin. Therefore, in a high-risk situation, pregnancy should not be considered a contraindication for vaccination with botulinum pentavalent toxoid.

4. Ka are should be administered a second or subsequent booster immunization unless laboratory test have shown antitoxin type B and or E to be below a satisfactory level.

## IMMUNOGENICITY

Experience with pentavalent botulinum toxoid has shown that: (A) it is effective in protecting animals against intraperitoneal challenge with toxins of types A,B,C,D, and E of *Clostridium botulinum*, (B) the serum antitoxin levels in animals as determined by mouse protection tests correlate with protective activity, and (C) the toxoid introduced into man produces levels of antitoxin thought to be protective as judged by extrapolation of data derived from animal experiments.

In experiments with the original lot of toxoid (2,3), 30 persons were immunized on a 0-2-12 week schedule. Antitoxin titers were detectable for all 5 types of toxin in about 80% of the volunteers 2 weeks after the third dose of the initial series. Only a small percentage had measurable titers by one year, just before the boosters were given. Eight weeks after the boosters, 100% of the recipients had measurable titers to all 5 types.

Since initiating the requirement for determining antitoxin levels in recipients due for boosters, the immunogenicity of the toxoid in humans has been reaffirmed. (Only types A, B and/or E antitoxins are routinely assessed.) While the antitoxin titers attained after the 3rd shot of the initial series are likely to decline in a matter of a few months, those established after the first booster are relatively stable and generally persist above the detectable level for at least 2 years. A titer of 1:16 (0.13-0.30 IU antitoxin per ml.) for either B or E antitoxin is considered satisfactory for deferring a booster for 2 more years. After evaluating sera from 183 recipients taken in 1986, 1987 and 1988 who were due for booster, 81 (43%) were able to postpone them.

The immunogenicities in humans of the two new lots of toxoid (lots A-2 and B-1) and of the original lot (181) were assessed by the U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID) and the results are available for comparison (1). The type B antitoxin levels attained after the 3rd injection of the new lots were significantly higher for the original lot.

In 1988 USAMRIID evaluated immunized individuals for neutralizing antibodies to type A & B botulinum toxins. After the primary series 91% had a type A titer ≥ 0.08 IU/ml, and 78% type B titer ≥ 0.02 IU/ml. After the first booster all individuals tested had a demonstrable titer for type A & B (4).

## REACTIONS

Since 1978, almost 10,000 injections of the toxoid have been administered to recipients who were subsequently observed for adverse reactions. The rate of moderate and severe local reactions was 5.8% for the initial series of shots and 10.7% for booster shots (Table 1). In addition, there was a low incidence of systemic reactions (3.0%) for both the initial series and the booster shots. The systemic reaction were generally mild consisting of fever, tiredness, headache, and muscle pain. Systemic reactions were often concurrent with local reactions. Moderate or severe systemic reactions and severe local reactions are not anticipated. Because of the documented increase in reactions, new lots of toxoid were manufactured in 1971, but distribution of the original lot was continued until 1981. A recent report on a very limited study on the reactogenicity of the new lots of toxoid indicated that they are probably no less reactogenic than the previous lot (1). Noting the higher incidence of local reactions following subsequent yearly boosters than following initial series shots, it was deemed advisable to evaluate the need for boosters by determining antitoxin levels and to boost only when necessary. This approach revealed that boosters subsequent to the first one are not necessary more frequently than at 2 year intervals and that many of these boosters can be avoided. Prior to 1976, yearly boosters were routinely given. Moderate local reactions include erythema, edema and induration. All such reactions reach a peak in 24 hours, then gradually subside and should be gone at 48 or at the most 72 hours. When a moderate local reaction occurs, reduction of the dose of each subsequent injections to 0.25 ml has been shown to alleviate the reaction without impairing the antitoxin response. Rarely, an individual may have a reaction characterized by a deep, painless, noninflammatory subcutaneous induration that may persist for 3 to 4 weeks. These rarely measure more than 2 to 3 centimeters in diameter and are absorbed without residue.

## SUPPLIES

The toxoid is supplied by the U.S. Army Medical Research and Development Command (USAMRDC), Ft Detrick, Frederick, Md. 21701. Inquiries for toxoid should be directed to:

U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID)
ATTN: SCRD-UIH (LTC McKee)
Medical Division
Ft. Detrick, Md. 21702-5011
Telephone: 301-663-7655

-OR-

U.S. Army Medical Material Development Activity
Biological Systems Project Management Division
Product Manager
Pentavalent Botulinum Toxoid (ABCDE)
Division of Biologics
Ft. Detrick, Md. 21702
Telephone: 301-663-7661

## REFERENCES


1. Andersen, J.H. and Lewis, G.E., Jr. Clinical Evaluation of Botulinum Toxoids. In Biomedical Aspects of Botulism. Academic Press, New York, pp. 233-244, 1981

2. Cardella, M.A. Botulinum Toxoids. In Botulism, Proceedings of a Symposium. PHS No. 999-FP-1, Public Health Service, Cincinnati, pp. 113-130, 1964.

3. Fiock, M. A., Cardella, M.A., and Gearinger, E.F. Studies on Immunity to Toxins of Clostridium botulinum. IX. Immunologic Response of Man to Purified Pentavalent A,B,C,D,E Botulinum Toxoid. J. Immunol. 967-702, 1963.

4. Siegel, L.S., Human Immune Response to Botulinum Pentavalent (ABCDE) Toxoid Determined by a Neutralization Test and by an Enzyme-Linked Immunosorbent Assay. J. Clin. Micro. 26: 2351-2356, 1988.


Table 1

Local Reactions to Botulinum Pentavalent (ABCDE) Toxoid (170-84)
Number of Reactions (%)

| Injection Number | None or Mild | Moderate | Severe* |
|---|---|---|---|
| 1 | 2356 | 90 | 3 |
| 2 | 2199 | 133 | 4 |
| 3 | 1967 | 148 | 5 |
| Subtotal | 6500 | 391(5.6) | 12(0.2) |
| **Booster Injections** | | | |
| 1 | 1079 | 141 | 14 |
| 2 | 496 | 53 | 5 |
| 3 | 290 | 28 | 5 |
| 4 | 886 | 77 | 1 |
| Unknown | 11 | 2 | 0 |
| Subtotal | 2760 | 301 | 25 |
| Subtotal % | (89.2) | (9.8) | (0.2) |
| Total | 9247 | 692 | 37 |
| Total % | (92.7) | (6.9) | (0.4) |

Key

None = No Reactions
Mild = Erythema only; edema or induration which is measurable but 30 mm or less in any one diameter.
Severe = any reaction measuring more than 210 mm in any one diameter or any reaction accompanied by marked limitation or motion of the arm or marked axillary node tenderness.

* MODERATE AND SEVERE REACTIONS AS DEFINED BY THESE CRITERIA ARE NOT INCAPACITATING.

## INFORMATION ABOUT BOTULINUM VACCINE

You are being given a vaccine called botulinum toxoid because you are considered at risk of exposure to botulism. Botulism can cause serious paralysis or death. It is caused by toxins that interfere with the normal transmission of nerve signals. Botulism can arise from: (a) contaminated food and water, (b) contaminated wounds, or (c) a biological warfare attack. Symptoms of botulism can begin as early as three hours or as late as several days after exposure to the toxin. Symptoms include blurred vision, generalized weakness, difficulty in swallowing and talking. Treatment after exposure is primarily supportive and there is an antitoxin/antidote which may be beneficial. Your primary protection against botulinum toxin is the use of your chemical protective mask and overgarment. Vaccination with botulinum toxoid is expected to provide additional protection for individuals exposed to the toxin. However, no vaccine is 100% effective. No other vaccine is available which can give you this protection.

This is an investigational (not yet licensed) vaccine that has been safely given to over 3,000 laboratory workers and scientists over the past 25 years. It will be administered as a series of three injections under the supervision of qualified medical personnel.

About 92% of people who are vaccinated report no significant side effects beyond the local pain experienced at the time the vaccine is given. However, like other vaccines you have been given, this one may have some side effects. Side effects occur in 4% to 8% of people. When they occur, they are usually at the site of injection and include pain, tenderness, swelling, redness, and/or itching. All these are common symptoms with the typhoid vaccine you have already received. The number of these local reactions tends to increase after the first injection. Rarely an individual may develop a small lump at the injection site which lasts for several days to weeks before going away. Local reactions that can interfere with performance of your duties are very uncommon. Generalized reactions may include fever, tiredness, headache and/or muscle pain and occur in less than 1% of people. Rarely (less than 1 in 1,000 injections) an individual may be unable to perform duties for a day or two. As with any vaccination, a very rare, unexpected, potentially severe, side effect not previously observed could occur. If you are pregnant it is not known if this vaccine will harm your unborn baby. However, most vaccines do not harm an unborn baby when given to the mother.

If a reaction that worries you occurs after you leave the area where the vaccine was given you should report to sick call.

You may be one of a group to receive a postcard in the next few weeks asking for information on your experiences with this vaccine.

I have read and understand the information above on the Botulinum toxoid vaccine. I voluntarily submit to the vaccine series.

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#12

Question: What measures were taken to ensure that military personnel in the Persian Gulf took pyridostigmine?

Answer: During ODS troops were given pyridostigmine in a blister pack containing twenty-one 30mg pyridostigmine tablets. The decision to begin, continue or discontinue pyridostigmine rested with each major unit commander, based on his chemical, medical, and intelligence staff officers' advice. Troops took one to 21 pyridostigmine tablets at the specified regimen of one tablet every 8 hours. Pyridostigmine tablets were self administered.

#13

Question: Please provide copies of all original reports by medical personnel on the adverse reactions experienced by military personnel in the Persian Gulf.

Answer: Medical reports on adverse reactions to pyridostigmine would have been maintained by local medical units. We are currently trying to obtain any such records. However, we can provide you with some accurate information from a retrospective study which was conducted on the XVIII Airborne Corps to determine the adverse effects of pretreatment with pyridostigmine tablets. The XVIII Airborne Corps instructed 41,650 soldiers (6.5% women) to take pyridostigmine tablets at the onset of ODS hostilities in January 1991. The dosage of pyridostigmine, prescribed as one tablet every 8 hours, was variable depending on the order issued by each unit commander; total dosage ranged from one to 21 tablets over 1 to 7 days, with 34,000 soldiers reportedly taking the medication for 6 to 7 days. With respect to acute side effects, in this retrospective study, thirty medical officers who provided medical support to the XVIII Airborne Corps were queried to determine the adverse effects of pyridostigmine. Gastrointestinal symptoms were noted in about half the troops. Urinary urgency and frequency were noted in between 5-30%, and headaches and tingling of extremities were noted in <5%. The need for a medical visit was reported for 1% and the need to discontinue use based on medical advise was reported for <0.1%. As indicated in the answer to question 3, ordinarily, discontinuing pyridostigmine should be adequate to alleviate the signs and symptoms of adverse side effects, allergic reactions, and overdose.

#14

Question: We have received information that some Persian Gulf soldiers were told they would not receive the second anthrax vaccine because the "vaccine had gone bad." Are you aware of any such discussions? Were any of the vaccines administered to Persian Gulf military personnel contaminated or deemed unsafe?

Answer: We are not aware of any vaccines that "had gone bad" during Operation Desert Storm. Moreover, we are not aware of any vaccines administered to Persian Gulf military personnel that were determined to be contaminated or deemed unsafe.

## QUESTIONS FROM SENATOR AKAKA

Posthearing Questions
For Dr. Edward Martin
from Senator Daniel Akaka
Senate Committee on Veterans Affairs

Q.15. To knowingly mislead military volunteers participating in medical experiments is a serious allegation. Is the practice of utilizing military recruits for human research protocols involving chemical or biological defense agents commonplace today? What steps have been taken to avoid such abuses? Do you think it wise to compensate volunteers of these earlier programs?

A.15. It is not common practice to use military recruits as subjects in research protocols involving chemical or biological defense agents. The Department of Defense (DoD) is committed to protecting fully human subjects who participate in military medical research. Procedures required to avoid abuse of any human subjects are detailed in Federal Regulations and DoD Instructions; compliance with these guidelines is ensured by the careful review of every human use research protocol by an independent Institutional Review Board (IRB). Approval of the IRB must be obtained and documented before any military medical research protocol is funded.

Specifically, the DoD follows Federal policy on the use of human subjects in medical research, *Title 32, Code of Federal Regulations, Part 219;* and has issued additional guidance in *DoD Directive 3216.2, Protection of Human Subjects in DoD Supported Research* and in *DoD Guidance for the Assurance of Compliance with the Federal Policy for the Protection of Human Subjects.* Additionally, research involving the use of a new drug or vaccine in human subjects must be reviewed and approval by the Food and Drug Administration.

These policies require that all uniformed and civilian persons to be used as human subjects in military medical research must be fully informed of the aims, methods, anticipated benefits, and potential hazards or discomforts associated with the study. Special care is given to informing potential volunteers who might be particularly vulnerable to coercion or misunderstanding (such as prisoners, mentally disadvantaged persons, non-English speaking persons, etc.); this same consideration would be given to young, military recruits. All potential subjects are informed of their freedom to withdraw from participating in the study, without repercussion, at any time. The IRB is responsible for ensuring that all aspects of the human use guidelines are met and has the ultimate authority to disapprove any research project if deficiencies in the protection of human subjects are found.

Q.16. Some say that criticism of current researchers for past medical research practices is like forcing the son to pay for the sins of the father. Do you feel further investigation into these alleged misdeeds would be justified, or do we grudgingly place these historical practices in proper perspective, and concentrate more on avoiding repetition of these mistakes?

A.16. Further investigation into alleged past misdeeds would be of little benefit, since the circumstances surrounding past decisions can never be fully reconstructed. It is better to concentrate now on avoiding repetition of any previous misguided events and devote our resources to helping former military personnel obtain full and accurate information on the extent of their participation in military medical research programs.

#17

Question: We have many active duty servicemen in Hawaii who served in the Gulf War. At least one has indicated that because of possible symptoms linked to his service in the Gulf War arena, records on his postwar treatment have been removed from his medical file.

a. What are the procedures for handling medical records of those military members identified as suffering from Gulf War illness?

Answer: No new or special policies have been established for handling medical records of Persian Gulf War veterans or their family members. Current Departmental policy requires inpatient treatment records to be retained at the hospital where the patient has been admitted. These records have limited access restricted to hospital staff. Patients must make written request to the patient administration division for copies of these records If the service member were admitted in Theater the administration and maintenance of the inpatient record is Service specific. However, by this time all intpatient records of Theater hospitalized service members will have been transferred for storage at the National Personnel Records Center (NPRC) in St. Louis, Mo. Copies of the records at NPRC are available on written demand by the service members. In addition, a cover sheet with diagnoses, dates of hospitalization, demographic information, and a narrative summary of the hospitalization are placed in the service member's outpatient record. The outpaitent medical record is a full access document. by both the hsopital staff and the service member. The field medical record is transported by the service members while in the theater of operations and when s/he departs from the theater and is combined with the permanent medical record upon repatriation.. The Assistant Secretary of Defense for Health Affairs has tasked the Military Departments to provide information on the actual process followed during Operations Desert Shield/Storm to combine the field outpaitent medical record with the permanent outpatient health record. This report should be available by the end of July 1994.

b. What are the procedures for treating family members of military members identified as possibly suffering from Gulf War exposures?

Answer: Family members who are entitled beneficiaries of the Military Health Services System may seek care for their health problems through military facilities or, in some cases, CHAMPUS.

c. Are such members told that their medical complaints may be linked to prior service in the Persian Gulf?

Answer: There is no Departmental policy which prohibits individuals with medical complaints that are linked to prior service in the Persian Gulf from being told that this is the case.

d. Are studies now underway to identify and treat these victims without the patient initiating the action?

Answer: Yes. The Assistant Secretary of Defense for Health Affairs (ASD[HA]) has established the Comprehensive Clinical Evaluation Program (CCEP) to provide extensive medical examinations to Persian Gulf War veterans or their family members who are experiencing illnesses which they believe are related to the Persian Gulf War. The overall objective of the CCEP is to determine, as well as is possible, the cause(s) of the illnesses being experienced by veterans and their families. Military Health Services System (MHSS) staff recognize patients' rights as an integral part of the CCEP diagnosis and treatment process. A description of CCEP patients' rights is provided below.

**Participants**

The following individuals who enroll in the DoD Persian Gulf Veterans Health Surveillance System after May 31, 1994 are currently candidates for participation in the CCEP:

Persian Gulf War veterans who are

- Active Duty
- Retired from military service
- Ready Reservists
- Full-time National Guard Duty

Family members of these veterans who are eligible beneficiaries of the Military Health Services System

**The CCEP Clinical Protocol**

The CCEP protocol is a three phase evaluation process. The protocol provides a framework for diagnostic evaluation, and is not all inclusive or restrictive. Physicians at military hospitals will conduct additional tests and examinations on an individual basis as appears necessary to fully evaluate each patient. The attached flowchart presents an overview of the clinical evaluation process. CCEP patients are entitled to quality care and treatment consistent with the highest standards of medical practice. Participation in the CCEP is purely voluntary. Patients have the right to decline to participate in the CCEP or to refuse recommended evaluations at any point during the evaluation process. In addition, patients may stop participating in the evaluation at any time. Individuals who initially decline to participate or stop participating at any time may resume their participation in the program at a later date if so desired.

**Phase I**

The purpose of the Phase I evaluation is to confirm and/or establish definitive diagnoses related to a patient's Persian Gulf related health complaints. All patients who have definitive diagnoses which are consistent with their complaints and which explain to their satisfaction their Persian Gulf related health concerns require no further evaluation within the CCEP. Individuals whose complaints are not explained to either the health care provider's or the patient's satisfaction shall be evaluated at a regional military medical center using CCEP protocol Phase II procedures.

**Phase II**

Persian Gulf veterans or family members who after completing Phase I evaluations do not have clearly defined diagnoses receive a Phase II evaluation consisting of supplemental baseline laboratory tests and consultations. Two tubes of blood will be drawn on each patient for submission to the Armed Forces Institute of Pathology (AFIP). All patients who have definitive diagnoses which are consistent with their complaints and which explain to their satisfaction their Persian Gulf related health concerns require no further evaluation within the CCEP. Individuals whose complaints are not explained to either

the physician's or the patient's satisfaction shall be evaluated at a regional military medical center using CCEP protocol Phase III procedures.

**Phase III**

Patients who still have undefined diagnoses receive Phase III evaluations consisting of special case-by-case evaluations. Patients whose problems have not been diagnosed after completing Phase III evaluation will be asked a list of supplemental questions concerning chemical intolerance.

Records of patients for whom a satisfactory diagnosis cannot be determined will be reviewed by a Special Clinical Review Committee sponsored by the ASD(HA).

**Reporting and Data Collection:**

Copies of all patient medical records including narrative summaries, laboratory results, diagnostic procedure reports, and available military and civilian records related to the onset of post Gulf War symptoms will be forwarded to the Naval Medical Information Management Center (NMIMC) in Bethesda, Maryland. Regional military medical centers will store CCEP medical records apart from other patient medical records, and maintain them in a secured/locked area. Copies of CCEP pertinent medical information will be maintained at the medical center, placed in the patient's medical record, and forwarded to NMIMC.

Regional military medical centers will forward all pathology specimens including whole blood and sera collected for AFIP, surgical specimens, and microscopic slides to AFIP.

**Respectful Treatment**

CCEP patients have the right to considerate and respectful care, with recognition of their personal dignity.

**Privacy and Confidentiality**

CCEP patients have the right, within the law and DoD regulations, to privacy and confidentiality. Medical information associated with CCEP evaluations will be processed according to existing laws protecting confidentiality of medical records. Patients will be asked to provide written consent for participation in the research component of the CCEP, blood collection, and release of personal medical information.

**Explanation of Care**

CCEP patients have the right to have their diagnoses, procedures, treatments, and prognosis explained in terms they can clearly understand.

**Informed Consent**

CCEP patients have the right to be given, in easily understandable terms, information needed to make knowledgeable decisions on diagnostic and treatment options. Such information should include anticipated complications, risks, benefits, and alternative available diagnostic procedures and treatments. CCEP patients are participants in a program designed to define, diagnose, and treat patients who have been identified as having medical problems which could be related to service in the Persian Gulf region.

**Patients' Complaints**

Patients are entitled to information about the evaluating medical facility's mechanisms for the review and resolution of patients' complaints. Patients who experience problems related to their CCEP evaluation which cannot be resolved at the local level should be referred to the Office of the Surgeon General of the Service which has jurisdiction over the facility.

Senate Committee on Veterans' Affairs
May 6, 1994
#18

Question: A variety of causes have been postulated as to the cause of illnesses attributed to service in the Persian Gulf arena. What historical baseline medical (epidemiological) studies have been done to date? Can you give us any results?

Answer: The Department has implemented an aggressive, comprehensive clinical diagnostic effort, to determine, as far as possible, the causes of the symptoms reported by our Persian Gulf War veterans. As a first step, those active duty Persian Gulf veterans who are in the DoD's Persian Gulf Veterans Health Surveillance System or the Veteran's Affairs Persian Gulf Registry and do not have clearly defined diagnoses will receive this intensive exam. In addition, the Department will develop approaches to conduct targeted Reserve evaluations. Within 120 days we expect to provide a report that describes the diagnostic and therapeutic outcomes of these examinations. In addition, this report will provide a description of the protocol being used as the DoD's clinical practice guideline for diagnosing and treating individuals experiencing the Persian Gulf Syndrome. In addition, the Department has completed, and is initiating, research studies into the Persian Gulf illnesses. These studies fall within the following broader research areas:

- Leishmania Research
- Stress-Related Surveys of Soldiers Deployed in ODS
- Studies Involving the Military Use of Pyridostigmine
- Survey of Troops Who Received Clostridium Botulinum Toxoid in the Gulf
- Epidemiologic Studies of Morbidity among Gulf War Veterans
- Epidemiologic Analysis of the Mortality Experience among Gulf War Veterans
- Environmental Toxicology Studies
- A Comprehensive Neuropsychological Study of Issues Associated with Gulf War Illnesses
- Low Level Chemical Sensitivity
- Health Effects of Depleted Uranium
- Antibiotic Therapy

Senate Committee on Veterans' Affairs
May 6, 1994
#19

Question: Many of the complaints concerning care and treatment of Persian Gulf War veterans mimic the Agent Orange experiences of doubt and delay.

a. Why were we apparently caught unaware of the possibility of postwar illnesses of this magnitude?

Answer: We were not caught unaware of the possibilities that illnesses might result from the deployment of U.S. forces to the Persian Gulf region. While the oil well fires were still burning in Kuwait, the Department sent a team from the U.S. Army Environmental Hygiene Agency to collect samples from the environment in order to estimate the possible health threats posed from environmental contaminants. The Department also established a personnel registry to document the names of individuals and the units which were deployed to the Persian Gulf. The Surgeons General of the Services have collected data on service members seen within the Military Health Services System (MHSS) who have experienced illnesses which were associated with Operations Desert Shield/Storm. In addition to these initiatives, numerous research projects have been sponsored by DoD and the Department of Veterans Affairs in an attempt to resolve the health problems of Persian Gulf veterans.

b. Would it not have been prudent to consider the need for immediate detoxification treatment and psychological counseling during and after the war, knowing that our troops were to be subjected to an unprecedented combination of toxins, biologicals, parasites, and high levels of stress?

Answer: With regard to the Persian Gulf War, there is no persuasive evidence that any of the proposed etiologies caused chronic illness on a significant scale in the absence of acute injury at initial exposure. In fact, the overall health experience of US troops in the Persian Gulf War was favorable beyond previous military precedent, with regard to non-combat as well as combat-related disease. The Department is reviewing the policies and procedures associated with deployments and demobilization in order to develop a doctrine for environmental health assessment and surveillance before, during, and after future deployments.

Senate Committee on Veterans' Affairs
May 6, 1994
#20

Question: Medical follow-up of those veterans given pyridostigmine tablets and botulinum vaccinations during the Gulf War has been less than satisfactory.

a Given the lead time prior to the start of the ground war, could we not have circumvented this problem?

Answer: No. Intelligence reports suggested the possibility that Iraq would use these chemical or biological agents during the war. It was essential that the troops deployed were protected against that potential military threat. The decision to use pyridostigmine bromide and botulinum vaccinations was made after full consultation with and concurrence by the Food and Drug Administration. Furthermore, we have no scientific evidence to date that any of the illnesses being experienced by veterans of the Persian Gulf War are related to pyridostigmine bromide or botulinum vaccination.

b. What improvements have been initiated since the end of the war to improve medical tracking of military members during wartime?

Answer: The Department is reviewing the policies and procedures associated with deployments and demobilization in order to develop a doctrine for environmental health assessment and surveillance before, during, and after deployments.

Senate Committee on Veterans' Affairs
May 6, 1994
#21

Question: By convention, we have focused our attention on medical experimentation using American servicemen and women. Yet there are many other countries, including our allies, which continue to pursue defense programs geared at medical defense of chemical and biological agent exposures.

a. Why is our experience with postwar illnesses so different from that of our allies?

Answer: We have no explanation of why our experiences have differed from that of other coalition nations. It is most perplexing because many troops from the coalition countries were exposed to all of the same contaminants which have been suggested as possible causes of the Persian Gulf Illnesses and yet have not developed symptoms. The Department is continuing to communicate with the Governments of the other allies in an effort to monitor their experiences related to Persian Gulf Illnesses.

b. How do we integrate lessons learned from prior wars and foreign country research into treatment regimens for victims of the Persian Gulf War?

Answer: Veterans of the Persian Gulf War are evaluated and treated within the Military Health Services System according to the current standards of medical practice. Scientific information from prior wars and research conducted in foreign countries published in scientific, peer reviewed, professional journals are a vital part of the current standards of medical practice.

## QUESTIONS FROM SENATOR MITCHELL

Senate Committee on Veterans' Affairs
May 6, 1994
#22

Senator Mitchell: The Compensation and Pension Service prepared a fact sheet on DoD cooperation in verifying exposure to mustard gas. It says it has been able to verify exposure for fewer than 200 veterans. It says that in March 1993, DoD assured VA it would assist in getting documentation. According to VA, this information was to have been compiled and available to VA before the end of FY 1993. None of these actions have yet taken place. Can you give this Committee some indication when these actions will be completed?

Dr. Martin: DoD received a copy of the referenced Compensation and Pension Service Fact Sheet from VA in a letter from Secretary Brown dated April 7. We will provide the Committee the answers to each statement in the fact sheet as soon as we have provided our response to VA.

In March of 1993, the Deputy Secretary of Defense responded in writing to Representative Montgomery, Chairman of the House Committee on Veteran's Affairs, on issues concerning the search for, location of, and collection of records that would assist VA in verifying veterans' exposures to mustard gas and other chemical agents. The Office of the Director of Defense Research and Engineering responded to Secretary Brown at the same time on identical issues. Copies of both letters are attached.

In March of 1993, the Deputy Secretary of Defense also directed the Military Departments to locate and provide the specified information. A copy of that memorandum is also attached. The Under Secretary of Defense for Personnel and Readiness, USD(P&R), was directed to oversee and monitor the performance and completion of the directed actions. Specified information was to be forwarded to the USD (P&R) by July 31, 1993. The Department stated at that time that our goal was to provide information to the VA as soon as possible. During hearings held in March of 1993 by the Subcommittee on Compensation, Pension, and Insurance of the House Committee on Veterans' Affairs, the Department stated we could not have the names of all test participants by July 1993. DoD did not commit to completing actions referred to in the fact sheet by the end of FY 1993. In fact, this effort will require years of research, collection, analysis, and cataloging to be prepared for use by VA, DoD, and the Department of Labor, which will need the information for verification on civilian exposures. We did commit to providing as much information as possible as soon as possible.

Since March of 1993, we have identified five major records repositories within DoD as well as records collections at the National Archives and the University of Chicago. We believe that additional documentation may be housed at other universities that participated in Defense programs as contractors, and at ancillary storage facilities in the National Archives system. Teams have reviewed the collections to determine whether they contain information on personnel exposed to chemical weapons agents as the result of human testing programs or during production, transportation and storage activities.

We have concentrated our efforts on locating information to verify full body exposures during chamber or field tests, and on other tests that specifically used human test subjects. We do not have the resources to immediately review all archived material relating to military installations and activities. We have targeted, with the help of archivists and records

management experts, those collections where we anticipate finding information specific to chemical weapons agent testing. We have recently completed our review of the repositories and tested an automated capability to facilitate extracting personnel data from the records.

We have contracted to compile a database of test sites, dates, and agents used. This will allow us to verify types of chemical agent testing, or other activities that took place at specific sites during particular time frames. This project is still in progress because of the extremely large amount of information to be gathered, reviewed, and entered into the database. Initial emphasis was on test site locations, but review of records and other archived materials has provided a tremendous amount of data on storage, production, and transportation activities, which were also potential causes of exposure. A preliminary copy of this 200-page site location database was provided to the VA in February. An updated version was been forwarded to the VA in May.

Our efforts to date have led to identification of new information that we have shared with VA. Among the findings were: identification of Hart's Island, New York as a test site; chamber test information from Great Lakes, Illinois; confirmation of the fact that a photo provided by a veteran showed mustard gas canisters in India; identification of Black Hills Ordnance Depot as a storage site; lesson plans stored at Fort Riley; and identification of several other sites where mustard gas may have been used in testing or training.

Most of the information found is not in medical or personnel records. Information is widely dispersed geographically and is interspersed in administrative, technical, and scientific documents. Thousands of linear feet of paper records must be reviewed page by page for personnel information. In some cases records are still classified. Much of the information is not conclusive concerning exposure, and personnel information is often incomplete. During our review of the records collections, we extracted names as we found them. However, records may refer to personnel by last name only, with no rank or title to indicate military or civilian; test subject numbers may be used instead of names; code names may be used instead of surnames; and often there are no service or social security numbers. Chemical agents are often referred to by number or by letters relevant only to the test site, which requires an index or guide to determine the agent. Extraction of pertinent information on human exposures, or potential exposures, is an extremely complex and labor-intensive task. Because the information is often incomplete, in code, and on technical topics, the research and collection must be carried out by trained, knowledgeable personnel and technical specialists.

The Military Departments are not staffed to carry out this task; and current and future personnel and fiscal constraints will further reduce our ability to collect, index, and automate the information to the extent requested by VA. There is not a centralized point designated to collect and analyze this vast collection of documents or to respond to agency and individual inquiries. In many cases we have not located any documentation on personnel used in the testing, nor have we located complete information on the testing protocols.

DoD continues to respond to inquiries from Congressional staff, VA, veterans organizations, and from individual veterans and their families. When an inquiry comes in, we conduct an exhaustive search on what documentation we do have, often calling the veteran to get additional information. Many other inquiries are researched and answered by the particular installations involved in the chemical defense activities or by the Service Headquarters. Information provided by veterans that will assist us in further expanding our database or search efforts is added to our files. This kind of information has assisted us in determining additional

test or storage sites and in assisting other veterans who had made inquiries concerning specific sites or incidents. Information is provided to VA as it is found.

We make every effort to assist veterans and give them the benefit of the doubt, since personnel or medical records are not usually available. However, until recently, except for 700 names found at the National Archives in Suitland, Maryland, we have not found many names to add to the original set provided by the Naval Research Laboratory.

We recently located 13 magnetic tapes from the 1970s that we believe contain test subject names, numbers, agents, doses, and other pertinent research information for personnel tested at Edgewood Arsenal during the period 1955 through the 1970s. The Army Chemical/Biological Defense Command, the Office of the Under Secretary of Defense for Personnel and Readiness, and the Defense Manpower Data Center are cooperating in having the tapes converted to a contemporary format for entry into a database. We estimate there are some 7,000 test subjects on these tapes. As soon as the tapes are converted to a readable format, the names and test information will be provided to VA. This May, the Naval Research Laboratory provided us and the VA with additional information on its World War II test subjects.

#23

Senator Mitchell: VA Secretary Brown has brought his concerns with the Defense Department's performance to the attention of Defense Secretary William Perry. I have asked for unanimous consent that Secretary Brown's letter of April 7, 1994--with attachments--be included in the records of the Committee's May 6, 1994, hearing. When can a response to this letter and the issues it raises be expected.?

Dr. Martin: The Office of the Under Secretary of Defense for Personnel and Readiness is currently coordinating a response to the letter from Secretary Brown. A response to each of Secretary Brown's concerns, including information provided here, will be forwarded prior to June 15, 1994.

## QUESTIONS FROM SENATOR JEFFORDS

**Question #24:** What is being done presently at DoD to streamline personnel and health records of servicemen and women in order to make information more readily available and make records more manageable?

**Answer:**
Current Departmental policy requires inpatient treatment records to be retained at the hospital where the patient has been admitted. Access to these records is limited to specific members of the hospital staff. Patients must initiate a written request to the patient administration division for copies of these records. If service members were admitted to a hospital in Theater, the administration and maintenance of their inpatient record is Service specific. All inpatient records of Theater hospitalized service members have now been transferred for storage at the National Personnel Records Center (NPRC) in St. Louis, Mo. Copies of the records at NPRC are available upon written request by the service member. In addition, a cover sheet with diagnoses, dates of hospitalization, demographic information, and a narrative summary of the hospitalization are placed in the service member's outpatient record. On the other hand, the outpatient medical record is a full access document by both the hospital staff and the service member. Field medical records are transported by the service member while in the theater of operations until s/he departs from the Theater. Close to departure, the field medical record is combined with the permanent medical record upon repatriation. The Assistant Secretary of Defense for Health Affairs has tasked the Military Departments to provide information on the procedures followed during Operations Desert Shield/Storm to combine the field outpatient medical record with the permanent outpatient health record. DoD has initiated a project with Veterans Affairs under a new DOD/VA Reinvention Partnership agreement to consider the processes and procedures for accessing information in both personnel and medical records.

#25

Question: Has the DoD established that any formerly presumed causes for Persian Gulf War illnesses are definitely not attributed to service in the Gulf?

Answer: None of the proposed causes for Persian Gulf Illnesses have been eliminated from our consideration in attempting to resolve the health problems being experienced by Persian Gulf War veterans.

Senate Committee on Veterans' Affairs
May 6, 1994
#26

Question: Could you briefly describe the 20 different Persian Gulf-related research activities being undertaken by the Federal Government?

Answer: A description follows.

# *Persian Gulf Veterans Coordinating Board*

## *Research*

DoD Research Activities

Review of the Health Consequences of Service During the Persian Gulf War.
Action: National Academy of Sciences (NAS) - Medical Follow-up Agency
Purpose: As directed by P.L. 102-585, the NAS will review existing scientific, medical and other information on the health consequences of military service in the Persian Gulf theater of operations during the Persian Gulf War.
Coordinations: DoD, VA and HHS.

Cooperative DoD/VA Research.
Action: DoD and VA Medical Scientists.
Purpose: Support for partial funding of research on the health consequences of exposure to environmental hazards during the Persian Gulf War. Some of this research will take place at VA Medical Centers.
Coordination: DoD, VA and HHS.

Leishmania Research.
Action: US Army Medical Research and Development Command.
Purpose: Develop a blood assay for leishmania.
Coordinations: DoD, VA and HHS.

Epidemiologic Assessment of Suspected Outbreak of an Unknown Disease Among Veterans of ODS at the Request of the 123d Army Reserve Command, FT. Benjamin Harrison, Indiana.
Action: US Army Medical Research and Development Command.
Purpose: Conducted medical examinations and in-depth surveys of 79 soldiers with symptoms or concerns potentially linked to service in ODS.
Coordinations: DoD, VA and HHS.

Stress-Related Survey of Soldiers Deployed in ODS.
Action: US Army Medical Research and Development Command.

Purpose: To identify correlations between post ODS symptoms and occupational and environmental stresses. These questionnaires were completed by active duty and reserve Army, Navy and Air Force personnel in Hawaii and Pennsylvania. Data analysis is in progress.
Coordinations: DoD, VA and HHS.

Retrospective Studies Involving Military Use of Pyridostigmine as a Pretreatment for Nerve Agent Poisoning.

Action: US Army Medical Research and Development Command.
Purpose: Obtain safety data for pending New Drug Application to FDA.
Coordinations: DoD, FDA and VA.

Retrospective Survey of Troops Who Received Clostridium Botulinum Toxoid in the Gulf War.

Action: US Army Medical Research and Development Command.
Purpose: To conduct a retrospective survey of troops who received clostridium botulinum toxoid in the Gulf War after troops returned to the US.
Coordinations: DoD, VA and HHS.

Environmental Toxicology Studies.

Action: Armed Forces Institute of Pathology and Army Environmental Hygiene Agency.
Purpose: To conduct a series of studies in environmental and toxicologic pathology relating to exposures during the Persian Gulf War.
Coordinations: DoD, VA and HHS.

Monitoring Gulf War Veterans With Imbedded Depleted Uranium Fragments.

Action: Armed Forces Radiobiology Research Institute.
Purpose: Conduct clinical follow-up of ODS patients with known or suspected imbedded depleted uranium fragments and assess health risks from imbedded depleted uranium fragments.
Coordinations: DoD, VA and HHS.

Working Group to Establish a Working "Case Definition" for Post-ODS/DS Unexplained Illness.

Action: Walter Reed Army Medical Center.
Purpose: Review and analyze medical records of ODS/DS veterans with unexplained symptoms to establish a working "case definition" for post-ODS/DS unexplained illness.
Coordinations: DoD, VA and HHS.

Epidemiologic Studies of Morbidity among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors.

Action: Naval Health Research Center.
Purpose: Conduct a definitive epidemiologic study of active duty members who deployed to ODS compared to those who did not deploy.
Coordinations: DoD, VA and HHS.

# *Persian Gulf Veterans Coordinating Board*

## *Research*

VA Research Activities

Children of PG Veterans in Mississippi.
Action: VAMC Jackson.
Purpose: An examination of children born to Persian Gulf veterans for evidence of possible genetically determined health effects related to their parents' service.
Coordinations: VA, DoD and HHS.

Review of the Health Consequences of Service During the Persian Gulf War.
Action: National Academy of Sciences (NAS) - Medical Follow-up Agency
Purpose: As directed by P.L. 102-585, the NAS will review existing scientific, medical and other information on the health consequences of military service in the Persian Gulf theater of operations during the Persian Gulf War.
Coordinations: VA, DoD and HHS.

Pilot Program to Investigate Medical and Psychological Effects of Exposure to Toxic Hazards.
Action: VAMC Birmingham.
Purpose: Conduct pilot program to investigate medical and psychological effects of exposure to toxic hazards. Results of examinations provided to about 11,000 veterans on VA's PG Registry are also being reviewed to determine if these individuals should be called back for testing.
Coordinations: VA, DoD and HHS.

Examining Neuropsychological-Psychological Profiles of Veterans Returning from the Persian Gulf Theater.
Action: VAMC Boston.
Purpose: Conduct a small-scale pilot program examining neuropsychological-psychological profiles of veterans returning from the Persian Gulf Theater.
Coordinations: VA, DoD and HHS.

Environmental Hazards Research Centers.
Action: Three VAMCs (to be determined).
Purpose: A request for proposals to establish up to three, VA-based, research centers for the study of the medical consequences of exposure to environmental and toxic hazards, initially focused on the problems cited by personnel in the PG conflict.
Coordinations: VA, DoD and HHS.

Persian Gulf Interagency Research Coordinating Council.
Action: VA, DoD and HHS.

Purpose: VA, DoD and HHS, make up the newly formed Persian Gulf Interagency Research Coordinating Council. The council, established by the Persian Gulf War Veterans' Health Status Act, will coordinate all research activities undertaken or funded by the Executive Branch of the Federal Government on the health consequences of military service in the Persian Gulf theater of operations during the Persian Gulf War. As an initial step, the council members agreed to organize a conference of experts from within and outside the federal agencies, with a goal of reaching a consensus definition of "Persian Gulf Syndrome."
Coordinations: VA, DoD and HHS.

Persian Gulf Advisory Committee.
Action: VA.
Purpose: A 16 member panel composed of experts in environmental and occupational medicine and related fields from both government and the private sector and representatives from veterans service organizations chartered to address issues related to the diagnosis, treatment and research of PG related health conditions.
Coordinations: VA, DoD and HHS.

Investigation of the Relation Between the Experience of ODS and Post-War Adjustment.
Action: VAMC Clarksburg.
Purpose: Assess difficulties in post-war adjustment among ODS soldiers.
Coordinations: VA, DoD and HHS.

Early Intervention with Appalachian Marine Reservists in ODS.
Action: VAMC Mountain Home, TN.
Purpose: To provide an early intervention debriefing to Marine reservists about the stresses of deployment and combat. Follow-up contacts and tests indicated a high degree of PTSD.
Coordinations: VA, DoD and HHS.

Desert Storm Reunion Survey.
Action: VAMC Boston.
Purpose: Study a broad range of combat and non-combat experiences associated with deployment during ODS. The study will delineate and quantify those experiences and determine their impact on subsequent patterns of adjustment.
Coordinations: VA, DoD and HHS.

Psychological Assessment of Operation Desert Storm Returnees.
Action: VAMC New Orleans.
Purpose: Conduct comprehensive psychological assessments and debriefings of troops mobilized in ODS.
Coordinations: VA, DoD and HHS.

Operation Desert Storm Follow-Up Survey.
Action: VAMC Salt Lake City.
Purpose: A survey designed to elicit VA medical center employees perceptions of ODS activation, deployment, and reintegration experiences.
Coordinations: VA, DoD and HHS.

Psychological Adjustment in ODS Veterans.
Action: VAMC Gainesville.
Purpose: A study of 542 National Guard and Reserve members was conducted with one group being actively involved in ODS and a Control group. Psychological tests were given to determine if differences existed between the service veterans and the control group in terms of overall mental health.
Coordinations: VA, DOD and HHS

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United States Senate

COMMITTEE ON VETERANS' AFFAIRS
WASHINGTON, DC 20510-6375

May 24, 1994

Dear John,

Thank you very much for your participation at the Committee's May 6 oversight hearing on military research, focusing on investigation compounds administered to Persian Gulf service members.

Unfortunately, we had limited time at the hearing to ask questions of the witnesses. Therefore, I am submitting the enclosed questions, and ask that you provide responses to these questions by June 6.

I look forward to working with you to ensure the best possible care for all our veterans.

If you have any questions, please contact Diana Zuckerman of the Committee staff at (202) 224-9126.

Sincerely,

John D. Rockefeller IV
Chairman

The Honorable R. John Vogel
Under Secretary for Benefits
Department of Veterans Affairs
Washington, DC 20420

## WRITTEN QUESTIONS FROM CHAIRMAN ROCKEFELLER TO THE DEPARTMENT OF VETERANS AFFAIRS AND THE RESPONSES

### Medical Records

*Question 1.* Many veterans have reported that decisions regarding their claims are postponed because their medical records cannot be found or are incomplete. What does VA propose to do to alleviate this problem? Should a claim be granted, even if on a temporary basis, if the VA fails to obtain or provide the service medical records?

[Letters from veterans detailing problems with medical records can be found in Appendix 4.]

*Answer.* If records needed to resolve a claim cannot be secured from the service department, VA assists the claimant in obtaining evidence from alternate or collateral sources. VA contacts the veteran explaining that the service department has been unable to locate specific records. We work with the veteran to explore possible alternate sources of evidence to support the veteran's claim. Alternate sources which might substitute for service medical records in decisions relating to service connection include statements from service medical personnel and reports from clinics and private physicians by which or by whom a veteran may have been treated, especially soon after discharge from service.

Although the service medical record is the primary source of evidence to support a veteran's claim, it certainly is not the only source. Even if service medical records are silent to treatment for a claimed condition or they are unavailable, a veteran's claim may be approved if alternate or collateral sources provide a basis to grant the claim. However, the ultimate responsibility for furnishing evidence needed to perfect a claim rests with the claimant. It is only when the service department indicates that no records exist and the request to the claimant does not result in receipt of alternate documents sufficient to establish entitlement that the claim is finally denied.

Should service records later be located that establish entitlement, VA regulations provide that compensation will be paid from the original date of claim.

*Question 2.* Please provide a list of all 1992 and 1993 research projects whereby veterans, acting as human subjects, received living biological agents (natural, genetically engineered, virulent, or avirulent) as part of a research protocol sponsored or approved by the VA or DOD?

*Answer.* Attached are lists of VA funded and Extra VA funded projects currently being performed at VA medical centers. These projects were searched using keywords which we felt were consistent with the request for projects using living biological agents. Also attached is a list of the criteria used in the search.

*Question 3.* VA officials have informed the Committee that all Persian Gulf claims based on exposure to environmental hazards are

sent to the Louisville regional office for processing. (a) Does this regional office process these claims in addition to all regional claims that are filed there? (b) Officials also stated that sending these claims to Louisville has resulted in a core of claims examiners in Louisville with expertise in rating environmental exposure claims. How many of these claims examiners are there and do they handle only these types of claims? (c) What is the average length of time it takes to adjudicate one of these environmental claims by the Louisville regional office, and how does that compare with average times for other types of claims? (d) GAO found that 37 percent of all claims at the Louisville VA regional office have been pending more than one year. How many of the pending claims at the Louisville regional office are claims for service connection based on exposure to environmental hazards?

*Answer 3(a).* In addition to processing claims for benefits based on exposure to environmental hazards in the Persian Gulf theater of operations, the Louisville regional office is also responsible for all claims filed by veterans residing in the Commonwealth of Kentucky.

*Answer 3(b).* At this time, Louisville has 12 claims examiners with the necessary expertise to resolve rating issues for disability and death resulting from exposure to environmental hazards. These same 12 decision makers also possess the expertise to resolve rating issues in all other claims.

*Answer 3(c).* We are unable to precisely report the average processing time for an environmental hazard claim since many factors influence the outcome. For example, medical records may be more accessible in one case than in another. Or, one veteran may complete his or her VA physical examination but another misses the examination and must be rescheduled.

We monitor claims processing by the type of claim (e.g., original claim for compensation, supplemental claim for compensation, etc.), and also by the date the claim is received. Additionally, for original compensation claims, we track the timeliness of the claim by the number of issues to be resolved.

Data as of April 30, 1994, show that processing of original compensation claims involving 1 to 7 issues averaged 240 days in the Louisville office, while the national average was 203. For original compensation claims involving 8 or more issues, Louisville averaged 319 days to complete and the national average was 231 days. These same data show that Louisville averaged 173 days to complete supplemental compensation claims and the national average was 114 days.

*Answer 3(d).* As of June 2, 1994, 6,306 compensation and pension claims were pending at the Louisville regional office. Of these, 1,142 or 18 percent are over 360 days old. Louisville is in various stages of developing evidence for nearly 2,000 environmental exposure claims and about 220 more claims are ready to be decided.

Because of recent modifications to our claims tracking system, we are unable to provide the age of the 2,000 environmental hazard

claims. However, we do know that at least 1,150 or 36 percent of these claims are over 360 days old.

## Persian Gulf

*Question 1.* Dr. Herbert H. Schaumburg, Professor and Chairman, Department of Neurology, Albert Einstein College of Medicine, was a panel member at the NIH Technology Assessment Workshop on The Persian Gulf Experience and Health, April 27-29, 1994. Please provide a copy of Dr. Schaumburg's conflict-of-interest forms for that panel and list any consultation or research that has involved Dr. Schaumburg on behalf of, or funded by, the Department of Veterans Affairs, or by companies that make pesticides or pyridostigmine.

*Answer.* The workshop on Persian Gulf Experience and Health was jointly sponsored by the Departments of Veterans Affairs, Defense, and Health and Human Services. Administrative responsibility for the conference organization resides with the Office of Medical Applications of Research (OMAR) at the National Institutes of Health. They maintain records related to panel members' conflict-of-interest reports, including those provided by Dr. Herbert Schaumberg. We have informed OMAR of your request for a copy of Dr. Schaumberg's conflict of interest statement and they have agreed to provide this information directly to your committee.

*Question 2.* To what extent is information on investigational drugs (i.e., pyridostigmine bromide and botulinum toxoid) included in the VA Persian Gulf Health Registry?

*Answer.* The original protocol for the Department of Veterans Affairs Persian Gulf Registry was designed in 1991 and implemented in 1992. At the time of its inception, little was known about the various exposures and symptom profile experienced by Gulf War veterans. The original registry protocol reflects the state of knowledge and concerns present in 1992. VA is currently revising and updating the Persian Gulf Registry protocol based on our present understanding of the health status and exposures of Gulf War veterans. Additions to the revised registry do include questions related to pyridostigmine ingestion, anthrax vaccination and botulinum toxoid injections.

*Question 3.* What would be required for VA to begin granting service connection to Persian Gulf veterans who claim a number of disabling symptoms, but who have no single, diagnosable disability?

*Answer.* As of June 7, 1994, approximately 95,000 veterans and beneficiaries are receiving monetary benefits based on the veteran's service in the Persian Gulf War period. Of this figure, nearly 11,000 veterans and beneficiaries are receiving monetary benefits based on the veteran's service in the Persian Gulf theater of operations.

Although some Persian Gulf War veterans have not received favorable decisions on their claims, this is not necessarily because we do not have the mechanism with which to grant service connection. For example, some veterans' claims are not allowed because the

claimed condition was not shown by the evidence of record to be related to military service. The issue is relating a disability to military service.

We recognize that some Persian Gulf veterans may be suffering from chronic disabilities that resulted from undiagnosed illnesses. The lack of a diagnosis often makes it difficult to establish a connection to military service. Since we are having the greatest difficulty in helping these veterans meet the requirements for disability benefits, we are seeking Congressional support to provide compensation to veterans suffering from a chronic disability as a result of an undiagnosed illness (or combination of undiagnosed illnesses).

*Question 4.* It is my understanding that VA has the authority to establish a temporary disability rating for veterans clearly disabled by a variety of symptoms, until such time that the science defines a diagnosable condition based on exposure to environmental hazards in the Persian Gulf. Is VA considering implementing such a procedure?

*Answer.* VA is permitted by paragraph 28 of the Schedule for Rating Disabilities (38 CFR 4.28) to provide immediate payment to veterans most likely to be in need and least likely to be self-sufficient. If a claim is received within 6 months from the date of the veteran's discharge from service and service medical records show the existence of an unstabilized condition from any disease or injury for which service connection may be granted, a "prestabilization" rating is made. This procedure addresses the problem of conditions the severity of which is not yet stabilized. It does not address the problems presented by an undiagnosed condition.

Any veteran, including Persian Gulf War veterans, who meets the criteria of section 4.28 may be awarded immediate payments.

Question 5. VA is using a definition of Chronic Fatigue Syndrome (CFS), Training Letter 93-5, that appears inconsistent with the Centers for Disease Control's definition and experts in the field. Please explain why VA developed a definition that appears to exclude most patients who have been diagnosed with CFS. Does VA plan to modify that definition in the near future? How many Persian Gulf veterans have been compensated for CFS to date?

*Answer.* VA's criteria for evaluating CFS are consistent with and modeled after the Centers for Disease Control's (CDC's) criteria. However, VA has modified the criteria somewhat to make them both simpler to use and less restrictive to veterans than the strict CDC criteria, which constitute a case definition for research purposes. VA has not added any stipulations to the CDC criteria, but, on the contrary, has afforded more flexibility by requiring only six minor criteria as opposed to 11 minor criteria set forth in CDC's definition. Clearly, the VA criteria include more veterans, not fewer, than the CDC criteria.

We have begun the rulemaking process to add CFS to our rating schedule as a new diagnostic code with its own evaluation criteria

and with a definition for VA rating purposes. As we progress through the stages of rulemaking, it is possible that there will be modifications in our criteria for CFS.

Four veterans have been granted service connection for CFS.

### Mustard Gas and Lewisite

*Question 1.* How many veterans exposed to mustard gas or Lewisite as part of DOD experiments currently receive service-connected disability compensation for conditions related to those exposures?

*Answer.* As of 3-7-94, 154 veterans have been granted service connection for disabilities recognized as secondary to exposure to mustard gas.

*Question 2.* How many claims are pending for service connection based on mustard gas or Lewisite exposure that will be adjudicated once final regulations are published?

*Answer.* 285 claims are pending finalization of our new regulation concerning service connection for disabilities secondary to exposure to mustard gas or Lewisite.

*Question 3.* What kind of publicity and outreach has VA generated to inform veterans of their potential eligibility for compensation based on participation in mustard gas and Lewisite tests?

*Answer.* Since June 1991, VA has issued three news releases to national media outlets announcing its decision to award disability compensation to veterans suffering from health problems related to exposure to mustard gas. In addition, VA's Office of Public Affairs (OPA) produced a 30-second mustard gas public service video and sent it to 1,000 commercial TV stations across the country in March 93. OPA also produced public service advertisements and sent them to all U.S. daily newspapers, major weeklies and national and regional publications of veterans service organizations and military associations.

While a specific number cannot be furnished, we know that in many instances our public affairs officers at VA regional offices re-issued or adapted national news releases and the public service advertisements for publication in local newspapers and periodicals. In all instances, VA's media campaign encouraged veterans and survivors of exposed veterans to call VA's national toll-free number for additional information about VA benefits available to exposed veterans.

VA regional offices have also incorporated mustard gas presentations into a variety of forums attended by exposed veterans, as well as meetings, conventions, conferences and training seminars with local representatives of major veterans organizations and State and local agencies who assist veterans.

In April 1993, VA released a training video on this important subject to Veterans Health Administration and Veterans Benefits

Administration employees. In addition, training has been conducted at regional offices to ensure that benefits counselors are able to answer questions and provide assistance to potentially eligible claimants.

*Question 4(a).* What problems, if any, has VA encountered in trying to obtain the military service records of veterans claiming service connection on the basis of exposure to mustard gas and Lewisite? (b). Have these records, once obtained, contained information about exposure to mustard gas and Lewisite?

*Answer 4(a).* DOD has sole responsibility for providing facts concerning a veteran's activities which may have resulted in exposure to mustard agents while on active duty. VA has experienced the greatest difficulty in obtaining information concerning the Army's mustard gas testing activities during WWII because of the Army's records maintenance methods. For example, we understand that the Army placed documentation about some veterans' participation in mustard gas testing in their individual service medical records. However, for others, the Army stored documentation about participation in a number of locations. Compounding the difficulty is the fact that test information was not always maintained under the name of the participant, that personnel records for some of the testing were never kept, or test information no longer exists.

*Answer 4(b).* Generally, yes. The Compensation and Pension Service has a list of approximately 2,400 Navy personnel who participated in the testing between August 1943 and October 1945. Until recently, this list essentially consisted of the participant's last name only. We have just received additional information concerning individuals who participated in testing at the National Research Laboratory which includes the first names of participants. We feel this is a major breakthrough.

*Question 5.* Does the VA have a registry for veterans who were exposed to mustard gas or lewisite? (a). If so, how do veterans know about the registry? What kind of publicity has there been with respect to the registry? (b). If not, why has VA not established a registry?

*Answer.* VA does not have a registry program for veterans exposed to mustard gas or lewisite during military service. The military experiments using mustard gas and lewisite came to public attention decades after exposure of these veterans. One of the major reasons to establish a registry is to provide a mechanism for long-term surveillance of the exposed populations. Health surveillance activities could have provided more timely information on remote health problems associated with exposure to these agents. Early medical surveillance was not possible with mustard gas and lewisite because of the delay in recognition of the exposure of military service members to these agents. VA does not believe that a registry program will facilitate medical care or compensation for veterans exposed to mustard gas or lewisite and does not propose to establish such a registry. However, plans are underway to identify a cohort of veterans exposed to mustard gas for possible further study.

## WRITTEN QUESTIONS FROM SENATOR AKAKA TO THE DEPARTMENT OF VETERANS AFFAIRS AND THE RESPONSES

*Question 1.* To knowingly mislead military volunteers participating in medical experiments is a serious allegation. Is the practice of utilizing military recruits for human research protocols involving chemical or biological defense agents commonplace today? What steps have been taken to avoid such abuses? Do you think it wise to compensate volunteers of these earlier programs?

*Answer.* This issue is under the jurisdiction of the Department of Defense.

*Question 2.* Some say that criticism of current researchers for medical research practices is like forcing the son to pay for the sins of the father. Do you feel further investigation into these alleged misdeeds would be justified, or do we grudgingly place these historical practices in proper perspective, and concentrate more on avoiding repetition of these mistakes?

*Answer.* Criticism of current researchers for the medical research practices of the past is neither fruitful nor fair. Informed consent, scientific peer review and protection of human subjects are practices which have become an accepted standard of contemporary medical research. Current researchers should not be criticized for the actions of their predecessors. We agree that a historical understanding of the failure to protect the rights of human research subjects in the early part of this century can help avoid repetition of similar ethical wrongs.

*Question 3.* We have many active duty servicemen in Hawaii who served in the Gulf War. At least one has indicated that because of possible symptoms linked to his service in the Gulf War arena, records on his postwar treatment have been removed from his medical file. What are the procedures for handling medical records of those military members identified as possibly suffering from Gulf War exposures? Are such members told that their medical complaints may be linked to prior service in the Persian Gulf? Are studies now underway to identify and treat the victims without the patient initiating the action?

*Answer.* This issue is under the jurisdiction of the Department of Defense.

*Question 4.* Recent reports by civilian physicians and veteran groups indicate that the mystery illnesses may be a result of multiple chemical sensitivity (MCS). Has VA investigated the MCS phenomenon and subsequent treatment regimen?

*Answer.* Some Persian Gulf veterans report symptoms which suggest intolerance to low-level chemical exposure. Some physicians have termed these symptoms chemical hypersensitivity or multiple chemical sensitivity (MCS) syndrome.

There is considerable debate about whether MCS represents a single diagnostic entity or is a manifestation of a number of diseases which may present with similar symptoms. Likewise, the proposed causes are equally diverse and have been characterized as chemical overload and toxicity, immunologic hypersensitivity, neurological dysfunction and as a form of post-traumatic stress. Presently, no basis exists for categorizing patients into this syndrome that has been widely accepted, however, several case definitions have been proposed. Cullen proposed a case definition in 1987, which was modified in 1992. The proposed definition is as follows:

- A change in health status identified by the patient
- Symptoms triggered regularly by multiple stimuli
- Symptoms experienced for at least six months
- A defined set of symptoms reported by the patient
- Symptoms that occur in three or more organ systems
- Exclusion of patients with other medical conditions

Others have proposed different classification procedures.

A number of medical organizations (American College of Physicians, American Academy of Allergy and Immunology, California Medical Association) have issued position statements on clinical ecology and MCS. They point to the absence of a generally accepted case definition and the lack of evidence upon which to base determinations of diagnostic accuracy and treatment efficacy. The dilemma which we face is that the available evidence is essentially a collection of case reports and case series reports which are not, at present, supported by carefully designed, controlled clinical studies. Scientific evidence does not exist at present which can conclusively establish the validity of MCS as a definitive medical diagnosis.

In order to clarify these scientific concerns, VA has actively sought proposals from the medical research community which address the problem of chemical intolerance or MCS. VA will establish Environmental Research Centers to address the effects of environmental and toxic exposures experienced by Persian Gulf veterans. Nineteen proposals have been received and are currently undergoing peer review. Several of these proposals address the problem of MCS. Future research efforts will be aimed at the establishment of MCS as a distinct diagnostic entity. If MCS is established as a valid diagnosis, the scientific community can then reliably proceed to establish a case definition and develop effective treatment methodology.

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## WRITTEN QUESTIONS FROM SENATOR JEFFORDS TO THE DEPARTMENT OF VETERANS AFFAIRS AND THE RESPONSES

*Question 1.* What is being done at VA to streamline personnel and health records of servicemen and women in order to make information more readily available and make records more manageable?

*Answer.* To more timely process disability compensation claims of recently discharged veterans, a VA Service Medical Records Steering Committee was established to work with the Department of the Army in devising an efficient approach to transferring and managing veterans' medical records. The Service Medical Records Center (SMRC) in St. Louis, Missouri was created as a result of the work of the steering committee.

The SMRC began receiving records for recently discharged Army veterans in October 1992. In February of this year, the SMRC began receiving records for Navy veterans. In May, the Air Force and Marine Corps began sending veterans' records to the SMRC.

*Question 2.* Is VA even close to establishing service connection for any of the illnesses that are being experienced by Gulf veterans? Could you briefly describe what illnesses are presently considered service-connected for veterans of the Persian Gulf War?

*Answer.* VA is granting service connection for any injury or disease which is shown by the medical evidence of record to be related to the veteran's military service. Persian Gulf veterans who file disability claims based on their belief that their disabilities are the result of exposure to environmental hazards may receive compensation if the medical evidence indicates that a disability or illness is related to service. Whether or not there is known exposure to a specific environmental agent, Persian Gulf veterans will have their claims rated for known residuals, much as we currently are doing in claims for compensation based on exposure to mustard gas.

*Question 3.* Has VA established that any formally presumed causes for the Persian Gulf War illnesses are definitely not attributed to service in the Gulf?

*Answer.* No.

*Question 4.* Could you briefly describe the 20 different Persian Gulf-related research activities being undertaken by the federal government?

*Answer.* Identified by the White House as the lead agency in the federal effort to address the physical and psychological health problems reported by veterans of the Persian Gulf conflict, the Department of Veterans Affairs (VA) has initiated significant action to help those veterans affected. Total projected Research and Development appropriated funding for Persian Gulf-related research is approximately $1.6 million in FY 1995.

Intramural research (utilizing VA's own investigators and facilities) was recommended as a high priority by the VA's Persian Gulf Working Group, formed in 1993 to determine the most effective course of action for VA on this issue. This recommendation was approved by Secretary Brown. VA immediately began supporting research programs addressing different aspects of potentially Persian Gulf-related afflictions.

In FY94, the VA Medical Research Service will initiate up to three major research centers for the study of the medical consequences of

exposure to environmental and toxic hazards. These centers will initially focus on the problems cited by personnel in the Persian Gulf conflict. The centers will be modeled on the highly successful VA AIDS centers. The Medical Research Service received 19 proposals in response to a special Request For Proposals (RFP). The proposals will be reviewed by a special ad hoc review committee in July and will be activated in the fourth quarter of FY94. Centers will be eligible to receive as much as $500,000 in annual funding for up to 5 years.

The VA Office of Research and Development has authorized $25,000 in annual funding for each of four small scale Pilot Programs into Persian Gulf related health consequences. The following section summarizes these programs.

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| VAMC Birmingham, AL | Researchers will investigate medical and psychological effects of suspected exposure to petrochemicals and other toxic hazards. The project will compare three groups: 1) Operation Desert Storm (ODS) veterans claiming exposure to environmental/toxic hazards; 2) ODS veterans stationed in the Gulf who do not claim exposure, and 3) ODS-era veterans who were not stationed in the Gulf. The three groups will undergo identical blind neuropsychological testing and the results will be compared to see if differences exist between the groups. |
| VAMC Boston, MA | This phase of Dr. Jessica Wolfe's ongoing work will examine neuropsychological profiles of veterans returning from the Persian Gulf theater. Using neuropsychological and PTSD protocols, the investigators will evaluate whether there are demonstrable cognitive change in these veterans, and whether these patterns differ from those found in a cohort of deployed veterans without health complaints. |
| VAMC Jackson, MS | The Jackson VAMC is acting as an initial clearinghouse for data on reported birth defects in children of members of the Waynesboro (MS) National Guard. It has been reported that as many as 13 of 15 children born to personnel since their return from the Persian Gulf have experienced medical problems. If VA investigations currently underway confirm the validity of these claims, additional studies will be initiated to ascertain if the reported ailments could possibly be the result of exposure to environmental/genetic hazards. |

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| Pittsburgh (HD), PA | Exposure to toxic substances is often associated with impairment of cognitive function, notably in the more complex cognitive abilities, such as maintenance of attention and short-term memory. The investigators will study a group of veterans with known exposure or definitive evidence of toxicity to evaluate whether the exposed veterans demonstrate the same cognitive and physiological deficits found in victims of chronic organic solvent exposure. If the results are positive, a second phase will be explored involving development of a screening assessment for individuals with claims of exposure. |
| | Additionally, several psychological and observational studies that do not receive direct funding support by the Office of Research and Development are currently being conducted by VA investigators. |
| VAMC Clarksburg, WV | "An Investigation of the Relation between the Experience of Operation Desert Storm and Post-War Adjustment." The study is designed to assess difficulties in post-war adjustment among Operation Desert Storm (ODS) soldiers. The study is being conducted as a joint effort with the Morgantown Vet Center and the University of West Virginia. |
| VAMC Mountain Home, TN | "Early Intervention with Appalachian Marine Reservists in Operation Desert Storm." The local Appalachian Marine Reservist Unit was contacted shortly after their return from the Persian Gulf and orally debriefed about the availability of health care services from VA and the types of stresses they might experience after their exposure to combat. Follow-up contacts and tests indicated a high degree of PTSD among the reservists even though they did not have heavy combat experience. |
| VAMC Boston, MA | "Desert Storm Reunion Survey." This survey is designed to study a broad range of combat and non-combat experiences associated with deployment during Operation Desert Storm. The study will delineate and quantify those experiences and determine their impact on subsequent patterns of adjustment. Advanced phases of the survey will involve extensive cognitive and neuropsychological testing. |

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| VAMC New Orleans, LA | "Psychological Assessment of Operation Desert Storm Returnees." This study involves comprehensive psychological assessments and debriefings of troops mobilized in ODS. |
| VAMC Gainesville, FL | "Psychological Adjustment in ODS Veterans." Two groups of National Guard and Reserve members (one group actively involved in Desert Storm, one group with no ODS involvement, 542 total) were studied. Psychological tests were given to determine if differences existed between the service veterans and the control group in terms of overall mental health. |
| VAMC Salt Lake City, UT | "Operation Desert Storm Follow-up Survey." A survey designed to elicit VA medical center employee perceptions of ODS, activation, deployment, and reintegration experiences. |

The VA Office of Environmental Medicine and Public Health is constructing a "Persian Gulf Registry" database based on diagnostic examinations and interviews administered to Persian Gulf veterans at VA Medical Centers (VAMC's) and Out Patient Clinics (OPC's). In addition to providing a way for veterans concerned about possible health problems to identify themselves to VA, the survey provides VA with a means of scientifically tracking the problems most commonly experienced by this cohort.

To properly address the issue of possible troop exposure to environmental hazards, all individuals who served in the Gulf region need to be identified. To this end, the Defense Manpower Data Center (DMDC) has prepared a computer file of 670,000 troops assigned to the Persian Gulf area during the war and transferred the file to VA's Environmental Epidemiology Service, giving the VA access to demographic data on all troops stationed in the Persian Gulf. Additionally, inpatient medical data on Gulf veterans are being closely monitored and analyzed in comparison to Gulf-era veterans not stationed in the Gulf. Computer matching of the PTF File with the DOD roster of Persian Gulf veterans has helped identify 6,092 Gulf veterans and 6,265 Gulf-era veterans treated in VA hospitals on an inpatient basis since the study began. Lastly, a mortality analysis of all 670,000 Persian Gulf veterans on the DMDC file will be compared with a sample of Gulf-era veterans who did not serve in the Gulf area. Cause-specific mortality for both veteran groups will be compared and also compared to the number of deaths expected in U.S. male population.

VA is also cooperating with other Federal agencies in government-wide research efforts to help Persian Gulf veterans. Under the direction of VA Secretary Jesse Brown, and comprised of top research officials from VA, DOD, HHS, and EPA, the Persian Gulf Interagency Research Coordinating Council serves as a central monitoring body

overseeing the federal research effort into the health implications of service in the Persian Gulf conflict. By establishing a single coordinating body, the government can streamline the federal research effort, ensuring cooperation among the separate agencies and preventing wasteful duplication of effort.

In April, 1994, VA participated in a special NIH Technology Assessment Workshop comprised of nationally-recognized experts in toxicology, environmental medicine, and other related disciplines. This workshop was convened with the purpose of establishing a consensus definition of the "Persian Gulf Syndrome", and produced a set of specific recommendations for further research initiatives.

The DOD response to the Health Problems of Persian Gulf Veterans can be divided into pure research activities and clinical research activities.

Included in the pure research activities are joint VA/DOD activities, such as the joint contract with the National Academy of Science to review existing scientific and other information on the health consequences of Gulf operations. Additional research projects include:

A working group established at Walter Reed Army Medical Center to review and analyze medical records of ODS veterans with unexplained symptoms to establish a working "case definition: for the constellation of symptoms commonly referred to in the media as "Persian Gulf Syndrome".

A series of studies in environmental and toxicological pathology relating to exposures during ODS. The purpose of these studies is to evaluate the mechanism and exposure thresholds for toxic effects of substances generated as a result of the Gulf War, (e.g., fumes from oil well fires).

Retrospective studies of troops stationed in the Persian Gulf including studies aimed at determining the possibility of health consequences of chemical attack pretreatments (including pyridostigmine), as well as studies into possible viral and parasitical infection (including leishmania).

DOD clinical research studies seek to establish the risks of possible exposure to toxic agents in the Persian Gulf theater. This process involves two steps, carried on concurrently. The first is identifying the potential hazards of possible environmental contaminants present in the Persian Gulf theater, including industrial contaminants. The second step is conducting an analysis of distribution patterns of known possible environmental/toxic hazards, troop location, and meteorological information to produce a "map" of the relative environmental hazards to troops stationed in the gulf. Studies in these areas are being conducted primarily by the U.S. Army Environmental Hygiene Agency (USAEHA).

Additionally, DOD efforts are underway examining the current health of veterans and active duty troops involved in ODS. These

include studies involving troops currently stationed in Georgia, North Carolina, Hawaii, Pennsylvania, and Indiana.

Numerous branches of the Department of Health and Human Services have been involved in Persian Gulf-related research. Representatives from the National Center for Infectious Diseases have participated in interagency efforts to address the health consequences of Operation Desert Storm. These include the Department of Veterans Affairs Persian Gulf Expert Scientific Panel, and the DOD Defense Science Board.

The Public Health Service (PHS) provided a great deal of support to other agencies and the Kuwait Task Force (KTF) under the direction of DOD. PHS observers and advisors helped on a range of public health issues affecting the restoration of Kuwait. In addition, the Office of Refugee Health medically screened United States citizens detained by the Iraqi government and made referrals for further evaluations and treatments.

Additionally, the National Center for Infectious Diseases at the Centers for Disease Control and Prevention has tested samples from ODS veterans for leishmania. The National Cancer Institute has also been involved in a "Biologic Surveillance Initiative" studying the health effects of Kuwaiti oil fires.

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## WRITTEN QUESTIONS FROM SENATOR MITCHELL TO THE DEPARTMENT OF VETERANS AFFAIRS AND THE RESPONSES

*Question 1.* On June 11, 1991, the VA issued a news release stating that World War II veterans who were exposed to mustard gas testing during military service and who suffer from certain long-term effects would become eligible for disability compensation under new rules to be proposed by VA. Quoting from the news release, then-Secretary Ed Derwinski said:

> "Because of the confidential nature of some of the mustard gas testing, we are giving the benefit of the doubt to those veterans who were involved in these tests. Criteria normally used in evaluating claims for VA disability compensation require documentation that the illnesses or condition occurred during military service. Because of the confidentiality of some of the testing, the possible lack of military medical records associated with those tests and the lack of long-term followup of veterans by the military branches, these criteria will not be applied to the mustard gas claims."

Materials provided to me by the Compensation and Pension Service, however, indicate that Department has made little progress in compensating those veterans in the intervening 3 years.

(a) How many veterans have filed claims for compensation for illnesses associated with exposure to mustard gas?

(b) What is the biggest stumbling block for allowing the remaining claims?

(c) How does VA reconcile its statements from June 11, 1991, that the criteria applied for awarding service-connected disability compensation will "not be applied" to mustard gas claims, with the reality? A veteran still must provide VA verification of full body exposure and VA must determine that an intervening cause is not identified. How can VA say that a mustard gas claim is treated any differently than any other claim?

*Answer 1(a).* As of March 7, 1994, 1,145 veterans have filed disability claims based on the belief that their disabilities are secondary to exposure to mustard gas.

*Answer 1(b).* The primary reason claims cannot be allowed is VA does not have verification of full body exposure to mustard gas. Other reasons for denying these claims are the claimed disability is not recognized as secondary to mustard gas exposure and no specific disability was claimed or detected.

*Answer 1(c).* Generally, a veteran is granted service connection if a disability is incurred in or aggravated by service or manifests within the applicable presumptive period, which in most cases, is one year following separation from service. For veterans exposed to mustard gas, presumptive service connection is permitted if the condition appears at *any* time after exposure.

In initially allowing presumptive service connection for disabilities related to mustard gas exposure, VA was influenced by the long history of secrecy surrounding the WWII tests, the inadequate documentation of participation, and the general unavailability of medical records, including long-term follow-ups. VA determined that, through no fault of the veterans involved, there was inadequate documentation of their participation in the tests, which were classified. Some participants have, in fact, indicated that they declined to seek medical help because they had been emphatically warned not to disclose the secret nature of the program. Those who did file claims may have experienced difficulty in establishing entitlement to benefits. For these reasons, VA determined to allow a presumption of service connection for certain illnesses with known mustard gas associations.

*Question 2.* Awarding service connection is needed for a veteran to be eligible for VA medical care in many cases. How does VA treat a veteran who has filed a claim for one of the diseases identified by VA as related to mustard gas exposure and whose claim is unresolved because of a failure to secure documentation? Is that veteran able to receive appropriate health care from VA at this time?

*Answer.* Veterans exposed to mustard gas and lewisite are treated under routine VA eligibility rules. No special regulations apply to this group of veterans.

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Title: **Etiology and Immune Response to Gastrointestinal Infections**

MC: 584 Iowa City, IA Name: **Stapleton, Jack T.** Proj No: 0004
Title: **Hepatitis A Virus Immunogenic Determinants and Cellular Interactions**

MC: 618 Minneapolis, MN Name: **Janoff, Edward N.** Proj No: 0008
Title: **Impact of HIV Infection on Mucosal and Systemic Immune Respones to Vaccines**

MC: 630 New York, NY Name: **Zolla-Pazner, Susan** Proj No: 0002
Title: **Protective Aspects of Antibodies Against HIV**

MC: 657 St. Louis, MO Name: **Gorse, Geoffrey J.** Proj No: 0004
Title: **Responses to and Efficacy of Influenza A Virus Vaccines**

MC: 671 San Antonio, TX Name: **Melby, Peter C.** Proj No: 0002
Title: **Identification of Vaccine Candidate Antigens in Leishmaniasis**

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Title: **Gastrointestinal Mucosal Immune Responses to Vaccines and Pathogens-387793-079101**

MC: 521 Birmingham, AL Name: **Bueschen, Anton J.** Proj No: 0003
Title: **Comparison of Bacillus Calmette Guerin and Mitomycin-C Therapy and Prophylaxis in Superficial Transitional Cell Carcinoma of the Bladder**

MC: 525 Brockton, MA Name: **Canoso, Rosa T.** Proj No: 0006
Title: **Antibody Titers to Influenza Vaccine in Patients Treated with Warfarin**

MC: 526 Bronx, NY Name: **Rosman, Alan S.** Proj No: 0001
Title: **Randomized Clinical Trial Comparing High Dose vs Standard Dose Recombinant Hepatitis B Vaccine in Alcoholic Patients**

MC: 528 Buffalo, NY Name: **Beam, Jr., Thomas R.** Proj No: 0020
Title: **Efficacy and Cost Effectiveness of Pneumococcal Vaccine**

MC: 528 Buffalo, NY Name: **Beam, Jr., Thomas R.** Proj No: 0030
Title: **Efficacy of Hepatitis B Vaccine in VA Health Care Personnel**

MC: 528 Buffalo, NY Name: **Pasko, Mary T.** Proj No: 0005
Title: **An In Vitro Model for Idiotype Induced Anti-Viral Antibodies**

MC: 535 Chicago, (Lakeside),IL Name: **Benson, III, Al B.** Proj No: 0141
Title: **NU 92I2: Assessing Sequential Active Specific Immunotherapy, Autologous Tumor Cell/BCG Vaccine--Treatment for Metastic Colorectal Cancer**

MC: 537 Chicago, (West Side),IL Name: **Sharifi, Roohollah** Proj No0055
Title: **SWOG-8795 Random. Prosp. Comp. of BCG & Mitomycin-C Therapy & Prophylaxis in Superficial Transitional Cell Ca of Bladder, w/DNA Flow Cytometri**

MC: 540 Clarksburg, WV Name: **Lamm, Donald L.** Proj No: 0004
Title: **Mitomycin vs BCG Immunotherapy for Superficial Bladder Cancer**

MC: 549 Dallas, TX Name: **Raj, Guna** Proj No: 0001
**TitleSafety of Intramuscular Influenza Vaccination in Patients on Anticoagulant Therapy**

MC: 553 Allen Park, MI Name: **Pontes, Edson J.** Proj No: 0001
Title: **A Pilot Study of Intravesical Alpha 2b, Intron A, in Carcinoma in situ (CIS) With or Without Papillary or Solid TCC**

MC: 553 Allen Park, MI Name: **Powell, Isaac J.** Proj No: 0002
Title: **A Pilot Study of Intravesical Alpha 2b, Intron A, in Carcinoma in situ (CIS) With or Without Papillary or Solid TCC**

MC: 553 Allen Park, MI Name: **Supena, Ronaldo B.** Proj No: 0009
Title: **A Phase III, Randomized, Comparative Trial of ZDV vs. DZV plus ddI vs ZDS plus ddC in HIV-infected Patients**

MC: 558 Durham, NC Name: **Hamilton, John D.** Proj No: 0032
Title: **A Research Study of Hepatitis B (Pre S2+S) Vaccine (Recombinant Yeast) in Dialysis Patients**

MC: 558 Durham, NC Name: **Hamilton, John D.** Proj No: 0046
Title: **Hepatitis B Mixed Particle Vaccine in Dialysis Patients**

MC: 573 Gainesville, FL Name: **Meuleman, John** Proj No: 0008
Title: **Influenza Vaccination & Warfarin Anticoagulation: A Comparison of Subcutaneous & Intramuscular Routes of Administration in the Elderly**

MC: 573 Gainesville, FL Name: **Toskes, Phillip P.** Proj No: 0012
Title: **Evaluation of Creon(R) in the Reduction of Pain Associated with Chronic Pancreatitis - A Double-Blind, Placebo-Controlled Crossover Study**

MC: 573 Gainesville, FL Name: **Wajsman, Zev** Proj No: 0018
Title: **A Phase III Study of Intravesical TICE BCG in Superficial (TC) Ca of the Bld: A Randomization of One Cycle vs Two Cycles of Tx**

MC: 578 Hines, IL Name: **Flanigan, Robert C.** Proj No: 0030
Title: **SWOG 8795 Comparison of Bacillus Calmette-Guerin & Mitomycin-C Therapy & Prophyla in Superficial Transitional Cell Carcinoma of the Bladder**

MC: 578 Hines, IL Name: **Ing, Todd S.** Proj No: 0045
Title: **Randomized, Double-blind, Placebo-controlled, Multi-center Clinical Trial to Assess the Safety & Efficacy HYPERVAX + STAPHA Vaccine**

MC: 580 Houston, TX Name: **Musher, Daniel M.** Proj No: 0017
Title: **90G09.HBP-Random. Multi-center Study of Safety & Immunogenicity of 3 Models of Pneumococcal 6A/23F-CRM197 Conjugant Vaccine in Two Dose Levels**

MC: 581 Huntington, WV Name: **Mufson, Maurice A.** Proj No: 0007
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Title: **Evaluation of Health Care Worker Compliance with Hepatitis B Vaccination**

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MC: 589 Kansas City, MO Name: **Williamson, Stephen K.** Proj No: 0050
Title: **SWOG-9035, Randomized Trial of Adjuvant Immunotherapy in Malignant Melanoma**

MC: 596 Lexington, KY Name: **Greenberg, Richard N.** Proj No: 0008
Title: **Healthy Adults / Investigational Formulation of Recombivax HB (SP1) Made From a New Recombinant Master Seed (IRB #91-30341)**

MC: 596 Lexington, KY Name: **Wood, Jr., David P.** Proj No: 0001
Title: **Phase I Eval of AD-32 Administered by Intravesical Instillation in Pts w/Superficial Transitional Cell Carcinoma of the Urinary (IRB#91-00**

MC: 598 Little Rock, AR Name: **Monson, Thomas P.** Proj No: 0006
Title: **Immunization of Persons at Risk of Exposure to C. Burnetii**

MC: 614 Memphis, TN Name: **Dale, James B.** Proj No: 0003
Title: **Chemistry and Immunology of Streptococcal M Proteins**

MC: 618 Minneapolis, MN Name: **Janoff, Edward N.** Proj No: 0007
Title: **Immunological Response and Function in the Advanced Elderly**

MC: 618 Minneapolis, MN Name: **Pomeroy, Claire** Proj No: 0004
Title: **The Immunogenicity and Antibody Response of HIV Seropositive Asymnptomatic Adults to Hemophilus Influenzae Vaccine**

MC: 629 New Orleans, LA Name: **Beltran, German S.** Proj No: 0029
Title: **SWOG 9035: Rand Trial of Adj Immunotherapy with an Allogeneic Vacc for Pts with Intermed Thick, Node Neg Malig Melanoma** Nelanoma

MC: 630 New York, NY Name: **Jacobson, Daniel R.** Proj No: 0001
Title: **Pneumovax Vaccination in Patients with Multiple Myeloma**

MC: 630 New York, NY Name: **Simberkoff, Michael S.** Proj No: 0013
Title: **Defenses and Vaccination Against S. pneumoniae in AIDS and Chronic Diseases**

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Title: **Cell-Mediated Immunity to Influenza in the Elderly**

MC: 657 St. Louis, MO Name: **Belshe, Robert B.** Proj No: 0001
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MC: 658 Salem, VA Name: **Barritt, A. Sidney** Proj No: 0013
Title: **Immunogenicity and Safety of Engerix-B Hepatitis B Vaccine given at 0,1,2, and 12 Months vs Recombivax given at 0,1, and 6 Months**

MC: 658 Salem, VA Name: **Garner, Dorothy C.** Proj No: 0008
Title: **Serologic Responses of Low Dose (5ug) to Standard Dose (10ug) Recombinant Hepatitis B Vaccine after Intramuscular Administration**

MC: 658 Salem, VA Name: **Schleupner, Charles John** Proj No: 0063
Title: **Immunogenicity and Safety of Engerix-B Hepatitis B Vaccine given at 0,1,2, and 12 Months vs Recombivax given at 0,1, and 6 Months**

MC: 664 San Diego, CA Name: **Looney, David J.** Proj No: 0004
Title: **The Laboratory Evaluation of an AIDS**

MC: 664 San Diego, CA Name: **Looney, David J.** Proj No: 0007
Title: **Laboratory Evaluation of Gene Therapy for AIDS**

MC: 664 San Diego, CA Name: **Oxman, Michael N.** Proj No: 0010
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Title: **SWOG 9035: Rand Trial of Adjuvant Immunotherapy w/Allogeneic Mel Vaccine for Pts w/Intermed Thickness, Node Neg Malig Mel (T3N0M0), III**

MC: 671 San Antonio, TX Name: **Weiss, Geoffrey R.** Proj No: 0256
Title: **SWOG 9140:Phase II Study of Oral Bropirimine Combined W/Intravesical Bacillus Calmette-Guerin (TICE) in Patients with Bladder Cancer**

MC: 673 Tampa, FL Name: **Ganguly, Rama** Proj No: 0004
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MC: 676 Tomah, WI Name: **Slater, Edward J.** Proj No: 0005
Title: **Influenza Vaccine Response in Adults**

MC: 678 Tucson, AZ Name: **Ahmann, Frederick R.** Proj No: 0031
Title: **SWOG 8507 - Maintenance vs No Maintenance BCG/Superficial Bladder Cancer Phase III**

MC: 678 Tucson, AZ Name: **Sampliner, Richard E.** Proj No: 0019
Title: **Safety, Tolerability and Immunogenicity of Hepatitis B (PreS2+S) Vaccine (Recombinant Yeast) in Dialysis Patients**

MC: 688 Washington, DC Name: **Gordin, Fred M.** Proj No: 0044
Title: **Immunization of HIV Infected Patients with Recombinant GP160 HIV Protein: Study of Toxicity and Efficacy**

MC: 688 Washington, DC Name: **Krasnow, Steven H.** Proj No: 0038
Title: **Phase I Clinical Trial of Intrapleural Tice BCG for Malignant Pleural Effusions: GWUMC Protocol No. 108902**

MC: 688 Washington, DC Name: **Seeff, Leonard B.** Proj No: 0022
Title: **Evaluation of Long-Term Immunogenicity of Hepatitis B Vaccine in Health care Workers**

MC 688 Washington, DC Name: **Wadleigh, Robert G.** Proj No: 0006
Title: **ECOG 1290 Combined Modalities in the Treatment of Dukes' C Colon Cancer**

MC: 688 Washington, DC Name: **Wadleigh, Robert G.** Proj No0007
Title: **ECOG 5283 Combined Modalities in the Treatment of Dukes' B Colon Cancer**

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# United States Senate

COMMITTEE ON VETERANS' AFFAIRS
WASHINGTON, DC 20510–6375

May 13, 1994

Robert J. Temple, M.D.
Director
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Temple:

Thank you very much for your participation at the Committee's May 6 oversight hearing on military research, focusing on investigational medical products administered to Persian Gulf veterans.

Unfortunately, we had limited time at the hearing to ask questions of the witnesses. Therefore, I am submitting the enclosed questions, and ask that you provide responses to these questions by June 1.

If you have any questions, please contact Dr. Diana Zuckerman at 202 224-9126.

Sincerely,

John D. Rockefeller IV
Chairman

cc: The Honorable Frank Murkowski

**Posthearing Questions**
**for Dr. Robert J. Temple**
**Director, Office of Drug Evaluation**
**Food and Drug Administration**

**from Senator John D. Rockefeller IV**
**Chair, Senate Committee on Veteran Affairs'**

1. Please provide all information provided to FDA on the long-term medical followup for those healthy men who participated as research subjects in experiments designed to determine the safety of pyridostigmine.

2. Information provided by numerous Persian Gulf veterans indicates that the Department of Defense did not warn them about side effects of the investigational drugs, did not ask about pregnancy status, coerced some who received the botulinum toxoid into signing an informed consent form, and provided no medical followup. Additionally, because the Department of Defense is unsure who received the investigational drugs, it is questionable as to whether any retrospective objective data can be obtained about the safety of these products under wartime conditions. What will the FDA do to follow up on these apparent flaws in the IND process?

3. There is evidence that the pyridostigmine and botulinum toxoid used in the Persian Gulf War may not have been efficacious. According to DoD's own data, pyridostigmine bromide may have reduced the efficacy for treating sarin toxicity. In addition, the atropine dose in the Mark I kit was questioned by FDA as inadequate (IND Amendment, Reference to IND# 28480, March 28, 1988). Please provide data which supports the dosage of atropine in the Mark I kit for enhancing the kit's efficacy for soman toxicity by pyridostigmine pretreatment.

4. Because only two doses of botulinum toxoid were administered to most military personnel who received the toxoid, it is doubtful if protection would have been conferred in time to protect during the war. Please comment how this misuse of botulinum toxoid and potential misuse of pyridostigmine (as described in #3) will influence further decisions by the Food and Drug Administration to waive informed consent on investigational products.

5. Please provide a copy of the letter informing DoD of FDA's decision not to file the NDA for pyridostigmine, and provide any subsequent documents describing the status of the NDA.

6. Please provide copies of all studies provided to FDA, from INDs or the NDA, indicating the safety of pyridostigmine for healthy women, including separately all studies of women taking birth control pills and pregnant women.

7. Please provide copies of all information provided to FDA, from INDs or the NDA, regarding long-term followup data indicating safety of pyridostigmine for patients with myasthenia gravis or healthy people receiving the drug as an antidote-enhancer for nerve gas.

8. Please provide copies of all studies provided to the FDA indicating safety of pyridostigmine for men and women with medical conditions which were permitted for military service in Desert Shield/Storm, but were excluded from most DoD studies, such as asthma.

9. What information does FDA have about the percentage of volunteers in DoD pyridostigmine studies who were excluded because they were sensitive to pyridostigmine? For these individuals who were deemed sensitive to the drug, or who had substantial adverse reaction in the studies, please provide all information on the medical followup of these individuals.

10. Please provide copies of all studies indicating safety for men and women receiving pyridostigmine bromide in combination with pesticides or other chemical exposures, and in combination with multiple vaccines (such as those administered to military personnel serving in the Persian Gulf).

11. Does the Food and Drug Administration have any information that manufacturing of the pyridostigmine which was provided to U.S. troops in Desert Shield/Desert Storm may have been less than optimal? Why was the percentage of military personnel who took pyridostigmine in the Persian Gulf higher than reported in studies of healthy men conducted by the Department of Defense?

12. We received information that some Persian Gulf soldiers were told they would not receive the second anthrax vaccine because the "vaccine had gone bad." Are you aware of any such discussions? Were any of the vaccines administered to Persian Gulf military personnel contaminated or deemed unsafe?

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 08 1994

The Honorable John D. Rockefeller IV
Chairman, Committee on Veterans'
Affairs
United States Senate
Washington, D.C. 20510-6375

Dear Mr. Chairman:

This is in partial response to you letter of May 13, 1994, addressed to Dr. Robert Temple, in which you requested responses to questions in follow up to the May 6, 1994, hearing on investigational medical products administered to Persian Gulf veterans. Your letter also requested additional documents from the files of the Food and Drug Administration (FDA).

At this time, we are enclosing documents from the New Drug Applications (NDA) and Investigational New Drug Applications (IND) for pyridostigmine as identified in the attached listing. These documents include original applications, protocols for studies in both male and female subjects, manufacturing and labeling supplements, and annual reports containing Adverse Drug Reaction reports and reviews of the published literature. These documents will provide information in response to numbers 1 and 6-10 of your inquiry.

There are an additional sixteen applications in storage at the Federal Records Center. These can be retrieved in the Committee wishes to review the documents.

Also enclosed is the Refusal to File letter, dated May 5, 1994, as requested in number 5.

We are preparing the responses to the remaining questions and will provide them as soon as they have been completed.

Some of the enclosed information is confidential and not releasable to the public under FDA's regulations implementing the Freedom of Information Act. Therefore, if the Committee intends to publish or otherwise make public any of this information, we request that the Committee staff contact us to discuss the confidentiality of the information. In addition, in accordance with Departmental policy, the documents have been purged of patient identifiers.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

cc: HFW-1
HFW-10(2)
HFW-12(Marrone)
HFD-8

R/D:JCMarrone:6/2/94
F/T:CUldriks:6/3/94
Init:CUldriks for DLanahan:6/3/94
Init:DStrickland
94-4436

[Documents referenced in the June 3 letter are located in Committee files; the letter provided in response to question 5 appears below.]

MAY - 5 1994

NDA 20-414

Office of The Surgeon General
Department of the Army
Commander, U.S. Army Medical Research
and Development Command
Attention: Col. C. Fred Tyner
Fort Detrick
Frederick, Maryland 21702-5012

Dear Colonel Tyner:

Reference is made to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pyridostigmine Bromide Tablets, 30 mg. The application was received by the agency on March 7, 1994.

Refuse to File Action:

As you note in your letter of March 4, 1994, your application does not contain a complete Chemistry, Manufacturing and Control [CMC] section. Specifically, the application does not contain information about the manufacture of the drug product by Roche Products Limited, United Kingdom and F. Hoffmann-LaRoche Ltd, Switzerland, nor does it provide letters of authorization granting access to alternative sources for this essential information. Accordingly, your NDA is not acceptable for filing under 21 CFR 314.101 because it fails to meet the requirements for an NDA set out under Section 505(b) of the Act and 21 CFR 314.50(b). You ask, nonetheless, that we file the application, asserting that a delay in filing would have a negative effect on the readiness of our military forces.

We believe the concerns expressed in your March 4th letter about the potential consequences of a 'refuse to file' action are unwarranted. It is not the time of filing of an NDA, per se, but the time at which formal regulatory action is taken that determines whether and when a new drug product may be legally marketed. However, we are mindful of the Department of Defense's view that this drug product is important to military readiness. In accordance with FDA's refusal to file policy, we have initiated a review of all the sections of your NDA that are complete because we believe that initiating the review of this NDA at the earliest possible time will better advance the public health. This strategy ensures that we will be able to complete our review of the application

without undue delay once you are able to submit it in the form required by law (i.e., with a complete CMC section).

Environmental Assessment

Our environmental assessment staff has completed a preliminary review of your EA and has asked that the following comments be forwarded.

1. Address the environmental impact at the production site(s) whether the product is manufactured in the United States or in a foreign country. FDA's environmental regulations require the Agency to consider the effects of its actions abroad, 21 CFR 25.50.

   Note that when submitting information for production in foreign countries, you may find that it is more convenient to obtain a letter or letters from the appropriate officer(s) of the foreign government stating that the manufacture of the product(s) that is the subject of the application has been evaluated by that government and that it meets their requirements for emissions and occupational controls. Provided that the letter(s) has some specificity about the drug substance and/or the drug product that would be manufactured under the NDA and the government's requirements, such a letter can be used in lieu of the information requested in section 6 of the EA format. Note that the letters must include the names and signatures of the appropriate officials, dates of signing and confirmatory seals or insignia where applicable. Letters written in a language other than English must be accompanied by a certified English translation. All documents submitted must be clear and legible.

2. Do not include confidential information in the EA, since the EA is publicly available, 21 CFR 25.30. Instead, submit confidential information pertinent to the environmental review in a separate section of your application (as an appendix). However, you should summarize confidential information to the extent possible in the EA.

3. Keep in mind that the EA must be a complete and independent document that will enable the Agency to decide whether an environmental impact statement (EIS) is necessary and that will permit the public to understand the basis for the Agency's decision.

4. Finally, note that FDA is required to ensure that the information contained in an EA is complete and accurate (21 CFR 25.41(c)) and to take responsibility for the scope and content of the EA once it is accepted (40 CFR 1506.5(b)). FDA therefore will carefully review your EA if it is not adequate for approval. An EA adequate for approval is one that contains sufficient information so that the

Agency can determine whether the proposed action may significantly affect the quality of the human environment, 21 CFR 25.22 (b).

Within 30 days of the date of this letter, you may request in writing an informal conference about FDA's refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

Should questions arise regarding this application, please contact Mr. Robbin Nighswander, Project Manager, at (301) 443-3504.

Sincerely yours,

5/5/84

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

The Honorable John D. Rockefeller, IV
Chairman, Committee on Veterans' Affairs
United States Senate
Washington, D.C. 20510-6375

AUG 2 4 1994

Dear Mr. Chairman:

This is in further response to your letter of May 13, 1994, addressed to Dr. Robert Temple, in which you requested responses to questions in follow-up to the May 2, 1994, hearing on investigational medical products administered to Persian Gulf veterans.

Previously, on June 3, 1994, we provided documents responsive to numbers 1 and 5-10 of your inquiry. We are enclosing responses to the remaining questions.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

Enclosure

cc: The Honorable Frank H. Murkowski
Ranking Minority Member
Committee on Veterans'Affairs
United States Senate
Washington, D.C. 20510-0202

**RESPONSE TO JOHN D. ROCKEFELLER IV'S**
**MAY 13, 1994 REQUEST**

Question 2.

**Information provided by numerous Persian Gulf veterans indicates that the Department of Defense did not warn them about side effects of the investigational drugs, did not ask about pregnancy status, coerced some who received the botulinum toxoid into signing an informed consent form, and provided no medical follow-up. Additionally, because the Department of Defense is unsure who received the investigational drugs, it is questionable as to whether any retrospective objective data can be obtained about the safety of these products under wartime conditions. What will the FDA do to follow up on these apparent flaws in the IND process?**

Response.

Both the DoD and the FDA recognized that the complete accounting of drug use ordinarily required of sponsors of INDs could not be assured in the extremely unusual setting of the Persian Gulf war. While the limitations on such accounting and follow-up of personnel receiving pyridostigmine were expected, there was an expectation at the outset that DoD would collect as much information about ultimate drug use (in the form of questionnaires both to medical staff and those receiving the treatment) as was deemed practical. Further, the FDA required DoD to inform soldiers of the potential risks associated with the treatment. As was noted at the hearing, FDA does not have the resources to investigate INDs routinely to ensure that sponsors comply with these requirements. Absent any reason to believe otherwise, we assume that sponsors will carry out their legal obligations. In those cases in which the FDA becomes aware that a sponsor is not fulfilling its obligations under the IND, the FDA has the authority to investigate the alleged violations and impose sanctions, as appropriate, on the sponsors if violations are proven and serious or substantial. We will be discussing further with DoD the success of their efforts to disseminate the information they agreed to provide, and follow-up, if necessary.

Although we cannot be entirely sure how many, and which, personnel received the treatment, it may still be possible to obtain some useful data about potential adverse reactions. Indeed, the report of Keeler, et. al., which reports on the experience of soldiers who received pyridostigmine, published in the Journal of the American Medical Association, suggests that this is possible. In addition, detailed reports of the experiences of individuals who received the drug may also be interpretable, and yield useful data about adverse reactions.

The fact that the IND for pyridostigmine did not explicitly require routine long term follow-up was not a flaw in the IND process. Rather, it reflects the generally held belief that short term treatment with low dose pyridostigmine is not associated with any chronic adverse effects. Longer-term follow-up could have been arranged, but based on what we knew, we did not think it was useful. Certainly, prudence would dictate that all cases of likely important adverse drug reactions should be followed up appropriately by DoD. DoD should submit such information to the FDA, whether or not such a requirement is stated explicitly in a protocol.

With regard to the botulinum toxoid vaccine, the written protocol specified that rosters with the names and other information that identified the vaccinated individuals were to be maintained by DoD. Furthermore, each dose of vaccine was to be recorded on the individual's permanent immunization record by DoD. As mentioned above, FDA does not routinely investigate INDs to ensure that sponsors are complying with the protocol requirements. In light of recent disclosures, we are concerned about DoD's compliance with the protocol. Consequently, representatives of the FDA have had a number of conversations with DoD about locating all the individual rosters.

Question 3.

**There is evidence that the pyridostigmine and botulinum toxoid used in the Persian Gulf War may not have been efficacious. According to DoD's own data, pyridostigmine bromide may have reduced the efficacy for treating sarin toxicity. In addition, the atropine dose in the Mark I kit was questioned by FDA as inadequate (IND Amendment, Reference to IND #28480, March 28, 1988). Please provide data which supports the dosage of atropine in the Mark I kit for enhancing the kit's efficacy for soman toxicity by pyridostigmine pretreatment.**

Response.

The maximum dose of atropine DoD ultimately decided to field for use in conjunction with 2-PAM and pyridostigmine was approximately 0.095 mg/kg. This dose was to be delivered via the Atropine Autoinjector (Atropen), an FDA approved product. It is approved as an antidote for organophosphate poisoning, and contains the equivalent of 2 mg of atropine sulfate. Current labeling permits up to three doses to be given acutely, resulting in a total atropine dose of 6 mg (approximately 0.095 mg/kg). The clinical data included in the NDA for the Atropen consisted of experience gained in the treatment of people accidentally exposed to organophosphates.

The DoD dosing recommendations for humans also call for up to three doses of atropine via the autoinjector to be given in case of exposure to nerve gas (in conjunction with 2-PAM and pyridostigmine). While formal human studies have not, of course, been conducted, it is reasonable to assume (though it is not proven), that the dose recommended as treatment for organophosphate poisoning may also be effective to prevent death associated with exposure to nerve gas.

In early animal studies designed to determine the effect of this combination of treatments on the survival of animals exposed to nerve gas, several atropine dosing regimens were studied. DoD decided that a total dose of 0.095 mg/kg yielded results (in terms of maximum concentration of atropine in the blood and other parameters) similar to those achieved in humans after 3 autoinjectors. For this reason, the dose of 0.095 mg/kg was initially chosen to be used in the animal studies of the effectiveness of the entire regimen.

DoD performed pilot studies in a few monkeys which suggested that this dose of atropine (0.095 mg/kg), when given to monkeys, did not decrease mortality when given in conjunction with pyridostigmine. For this reason, they increased the atropine dose used in the definitive monkey study to 0.4 mg/kg, a dose which, when given in conjunction with pyridostigmine, was associated with protection from nerve agent induced death.

The DoD's conclusion that the lower dose was not shown to be effective in monkeys when given with pyridostigmine needs to be examined more closely. This is because the study which gave rise to this conclusion was, as stated above, a very small study, using only a few animals. This study did not have the ability to demonstrate a positive effect of the treatment, unless that effect was extremely large. That is, even if the dose of atropine was effective, there was a good chance that this effect, unless overwhelming, would not have been demonstrated.

Beyond this, there is evidence that humans and monkeys handle atropine differently. First, there is reason to believe that atropine is eliminated from monkeys more rapidly than it is in humans, so that it is likely that a greater dose needs to be given to monkeys to maintain a given concentration in the blood. Further, there is also evidence that monkeys are less sensitive to the effects of a given concentration of atropine than are humans. For this reason, it is also possible that higher doses need to be given to monkeys in order to elicit a given response.

Finally, doses of 0.4 mg/kg of atropine (again, the dose of atropine shown to be useful in the definitive monkey study) would generally be considered to be extremely toxic, even life

threatening, to normal humans. On the other hand, the doses proposed for this study are known to be generally well tolerated.

Question 4.

**Because only two doses of botulinum toxoid were administered to most military personnel who received the toxoid, it is doubtful if protection would have been conferred in time to protect during the war. Please comment how this misuse of botulinum toxoid and potential misuse of pyridostigmine (as described in #2) will influence further decisions by the Food and Drug Administration to waive informed consent on investigational products.**

Response.

The protocol called for the administration of the three recommended doses of the botulinum toxoid vaccine. The vaccinations, however, were not started by DoD in time to allow all doses to be administered prior to the completion of the Persian Gulf war. It would not have been appropriate for DoD to continue to administer the vaccine without informed consent following the resolution of the threat. Obviously, it would have been preferable if DoD could have started the vaccinations in time to allow the complete series of vaccinations to occur. At the same time, however, it would have been inappropriate for FDA to deny the waiver entirely based on a prospectively unknown time factor, i.e., duration of a military emergency. Certainly, this experience will be considered by FDA in similar situations in the future.

You should also be aware of some additional information. A publication, Ellis, R.J: Immunobiologic Agents and Drugs Available from the CDC: Descriptions, Recommendations, Adverse Reactions, and Serologic Responses, 3rd Edition, March 1982, contains data to indicate that antibodies were not detected in humans following two doses of the botulinum toxoid vaccine. However, given our experience with other toxoid vaccines, such as tetanus toxoid, and our understanding of the immune system, it seemed unlikely that there would be absolutely no antibody response after two immunizations and an adequate response after three. FDA therefore requested that the DoD obtain some sera from individuals after the 2nd immunization and prior to the 3rd immunization using a lower threshold for detecting antibody. Upon further examination of their database in June 1994, DoD discovered some post-2nd dose immunization data. Evidently, at the time of Desert Shield/Desert Storm, there was some urgency to admit lab workers to the suites as soon as possible. Therefore, sera were obtained from some workers at

the time of the visit for the 3rd immunization. All seven of the vaccinees had detectable antibody following the 2nd dose, indicating that some protection might have been provided at least temporarily by two doses. Given the limited amount of data, however, the FDA views this information as preliminary, and FDA has requested DoD to provide data on more substantial numbers of vaccinees at a variety of timepoints during and following the immunization series.

In the publication, Cardella, M.A. "Botulinum Toxoid," Botulism. Proceedings of Symposium, PHS Publ. No. 999-EP-1, PHS Cincinnati, Ohio, December 1964, 113-130, the author noted that, in his experience, some vaccinated animals with no demonstrable antibodies have been protected from challenge. A copy is attached for your information.

With regard to pyridostigmine, as mentioned in the response to Question #2, we plan to discuss with DoD several aspects of dissemination of information and collection of data during such a military operation. Certainly, this experience will be considered by FDA in similar situations in the future.

Question 11.

**Does the Food and Drug Administration have any information that manufacturing of the pyridostigmine which was provided to U.S. troops in Desert Shield/Desert Storm may have been less than optimal? Why was the percentage of military personnel who took pyridostigmine in the Persian Gulf higher than reported in studies of healthy men conducted by the Department of Defense?**

Response.

On April 29, 1994, FDA provided the Committee with information on the suppliers of pyridostigmine. Specifically, in response to your question asking if two manufacturers of pyridostigmine were in compliance with FDA's Good Manufacturing Practice Regulations (GMPs), we informed you that both manufacturers of pyridostigmine, Duphar in the Netherlands and Roche in the United Kingdom, had been inspected by FDA and found to be in compliance with GMPs. We stated further that these two manufacturers were the only suppliers of pyridostigmine.

We have been reviewing our files in order to respond to your current inquiry and would like to provide clarification with respect to the suppliers of pyridostigmine. Duphar and Roche were the suppliers of the finished dosage form, 30 mg tablets. In the case of Duphar, however, the active drug substance used for the tablets was produced by Raschig A.G., Ludwigshafen, Germany; the active drug substance for the Roche product was

supplied by the firm's Basel, Switzerland facility. These facilities had been inspected and found to be in compliance with GMPs.

Also, according to FDA's Division of Medical Products Quality Assurance files, active bulk pyridostigmine was to be provided by either Helsinn Chemicals, Chiasso, Switzerland or CL Pharma AG, Linz, Austria to DoD under the terms of the DoD contract with the manufacturers. An FDA Inspection at Cl Pharma AG and a Swiss inspection at Hilsinn Chemicals resulted in determinations that the manufacturing processes were acceptable.

In order to respond to the more specific nature of this current inquiry, we are providing the FDA Form 483 (inspectional observations left by an investigator at the conclusion of an inspection) and the Establishment Inspection Reports for the inspections conducted by FDA. FDA does not have a copy of the Swiss inspection report for Helsinn Chemicals.

As you will note during your review of these documents, a number of deficiencies were observed during the inspections. Based on commitments to take corrective action, it was determined that these deficiencies did not raise any significant public health concerns and, therefore, did not warrant regulatory action by the agency.

With regard to the incidence of adverse events, it appears that the incidence of gastrointestinal-related events (diarrhea, flatulence, abdominal cramps, etc.) reported in soldiers taking pyridostigmine in the Persian Gulf (approximately 50 percent) was greater than would have been expected based on the experience garnered in studies in healthy volunteers performed under the IND. The explanation for this difference is not obvious. Assuming that the incidence reported in the Desert Storm experience accurately reflects the true incidence, a number of factors might have contributed to this discrepancy, such as diet, psychological factors (anxiety, etc.), infectious causes, other environmental factors (oil well fires, etc.), underlying medical conditions, or concomitant medications. This issue will be one of our agenda items when, as was mentioned above, we meet with DoD. It bears repeating, however, that even though the incidence might have been greater, there were few, if any, truly serious events noted.

**Question 12.**

**We received information that some Persian Gulf soldiers were told that they would not receive the second anthrax vaccine because the "vaccine had gone bad." Are you aware of any such discussions? Were any of the vaccines administered to Persian Gulf military personnel contaminated or deemed unsafe?**

Response.

All of the Anthrax vaccine was of acceptable quality, that is, when FDA reviewed the Anthrax vaccine, FDA did not fail any of the Anthrax vaccine lots in the Desert Storm/Desert Shield time period. Likewise, FDA is not aware of any problems with test results for other vaccines that might have been used for the military. FDA was formally informed, however, that following the conclusion of the Persian Gulf War, the refrigerator units at the supply area in Saudi Arabia failed, and that vaccine vials stored at the site that lost refrigeration were quarantined and subsequently not used. You may wish to contact DoD for additional information.

QUESTIONS FROM SENATOR DANIEL AKAKA

Question 1.

**To knowingly mislead military volunteers participating in medical experiments is a serious allegation. Is the practice of utilizing military recruits for human research protocols involving chemical or biological defense agents commonplace today? Do you think it wise to compensate volunteers of these earlier programs?**

Response.

We are not aware of current or recent studies in which recruits were deliberately exposed to chemical or biological agents by DoD. Indeed, one of the difficulties in assessing potential antidotes (like pyridostigmine) or vaccines (like botulinum toxoid) is the investigator's inability, on ethical grounds, to expose humans to the toxic agents. The potential antidotes and vaccines themselves have been studied in humans; as described at the hearing, pyridostigmine has been used in a modest number of military volunteers in short-term studies and has long been marketed for the treatment of myasthenia gravis. We are not aware of any studies in which the military volunteers were misled. Whether military volunteers in previous studies need compensation is not an issue on which FDA can comment.

Question 2.

**Some say that criticism of current researchers for medical research practices is like forcing the son to pay for the sins of the father. Do you feel further investigation into these alleged misdeeds would be justified, or do we grudgingly place these historical practices in proper perspective, and concentrate more on avoiding repetition of these mistakes?**

Response.

FDA has no information on the past military practices mentioned. Current practices are regulated by current U.S. law and regulations pertinent to studies of investigational agents in humans.

# APPENDIX 4.—STATEMENTS SUBMITTED FOR THE RECORD

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## STATEMENT OF JOHN W. ALLEN, MUSTARD GAS-EXPOSED VETERAN, OREFIELD, PA

My name is John William Allen, and my name is recorded in the N.R.L. Scientific Notebook (S/N) #6AKA S/N 5445 on page 627. This confirms my taking part in Exp. #104.C. This series of experiments as stated on page 624a, of this S/N is: "Effect of temperature and humidity on chamber exposure."

In these experiments in which my name appears, the exposure to "volunteers" in the gas chamber are confined to the use of Crude Sulphur Mustard Gas, under the following conditions. The chamber was heated to 90° F with 30% humidity, to simulate tropical conditions, in which mustard might have been used by the enemy.

This series of experiments was titled "Man Break." This means I was issued clothing consisting of one pair of pants, undershorts, gas mask, and shirt. These had been used before and were impregnated by gas. There is no way of knowing how many times they had been worn before they were issued to me.

This experiment is to determine how long a human can function under these conditions. The purpose is to break the man, not the so-called protective clothing.

I was subject #865 wearing gas mask #335 and protective suit #865, I will say one more time the "protective suit" consisted of pants, shirt, undershorts, and gas mask, which had been used numerous times before.

S/N #5445 confirms these dates of exposure to crude sulphur mustard:

1. date 45-04-30 exposure #1 Exp. #104.1C

2. date 45-05-1 exposure #2 Exp. #104.2C

3. date 45-05-2 exposure #3 Exp. #104.3C

4. date 45-05-3 exposure #4 Exp. #104.4C

I was pulled from further exposure on 45-05-04 when I passed out in the chamber. I woke up on a stretcher, not knowing how I got there. I received no medical treatment or followup. I was sent home the next day on an 11-day leave.

I returned from leave 45-5-14. The physical examination at this time showed I had many scars as the results of exposure to the mustard gas. I was then sent to Bainbridge, then on to Norfolk, and then aboard *U.S.S. Harcourt IX 225.* While aboard ship, my neck rubbed open from the blisters, and I was given a white salve to put on it. They thought it was from sunburn, because we couldn't tell anyone we had been gassed. This was the extent of my medical followup or treatment.

It took me over 50 years to receive these records. I tried in 1953 to get them, but was told there were no records of mustard gas testing. There is nothing on either of my discharges either, about my exposure.

The war was on, I was a young kid, and I volunteered for extra leave to "just test summer uniforms," so I could go home again before shipping out.

I enlisted in the U.S. Navy on January 19, 1945. I have proved over and over again that I was in these tests and that I have health problems, yet I have been turned down twice in Philadelphia by the VA.

I went to Washington, DC on December 14, 1993, but have not heard one word from them. I was represented by the DAV at that time. The Department of Veterans Affairs in Philadelphia gave, as their reason for not giving service connection and disability—"We reach this decision because the law defines those disabilities as a result of mustard gas exposure are laryngitis, bronchitis, emphysema, asthma, conjunctivitis, keratitis and corneal opacities."

I've also been told by the DAV that most service connection has come from "field testing." How can anyone that sits on a board for the veterans say this, when we were sealed in a room for 1 hour each day with mustard gas circulating on us at all times? The effects of exposure are cumulative, as well as radiomimetic, and you must, in all fairness, take this into consideration.

My wife tells me that it is my fault because some of my problems are not on my records, because I will tell them I am fine, or deny that I hurt, or have problems until they get to be too much. When I went through 8 weeks of radiation I did not let them know I was in pain, and when I took chemo I just wanted to go home from the hospital and never told them I was sick. And I denied having the bad headaches until I could not stand it any longer. I've had them for about 8 or 9 years now, and they are getting worse.

During the years I have had numerous medical problems, and when I ask doctors if they could be caused by exposure to mustard gas, they laugh at me. The VA doctors do not know what to look for and do not have time to find out about mustard gas exposure. Too many of the doctors in VA hospitals do not speak English clear enough that you can understand them, or they can not understand you.

I guess one reason I don't tell the doctors about symptoms is because I'm afraid of being used as a human "guinea pig" again. When they first found the spot in the lobe of my left lung they were ready to cut the left side of my lung out. I said no, leave it alone. I did consent to try to get a biopsy.

In 1949 I had bleeding ulcers; ever since I was gassed, I have had eye problems. I get small white pimples under my eyelids (it feels like I have sand in my eyes). Finally, in 1981, I was pronounced legally blind and received my first surgery in 1981, followed by the second in 1982. I have scars on my back, shoulders, arms, and hands. I break out from time to time around my

wrists with small sores. My skin is sensitive to electric razors, certain soaps, shaving creams, and deodorants. I had tumors taken from my bladder in 1989 and bladder cancer in 1991. In 1950, all my top teeth had to be removed—I had perfect teeth when I went into the Navy. My tonsils were burnt out by the gas. I have a narrowing of my esophagus. I have to sleep on my stomach with two pillows under my chest to get air into my lungs. I've had mood changes for years that I did not understand, nor did my family. I just want to be alone, shut myself into a room and not talk to anyone. I often have to swallow water to push food on down my esophagus, because it won't go down.

I have circulation problems in arms, hands, and legs. In fact, the left leg is so bad they cannot find a pulse in it. I am on medication now and if it does not correct it, I may lose the leg. I had to retire early because of the pain in my legs.

The government has lied to us for 50 years over and over again. If I would have been shot on the front lines, at least I would have had it on my record and would have received medical treatment.

Our only daughter has M.S. I notice in the book "Veterans at Risk," that several of the men who were exposed have M.S. Maybe if the government had not denied us followup, they would have found that some of the chemicals we were exposed to might be causing this disease, and they could find out what causes it.

I'm also tired of younger men in the VA saying, "I wasn't even born when they did this to you." They don't realize they may not have had a free country to be born in, if it hadn't been for some of us older men doing what we thought was right.

I feel that my long term suffering is a direct result of my being exposed to mustard gas in these secret tests. I cannot see how this government of ours can deny any of us who went through this our rightful service connection and disability.

# STATEMENT OF DAVID L. MCGEE, SGT., UNITED STATES MARINE CORPS, PERSIAN GULF WAR VETERAN, LISBON, OH

AM I DYING OR IN HELL?

Where do we turn now? Who will help us after we have helped somany? At a point in our lives we stepped forward and took an oath to defend this country, its people, and its ideas. We went unquestionably to the places most would never go. We did the things most could not imagine or refuse to admit to their conscience would be humanly possible. We survived through the extremes and pressures that are not told by the government or media. We came back... or did we?

I am a Desert Shield and Desert Storm Veteran. I am 27 years of age. I am looking for an answer to why my life is filled with so much pain. I now wake every morning asking myself how bad will it be today, and how will I keep it from troubling my family.

It began as a headache. As the headaches became more common and more severe, steady shoulder and neck pains began to persist.

When returning home from the Persian Gulf, the headaches and pain continued to get stronger. A few times I entered a seizure-like episode and was admitted to our local community hospital. Continually for two years, I made trip after trip to the Veterans Hospitals, complaining of pain, headaches, vomiting, passing out, and seizure-like episodes.

This continued for month after month. The pain grew even stronger and the headaches worse and more frequent, seizure-like episodes continued, the pain moved to my joints and extremities. I began to forget things. I lost sensation in parts of my body and little blister type rashes developed here and there all over my body.

A doctor in Neurology in Wade Park V.A. Hospital, admitted me immediately. He discovered other problems that had not been noticed; a droop in the left side of my face, one pupil larger than the other, a slurring of speech, memory loss, loss of sensation in more than one area, an overall slowness of the brain and the left side reactions slower than the right.

I was discharged to Highland Drive Veterans Hospital for treatment of possible chemical poisoning due to an elevated level of protein in my spine. He also suspected post-traumatic stress disorder. Due to my multiple complaints, they could not adequately treat me.

So here I sit, wondering what I did to deserve treatment like this. How will I provide for my family who take care of me daily? I wonder why I must suffer this pain that everyone tells me is not there. Tell me there is no pain when my wife lifts me out of bed, or finds me on the floor. Tell that to my baby daughter who I cannot even lift or manage to hold. Tell that to my family as they watch me daily as if I were a child again. Tell my brothers and sister when I don't know their children whom I have known for years. Tell it to my neighbors when they find me wandering in the yard in the dead of winter with no jacket or shoes. Tell it to our friends who carry me into the hospital because I have passed out and they can't revive me. Tell it to ME when I break into tears from pain that I cannot escape from or relieve, or when I wake up and don't know whose house I am in or who is around me.

Meanwhile my condition gets worse as I walk with my cane, and experience, bloody bowl, irritability, anger, bleeding gums, fatique, diarrhea, insomnia, sensativity to light, sensativity to noise and smells, blurry vision, problem concentrating, unknown lumps, cough, heavy chest pressure, constant ringing in ears, confusion, numbness and coldness in hands and feet, numbness of arms and legs.

What could have caused this to happen to me? Chemicals or Biological Agents? Parisites? Burning oil fields? Or could it have been the same thing that killed the animals that I saw by the dozens while I was there serving our country? OR could it have been the series of shots and pills administered countlessly, and never recorded in our medical records?

# STATEMENT OF MICHAEL S. AND DEBRA A. MOORE, PERSIAN GULF WAR VETERAN AND SPOUSE, SMITHS, AL

February 27, 1994

Debra A. Moore
96 Lee Road 973
Smiths, AL 36877

To Anyone Who Will Listen:

I have wanted an opportunity many times in the last three years to express my feelings about the Gulf War, it's Veterans, and the sadness of it all. I am the wife of Michael S. Moore, a Navel Reservist with NMCB 24, Columbus, Georgia. I can recall vividly my dread and fear when my husband and the father of my children was called to active duty for Dessert Storm. I begged him to please get out of going. His response to me was that he had men counting on him and that it was his duty to his country to go and serve when "she" called.

I'm sure many families experienced the heartache and fear that we did. My children had never been separated from their father. My son was 15 at the time and started to develop ulcers because he couldn't handle his father being gone. My daughter was 12 and she supported her brother and I as much as possible and held her feelings inside. Anyway, we made it through.

My husband returned home on March 15, 1991. I met him at the emergency room door of Eisenhower Memorial Hospital in Augusta, Georgia. Our children did not go with me because I did not know what kind of shape their father was in and did not know if they could face that reunion. All I knew was that my husband had been having heart problems and was in critical condition. When he arrived home, I thought our nightmare was over. Little did I know that it had only just begun.

My husband was perfectly healthy when he left for training and duty in November of 1990. He had never had any major illnesses since our marriage in 1973. He was always energetic, hard working, and even tempered. We had a good family life. In my husband's statement of July 23, 1993, he listed all the symptoms he has continued to experience since his return. I can vouch for every one of them. I could be specific about some of our family experiences with him since his return, but I won't. I will only tell you that our family is important to us and we have had to do a lot of adjusting and talking with each other to understand the complexity of this "Gulf War Syndrome."

Dealing with one family member being sick is tough. I can usually handle a lot. However, when someone messes with my children it's a whole different story. In August of 1992 my daughter was diagnosed with hypothyroidism. It reacts opposite of my husband's illness, but it is still caused from a disturbance to the immune system. I became concerned but tried not to let it get the best of me. In the past year and a half, my daughter's activity level has decreased. She does not have the same stamina and drive that she had in the past. She has had problems with depression, fatigue, insomnia, and memory loss. Our family doctor says it's due to the stress of the fears caused from the uncertainty about the "Gulf War Syndrome" and the fact that we know so many sick Veterans. I have had to go pick her up from school on several occasions because she was so weak and exhausted she couldn't make it through the day. My husband and I have laid in the bed at night crying because we don't honestly know what the future holds for any of us. We know that there is

definitely a reason for concern and nobody is giving us any answers that are comforting.

My son has also experienced some problems with his heart and asthma. Fortunately, he was treated and his symptoms have not reoccurred.

I have experienced fatigue, memory loss, internal trembling, insomnia, depression, and stomach problems (duodenal ulcer). In the fall of 1993 I had to take a leave of absence from work for chronic fatigue. Now I have to really watch my activity level and make sure I get plenty of rest to make it through the work day.

I am 39 years old and have had to deal with a lot of stress in my life. I feel like I have experienced enough in my life to know that what I have felt since 1991 is like nothing I have ever felt before. I know deep down inside that there is something wrong and we aren't all just stressed out.

My biggest problem is knowing that when the U.S.A. called my husband to active duty in the Gulf, he went without hesitation. Now my husband and thousands of other Veterans, and their family members are calling on the U.S.A. to help them. We made our sacrifices for her and she is playing politics with us. We shouldn't have to continue waiting month and month, and year after year, for the V.A., D.O.D., or Congress to decide who did what and what happened. This should have already been taken care of with the speed in which the Gulf War was. Where are our priorities? What would happen if the next time the U.S.A. called its men and women to go to war, and we played politics for years. This country wouldn't be in existence. We all deserve some answers.

Thanks for listening!

Sincerely,

Debra Moore

Debra A. Moore

## STATEMENT OF CURRENT PHYSICAL CONDITION

Michael S. Moore July 23, 1993

I have continued to experience health problems since March 8, 1991, which are, in my opinion, directly related to my deployment to Saudi Arabia in support of Desert Storm and to one or more of the events that happened there within the period of January 15, 1991 to February 3, 1991. The events are as follows:

| | |
|---|---|
| January 15, 1991: | I received my first injection of the Anthrax vaccine on January 15, 1991, and we were then placed on two types of pills. We were told that one pill was a very high dosage of antibiotic, and the other pill was to build our immunity to nerve gas should be be attacked with any. |
| January 20, 1991: | There were two explosions on the night of January 20, 1991, which I feel contained chemicals due to the circumstances surrounding them. |
| February 3, 1991: | On February 3, 1991, we received a second Anthrax vaccination. |

On the morning of February 4, 1991, I woke up with flu like symptoms: chills, sore achy muscles and just generally feeling bad. I fainted twice during the day. I reported to the Medical Department that evening and was placed under medical care. On March 8, 1991, I was medically evacuated out of Saudi Arabia. In a period of 51 days, I went from a perfectly healthy individual to a bedridden patient in ICU.

Some of my current problems are the same problems I was having when I was first admitted to ICU. These problems have caused me to miss nine days of work in the past six months. They are as follows:

- Heart complications. I have a copy of an EKG that says I could have had a heart attack during my initial medical evacuation from Saudi. My heart still continues to skip beats, race, and sporadically does what feels like flip-flopping.
- Shortness of breath. I experience shortness of breath and I tire very easily with any physical activity.
- High blood pressure. My blood pressure has been elevated on several occasions, mostly during periods of stress.
- Chest pain. I have experienced chest pain on several occasions, mostly during period of stress.
- Daily medication. I am taking Synthroid on a daily basis because of the I-131 treatment I was given to eliminate my thyroid. I am on this medication for the rest of my life and without it I could die from heart failure and low blood pressure.

- Vision impairment. My vision has been going downhill since my return and even though my eyeglass prescription has been changed numerous times, I still have difficulty seeing and focusing.

- Toenail loss. I have had some sort of rash or fungus on my feet and several of my toenails have fallen off.

- Headaches that are unexplainable and severe at times. I also have more sinus problems than I have ever had before.

- Fainting, dizziness, and poor balance. I have fainted three times since Saudi, once falling from a ladder and landing on a glass picture, cutting myself badly.

- Stress Intolerance. My tolerance for stress is almost non-existent. My superiors, co-workers, and family members have noticed it and commented about it. When I do get stressed out I sometimes feel as though I am not a real part of myself, sort of like my consciousness is taking me away from it. I don't currently know how long I will be able to continue work at my present job as stress is a daily part of it.

- Unexplained tiredness. I am physically drained at the end of the day.

- Internal nervousness. I have periods of internal nervousness that often make me feel as though an earthquake is happening inside me or that I may explode inside. I often ask my family if they feel the house shaking to determine if it's within me or not.

- Typhoid level. My blood tests have indicated that my Typhoid level is high and there is a possibility of Hepatitis B. I was referred back to the VA Hospital in Tuskegee for further testing.

- Joint and muscle aches. My joints stay sore and swollen, sometimes worse than others. I have muscle cramps in my thighs and upper arms.

- Night sweats and chills. I experience night sweats and chills periodically.

- Memory loss. Sometimes I become confused and experience a temporary loss of memory. I lost my truck at the Mall on two occasions. I can be driving around to a particular location and forget where I am going. My wife has started to worry about me driving a car alone.

  I sometimes become dissoriented and forget what I am doing or supposed to be doing.

  I have also noticed that my hand and eye coordination is off at times causing me to have some problems I have never had before.

I strongly feel that the above mentioned problems are directly related to the events which took place between January 15 and February 3, 1991 in Saudi Arabia. I only know that I left on a plane in December, 1990 as directed by the U.S. Navy and when I returned home I was not and have not been physically able to maintain my lifestyle in the same manner. My health seems to be going downhill and becomes more noticeable each day. I also know that many of my fellow service members that were stationed with me in Saudi are having similar problems.

# STATEMENT OF NATHAN J. SCHNURMAN

Mr. Chairman, Honored Members of the Senate Veterans Affairs Committee, May I respectfully submit this statement and request it be included in the record by this Committee.

Recognition of veterans used as human guinea-pigs by government agencies in covert experiments, designed to intentionally injure humans, for study by the Committee For Medical Research (CMR), that produced long-term medical consequences, resulting in acute, chronic, primary and secondary injuries are long overdue.

The use of Humans was made available by the Secretary of Navy in a letter dated: May 8, 1942, signed by: James Forrestal, Acting Secretary of the Navy and Robert P. Patterson, Acting Secretary of War. Consent was requested and approved by Rear Admiral Ross T. McIntire, Bureau of Medicine and Surgery (BuMed&Sur.), The Navy Bureau of Personnel (BuPers), and Commanding Officer (C/O), Bainbridge Naval Training Center.

This was a Bureau of Ships (Bu/Ships) project, but taken under BuMed&Sur. due to known physiological effects of exposure by vesicants. (Reference: BuMed&Sur Project X-547 Subj.#116 Dated: 23 March, 1945 "Studies in C/W Defense" BuShips Project, taken under BuMed&Sur Cognizance Project, in view of the physiological aspects and Gilbert W. Bebee, Ph.D., National Academy of Sciences-National Research Council Follow-up Agency (J. Nat. Cancer Inst. 25: 1231-1252, Washington DC, 1960).

Humans were obtained under any pretense and identified as "volunteers." The volunteers were obtained under the guise of "volunteering" to test Navy Summer Clothing, for which they would be afforded a three day pass. No record was to be made available that would or could confirm the etiology of the "volunteers" medical injuries. Many were denied the three day pass, and many went to their grave without revealing this story.

The volunteers were threatened with Court Martial, and to be charged with "Treason", if they refused a direct order to enter the chamber or reveal to anyone, where, how or what caused their injuries. After all, we volunteered for this duty. You note, I use the word, "volunteer." That is exactly what we were, unwitting volunteers.

During my participation (January 1944) it was winter in Maryland, cold, snow, ice and chilling wind. Navy Summer clothing tests surely would be conducted where the weather was warm and the sun would shine. This could be, Florida, Georgia or anywhere the weather was warm; or so I assumed. This became more than just a bad dream. It was a horrible nightmare where injuries were produced daily by the vesicants and compounded.

How could such a program even begin? Human volunteers were difficult to obtain at the beginning of this program, as confirmed in a "Weekly Report" To: BuMed&Sur. Experimental Section, Dated: 43-04-03 TO: Bu.Med. & Sur. Attn: R/A H. W. Smith From: Lt. Cmdr. L. E. Daily (M.C.) U.S.N. Friday: "Went with Comdr. Dole to Navy Yard to arrange for human volunteers for gas testing work. This idea was found to be unsatisfactory. It was suggested we contact the Naval Training Center, Bainbridge, MD."

In a weekly report to the BuMed&Sur., Research Division, Dated: 20 August 1943, From NRL "The men are definitely volunteers when they are obtained. However, The attitude is adopted that once they are at [sic] the experimental station their volunteer status ceases and they are under direct orders to participate in the tests."

Volunteers were sent to the Naval Research Laboratory (NRL), on a weekly basis. Injuries were produced by the high concentrations of vesicant agents and by ordering the human subjects to enter the gas chamber for repeated exposing until they reached a casualty level of injury.

Injuries were produced by each exposure, compounded and manifested by multiple exposures. The average number of exposures a man could tolerate was three. The "protective clothing" was incapable of preventing injury. Likened unto the gas masks furnished these humans, the vesicant agents penetrated the rubber, and the canisters furnished during this time frame as the gas masks were fitted with asbestos filters. Life of the canisters for the Navy Mark III and Navy Mark IV gas masks varied. The average complete protective time was 15 minutes. Volunteers were locked in the gas chamber 60 minutes daily and exposed to vesicants.

The men were issued "Protective Clothing" that was treated to prevent injury, or so we thought. There was little protection. If the clothing was to prevent injury, why were these painful injuries being produced on a daily basis? We were ordered to return to the gas chamber every day wearing the same inadequate protective clothing and gas mask.

The used protective clothing and gas masks were reissued to new incoming drafts of volunteers, until confirmed there was no protective value left. A new man would be issued the depleted protective clothing and injured during his first exposure in the chamber. Confirmation of the lack of protection is assured by affording the same clothing to additional men. They too were also severely injured by the first exposure and defined as Casualties.

What was the name of the agents to which we were being exposed? Mustard gas, (H) mixed with an equal volume of Lewisite (L) to produce H/L. I had heard of Mustard being used during World War I. What was Lewisite? I didn't know. However, this is America. Surely they would not do anything that would produce damaging injury to us. These were honorable people. People to be trusted. I should not worry, but why was I being repeatedly injured every day?

Walking, sitting, lying down or trying to sleep, produced pain. I dare not change my position, once I would lie down on this Army Cot; if I did, it would rupture another large blister on my body. This Florida sunshine was too warm for me. Another sad story, this was not Florida. I was still in Maryland; Edgewood Army Chemical Center, Edgewood, Maryland.

We wore the contaminated clothing during lunch. Upon returning from lunch, we would lie on the Army cot, with Army blankets, wherein, even the blankets became contaminated. The contaminated clothing was to be worn a minimum of five hours daily. The experiments were designed to produce medical injuries by exposure to vesicant agents under tropical conditions. This was titled "Man Break" experiments. Vesicant agents were administered in vapor form to bring the desired concentration to the targeted value, sufficient to produce injuries, and by multiple exposures capable of producing systemic damage to the cells, the most important of which is DNA.

Human subjects were intentionally injured in the "Man Break" experiments; locked in a gas chamber and repeatedly exposed on a daily basis to high concentrations of vesicant war gasses until visible injuries appeared and could be classified as casualty. (NRL TO. Bu Med. & Sur. Date: 43-10-02) We were injured by the vesicants due to defective gas masks, canisters and contaminated clothing; by inhalation; ingestion; and absorption by body contact with the vesicants on a daily basis, and sent home to recover.

Unfortunately, while at home on a ten day leave, the effects of the exposures manifested additional abnormalities, to include pneumonia, additional rupture of blisters, labored breathing, extreme pain continued in the eyes, the throat and expelling of the mucous membrane of both nostrils. Pain was produced just by breathing. I finally gave in to the pain and sought medical treatment prior to returning directly to Bainbridge. Upon my return to Bainbridge, the medicated packing was still in my nostrils, and held in place by adhesive. I could hardly speak above a whisper, I could not eat, all of which produced severe pain to my throat.

The vesicants of choice was either Crude Sulphur Mustard, identified by The Chemical Warfare Service (CWS) as Agent "H" or Nitrogen Mustard, identified as Hn1, Hn2, or Hn3 to include Lewisite, identified as agent "L." Lewisite contains Arsenic. In addition to its heavier molecular weight used in equal volume with any of the mustards.

The primary purpose of the Lewisite was to bring the mustards down on target, either by burster munitions, or aerosol spray from low flying airplanes. The Arsenic effect was a bonus. These vesicants are radiomimetic, as noted by the gamma symbol (∂). Some experiments were conducted with one vesicant agent, others in concert with Lewisite; identified as H/L. Unfortunately, most of the exposures were multiple, therefore, the effects are cumulative.

The concentration of the vesicants in the chamber was checked every five minutes and additional vesicant added to correct for absorption of the vesicant into the protective clothing, gas mask, onto and into the skin, and ultimately picked up by the blood and carried to every organ of the body within five minutes. This procedure was necessary to maintain the desired concentration. Therefore, it is impossible to determine the total

volume of vesicant to which subjects were exposed. But I assure you, the concentration and multiple exposures were sufficient to produce systemic injury as stated in a letter to me, from Alfred Gilman, Ph.D. (Yale) Dated: 12 December, 1977. (Alfred Gilman, Ph.D. Yale, Co-author. Goodman & Gilman "Physicians Handbook on Pharmacology; Still used in medical schools today")

It was decided, something should be added to the man's service record, to account for his absence. Intra-agency correspondence From: NRL Lt. Cmdr. Daily, TO: Ch. Dir. Navy Personnel Via: Ch. Bu.Med. & Sur. Date: 44-04-25: "Recommendation for Entry of Defensive Gas Warfare Training Course in Men's Service Records." (No statement was included as to how or why the men returned to Bainbridge with burn type injuries, et al. No statement was included to confirm the man was locked in a gas chamber, repeatedly and intentionally exposed to deadly vesicants until he could be classified a casualty. No medical treatment was to be afforded the "volunteer.") Unfortunately, the entry relating to the training course was not included in most of the volunteers personnel or medical file. There was no follow-up for medical attention.

The records of NRL confirm 2,930 men were obtained from Bainbridge Naval Training Center, Bainbridge, MD, which was accessible to both the NRL and the Navy Unit stationed at Edgewood Army Chemical Center. As both were units, or branches of the parent agency, NRL and charged with reporting to the Bureau of Medicine and Surgery (BuMed/Sur) on a weekly basis by the Medical Liaison Officer.

Of the 2,930 humans a total of 6,450 exposures or experiments were conducted by NRL with 2,085 different humans. Why should it now take The Department of Veterans Affairs (DVA), years to afford the few remaining claimants due process? I can appreciate the difficulty in adjudicating these claims, especially in light of declining funds, however, most claims were previously denied as fantasy. But truth is here, and with the ability to verify participation and injuries. (Summary Technical Report Of Division 9, NDRC "Chemical Warfare Agents, And Related Chemical Problems, Parts 1 - II and III - VI (Office Of Scientific Research And Development, Vannevar Bush, Director and National Defense Research Committee, James B Conant, Chairman, Division 9 W. R. Kirner, Chief Washington DC, 1946 )(Declassified)

In filing claim with the DVA in 1975, for service connected injuries, government agencies denied such a project ever took place, especially here in the United States; let alone using humans as the guinea pig.

Denial of claims, due to lack of documentation was and is standard practice. How many times did my claim receive this same phrase; "Claim Denied." Many times, I assure you. "No evidence of record." Of course there would be no record to confirm the claim. All personnel and service records were sanitized for any and all confirmation of this atrocity. It took seventeen years for the DVA to recognize my claim as service connected. It is now in the appeal process since August 27, 1991. When will this claim be adjudicated? This year. Next year. I don't know. It was remanded [back] to the Regional Office (VARO) from the BVA in November of 1993. DVA Regional Rating Boards need to know of the toxic effects these vesicants produce to veterans. Qualified medical personnel, practicing in Veterans' Administration Medical Centers should be made aware of the [now] declassified medical research relating to acute, long-term chronic medical effect of injury by vesicants.

It is unfortunate, government agencies felt human subjects could only be obtained by lies, half-truths, and threats of a charge of treason to their country, if they (we) ever revealed the facts. Being enlisted personnel, we were used, abused, lied to, lied about, denied medical treatment and service related benefits. All of which is wrong.

This program was closed 20 May, 1946. To retain secrecy, a notation would be recorded on some men's Scientific Log to denote what would belie the creditability of any statement by the quotation, "Psycho." However, no record was included in any of the participant's medical or service record to confirm exposure by vesicants or injuries due to exposure in a gas chamber.

May I take this opportunity to thank the Naval Research Laboratory, Information Services Branch, Mr. James W. Gately, Jr. and Ms. Maria Lloyd for their assistance and cooperation in obtaining confirmation of participation and exposures for many of the claimants in these experiments.

Mr. Chairman, Fifty years is too long for the truth to be denied. It is fortunate confirmation pertaining to this issue is now declassified and without threat to the security of the United States, especially, considering most of the claimants are deceased. Delaying adjudication is lowering the number of claims filed by former Army and Navy personnel with the Department of Veterans Affairs (DVA), for the service connected benefits, due to long-term multiple medical effects of exposure and injuries produced by the vesicants. Justice delayed is justice denied.

Mr. Chairman, and honored members of this committee, on behalf of the remaining survivors of these heinous actions on humans; we thank you for your indulgence and pray your actions will mimic the words of Abraham Lincoln's address to an Indiana Regiment (March 17, 1865): "With malice toward none, with charity for all, with firmness in the right as God gives us to see the right, let us strive on to finish the work we are in, to bind up the nation's wounds, to care for him who shall have borne the battle and for his widow and his orphan, to do all which may achieve and cherish a just and lasting peace among ourselves and with all nations."

Thank you

# APPENDIX 5.—GAO INFORMATION

GAO

United States
General Accounting Office
Washington, D.C. 20548

Human Resources Division

B-257173

May 4, 1994

The Honorable John D. Rockefeller, IV
Chairman, Committee on Veterans' Affairs
United States Senate

Dear Mr. Chairman:

This letter provides information that you requested on March 25, 1994, concerning veterans' service medical records. After discussions with your staff we agreed to (1) describe the service medical records control procedures followed by the Department of Defense (DOD) and the Department of Veterans Affairs (VA) after a servicemember is discharged and (2) identify some of the reasons that some records may be hard to find. We agreed to focus on procedures applicable to Persian Gulf veterans, basically those followed since 1991.

To obtain this information, we reviewed documents prepared by each military service that outlined the procedures that were in place in 1991. We obtained updated information from interviews with DOD officials. We also reviewed applicable portions of the VA claims processing manual and interviewed VA officials. Some of the information is based solely on interviews with DOD and VA officials. These officials reviewed the flow charts that we developed and agreed that the charts present an accurate overview of the service medical records control procedures.

As requested by your office, attached are the following:

-- Flow charts, with explanatory text, illustrating the service medical records control procedures. There is a chart for each of the four military services. As shown on the charts, services have implemented new procedures that transfer records directly to VA. The new procedures have simplified the process. However, the possibility of medical records being misplaced, which has been a longstanding problem, remains because there are still many locations where records could be found within the new system.

-- A map indicating the locations of facilities included in the procedures as well as other places officials said that records are sometimes found. There are 126 U.S. facilities shown on the map. There are over 10,000

B-257173

other places where records might be found, including Reserve and National Guard units and over 600 medical treatment facilities that are not identified on the map.

-- Data on the estimated number and age of Persian Gulf veteran compensation claims pending at the Louisville VA Regional Office--the office responsible for adjudicating all Persian Gulf claims involving environmental issues. VA reported that there are about 1,100 Persian Gulf claims pending, of which 37 percent are over 1 year old, 33 percent 6 months to 1 year old, and 30 percent less than 6 months old.

-- A chart illustrating examples of VA's inability to obtain service medical records for 20 veterans who have filed compensation claims with the Louisville VA Regional Office. With two exceptions, Louisville has made at least two requests to the U.S. Army Reserve Personnel Center (ARPERCEN) for these records since January 1993; these claims are still awaiting service medical records as of March 1994. The officials reported that they were awaiting records from ARPERCEN for many other claims.

In addition, we are providing enlarged copies of the Army flow chart and the map for possible use during upcoming hearings. If you have further questions about this information, please call Ruth Ann Heck of my staff on 202-512-7007.

Sincerely yours,

Flora H. Milens for

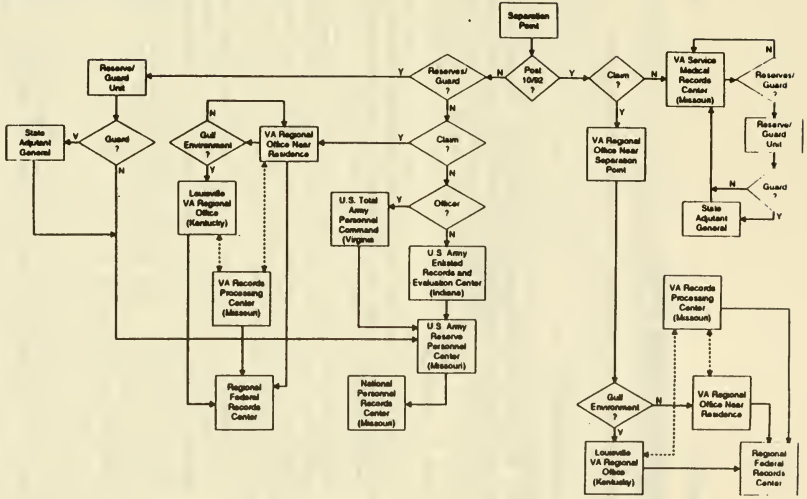
David P. Baine
Director, Federal Health Care
Delivery Issues

Attachments - 4

ATTACHMENT I

## FLOW CHARTS OF SERVICE MEDICAL RECORDS CONTROL PROCEDURES AFTER DISCHARGE

**Figure I.1: Service Medical Records Control Procedures After Discharge, Army Records**



ATTACHMENT I ATTACHMENT I

SERVICE MEDICAL RECORDS CONTROL
PROCEDURES AFTER DISCHARGE, ARMY RECORDS

The separation point assembles records from the medical treatment facility.

Before October 1992

1. The separation point sends the record to the Reserve or Guard unit if the servicemember is joining the Reserves or Guard. The Reserve unit will send the record to the U.S. Army Reserve Personnel Center (ARPERCEN), St. Louis, Missouri, when the servicemember leaves the unit; the Guard unit will send the record to the State Adjutant General, who will then send the record to ARPERCEN.

2. a. The separation point sends the record to the VA regional office nearest the servicemember's residence, if the servicemember indicates he/she is filing a claim with VA.

   b. Since December 1992, the Louisville VA Regional Office has been responsible for adjudicating all claims involving Persian Gulf environment issues. Other regions were to forward all such claims filed before that date, and associated medical records, to the Louisville office.

   c. The cognizant VA regional office will send the record to the appropriate Federal Records Center (FRC) when the veteran dies and VA no longer needs the record. [Note: If the record becomes inactive, the regional office will send the record to the VA Records Processing Center (RPC), St. Louis, Missouri. RPC will return the record to the regional office if a claim is filed or retire it to the FRC when the veteran dies.]

3. The separation point sends records for all other officers (those not filing claims or joining the Reserves or Guard) to the U.S. Total Army Personnel Command (PERSCOM), Alexandria, Virginia. PERSCOM will send records to ARPERCEN.

4. The separation point will send records for all other enlisted members (those not filing claims or joining the Reserves or Guard) to the U.S. Army Enlisted Records and Evaluation Center (EREC), Ft. Benjamin Harrison, Indiana. EREC will send the records to ARPERCEN.

5. ARPERCEN maintains records of retirees and members of the Individual Ready Reserve and of others who still have a service obligation. When the obligation ends or the veteran

dies ARPERCEN will send the record to National Personnel Records Center (NPRC).

> ". . .Because of delays in forwarding records from one point to another, the records may not be where they are supposed to be. It is also possible that the records might never have left the separation center or treating facility or that the records might be in the veteran's possession. If the veteran had a terminated Reserve/Guard connection, the veteran's records might never have left the Reserve/Guard Unit." (Veterans Benefits Administration Manual M21-1, Part III, p. 4-I-3.)

After October 1992

1. The separation point sends records to the VA Service Medical Records Center (SMRC), St. Louis, Missouri, if the servicemember does not indicate he/she is filing a claim with VA. [Note: VA has made no decision concerning how long SMRC will maintain records. The military services have not decided whether records will be retired to NPRC or to them.]

2. SMRC sends the record to the Reserve or Guard unit if the servicemember is joining the Reserves or Guard. The Reserve unit will return the records to SMRC after the servicemember leaves the unit; the Guard unit will send the record to the State Adjutant General, who will then send the record to SMRC.

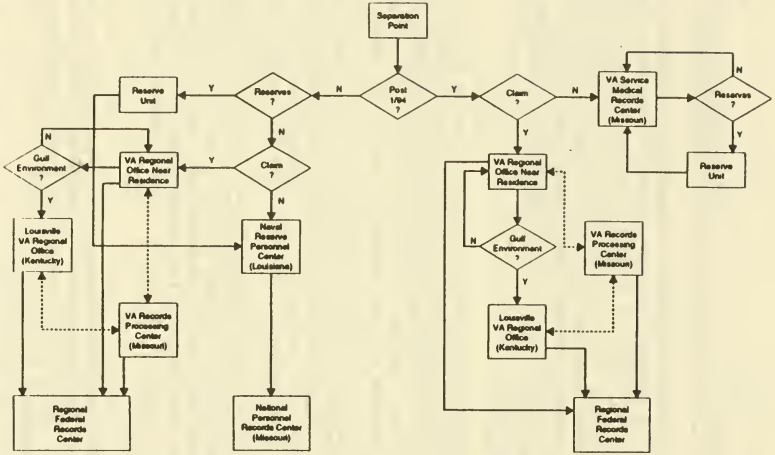
3. The separation point sends the record to the VA regional office nearest the separation point if the servicemember indicates he/she is filing a claim with VA. [Note: Initial implementation of this procedure was a test. An Army official said that the Army will be issuing guidance to change the procedures to send the record to the regional office nearest the servicemember's residence if he/she indicates a claim is being filed.]

4. The VA regional office nearest the separation point will send the record to the Louisville VA Regional Office if the claim involves Persian Gulf environment issues; otherwise it will send the record to the VA regional office nearest the servicemember's residence.

5. The cognizant VA regional office will send the record to the appropriate FRC when the veteran dies and VA no longer needs the record. [Note: If the record becomes inactive, the regional office will send the record to the VA RPC, St. Louis, Missouri. RPC will return the record to the regional office if a claim is filed or retire it to the FRC when the veteran dies and VA no longer needs the records.]

ATTACHMENT I

Figure I.2: Service Medical Records Control Procedures After Discharge, Navy Records



ATTACHMENT I

ATTACHMENT I

SERVICE MEDICAL RECORDS CONTROL
PROCEDURES AFTER DISCHARGE, NAVY RECORDS

The separation point assembles records from the medical treatment facility.

Before January 31, 1994

1. The separation point sends the record to the Reserve unit if the servicemember is joining the Reserves. The Reserve unit will send the record to the Naval Reserve Personnel Center (NRPC), New Orleans, Louisiana, when the servicemember leaves the unit.

2. a. The separation point will send the record to the VA regional office nearest the servicemember's residence if the servicemember indicates he/she is filing a claim with VA.

   b. Since December 1992, the Louisville VA Regional Office has been responsible for adjudicating all claims involving Persian Gulf environment issues. Other regions were to forward all such claims filed before that date, and associated medical records, to the Louisville office.

   c. The cognizant VA regional office will send the record to the appropriate FRC when the veteran dies and VA no longer needs the record. [Note: If the record becomes inactive, the regional office will send the record to the VA RPC, St. Louis, Missouri. RPC will return the record to the regional office if a claim is filed or retire it to the FRC when the veteran dies.]

3. The separation point will send records of retirees, members of the Individual Ready Reserve, and all other discharged members to NRPC. NRPC will retain records of those who still have a service obligation.

4. NRPC sends the record to NPRC when no service obligation remains or the veteran dies.

". . .Because of delays in forwarding records from one point to another, the records may not be where they are supposed to be. It is also possible that the records might never have left the separation center or treating facility or that the records might be in the veteran's possession. If the veteran was in a Naval Reserve unit, the veteran's service records might never have left the Reserve unit." (Veterans Benefits Administration Manual M21-1, Part III, pp. 4-I-3, 4.)

ATTACHMENT I ATTACHMENT I

After January 31, 1994

1. The separation point sends the record to the VA SMRC, St. Louis, Missouri, if the servicemember does not indicate he/she is filing a claim with VA. [Note: VA has made no decision concerning how long SMRC will maintain records. The military services have not decided whether records will be retired to NPRC or to them.]

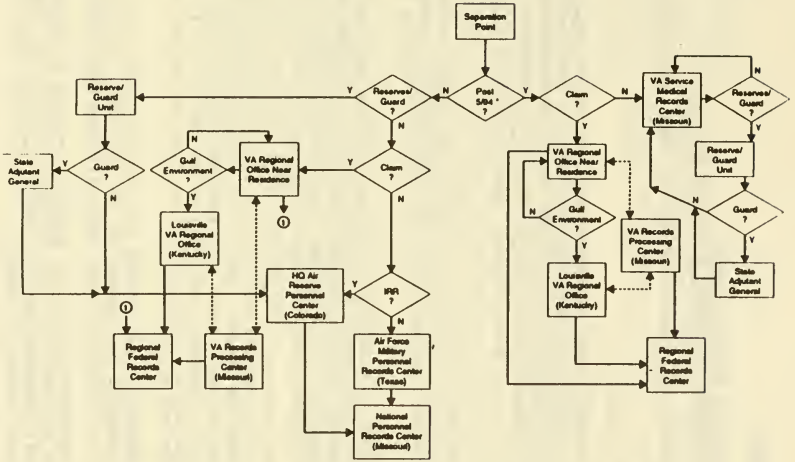
2. SMRC sends the record to the Reserve unit if the servicemember is joining the Reserves. The unit will return the records to SMRC after the servicemember leaves the unit.

3. The separation point sends the record to the VA regional office nearest the servicemember's residence if the servicemember indicates he/she is filing a claim with VA. If the claim involves Persian Gulf environment issues, the record is sent to the Louisville VA Regional Office.

4. The cognizant VA regional office will send the record to the appropriate FRC when the veteran dies and VA no longer needs the record. [Note: If the record becomes inactive, the regional office will send the record to the VA RPC, St. Louis, Missouri. RPC will return the record to the regional office if a claim is filed or retire it to the FRC when the veteran dies and VA no longer needs the records.]

ATTACHMENT I

Figure I.3: Service Medical Records Control Procedures After Discharge, Air Force Records




* Air Force is expected to implement the new system by May 1, 1994

ATTACHMENT I ATTACHMENT I

SERVICE MEDICAL RECORDS CONTROL
PROCEDURES AFTER DISCHARGE, AIR FORCE RECORDS

The separation point assembles records from the medical treatment facility.

Before April 30, 1994

1. The separation point sends the record to the Reserve or Guard unit if the servicemember is joining the Reserves or Guard. The Reserve unit will send the record to Headquarters, Air Reserve Personnel Center (ARPC), Denver, Colorado, when the servicemember leaves the unit; the Guard unit will send the record to the State Adjutant General who then sends it to ARPC.

2 a. The separation point will send the record to the VA regional office nearest the servicemember's residence if the servicemember indicates he/she is filing a claim with VA.

b. Since December 1992, the Louisville VA Regional Office has been responsible for adjudicating all claims involving Persian Gulf environment issues. Other regions were to forward all such claims filed before that date, and associated medical records, to the Louisville office.

c. The cognizant VA regional office will send the record to the appropriate FRC when the veteran dies and VA no longer needs the record. [Note: If the record becomes inactive, the regional office will send the record to the VA RPC, St. Louis, Missouri. RPC will return the record to the regional office if a claim is filed or retire it to the FRC when the veteran dies.]

3. The separation point sends the record to ARPC if the servicemember is a member of the Individual Ready Reserve. When the obligation ends, ARPC will send the record to NPRC.

4. The separation point will send the records of retirees and others discharged without further obligation to the Air Force Military Personnel Center (AFMPC), Randolph AFB, Texas. AFMPC will send records to NPRC.

". . .Because of delays in forwarding records from one point to another, the records may not be where they are supposed to be. It is also possible that the records might never have left the separation center or treating facility or that the records might be in the veteran's possession." (Veterans Benefits Administration Manual M-21-1, Part III, p. 4-I-4.)

After April 30, 1994

1. The separation point sends the record to the VA SMRC, St. Louis, Missouri, if the servicemember does not indicate he/she is filing a claim with VA. [Note: VA has made no decision concerning how long SMRC will maintain records. The military services have not decided whether records will be retired to NPRC or to them.]

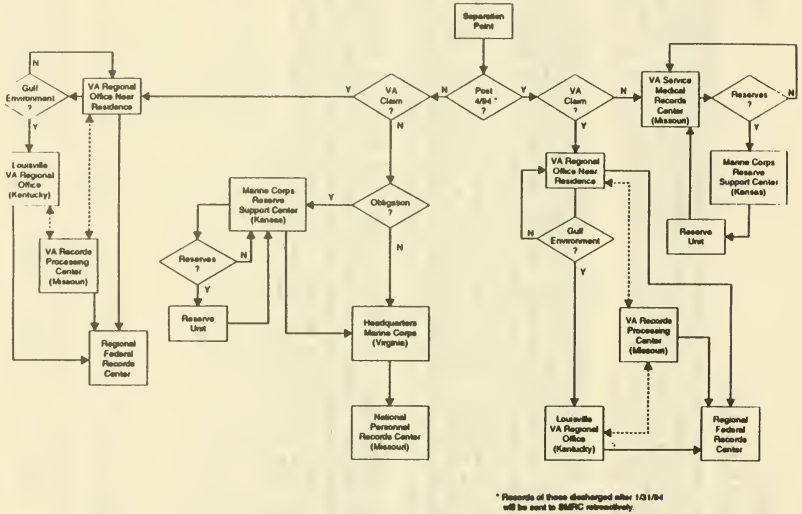
2. SMRC sends the record to the Reserve or Guard unit if the servicemember is joining the Reserves. The Reserve unit will return the records to SMRC after the servicemember leaves the unit; the Guard unit will send it to the State Adjutant General, who will then send it to SMRC.

3. The separation point sends the record to the VA regional office nearest the servicemember's residence if the servicemember indicates he/she is filing a claim with VA. If the claim involves Persian Gulf environment issues, the record is sent to the Louisville VA Regional Office.

4 The cognizant VA regional office will send the record to the appropriate FRC when the veteran dies and VA no longer needs the record. [Note: If the record becomes inactive, the regional office will send the record to the VA RPC, St. Louis, Missouri. RPC will return the record to the regional office if a claim is filed or retire it to the FRC when the veteran dies and VA no longer needs the records.]

ATTACHMENT I

Figure I.4: Service Medical Records Control Procedures After Discharge, Marine Corps Records



ATTACHMENT I ATTACHMENT I

SERVICE MEDICAL RECORDS CONTROL PROCEDURES
AFTER DISCHARGE, MARINE CORPS RECORDS

The separation point assembles records from the medical treatment facility.

Before April 30, 1994

1. a. The separation point will send the record to the VA regional office nearest the servicemember's residence if the servicemember indicates he/she is filing a claim with VA.

   b. Since December 1992, Louisville VA Regional Office has been responsible for adjudicating all claims involving Persian Gulf environment issues. Other regions were to forward all such claims filed before that date, and associated medical records, to the Louisville office.

   c. The cognizant VA regional office will send the record to the appropriate FRC when the veteran dies and VA no longer needs the record. [Note: If the record becomes inactive, the regional office will send the record to the VA RPC, St. Louis, Missouri. RPC will return the record to the regional office if a claim is filed or retire it to the FRC when the veteran dies.]

2. The separation point sends the record to Headquarters, Marine Corps (HQMC), Quantico, Virginia, if the servicemember has no remaining service obligation.

3. The separation point sends the records to the Marine Corps Reserve Support Center (MCRSC), Overland Park, Kansas, if the servicemember has any remaining service obligation.

4. MCRSC retains the records of those members of the Individual Ready Reserve, and of retirees and others who still have a service obligation remaining. When the obligation ends or the veteran dies, MCRSC will send the record to HQMC.

5. MCRSC will send records to the Reserve unit if the servicemember is joining the Reserves. When the servicemember leaves the Reserve unit, the unit will return the records to MCRSC.

6. HQMC sends the record to NPRC.

". . .Because of delays in forwarding records from one point to another, the records may not be where they are supposed to be. It is also possible that the records might never have

left the separation center or treating facility or that the records might be in the veteran's possession." (Veterans Benefits Administration Manual M-21-1, Part III, p. 4-I-5)

After April 30, 1994[1]

1. The separation point sends the record to the VA SMRC, St. Louis, Missouri, if the servicemember does not indicate he/she is filing a claim with VA. [Note: VA has made no decision concerning how long SMRC will maintain records. The military services have not decided whether records will be retired to NPRC or to them.]

2. SMRC sends the record to MCRSC if the servicemember is joining the Reserves. MCRSC sends the record to the Reserve unit, which will return it to SMRC when the servicemember leaves the unit.

3. The separation point sends the record to the VA regional office nearest the servicemember's residence, if the servicemember indicates he/she is filing a claim with VA. If the claim involves Persian Gulf environment issues, the regional office sends the record to the Louisville VA Regional Office.

4. The cognizant VA regional office will send the record to the appropriate FRC when the veteran dies and VA no longer needs the record. [Note: If the record becomes inactive, the regional office will send the record to the VA RPC, St. Louis, Missouri. RPC will return the record to the regional office if a claim is filed or retire it to the FRC when the veteran dies and VA no longer needs the records.]

[1]The Marine Corps began implementing the new system on April 30, 1994. But to be consistent with the Navy, records of those separating after January 31, 1994, will be sent to SMRC, retroactively.

ATTACHMENT II

LOCATIONS WHERE SERVICE MEDICAL RECORDS MIGHT BE FOUND

Figure II.1: Locations Where Service Medical Records Might Be Found



ATTACHMENT II

ATTACHMENT II

NUMBERED LOCATIONS ON MAP

Army

1. U.S. Total Army Personnel Command
   Alexandria, VA

2. U.S. Army Enlisted Records and Evaluation Center
   Ft. Benjamin Harrison, IN

3. U.S. Army Reserve Personnel Center
   St. Louis, MO

Navy

4. Naval Reserve Personnel Center
   New Orleans, LA

Air Force

5. Air Force Military Personnel Center
   Randolph AFB, TX

6. Headquarters Air Reserve Personnel Center
   Denver, CO

Marine Corps

7. Marine Corps Reserve Support Center
   Overland Park, KS

8. Headquarters Marine Corps
   Quantico, VA

Department of Veterans Affairs

9. Department of Veterans Affairs
   Service Medical Records Center
   St. Louis, MO

10. Department of Veterans Affairs
    Regional Office
    Louisville, KY

ATTACHMENT II

ATTACHMENT II

11. Department of Veterans Affairs
Records Processing Center

12. National Personnel Records Center
St. Louis, MO

Regional Federal Records Centers

Unnumbered Locations on Map

o Department of Veterans Affairs Regional Offices

x State Adjutants General Offices

Other Locations Records Might Be Found

Reserve/Guard Units (over 10,000)

Medical Treatment Facilities (over 600)

Employers (for example, first employer after discharge or most recent employer)

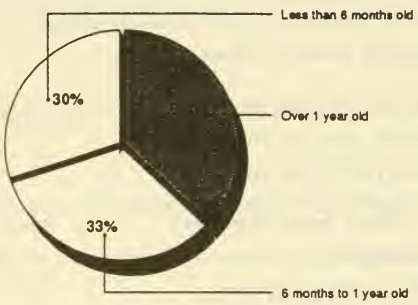
In veteran's possession

DOD offices, for research purposes

ATTACHMENT III ATTACHMENT III

DATA ON PERSIAN GULF VETERAN COMPENSATION CLAIMS

Figure 1: Estimated Number and Age of Persian Gulf Veteran Compensation Claims at the Louisville VA Regional Office




VA reports that there are about 1,100 Persian Gulf veteran compensation claims pending at the Louisville VA Regional Office.

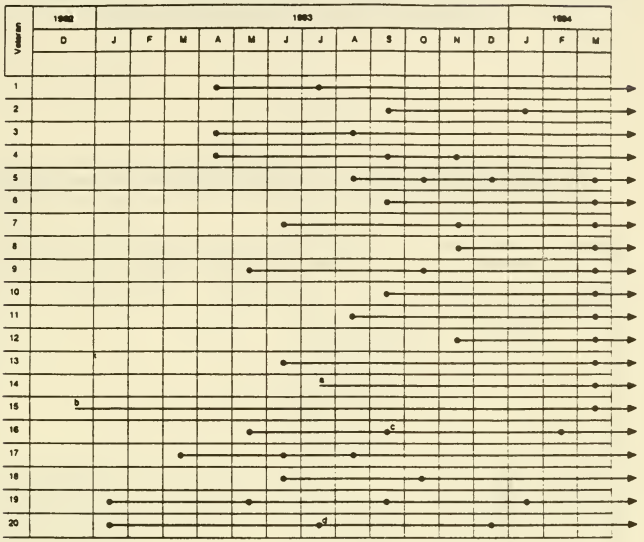
VA reports that many Persian Gulf veteran claims are already over 6 months old when they are transferred to the Louisville VA Regional Office.

ATTACHMENT IV

ATTACHMENT IV

## TWENTY EXAMPLES OF VA'S INABILITY TO OBTAIN SERVICE MEDICAL RECORDS

Figure IV.1: Examples of VA's Inability To Obtain Service Medical Records




Legend

- ● Number of requests made
- → Still awaiting records
- a Transferred to control group within ARPERCEN
- b National Personnel Records Center indicates service medical records charged out to ARPERCEN since December 1992
- c Records not at ARPERCEN as of September 1993
- d Received notice that partial records only were available. Resubmit in 120 days

Note: Examples provided by VA. These requests were by the Louisville VA Regional Office to the Army Reserve Personnel Center (ARPERCEN).

(101452)

# APPENDIX 6.—INFORMATION ABOUT DOD STUDIES OF PYRIDOSTIGMINE BROMIDE

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Studies, Memoranda, and Notes Cited in FDA Documents Regarding the Efficacy and Safety Studies for Pyridostigmine Bromide (PB) (documents were requested by the Staff, Senate Committee on Veterans' Affairs)

| Investigation | Human Subjects M/F | No. | Results | Comments |
|---|---|---|---|---|
| McNall, 1969 | | 133 | Infrequent side effects in patients receiving PB to reverse neuromuscular blockade following surgical procedures | average dose = 7 mg PB |
| Moylan-Jones, Technical Paper No 258, March 1979, unclassified | 39 men | 39 | Study determined kinetics of PB following administration | average weight of men = 156 pounds |
| CDE Technical Paper 258, March 1979 | | | Caution: increased absorption of PB may occur if serviceman were to use his atropine autojet by mistake | |
| Fundamental and Applied Toxicology, 1981;1:214-216 (Gall) | all men | | No change in performance while taking PB; some experienced minor GI upset | 90 mg PB/day in divided doses |
| TR-84-004, Air Force Aerospace Medical Research Lab, 1984 (Williams) | 24 men | 24 | No adverse effects | 90 mg PB/day in divided doses x 5 d |

| | | | | |
|---|---|---|---|---|
| TR-84-052, Air Force Aerospace Medical Research Lab, 1984 (Graham) | all men | | PB reduced probability-monitoring in a vigilance task and degraded performance in a dual task that required time-sharing between visual tracking and short-term memory | 90 mg PB/day in divided doses for 5 days, and repeated after 7 d of rest |
| DAMD17-85-C-5133, Task Order 2 (Kornhauser) | 24 men | 24 | 1 - increased creatine kinase; 2 - increased liver enzymes; 1 - increased LDH; 3 decreased hemoglobin conc; 2 - eosinophilia; changes in electrocardio-gram noted | Women were excluded from the study |
| IND Information Amendment, Krutz et al., serial 001, Dec 1987 | 12 men | 12 | No adverse reactions with PB treatment | 30 mg PB x 4 doses; study tested PB with mild hypoxia and rapid decompression |
| Annual Report, IND 23,509, (Leslie and Altstatt) March 20, 1987 (study completed) | 32 men | 32 | No adverse affects | 0.4 - 0.9 mg/kg PB given once |
| IND Information Amendment, Schiflett et al., serial 001, Dec 1987 | 12 men | 12 | Tapping performance and short-term memory were affected by PB and altitude interaction | 30 mg PB x 4 doses; study tested effect of PB and altitude on performance |

| | | | | |
|---|---|---|---|---|
| Proceedings of the Sixth Medical Chemical Defense Biosciences Review, 1987; 605-607 | | | PB did not appear to alter overall performance or interact with moderate decreases in barometric pressure | 30 mg PB every 8 h x 4 doses (120 mg total) |
| Proceedings of the Sixth Medical Chemical Defense Biosciences Review, 1987; 609-611 | | | PB provided safe operational pretreatment for tactical transport crews | 30 mg PB was ingested 90 min prior to takeoff |
| IND Annual Report, 1987-1988, IND 23,509 | | 32 | 1 of 32 male subjects studied in one experiment lost consciousness following visual change and headache for 5 minutes | adverse reaction occurred 18 h after PB infusion had been discontinued; subjects were ages 18 to 35 and in good health |
| IND Amendment, 28 March 1988, IND 28,480 | | 28 | 1 respiratory arrest with subsequent recovery following artificial respiration | adverse reaction occurred 91 minutes after ingesting the third in a series of 30-mg PB tablets |
| Proceedings Medical Defense Bioscience Review, USAMRDC, 1989, 841-844 (Wenger) | | 5 | No adverse effects; PB increased sweating in all 4 environments | 5 soldiers in 4 pairs of heat stress tests; subjects were tested 100 min after ingesting 30 mg PB |

| | | | | |
|---|---|---|---|---|
| IND Annual Report, May 1987-June 1989, IND 23,509 (Kornhauser) | 12 men | 12 | PB was well tolerated in 10 subjects; 2 subjects dropped out of study | 6-9 mg PB over 8 h; 6 subjects were caucasian and 6 were non-caucasian |
| Kolka, MECD-1-89 | | | | Proposal states that prior to this study a total of 19 subjects have been 30 mg PB with no untoward events |
| Stephenson and Kolka, 1990, Am J Physiol | | 5 | Skin blood flow decreased 37% after PB treatment | 1 - 30 mg PB tablet was ingested 150 min before cycle ergometer exercise at peak oxygen consumption |
| Avia Science Environ Med 1990; 61:220-224 (Kolka and Stephenson) | 4 men | 4 | No adverse effects | studied temperature regulation during exercise; exercise stated 30 min after ingesting 30 mg PB; second experiment was done on a separate day with no PB |

| | | | | |
|---|---|---|---|---|
| USAMRICD Technical Memorandum 90-4 | | | Memo notes that PB decreases performance at high altitude, including performance requiring short-term memory; hyperthyroid patients could undergo atrial fibrillation if administered PB | Reflux esophagitis, peptic ulcers, and asthma may be exacerbated by PB; PB + quinidine may make A-V block more attainable; incidence of people with pseudo-cholinesterase is 4% for heterozygotes and 0.03% for homozygotes |
| J Neurosci Nurs 1990, 22(6):358-364 (Hood) | | 218 | 218 patients with myasthenia gravis responded to mail-survey; 104/194 of those being treated with PB reported side-effects | |
| Annual Report, IND 23,509, 1990-1991 (Prusaczyk) | 16 men | 16 | 4 subjects dropped; 1 test subject taking PB and exposed to cold water was removed from testing due to moderate to severe abdominal and hip flexor cramps | single dose of 30 mg PB; subjects were ages 18-35 |

| | | | | |
|---|---|---|---|---|
| Annual Report, IND 23,509, 1990-1991 (Wenger) | 7 men | 7 | No adverse reactions | 30 mg PB every 8 h for 4-7 d' studied effect of PB on physiological responses to heat and moderate-to-intense exercise |
| Annual Report, IND 23,509, 1990-1991 (Thornton) | 12 men | 12 | One control and one PB-treated subject withdrew from experiment | 1 - 30 mg PB tablet 1 h before flight |
| Annual Report, IND 23,509, 1990-1991 (Wiley) | 4 men | 4 | PB caused decreased absolute light sensitivity | studied the effect of PB on vision |
| Annual Report, IND 23,509, 1990-1991 (Kolka) | 6 men | 6 | No adverse reactions | men were ages 18-35 years, studied the effect of PB on heavy exercise in hot environments |
| Annual Report, IND 23,509, 1990-1991, (Wenger) | 5 men | 5 | No adverse reactions | men were ages 18-43 years, studied the effect of PB on physiological responses to heat, exercise, and hypohydration; single dose of 30 mg PB given |

| | | | | |
|---|---|---|---|---|
| Annual Report, IND 23,509, 1990-1991, (Kolka) | 7 men | 7 | PB decreased resting skin blood flow and heart rate; no adverse reactions | studied the effects of PB pretreatment in different environments; PB given on 3 separate days; report states that PB can enter CNS when high levels of AChE are inhibited |
| Avia Space Environ Med 1990, May 61(5):430-432 (Izraeli et al.) | | 10 pilots | PB did not influence pilot performance during short missions | tested 2 h after 4th dose of PB |
| Hum Factors 1990 Feb, 32(1):79-94 (Gawron et al.) | | 21 pilots | No difference in performance between controls and PB-treated subjects | |
| JAMA 1990, 263(8):1121-1122 (Rothenberg et al.) | | | report on a woman with myasthenia gravis that develops a psychosis thought to be due to bromide toxicity from PB | |
| Memorandum Thru Director, Military Ergonomics Division, 9 August 1990, For Commander, USARIEM | | | Symptoms associated with administration of PB up to 72 h prevented a number of test subjects from exercising in the second or third day of PB administration | effects of PB were studied in subjects undergoing heavy exercise in hot environments<br><br>HURC #377 |

| | | | | |
|---|---|---|---|---|
| Avia Space Environ Med, April 1990, pp 310-313 | 8 men | 8 | PB does not increase physiological strain from CW garments worn during exercise in hot conditions | 30 mg x 4 tablets |
| Isr J Med Sci 1991; 27:659-663 | 6 men | 9 | 1 cardiac arrest; other signs: vomiting, abdominal pain, diarrhea, blurred vision, muscle tremors, nausea, increased heart rate, weakness, salivation, involuntary urination, drowsiness | 9 patients were hospitalized with diagnosis of PB overdose during the Gulf War (acute intentional exposure)<br><br>doses ingested were 390 - 900 mg |
| Isr J Med Sci 1991; 27:656-658 | | 213 | 37% said they had at least one severe symptom related to PB; 75% of respondents had at least one moderate symptom | 30 mg x 3 tablets; soldiers were asked to fill out survey 24 h after starting PB |
| JAMA 1991; 266(5):693-695 | | | 50% of 41,650 Persian Gulf War soldiers had side effects from PB; 6.5% were women | 30 medical personnel were surveyed to provide information on behalf of 41,650 military personnel they served |

| | | | | |
|---|---|---|---|---|
| J Clin Endo Metab 1991; 73(1):75-78 | 8 men 8 wom | 16 | Only 5 females could finish experiment because of side effects at highest dose, women and men responded differently to PB-induced changes in Growth Hormone | 30 - 120 mg PB given orally |
| J Appl Physiol 1991; 71(2):432-437 | 6 men | 6 | 3/6 experiments were terminated because of abdominal discomfort in PB-treated men (no similar discomfort in controls) | 1 - 30 mg PB tablet given to men immersed in cold water |
| Technical Report 11, Nov 1991, (Kornhauser) | 8 men | 8 | 3/8 developed GI symptoms; 1 - decreased diastolic BP; 2 - became sleepy; 1 - nausea; 1 - diarrhea | compared single oral dose of PB to osmotic-delivery system |
| Annual Report, IND 23,509, March 1991-Feb 1992, (Thornton) | 2 men | 2 | Increased sweating after PB; one also had increased rectal and skin temperature | |
| Annual Report, IND 23,509, March 1991-Feb 1992, (Roberts) | 7 men | 7 | 2 men dropped out due to soft tissue injuries; no adverse reactions | studied the effect of PB administration on thermo-regulation during exercise in cold air |

| | | | | |
|---|---|---|---|---|
| Annual Report, IND 23,509, March 1991-Feb 1992, (Kolka) | 6 men | 6 | No adverse reactions | 30 mg PB every 8 h for 72 h |
| Mil Med 1992; 157(5):250-254 (Cook et al.) | 7 men | 7 | Soldiers could not differentiate treatment from placebo; PB resulted in lower resting BP, smaller pupil diameter, decreased handgrip, and higher rectal temperature | 30 mg PB every 8 h x 7 d; studied the side-effects of PB in treated soldiers in desert environment |
| Avia Space Environ Med 1992; 63(1):37-45 Wenger et al.) [repeat of annual report, see above] | 5 men | 5 | PB had little effect on physiological responses to moderate exercise-heat stress | 1 - 30 mg PB tablet |
| Mil Med, 1992, 157(4):210-214, (Arad et al.) | 8 men | 8 | PB did not affect performance | men complained about discomfort of wearing protective clothing |
| Survey 1, IND 23,509, Operation Desert Shield/Storm, May 27, 1992 | | | 26-27 military personnel were ordered to discontinue PB by medical order; 16 medical personnel indicated no information sheets were given to those who were taking the drug; some thought the dose was too high for women | 23 selected medical personnel who cared for 8,366 military personnel during ODS/DS |

| | | | | |
|---|---|---|---|---|
| Survey 2, IND 23,509, Operation Desert Shield/Storm, May 27, 1992 | 138 men<br><br>8 wom<br><br>3 ??? | 149 | 38% of 133 who took PB experienced side-effects | |
| Survey 3, IND 23,509, Operation Desert Shield/Storm, May 27, 1992 | | 108 | 22% experienced side effects, the majority of which were headaches and diarrhea | some aviators said they did not, or would rather not, fly while taking PB |
| DAMD17-85-C-5133, February 16, 1993 (Kornhauser) | 16 men | 16 | 3 - increased liver enzymes; 11 - had minor adverse side effects possibly or probably related to PB; 2/3 subjects asked to return for follow-up did not | 6 mg PB in saline was given IV over 6 h; followed by 1 or 2 PB tablets. Two days later the subjects began multiple dosing with same tablet (30 mg standard or 90 mg sustained release) |

Selected Animal Studies on Pyridostigmine Bromide Side-Effects

| Investigation | Results |
|---|---|
| Teratological study, IND 270,710, 1984 | Phase II study revealed no higher incidence of birth defects in rats |
| Annual Report, Feb 2 1984 - April 30 1987, IND 23,509 | 3 rats were found dead and 3 others died of dose-related injuries of PB |
| Fund Appl Toxicol 1985; 5:260-269 | PB was associated with neuromuscular toxicity in the diaphragm extensor digitorum longus soleus muscles of rats |
| Neurotoxicology 1986;7:167-186 | Ultrastructural cellular changes were found at the junction between nerve terminals and muscle fibers (end plates) under electron microscopy at doses low enough to cause only about 10% reduction in AChE |
| Study Report 8740-86-8, COntract No DAMD17-84-C-4088, Battelle, 1986 (Page) | 4 rats receiving 1.25 mg/kg PB single oral dose died during a swim exercise test |
| Final Study Report, G8740-87-1, January 6, 1987 | Study was designed to evaluate PB toxicity in dogs. No tissues were saved at necropsy. |
| Fund Appl Toxicol 1989; 13(1):110-117 | Subchronic feeding of PB to rats induced electron microscopic changes in muscle morphology |
| Toxicol Pathol 1990:18(3):387-395 | Within one day of PB treatment, inflammatory cells invaded 3% of extraocular myofibers in rats |
| | |

# APPENDIX 7.—INFORMATION ON BOTULISM VACCINE

---

**MEMORANDUM**

Date: September 1, 1990

To: IND 161

From: Ann Sutton, Vaccines and Allergenics, DBIND

Subject: Brief review of product status persuant to its current proposed use by the U.S. military.

The sponsor of this file is the Center for Disease Control, which dispenses the vaccine on request for immunization of persons at risk for exposure to botulinum toxin, e.g., public health laboratory workers, researchers working with C. botulinum or its toxins, etc. The vaccine is made under contract for the U.S. Army which provides a portion of each lot to the CDC. An accounting of the number of doses administered by the military and reports of adverse reactions are sent to CDC for incorporation in their annual progress reports to this file.

The vaccine was originally manufactured by Parke Davis according to U.S. Army contract specifications for manufacture and lot release testing. At one point (about 1975), the Army considered discontinuing distribution of the product, due to high reaction rates. They agreed to continue providing it to CDC for administration to persons who were clearly at high risk of exposure (and death). At this time, the Army was seeking another source of vaccine with less reactogenicity.

OS. Source of vaccine given as Parke-Davis, according to specifications of US Army Biologicals.

Suppl. 5. CDC looking for alternate supplier, due to high rate of reactions. Investigators' Brochure.

Suppls. 11-17 refer to lot 1-B1.

Suppl. 23. Note "..continue...distribution of current lot of toxoid produced by Parke-Davis in 1958."

Suppls. 24-27. Progress reports refer to lot 1B1-F3.

Suppl. 26. Memo discussing the meaning of the guinea pig potency test. Indicates that Michigan Dept. Public Health vaccine replaced the Parke-Davis lot in 1971.

Suppl. 29: First submission of MDPH toxoid made "according to the method of Parke-Davis," with release documents for lots A2, B1, and B2. The 5 strains used are listed and described as having been obtained from Fort Detrick and as being the same strains used by Parke-Davis. Each monovalent toxoid is described. The three lots were made from the same bulk toxoids;

lot A2 differs in having less formaldehyde (0.022%). Detoxification verified by animal testing for each of the 5 toxoids.

The following potency tests were (apparently) performed by CDC:

a. Potency test in 10 immunized guinea pigs per toxin challenged with $10^3$ mouse $LD_{50}$ of toxin. Those challenged with toxins A, B, or C survived at 100%; 90% survived challenge with toxin D; 40% survived challenge with toxin E. The specification for potency is at least 50% survival. All control animals (2/toxin) died from challenge.

c. Neutralizing antitoxin was titrated in the serum [of same animals]. The specifications and titrated antibody levels are given:

| Type: | Spec: | Antitoxin u/ml: | Status: |
|---|---|---|---|
| A | 0.03 | >.160 | Pass |
| B | 0.01 | 0.0108 | Pass |
| C | 0.4 | 0.18 | Failed |
| D | 0.12 | 1.14 | Pass |
| E | 0.035 | 0.019 | Failed |

Suppl. 45. First use of lot A2 (currently used lot) in November, 1981. Therefore, the data contained in CDC's "Immunobiologic Agents and Drugs Available from the Centers for Disease Control" published March 1982 do not reflect experience with this lot.

Antibody titers in n=13 humans after immunization with lot A2 are given as 0.46 IU anti-A, 0.10 IU anti-B, and 0.03 IU anti-E. (There were no standard antitoxins for the other two types) These data appear to be better than the guinea pig data, but may be expressed in different units.

Suppl. 48. Publication noted above submitted. Local reactions to primary immunization listed as "moderate" in 4.5%, "severe" in 0.2%. Systemic reactions in 2.9%, mostly malaise and generalized pains. Antibody conversion after the primary series is given for 2 subjects. It appears that 3 injections are need for detectable antibody titers.

Suppl. 55. General Safety test results for lot A2: pass in 4 guinea pigs, 6 mice.

Suppl. 56. Neutralization titers in n = 23 subjects immunized by the Army at 2-3 weeks post 3rd injection:

| Type | number $\geq$0.25 IU/ml: |
|---|---|
| A | 17/23 |
| B | 4/23 |

Suppl. 57. Reactions to lot A2 reported by USAMRIID for calender year 1988: 3 local reactions mild-moderate in 58 primary injections (approx. 5%).

CDC Progress Report for 3/88 to 3/89, reactions (my calculations):

| Injection: | local, mod-severe: | systemic: |
|---|---|---|
| 1 | 10% | 4.6% |
| 2 | 13% | 1.7% |
| 3 | 20% | 0 |

Comments.

The CDC has promptly filed annual reports for many years detailing the disposition of the vaccine and the reactions which have been observed. Investigators are requested to return a reaction report for each subject after their primary series and for subsequent boosters. Severe reactions occaisionally occur, primarily local (pain, swelling, unable to use arm). The incidence of local reactions appears to increase with each injection but systemic reactions appear to decrease.

Immunogenicity data has not been routinely acquired due to lack of standardized antisera for some of the types and to the expense of performing the neutralization test. Titrations are sometimes done to determine the need for an individual to receive a booster injection.

There are no efficacy data in humans. The presummed efficacy of the vaccine is extrapolated from its ability to protect animals from challenge. The protective antibody levels in humans have been proposed based on calculation from the protective levels in guinea pigs.

161.mem
cc:
Dr. Woodcock
Dr. Scribner
Dr. Habig
Dr. Goldenthal

RECORD OF TELEPHONE CONVERSATION

IND: 161 Date: ~~September~~ August 30, 1990

Product: Botulinum Toxoid, Pentavalent, Vaccine.

Initiated by: Ann Sutton, BIND

Firm Name: USAMRIID, Fort Detrick

Person with whom conversation was held: Dr. Walt Brandt, Ms. Anna Johnson-Wineger

Telephone No.: 301-663-7564 (-7567)

Dr. Brandt clarified their plans for obtaining sufficient doses of the vaccine to begin mass immunization approximately October 1. Michigan Dept. Public Health has stocks of the identical bulk toxoids which were formulated into lots A2, B1 and B2. They will formulate and fill for the Army over the next several months.

I told him that we had very little detail about manufacturing in the IND and suspected that there have probably been technical changes over the years. This should be updated. The fact that they are using the same bulks makes life simpler for us. We will need lot release documents with final container test results and whatever info is available on potency and immunogenicity.

I also noted that the informational brochure from CDC is probably out of date with respect to the change to lot A2. The Army probably has the most/best data on experience with this lot.

He suggested that the Army might file a new IND for the new lots, which I think is a good idea. He will contact CDC about this and about updating an "Investigators' Brochure." I also asked about possible changes in immunization schedule from that recommended by CDC; he will check.

Anna Johnson-Winegar will be the contact person for this product and can be reached at 301-663-7567.

161a.tel
cc: Dr. Woodcock
Dr. Scribner
Dr. Habig
Dr. Goldenthal

RECORD OF TELEPHONE CONVERSATION

IND: 161 Date: September 1, 1990

Product: Botulinum Toxoid, Pentavalent, Vaccine.

Initiated by: Dr. Walt Brandt

Telephone No.: 301-663-7564 (-7567)

Firm Name: USAMRIID, Fort Detrick

Person with whom conversation was held: Ann Sutton, BIND

He reviewed the CDC recommended immunization schedule and found that the schedule the Army is using is the same. He has contacted the CDC and offered to write and update for the information guide/ investigators' brochure. I said the most important elements to update would be the reactogenicity profile (CDC has this information) and immunogenicity data (Army has the most, and the most current, data).

161b.tel
cc: Dr. Woodcock
Dr. Scribner
Dr. Habig
Dr. Goldenthal

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Acting Director, IND Branch

DATE: September 12, 1979

THROUGH: Dr. John B. Robbins, Director, DBP

FROM : Director, Bacterial Toxins Branch

SUBJECT: Botulinum Toxoid, IND 161/33, CDC

IND Supplement 161/33 has been submitted for review to this Branch. Although the IND was submitted several years ago, it does not appear that this staff has previously written comments.

The U.S. Army Medical Research Institute of Infectious Diseases wishes to compare the response of volunteers to two new lots of Botulinum Toxoid Adsorbed with a lot previously used. This may be in anticipation of using this product in the immunization of donors for a botulinum plasma program also being done under IND.

The following comments are for your consideration.

1. In 1971 lots of Pentavalent Botulinum Toxoid were produced by Michigan and then packaged as lots MDPH A-2 and MDPH B-1 in 1978. According to the submission received June 23, 1979 it is stated that the product is identical to that made by the first manufacturer, Parke-Davis. However, this reviewer would suggest there may be some differences.

a. The report from Michigan in supplement 161/31 does not describe the media used for each of the different strains. It is not present for Parke-Davis material either. Only a reference which is a technical report is cited. Different manufacturers filled the product also.

b. In supplement 161/31 it is stated that the adjuvant is aluminum phosphate. At no time is reference made to aluminum phosphate gel as described for the Parke-Davis material which apparently contained some aluminum hydroxide as well. The actual aluminum content per ml of product was not cited.

c. From the data provided (Study 81) it would appear that the MDPH lots contain twice the Lf/ml content of Type B than does the Parke-Davis lot.

d. One of these lots has had adjustment with succinate buffered saline to lower the formaldehyde content. This also resulted in a decrease in the nitrogen content.

e. The specifications for the products were apparently not met *in toto* by these two products.

f. In 1974 it was stated that the Type E was unsatisfactory..

2. It is suggested that a summary chart of the properties of all three lots to be given to man be provided to show composition. In addition, it is suggested that the potency of all three lots be compared in a comparable experiment. There appears to be variation in the antitoxin response. Otherwise the human data may be difficult to relate to potency tests in animals.

3. What tests have been done to show that reversion to toxicity with storage does not occur? Last detoxification tests appear to have been performed in 1969-1970.

4. The consent form does not include all elements of informed consent. The form should include name, not just initial.

5. It is noted that this study has been initiated.

Carolyn Hardegree, M.D.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
ATLANTA, GEORGIA 30333
TELEPHONE: (404) 633-3311

February 19, 1974

TO: Pentavalent (ABCDE) Botulinal Toxoid Investigators (IND-BB-161)

SUBJECT: Proposed Termination of the Distribution of Pentavalent (ABCDE) Botulinal Toxoid on April 1, 1974

Several years ago the Michigan Department of Health, under contract with the Center for Disease Control, prepared a new pentavalent (ABCDE) botulinal toxoid to replace the toxoid produced by the Parke-Davis Company in 1958 for Fort Detrick, which we currently distribute. When the new Michigan product was tested for immunogenicity in guinea pigs it was found that there was satisfactory protection against botulinal toxins A,B,C, and D, but not type E toxin. Essentially the same results were obtained with a pilot lot of trivalent (ABE) toxoid, i.e., the type E component was unsatisfactory in combination with the other toxoids. However, a monovalent type E toxoid gave satisfactory protection of guinea pigs. Therefore, it was concluded that it would be necessary to immunize with two toxoids - monovalent type E and polyvalent (ABCD) - instead of a single pentavalent toxoid.

A meeting of six representatives from the Bureau of Epidemiology and the Bureau of Laboratories, Center for Disease Control, was held in November 1973 to decide on the proper action to take in respect to the botulinal toxoids. It was agreed by this group and endorsed by the Office of the Director, CDC, that CDC should terminate the distribution of botulinal toxoid for immunization of laboratory workers for the following reasons:

1. A significant number of individuals immunized with the Parke-Davis product currently distributed by CDC have demonstrated apparent hypersensitivity or untoward reactivity to the toxoid. A review of the data on local reactions during the period 1966-1971 revealed that 4.5% of a total of 3,062 injections in the initial series resulted in moderate local reactions and 0.5% caused severe reactions. The number of reactions following booster injections of the toxoid was even higher - 10.7% resulted in moderate reactions and 3.7% severe reactions.

2. We have no data on humans with the new lot of botulinal toxoid (ABCD with unsatisfactory type E) produced by the Michigan Department of Health, and we have no idea of the degree of untoward reactivity or potential to induce hypersensitivity of the new products. We have no scientific or medical basis to establish an appropriate immunization schedule with the new products without clinical data. The three toxoids (the old Parke Davis Company ABCDE, new Michigan types ABCD, and the Michigan type E) will be stockpiled at CDC for possible emergency use.

3. We feel that the unknown risks of hypersensitivity or reactivity to the products are too great to justify the immunization of laboratory personnel.

4. Therapeutic equine trivalent (ABE) botulinal antitoxin is available within 4 to 6 hours of request at about 25 locations in the U. S. We know of no individuals working with foods or botulinal toxins in the laboratory who have developed botulism. This would be an excellent time to review the safety of your operations to minimize possible exposure.

Inasmuch as the termination of the distribution of botulinal toxoid by CDC is scheduled for April 1, 1974, I would appreciate receiving your comments by March 15.

Robert J. Ellis

Robert J. Ellis, Ph.D.
Chief, Immunobiologics Activity

**TABLE 7**

Systemic Reactions to Botulinum Pentavalent (ABCDE) Toxoid 1970-1992
Number of Reactions (% of 12,499)

| Year Ending in March | General Malaise | Chills, Fever | Headache | Swelling Lumps Soreness, Stiff Back, Stiff Neck | Blurred Vision, Dizziness | Nausea Diarrhea Vomiting GI | Itching Hives | Total No. of Systemic Reactions |
|---|---|---|---|---|---|---|---|---|
| 1970 | 2 | 7 | 2 | 1 | 3 | 5 | - | 20 |
| 1971 | 3 | 1 | 1 | 2 | 1 | 1 | - | 9 |
| 1972 | 6 | 4 | 6 | 2 | - | 2 | - | 20 |
| 1973 | 4 | 5 | 2 | 1 | 4 | 4 | - | 20 |
| 1974 | 5 | 9 | 1 | 3 | 3 | 3 | - | 24 |
| 1975 | 2 | 1 | 2 | 1 | 3 | 4 | - | 13 |
| 1976 | - | 1 | - | 2 | 1 | 1 | - | 5 |
| 1977 | - | 1 | - | - | - | 2 | - | 3 |
| 1978 | 3 | - | 1 | 2 | 1 | - | 1 | 8 |
| 1979 | 1 | 1 | 1 | - | 5 | 1 | 1 | 10 |
| 1980 | 1 | - | 1 | 10 | - | - | 4 | 16 |
| 1981 | 2 | 3 | 4 | 6 | 3 | 4 | 1 | 23 |
| 1982 | - | - | - | 2 | - | 1 | - | 3 |
| 1983 | - | - | - | 2 | 1 | - | - | 3 |
| 1984 | - | - | - | - | - | 1 | - | 1 |
| 1985 | 2 | - | 1 | 12 | - | 1 | 3 | 19 |
| 1986 | 3 | 3 | 2 | 5 | 3 | 1 | - | 17 |
| 1987 | 5 | 4 | 4 | 15 | 1 | - | 7 | 36 |
| 1988 | 3 | 7 | 2 | 31 | - | - | 6 | 49 |
| 1989 | 1 | - | 1 | 32 | - | - | 4 | 38 |
| 1990 | 6 | 2 | 2 | 22 | - | 3 | 2 | 37 |
| 1991 | 2 | 4 | 6 | 29 | 1 | 3 | 12 | 57 |
| 1992 | 1 | 3 | 2 | 18 | 1 | - | 8 | 33[a] |
| TOTAL | 52(0.4) | 56(0.5) | 41(0.3) | 198(1.6) | 31(0.2) | 37(0.3) | 49(0.4) | 464(3.7) |

[a] From Table 5

red copy — MEMO SECTION — IND 161

## CONVERSATION RECORD

| | | | |
|---|---|---|---|
| DATE: 9MAR89 | TIME: 430 AM (PM) | CHECK ONE: ☒ INCOMING ☐ OUTGOING ☐ MEETING | CIRCULATION: cc/Dr. Hardegree |
| CENTER FOR DRUGS AND BIOLOGICS REPRESENTATIVE: WILLIAM HABIG | | | cc K. Goldenthal DBIND (file in IND 161) |
| ORGANIZATION REPRESENTATIVE: PAUL BLAKE | TELEPHONE NO. | | |
| ORGANIZATION: CDC | | | |

SUBJECT: Adverse reactions to Botulinum Toxoid.

| TEXT | ACTION REQUIRED |
|---|---|
| Dr. Blake called to discuss adverse reactions to Botulinum Toxoid. A physician reported local reactions in 6 of 6 recipients. The worst reaction occured in a woman who was receiving second dose; she had 75 mm induration/erythema. Others had "knots" at injection site and local reactions. The MD was giving injections subcutaneously - Dr. Blake thought perhaps they were not deep subcutaneous injections as recommended.<br>This is same lot as has been used for ~10 years and no other increased frequency of reactions has been reported. We discussed improper injection technique and vial contamination as possible factors. A new vial is being sent to physician who may administer reduced dose for next injection for the reactive woman. If still reaction is seen, her serum will be titrated. I stated that I agreed that it might not be warranted to take much action based on this single report at this time. He will include these reactions in his annual report for IND 161, unless he hears otherwise. He will keep us informed also. | |

FORM FDA 2674 (10/84) PREVIOUS EDITIONS ARE OBSOLETE W. Habig

U.S. GOVERNMENT PRINTING OFFICE: 1985 458-070/20073

ATTACHMENT B

Telephone :
NORWICH 810250
and
NORWICH 811323

DR. A. M. PRESS

THE SURGERY,
GREAT MELTON ROAD,
HETHERSETT,
NORFOLK,
NR9 3AB.
UK

AMP/SC

14th May 1992

Dept of Health & Human Services
Centers for Disease Control
Division of Host Factors
Atlanta
Georgia 30333

Dear Doctor

MWP

I understand this gentleman has had immunisation against Botulinum, the last being in September, 1991. I thought it prudent to report the following medical problem in case it could be at all attributable to the vaccine, although the time interval from the last innoculation to the onset of symptoms is somewhat prolonged.

Mr Peck has had pain in his right arm for about a month and has developed a palsy of the right long thoracic nerve. I believe this to be a form of neuralgic amyotrophy. This condition usually follows an acute non-specific infection or may complicate any febrile illness. Indeed he suffered a febrile episode a few days before the onset of the symptoms. It therefore seems most likely that it is not related to the Botulinum at all, but I would appreciate any comments that you have and whether there is any contra-indication to further vaccination. This latter point is important because it relates directly to his work.

He is recovering from the episode, his pain is going and I would anticipate that the paralysis would recover.

Thank you for your help.

Yours sincerely

A M PRESS

cc. Mr M Peck
Dr P Knights, Medical Adviser AFRC Institute of Food Research, Norwich

**MEMORANDUM**

Date: November 14, 1990

To: IND 3723

From: Ann Sutton

Subject: Original Submission. Protocol for the use of Pentavalent Botulinum Toxoid by the US military under the conditions of Operation Desert Shield.

Product: The sponsor of the cross-referenced file is the Center for Disease Control, which dispenses the vaccine on request for immunization of persons at risk for exposure to botulinum toxin, e.g., public health laboratory workers, researchers working with C. botulinum or its toxins, etc. The vaccine is made under contract for the U.S. Army which provides a portion of each lot to the CDC. An accounting of the number of doses administered by the military and reports of adverse reactions are sent to CDC for incorporation in their annual progress reports to this file.

The vaccine was originally manufactured by Parke Davis according to U.S. Army contract specifications for manufacture and lot release testing. Vaccine produced by Michigan Dept. Public Health according to same specifications replaced the Parke-Davis lot in 1971. At one point (about 1975), the Army considered discontinuing distribution of the product, due to high reaction rates. They agreed to continue providing it to CDC for administration to persons who were clearly at high risk of exposure (and death). At that time, the Army was seeking another source of vaccine with less reactogenicity.

The following potency tests were performed on lot A2:

a. Potency test in 10 immunized guinea pigs per toxin challenged with $10^3$ mouse $LD_{50}$ of toxin. Those challenged with toxins A, B, or C survived at 100%; 90% survived challenge with toxin D; 40% survived challenge with toxin E. The specification for potency is at least 50% survival. All control animals (2/toxin) died from challenge.

c. Neutralizing antitoxin was titrated in the serum [of same animals]. The specifications and titrated antibody levels are given:

| Type: | Spec: | Antitoxin u/ml: | Status: |
|---|---|---|---|
| A | 0.03 | >.160 | Pass |
| B | 0.01 | 0.0108 | Pass |
| C | 0.4 | 0.18 | Failed |
| D | 0.12 | 1.14 | Pass |
| E | 0.035 | 0.019 | Failed |

Previous human use: Antibody titers in n=13 humans after immunization with lot A2 are given as 0.46 IU anti-A, 0.10 IU anti-B, and 0.03 IU anti-E. (There were no standard antitoxins for the other two types) These data appear to be better than the guinea pig data, but may be expressed in different units. It appears that 3 injections are needed for detectable antibody titers.

Neutralization titers in n = 23 subjects immunized by the Army at 2-3 weeks post 3rd injection:

| Type | number $\geq$0.25 IU/ml: |
|---|---|
| A | 17/23 |
| B | 4/23 |

Local reactions to primary immunization listed as "moderate" in 4.5%, "severe" in 0.2%. Systemic reactions in 2.9%, mostly malaise and generalized pains. The incidence of local reactions appears to increase with each injection but systemic reactions appear to decrease.

There are no efficacy data in humans. The presumed efficacy of the vaccine is extrapolated from its ability to protect animals from challenge. The protective antibody levels in humans have been proposed based on calculation from the protective levels in guinea pigs.

Protocol: The administration of the vaccine (dose and schedule) is identical to the recommendations of CDC and to previously used protocols.

Comments: As requested following our initial reveiw of the protocol in draft, a mechanism (postcards) for passive reporting of adverse reactions in a subset of 100 individuals. The collection of such data in subjects who receive lot 2, previously used and monitored in hundreds of subjects, is not critical. I am more concerned with follow-up for safety for subsequent lots of vaccine planned to be filled by Mich. Dept. Public Health. If reaction rates to the first injection are within the expected range, reactions to further injections would also be expected to be similar to past experience. A subset of 100 should reveal any increase in greater than mild local reactions. Systemic reactions are rare following primary immunization and increases may not be detected. Such data will alert us to the possibility of a "hot" lot or other manufacturing concerns, but need not preclude continued use of the vaccine, considering the benefit to risk.

I have no objection of the initiation of the protocol as written.

3723-0.mem

RECORD OF TELEPHONE CONVERSATION

IND: 161 Date: December 4, 1990

Product: Botulinum Toxoid Vaccine

Incoming: Ann Sutton

Firm Name: USAMRIID

Person with whom conversation was held: Maj. Mike Balady

Telephone No.: 301-663-7661

He is trying to get a copy of the manufacturing scheme which Michigan DPH used to manufacture the current lots of vaccine, distributed/investigated by CDC under IND 161. Michigan DPH is unable to supply this; the bulk toxoids were manufactured about 20 years ago. I told him I thought there wasn't much in the way of manufacturing in the IND, but I will see what is available. The vaccine was made by Parke-Davis and Mich. DPH according to specifications of the Army.

They are looking for an additional manufacturer for vaccine, want to use the same manufacturing scheme. I suggested that CBER would regard any such vaccine as a new product, regardless of whether it was made according to the original scheme, simply because of the change in manufacturer. I also suggested that we would look favorably on improved technology in manufacture. Any new vaccine/new lots of old vaccine would have to meet specifications for purity, identity, animal potency; simply making vaccine the same way (even at Michigan) would not speed up the process.

Regarding another issue: Porton is making Botulinum Toxoid F for Army studies. Porton is also making Anthrax Vaccine in a separate facility, but at later stages there are some common areas. Could this be a problem? I told him it could, but would depend on validation of killing of spores. Suggested he call Bill Habig.

USAMRIID is thinking of renovating some facilities for production (of vaccines?); could we arrange for FDA walk-through, advice, etc.? I referred him to Bill Habig, I don't think we would have any problems with this.

161c.tel
cc: Dr. Habig Dr. Goldenthal

RECORD OF TELEPHONE CONVERSATION

IND: 3723 Date: January 2, 1991

Product: Pentavalent Botulinum Toxoid Vaccine

Outgoing: Ann Sutton, DBP

Firm Name: Division Product Quality Control

Person with whom conversation was held: Dr. Fitzgerald, Dr. Hochstein

Telephone No.: 496-4937

Update on several phone calls (Major Balady to Dr. Goldenthal, Major Balady to Dr. Anthony, Dr. Brandt to Dr. Fitzgerald) regarding testing of investigational vaccine to be used in Operation Desert Shield:

A new lot has been formulated at Michigan DPH from existing stocks of monovalent toxoids. A potency test is in progress on the bulk vaccine, also a general safety test on the bulk. Michigan will send sample of bulk (12 ml) to DPQC for general safety test. General safety on bulk sample is routine for toxoid vaccines, e.g., DT; also done on final container by the manufacturer. Dr. Fitzgerald needs to know if an adjustment of dose is used by Mich. DPH for this product. We discussed whether CBER should also do final container sterility test. Dr. Fizgerald felt that in the interests of time, and considering the possibility of false positives, we should review manufacturer's testing for acceptability rather than repeat the testing at CBER.

Dr. Brandt indicated that lots B-1, A-2, and B-2 were on their way to their destination. I will call Brandt/Balady to request approx. 3 vials each to be sent to CBER for general safety test, as discussed with Maj. Balady on Jan. 31 and noted in pending letter from CBER. Dr. Fitzgerald said that enough guinea pigs of the right weight to test all 4 lots may not be available at this time. We decided that priority will be given to the new lot, then to lot B-1, since lot A-2 was retested 3 years ago. B-2 could be considered identical to A-2.

The test results will be given to Dr. Brandt over the phone and memos will be filed to the IND.

3723.tel
cc:
Dr. Fitzgerald/Dr. Hochstein
Dr. Quinnan/Dr. Woodcock
Dr. Anthony
Dr. Goldenthal

IND 3723 December 30, 1990
Pentavalent Botulinum Toxoid
US Army

Memorandum of Telephone Conversation
Between
MAJ Mike Balady
(301) 663-7661
and
Myself

I called MAJ Balady to ask if DOD was aware of any other organization, agency, such as NATO, other duly constituted bodies, or countries that have sanctioned the use of botulinum toxoid. (This information, required by the draft FDA Procedures for Informed Consent Waiver, had not been included in the IND submissions received.) He said no, DOD was not aware of any other organization that had approved its use.

Roger Eastep
Deputy Director, DBIND, HFB-230

cc: Dr. Goldenthal

RECORD OF TELEPHONE CONVERSATION

IND: 3723 Date: January 30, 1991

Product: Botolinum Toxoid Vaccine

Incoming: Ann Sutton

Firm Name: Army

Person with whom conversation was held: Dr. Alexis Shelikoff

Dr. Shelikoff of The Salk Institute, Swiftwater, PA, is a contractor for production of botulinum toxoid bulks at Ft. Detrick. He called for information regarding the immunization of personnel who have applied to work in the new facility to prepare the bulk toxoids. The full 3-dose immunization schedule takes 12 weeks. The have a 65-year old applicant who has already been immunized with the primary series but, pending serology results, may need a booster. They would like to use him but the clinical trial protocol has age limits of 18-65 yrs. Similarly, they have a healthy 71 yr old who has applied.

I suggested that a letter be written which describes the health status of the two individuals and requests a variance from the protocol. I thought that FDA would have no objection.

Note: local IRB approval may also be required; I will call Walt Brandt. They may wish to amend the protocol proper as well.

cc:
Dr. Habig HFB-600
Dr. Goldenthal HFB-230

3723b.tel

# APPENDIX 8.—DEPARTMENT OF DEFENSE DOCUMENTS DESCRIBING RISKS OF PYRIDOSTIGMINE

SGRD-UE-MEP (70) 23 October 1989

MEMORANDUM THRU

C, Physiol Br, Mil Erg Div

Dir, Mil Erg Div

FOR Commander, USARIEM

SUBJECT: Amendment to Protocol HURC #378

1. The protocol HURC #378, entitled "Effects of Pyridostigmine Bromide on Thermoregulatory, Metabolic and Cardiorespiratory Responses to Cold Stress" states on page 9 that persons with a positive history of pulmonary disease will be excluded from participation in the study.

2. Because of the existing incidence of asthma in soldiers in the U.S. Army, the medical monitor believes there is scientific merit in the study of responses of subjects with asthmatic histories to the administration of pyridostigmine.

3. This memorandum is to request an amendment to the exclusionary criteria of the protocol as approved. It is requested that this section be amended to allow testing of subjects with recorded histories of currently inactive pulmonary disorders at the discretion of the Test Subject Medical Officer (TSMO) and the assigned medical monitor for the protocol.

4. Sentence 4 on page 9 of the amended protocol should read: "Any subject presenting a positive history for any of the above will be excluded from participation unless cleared by the appropriate medical authorities" (amendment underlined). This will allow participation of subjects with recorded histories of childhood illnesses which have resolved or have had periods of prolonged inactivity and who are approved for participation by the TSMO and the medical monitor.

WILLIAM K. PRUSACZYK
CPT, MS
Research Physiologist

SGRD-UAS-NS (70-1n) 13 August 1990

MEMORANDUM THRU Chairman, SRC 14 Aug 90

FOR Commander, USAARL

SUBJECT: Approval of Abbreviated Protocols Entitled "The Effect of Pyridostigmine Bromide on Vision" and "Physiological Effects of Wearing the Aircrew Uniform Integrated Battlefield (AUIB) While Flying the UH-60 Simulator in a Controlled Heat Environment After Pyridostigmine Administration"

1. A meeting was held this date to review the above subject protocols. The following Human Use Committee members were in attendance: Dr. Kirby, Dr. Comperatore, CPT Sommerkamp, Mr. Reynolds, and Ms. Smith. This constitutes a quorum of the nine committee members.

2. Changes were recommended to the subject briefing for the protocol "The Effect of Pyridostigmine Bromide on Vision."

a. The risk section should be rearranged so that those risks related to pyridostigmine ingestion are specified first. One member thought that the possibility of death from pyridostigmine overdose should be mentioned. After a short discussion it was determined that this is not a real issue because of the dose levels involved.

b. The members voted unanimously to recommend approval of the protocol, but found it to be greater than minimal risk.

3. Changes were recommended to the protocol "Physiological Effects of Wearing the Aircrew Uniform Integrated Battlefield (AUIB) While Flying the UH-60 Simulator in a Controlled Heat Environment After Pyridostigmine Administration."

a. To be more meaningful to the volunteers, temperatures should be specified in both fahrenheit and centigrade.

b. Typographical errors need to be corrected.

c. It must be made clear that the medical monitor is not one of the principal investigators on the protocol.

d. Side effects of pyridostigmine administration should be specified in the subject briefing as well as the availability of atropine, if needed.

Encl 2

SGRD-UAS-NS (70-1n) 13 August 1990
SUBJECT: Approval of Abbreviated Protocols Entitled "The Effect of Pyridostigmine Bromide on Vision" and "Physiological Effects of Wearing the Aircrew Uniform Integrated Battlefield (AUIB) While Flying the UH-60 Simulator in a Controlled Heat Environment After Pyridostigmine Administration"

e. The members voted unanimously to recommend approval of the protocol with the recommended changes. It was found to be greater than minimal risk.

Albert Kirby

ALBERT W. KIRBY
Chairman, Human Use Committee

APPROVED/~~DISAPPROVED.~~

DAVID H. KARNEY
Colonel, MC, SFS
Commanding

DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

REPLY TO
ATTENTION OF

SGRD-HR (70-1n)

14 AUG 1990

MEMORANDUM FOR Commander, U.S. Army Aeromedical Research Laboratory, ATTN: SGRD-UAC, Fort Rucker, AL 36362-5292

SUBJECT: Protocol Entitled "The Effects of Pyridostigmine Bromide on Vision," submitted by Dr. Roger W. Wiley, USAARL (Log No. A-5378)

1. Subject protocol has been reviewed. Although this protocol would normally be considered by the membership of the Human Subjects Research Review Board (HSRRB), review by the USAARL Human Use Committee will satisfy the requirements of the Food and Drug Administration and the Department of Health and Human Services regulations governing the use of humans in research. The urgency of the situation justifies review by the Acting Chairman, HSRRB.

2. This protocol is approved for implementation.

3. If you have any questions concerning this matter, please contact Ms. Marty Myers at AUTOVON 343-2165 or (301) 663-2165.

HARRY G. DANGERFIELD, M.D.
Colonel, MC
Acting Chairman
Human Subjects Research Review Board

CF: USAMMDA, ATTN: SGRD-UMP
USAMRDC, ATTN: SGRD-PLE

S/

DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

REPLY TO ATTENTION OF

August 15, 1990

Human Use Review and
Regulatory Affairs Office

SUBJECT: IND 23509 - Pyridostigmine Bromide -
WR 270,710 (Serial No. 016)

Director
Division of Neuropharmacological
Drug Products (HFN-120)
Office of Drug Review I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir:

Enclosed in triplicate is an additional clinical study entitled "The Effects of Pyridostigmine Bromide on Vision" to be conducted by Dr. Roger W. Wiley, under this IND. Although Dr. Wiley is listed as the principal investigator, the test article will be administered under the supervision of Major Darcelle Delrie, Medical Corps. A Form FDA 1572 and curriculum vitae have been requested for Major Delrie and will be forwarded upon receipt.

This study was approved by the U.S. Army Aeromedical Research Laboratory Human Use Committee on August 13, 1990 and by the Acting Chairman of The Surgeon General's Human Subjects Research Review Board on August 14, 1990. Copies of those approvals are enclosed.

If you have any questions concerning this submission, please contact the undersigned at (301) 663-2165.

Sincerely yours,

Martha H. Myers

Martha H. Myers
Acting Chief
Human Use Review and
Regulatory Affairs Office

CENTER FOR
REC'D
AUG 23 1990
HFN-120
DRUGS AND BIOLOGICS

ABBREVIATED PROTOCOL

DTIC Search Accomplished 10 August 90. Numbers XIN42D and XIN43C

Title of Project. The Effects of Pyridostigmine Bromide on Vision

Coinvestigators: Roger W. Wiley, Isaac Behar, Tom Harding, and John Kotulak

Funding Source: In-house - D4NG

Required Man Days. 35 days. Inclusive Dates of Project. 13 Aug - 18 Aug 90.

| Personnel | Title | Hours |
|---|---|---|
| Roger Wiley | Research Optometrist | 60 hours |
| Isaac Behar | Research Psychologist | 60 hours |
| Tom Harding | Research Physiologist | 60 hours |
| John Kotulak | Research Optometrist | 60 hours |

Project Objectives: To evaluate visual performance following doctrinal amounts of the pretreatment drug, pyridostigmine bromide.

Background: Pyridostigmine bromide, a quaternary carbamate, is the pretreatment drug of choice for protection against the effects of nerve agent exposure. Carbamates are reversible inhibitors of cholinesterase, the enzyme which terminates the action of acetylcholine in the body. Carbamates reversibly bind to cholinesterase, making it inaccessible to irreversible inhibition by nerve agent. Over a period of time, the enzyme spontaneously decarbamylates, making it available once again to degrade acetylcholine. Pyridostigmine does not cross the blood central protection, but neither does it result in centrally induced deficits.

The doctrinal dose of pyridostigmine bromide for protection against possible nerve agent exposure is 30 mg every 8 hours for three days. A decision then is made as to whether or not the threat still exists. If so, the dose is continued for four additional days. Up to 3 seven day cycles of pyridostigmine administration can be approved. The doctrinal dose should be safe, since patients suffering from myasthenia gravis routinely receive 600 mg/day, and often receive much more. Thirty milligrams every 8 hours is expected to result in 20-40% inhibition of blood cholinesterase. The plasma half life for orally administered pyridostigmine in man is 1.78 hours. It is anticipated that loss of 20-40% of blood cholinesterase will

result in few if any deficits, since there appears to be tremendous excess of cholinesterase in the body. Based upon a limited sample in animal studies , central visual processing appears not be affected until inhibition of blood cholinesterase approaches 80%. If true in humans as well, 80% inhibition of blood cholinesterase should be well beyond that obtained by even the most extreme outriders receiving the doctrinal dose.

Experimental Design: Each of four volunteer subjects will be administered a battery of visual tests which will be given on two days immediately preceding drug treatment, three days during which pyridostigmine bromide will be administered, and one day following drug administration. In addition, a blood sample (2 cc) will be obtained daily to assess cholinesterase activity, thereby providing an indication of the efficacy of the drug.

All of the performance tests are noninvasive; several are used in standard clinical vision examinations, and all testing procedures have been used previously in other experiments. The following visual function tests and measurements will be included in the test battery and administered in the order listed:

Pupil diameter measurement
Autorefraction
Accommodative amplitude
Oculomotor assessment (phoria and vergence measurements)
Dark adaptation
High and low contrast visual acuity at 3 illumination levels
Contrast sensitivity at 3 illumination levels

Because of the urgent requirement for the information, four subjects will be included in the initial trial. An additional 8-12 subjects will be necessary to provide valid statistical inferences. A repeated measures design will be used with each subject providing his own pretreatment baseline data. Day 1 will be a training day during which subjects will be familiarized with the various tests. Day 2 will provide baseline test data for all of the tests. Days 3, 4, and 5 are drug treatment days. On these days, each subject will ingest 30 mg tablets of pyridostigmine bromide on a three per day schedule (0600 hours, 1400 hours, 2200 hours). They will continue to follow the testing schedule. Day 6 is a posttreatment day during which the subjects again will be tested and monitored. It is expected that subjects will be released following testing on Day 6. All subjects will be admitted as inpatients of Lyster Army Hospital which will provide medical monitoring during nontesting periods.

Human Subject Implications: Participation of human subject volunteers is essential for these experiments. No risks are anticipated from the various vision measurements. Some of the

tests are used routinely in clinical examinations. The television screens on which various vision targets are displayed are commercially available. The light levels selected are quite low. However, as with all drugs, some risks are related to the ingestion of pyridostigmine. These are primarily related to overdosage although the drug is also contraindicated for subjects having bronchial asthma, peptic ulcer, liver, kidney, heart disease or hypersensitivity to pyridostigmine or related drugs. Possible adverse side effects include nausea, vomiting, slow heart rate, sweating, diarrhea, abdominal cramps, increased salivation, increased bronchial secretions, and pupil constriction. Other side effects are weakness, muscle cramps, and muscle twitches. In addition, subjects will likely experience slight discomfort during venipuncture for blood samples. Because of these side effects, all subjects will be admitted to Lyster Army Hospital as in-patients so that they will be medically monitored during evening periods of nontesting. A drug will be available at the test site to counteract the possible adverse side effects. Pyridostigmine is experimental for the purposes to be investigated in this research study. The blood samples will be obtained by trained medical laboratory technicians at the hospital laboratory and brought to USAARL for analysis of cholinesterase activity. Representatives of U.S. Army Medical Research and Development Command and Food and Drug Administration may inspect the results of this research study.

Name of Medical Monitor: MAJ Darcelle Delrie, MC

I have read, understand, and will comply with USAARL Policy No. 70-3 and USAMRDC Regulation No. 70-25 in conducting the study, including the necessity for informed consent, based on the accurate presentation of this protocol and the right of withdrawal of the subject.

Roger W. Wiley

I have read and am familiar with protocol entitled, "The Effects of Pyridostigmine Bromide on Vision," and agree to serve as Medical Monitor.

Darcelle Delrie
MAJ, MC
Medical Monitor

**VOLUNTEER AGREEMENT AFFIDAVIT**

For use of this form, see AR 40-38; the proponent agency is the Office of the Surgeon General

THIS FORM IS AFFECTED BY THE PRIVACY ACT OF 1974

1. AUTHORITY: 10 USC 3012, 44 USC 3101 and 10 USC 1071-1087.

2. PRINCIPAL PURPOSE: To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purposes.

3. ROUTINE USES: The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs; teaching; adjudication of claims; and for the mandatory reporting of medical condition as required by law. Information may be furnished to Federal, State and local agencies.

4. MANDATORY OR VOLUNTARY DISCLOSURE: The furnishing of SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

**PART A - VOLUNTEER AFFIDAVIT**

VOLUNTEER SUBJECTS IN APPROVED DEPARTMENT OF THE ARMY RESEARCH STUDIES

Volunteers under the provisions of AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____ SSN _____ having
(last, first, middle)

full capacity to consent and having attained my _____ birthday, do hereby volunteer to participate in
(research study)

The Effects of Pyridostigmine Bromide on Vision

under direction of Roger W. Wiley, Isaac Behar, Tom Harding, John Kotulak conducted at U.S. Army Aeromedical Research Lab
Telephone: 255-6810 (Name of Institution)

implications of my voluntary participation; the nature, duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights on study-related injury I may contact

Command Judge Advocate, Telephone (301) 663-2065 or AUTOVON 343-2065

at U.S. Army Medical Research and Development Command, Ft. Detrick, Frederick, MD 21702-5012
(name and address of hospital & phone number (include area code))

I understand that I may at any time during the course of this study revoke my consent and withdraw from the study without further penalty or loss of benefits however, I may be ☐ required (military volunteer) or ☒ requested (civilian volunteer) to undergo certain examination if, in the opinion of the attending physician, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

**PART B - TO BE COMPLETED BY INVESTIGATOR**

INSTRUCTIONS FOR ELEMENTS OF INFORMED CONSENT:( Provide a detailed explanation in accordance with Appendix E, AR 40-38 or AR 70-25.)

PURPOSE

The purpose of this investigation is to examine possible changes in visual performance during the time in which doctrinal doses of pyridostigmine bromide are ingested over a three day period.

PROCEDURES

Each subject will be requested to complete a series of vision tests. These require only that the subject report what he sees. These responses will be used as indication of the subject's visual acuity using both very black letters and gray letters, night vision sensitivity, coordination of his two eyes, and ability to see light and dark bars of various sizes. These tests will be repeated over 6 days: two days of test practice and

(CONTINUE ON REVERSE)

PART B - TO BE COMPLETED BY INVESTIGATOR (cont'd)

ba \ne data, 3 days during which doctrinal doses (1 tablet, three times per day) are ti brally, and 1 day following the last drug ingestion. In addition, a small blood sam\e (less than 1 teaspoon) will be taken on all but the first day of the investigation. During the investigation, all subjects will be admitted to Lyster Army Hospital to ensure appropriate medical control and monitoring.

BENEFITS

Test participants will derive no direct benefits from their participation in this study. The information obtained will be used to determine the effects of pyridostigmine bromide on visual performance. Pyridostigmine bromide is a pretreatment drug which, by Army doctrine, is ingested by military personnel when there is a threat of exposure to nerve agent poisoning.

RISKS

As with all drugs, some risks are related to the ingestion of pyridostigmine. These are primarily related to overdosage although the drug is also contraindicated for subjects having bronchial asthma, peptic ulcer, liver, kidney, or heart disease, or hypersensitivity to pyridostigmine or related drugs. Possible adverse side effects include nausea, vomiting, slow heart rate, sweating, diarrhea, abdominal cramps, increased salivation, increased bronchial secretions, and pupil constriction. Other side effects are weakness, muscle cramps, and muscle twitches. In addition, subjects will likely experience slight discomfort during venipuncture for blood samples daily. Because of these side effects, all subjects will be admitted to Lyster Army Hospital as in-patients so that they will be medically monitored during nontesting periods. The blood samples will be obtained by trained medical laboratory technicians at the hospital laboratory at the conclusion of \e \esting day. As with all experiments involving human subjects, an Army physician fa\ \ar with investigation and possible risks has been assigned to provide medical oversight during the conduct of the investigation. A drug will be available at the test site to counteract the possible adverse side effects. No risks are anticipated from the various vision measurements. Some of the tests are used routinely in clinical examinations and the light levels selected are quite low. Pyridostigmine is experimental for the purposes to be investigated in this research study.

ADDITIONAL INFORMATION: Questions concerning this investigation are encouraged throughout the course of the study.

Subjects are free to withdraw from the study at any time without prejudice or penalty.

No information that could be linked to any one individual will be released without your expressed written consent. Representatives of U.S. Army Medical Research and Development Command and Food and Drug Administration may inspect the records of this research.

I have received a copy of this volunteer consent form.

| \N OF VOLUNTEER | DATE SIGNED | SIGNATURE OF LEGAL GUARDIAN (If volunteer is a minor) |
|---|---|---|
| PERMANENT ADDRESS OF VOLUNTEER | TYPED OR PRINTED NAME AND SIGNATURE OF WITNESS | DATE SIGNED |

# ANNUAL REPORT
# IND # 23,509
# PYRIDOSTIGMINE BROMIDE

## (JANUARY 1989 - FEBRUARY 1990)

SUBMITTED BY

OFFICE OF THE SURGEON GENERAL
DEPARTMENT OF THE ARMY
WASHINGTON, D.C. 20310-2300

83-530 95 – 10

ANNUAL REPORT
IND # 23,509
PYRIDOSTIGMINE BROMIDE
(JANUARY 1989 - FEBRUARY 1990)

**1.0 INDIVIDUAL STUDY INFORMATION**

TITLE: Effect of Chronic Pyridostigmine Administration on Heavy Exercise in Hot Environments

INVESTIGATORS: Kolka, M.A. et al.

INSTITUTION: U.S. Army Research Institute of Environmental Medicine, Natick, MA

PURPOSE: This investigation will examine the effect of an orally administered pyridostigmine bromide, 30 mg, t.i.d., on the ability to do cycle exercise in the heat for three days as compared to responses obtained for three days when not taking the drug.

PATIENT POPULATION: The subjects will be healthy male soldiers (18 to 40 years old), recruited from personnel assigned to the Natick test subject pool.

STATUS: In progress

TOTAL NUMBER OF SUBJECTS

ORIGINALLY PLANNED FOR STUDY INCLUSION: 6
ENTERED INTO THE STUDY TO DATE: 2
COMPLETED STUDY AS PLANNED: 2
DROPPED FOR ANY REASON: 0

RESULTS SUMMARY: In progress

TITLE: Effects of Pyridostigmine Bromide on Thermoregulatory, Metabolic and Cardiorespiratory Responses to Cold Stress

INVESTIGATORS: Prusaczyk, W.K. et al.

INSTITUTION: U.S. Army Research Institute of Environmental Medicine, Natick MA

PURPOSE: This investigation will examine the effect of a small dose of pyridostigmine bromide, 30 mg, taken by mouth, on the physiological responses to rest in cold water (20° C or 68° F) and in cold air (5° C or 41° F). This study is part of a larger program which is designed to evaluate the soldier's ability to continue to perform duties following treatment with pyridostigmine under a variety of conditions.

PATIENT POPULATION: The subjects will be healthy male soldiers (18 to 35 years old), recruited from personnel assigned to the Natick test subject pool.

STATUS: In progress

TOTAL NUMBER OF SUBJECTS
ORIGINALLY PLANNED FOR STUDY INCLUSION: 8
ENTERED INTO THE STUDY TO DATE: 7
COMPLETED STUDY AS PLANNED: 3
DROPPED FOR ANY REASON: 4

RESULTS SUMMARY: Study completed. Patient dropped due to equipment failure.

TITLE: Effect of Chronic Pyridostigmine Administration During Rest and Exercise at Acute Altitude

INVESTIGATORS: Kolka, M.A. et al.

PURPOSE: This investigation will examine the effect of an orally administered pyridostigmine bromide, 30 mg, on the ability to exercise at sea level and during acute altitude exposure (10,000 feet) for three days while taking the drug and compare responses to two days when not taking the drug.

PATIENT POPULATION: The subjects will be healthy soldiers (18 to 35 years old), recruited from personnel assigned to the Natick test subject pool.

STATUS: In progress

TOTAL NUMBER OF SUBJECTS

ORIGINALLY PLANNED FOR STUDY INCLUSION: 6
ENTERED INTO STUDY TO DATE: 0
COMPLETED STUDY AS PLANNED: 0
DROPPED FOR ANY REASON: 0

RESULTS SUMMARY: In progress

TITLE: Effects of Pyridostigmine Pretreatment on Physiological Responses to Heat, Exercise, and Hypohydration.

INVESTIGATORS: Wenger, C.B., et al.

INSTITUTION: U.S. Army Research Institute of Environmental Medicine, Natick, MA

PURPOSE: This investigation is designed to determine the effect of a single oral 30 mg dose of pyridostigmine and three hydration states on thermoregulatory, cardiovascular, and fluid balance responses of soldiers during two-hour walks in dry and humid heat. Subjects will be tested 90 minutes after taking pyridostigmine and having taken no drug in the last 24 hours.

PATIENT POPULATION: The subjects will be healthy male soldiers (18 to 35 years old), recruited either from personnel assigned to the Natick test subject pool or specifically to this study.

STATUS: Data collection completed.

TOTAL NUMBER OF SUBJECTS

ORIGINALLY PLANNED FOR STUDY INCLUSION: 8
ENTERED INTO THE STUDY TO DATE: 5
COMPLETED STUDY AS PLANNED: 5
DROPPED FOR ANY REASON: 0

RESULTS SUMMARY: In progress

TITLE: Physiological and Biophysical Evaluation of Pyridostigmine Pretreatment in Different Environments

INVESTIGATOR: Kolka, M.

INSTITUTION: U.S. Army Research Institute of Environmental Medicine, Natick, MA

PURPOSE: This investigation will determine the effect(s) of acute pyridostigmine administration (30mg orally) on various physiological and biophysical parameters of human temperature regulation. Subjects will be tested during both rest and submaximal exercise in different environmental conditions.

PATIENT POPULATION: The subjects will be healthy male soldiers (18 to 35 years old) recruited either from personnel assigned to the Natick test subject pool or specifically to this study.

STATUS: Data collection completed.

TOTAL NUMBER OF SUBJECTS

ORIGINALLY PLANNED FOR STUDY INCLUSION: 8
ENTERED INTO THE STUDY TO DATE: 7
COMPLETED STUDY AS PLANNED: 7
DROPPED FOR ANY REASON: 0

RESULTS SUMMARY: In progress

2.0 SUMMARY INFORMATION

2.1 Safety

2.1.1 Most Frequent and Most Serious Adverse Experiences

There were no reported frequent or serious adverse experiences attributed to pyridostigmine bromide administration

during these investigations.

2.1.2 IND Safety Reports Summary

Since the last annual report was submitted, no IND safety reports have been submitted.

2.1.3 Deaths

Since the last annual report was submitted, no deaths have been reported.

2.1.4 Subject Drop-outs

Since the last annual report was submitted, no subjects have dropped-out of any investigation under this IND>

2.2 Drug Action - Summary of Major Clinical Findings:

"Acetylcholinesterase Inhibitor, Pyridostigmine Bromide, Reduces Skin Blood Flow in Humans" Stephenson, L.A. and Kolka, M.A., Am. J. Physiol. (Regulatory, Integrative and Comparative Physiology 1990) 258: (In Press)

Five subjects exercised on a cycle ergometer for 30 min at 55% peak oxygen consumption on two occasions in an environmental test chamber (ambient temperature = 29°C; T = 10°C). Pyridostigmine bromide (PRY), an acetylcholinesterase (AChE) inhibitor, was ingested (30 mg) 150 min before one experiment, and no drug was administered during the other experiment (control). Red blood cell AChE inhibition averaged 40 (±7)% during PYR treatment. Esophageal temperature ($T_{es}$), an eight site-derived mean skin temperature, forearm blood flow (FBF; venous occlusion plethysmography), skin blood flow (SkBF; laser-Doppler velocimetry), and metabolic rate (indirect calorimetry) were measured. SkBF decreased 37% after PYR treatment compared with control ($P \leq 0.05$). The $T_{es}$ threshold for initiation of

cutaneous vasodilation was 36.8 (±0.3)°C for the control treatment and 37.0 (±0.3)°C for the PRY treatment ($P \leq 0.01$). FBF was not significantly different between treatments, whereas heart rate was reduced by 7 and 9 beats/min during rest and exercise, respectively ($P \leq 0.01$). The increased threshold for initiation of cutaneous vasodilation with AChE inhibition by PYR is compatible with nonthermal modulation of the control of thermoregulation through increased acetylcholine (ACh) accumulation. This could potentiate preganglionic transmission to enhance adrenergic vasoconstrictor tone. One suggested mechanism possible at the neuroeffector junction of the sweat gland may be that accumulated ACh diffusion across the adventitia of adjacent arterioles to muscarinic receptors initiates contraction of the smooth muscle. Alternatively, a low-pressure baroreflex, perhaps resulting from the negative inotropic effect of ACh in atrial muscle, may have initiated the relative vasoconstriction with PYR.

"Human Temperature Regulation During Exercise After Oral Pyridostigmine Administration" Kolka, M.A. and Stephenson, L.A., Aviat. Science Environ. Med. 1990; 61:220-224.

Four healthy males exercised in two experiments at ambient temperatures of 22, 19 and 36°C with the relative humidity at 30% in all environments Tdp = 3.9, 9.9, and 15.8°C)>. One experiment in each environment was done 150 min after 30 mg oral pyridostigmine bromide (PYR) administration, and the second experiment was done on a separate day with no medication (CON). Red blood cell cholinesterase was 39 ± 7% lower after PRY (11.8 vs. 7.2 $mol \cdot ml^{-1} \cdot min^{-1}$). Esophageal ($T_{es}$) and mean skin temperature ($T_{sk}$), forearm blood flow (FBF), forearm sweating, and skin blood flow (SkBF) were measured twice each minute during a 15-min rest period and during 30 min of seated cycle exercise at 58% $Vo_2$ peak. Whole body sweating was determined from weight

"Pyridostigmine Counteracts the Blunted Growth Hormone Response to Growth Hormone-releasing Hormone of Obese Children" Loche, S., Pintor, C., Cappa, M., Ghigo, E., Puggioni, R., Locatelli, V., and Muller, E.E., Acta Endocrinol (Copenh) 1989 May;120(5):624-8.

The investigators have evaluated the effect of acute administration of pyridostigmine bromide, a cholinesterase inhibitor, on the GHRH-induced GH rise in 11 obese children and in 8 age-matched controls. The GH response to GHRH (hpGRF 1-40, 1 microgram/kg iv), evaluated both as maximum GH peak and as integrated area under the curve, was significantly lower in the obese children than in the controls. Pretreatment with pyridostigmine bromide (60 mg orally 60 min before the GHRH injection) significantly increased both baseline GH levels and the GH response to GHRH in all the obese subjects, so that their mean baseline GH, peak GH levels and integrated area under the curve after pyridostigmine bromide plus GHRH were similar to those of the control children after GHRH. Also in control children pyridostigmine bromide increased (though not significantly) baseline GH levels. and caused a significant augmentation of the GH response to GHRH. Mean peak GH levels and mean integrated area under the curve after pyridostigmine bromide plus GHRH were significantly higher in the controls than in the obese children given the same treatment. Mean baseline Sm-C levels were significantly higher in the obese than in control children. These data show that enhancement of cholinergic neurotransmission, likely in the hypothalamus, counteracts the blunted GH response to GHRH present in the obese children, and that in simple obesity the potential of the pituitary to make a secretory response to a direct GH secretagogue is preserved.

"Temperature Regulation Following Systemic Anticholinergic or Anticholinesterase Therapy," Kolka, M.A. and Stephenson, L.A. In: Thermal Physiology (Proceedings of Satellite thermal Physiology Symposium, International Congress of Physiological Science, Tromso, 1989, Amsterdam: Elsevier 259-264.

The systemic administration of either cholinolytic or anticholinesterase drugs affects temperature regulation in humans. Cholinergic receptors are blocked by an anticholinergic such as atropine, thus at effector organs a given concentration of neurotransmitter produces an attenuated response. Two consequences are 1) the inhibition of cardiac vagal stimulation and therefore increased heart rate at rest and during exercise; and 2) attenuated secretion from eccrine sweat glands. Conversely pyridostigmine, an anticholinesterase, increases cholinergic stimulation at receptors because acetylcholine is not rapidly hydrolyzed and binds with available receptors in the synaptic area. By this action 1) eccrine sweat glands secrete more fluid which becomes available for evaporative heat loss and 2) bradycardia predominates by an enhanced vagal stimulation.

This paper concerns an investigation of alterations in skin blood flow which occur after systemic anticholinergic or anticholinesterase drug application. The anticholinergic drug used in these studies was atropine sulfate (ATR), administered i.m. in a dose which decreased whole body sweating by 55% and increased resting heart rate by 30 $b \cdot min^{-1}$. The second set of experiments examined the effect of oral administration of the anticholinesterase, pyridostigmine bromide (PYR) in a dose which decreased red blood cell cholinesterase activity by 39% and caused bradycardia 10 $b \cdot min^{-1}$.

"Effects of Pyridostigmine Pretreatment on Physiological Responses to Heat, Exercise and Hypohydration," Wenger, C.B. and Latzea, W.A. in: Proceedings Medical Defense Bioscience Review, U.S. Army Medical Research and Development Command, Maryland, 1989, 841-844.

Pyridostigmine bromide (PYBr), a carbamate anticholinesterase, has been fielded as a pretreatment drug against organophosphate nerve agent poisoning. To examine the short-term effects of PYBr on exercise-heat tolerance, five soldiers participated in four pairs of heat stress tests (HSTs) at 35°C, each consisting of four 25-min treadmill walks separated by 5-min rests. Exercise elicited about 35% of each subject's maximal $O_2$ uptake. In each pair of HSTs, subjects were tested once 100 min after ingesting 30 mg PYBr [mean inhibition of red cell cholinesterase, 30.8±7.6% (SD)], and once after a placebo. HSTs occurred under four conditions: (1) 20% relative humidity (rh), euhydrated, drinking water ad libitum; (2) 20% rh, euhydrated, drinking to maintain initial weight; (3) 75% rh, euhydrated, drinking to maintain initial weight; and (4) 20% rh, hypohydrated by 3% of body weight, drinking to maintain initial hypohydrated weight. Measurements included rectal temperature ($T_{re}$) and skin temperatures on chest ($T_{chest}$), upper arm, and calf; heart rate (HR); and fluid intake, urine and stool output, and nude weights. Venous blood samples were taken before entering the heat and during each treadmill walk. Overall, PYBr lowered HR an average of 3 beats/min (P=0.004); this effect was greatest during hydration, and disappeared in the 75% rh environment. PYBr tended to increase sweating in all environments, but this effect was not significant. Over the course of exercise at 20% rh, $T_{chest}$ decreased more, and the $T_{re}$-$T_{chest}$ gradient widened more, with PYBr than with placebo, but these effects were significant only in condition 2. PYBr tended to reduce the rise in $T_{re}$ at 25% rh, but this effect was statistically significant only during

hypohydration. In euhydrated subjects, PYBr slightly decreased the expansion of plasma volume that occurred during heat exposure, but this effect was significant only at 75% rh. PYBr had no significant effect on hematocrit, hemoglobin, total plasma protein, osmolality, ad libitum water consumption, $O_2$ water consumption, or subject ratings of temperature, discomfort, or exertion. PYBr had only minor effects on tolerance to moderate exercise-heat stress, and did not aggravate the strain of hypohydration.

"Temperature Regulation After Oral Pyridostigmine Bromide Administration," Kolka, M.A. and Stephenson, L.A.. USARIEM Technical Report, 1989, May, T16-89.

Four healthy subjects exercised in three environments (22°C, 29°C and 36°C). Three additional subjects were tested at the two hottest temperatures. The relative humidity was 30% for all experiments. Two experiments were done in each condition; one, 150 minutes after oral (30 mg) pyridostigmine bromide (PRY) administration, and the second with no medication (CON). PYR decreased red blood cell cholinesterase activity by an average (±SD) pf 39 (±6) %. Esophageal ($T_{es}$) and mean skin temperature ($T_{sk}$), forearm blood flow (FBF) and cutaneous perfusion (SkBF) were measured twice each minute during a 15-min rest period and during 30 minutes of seated cycle exercise. Oxygen uptake and heart rate were frequently measured both at rest and during moderate exercise. PRY decreased heart rate at rest (6 $b \cdot min^{-1}$) and during exercise (9 $b \cdot min^{-1}$) at 29°C and 36°C ($P<0.05$). Resting SkBF was ~ 30% lower at 29° and 36° after PYR compared to CON ($P<0.05$). There was no effect of PYR on heat production at rest or during exercise (52 $W \cdot m^{-2}$ during exercise). $T_{sk}$ was different in the three environments by design, but was unchanged by PYR. $T_{es}$ was not different at rest in any condition, but was elevated during exercise at 29° and 36°C (0.1°C, $P < 0.05$) in PYR compared

to CON. Anticholinesterase administration increased dry heat gain during exercise in the hot environment. The data suggest that temperature regulation would be further compromised in health adults by increasing exercised intensity, exercise duration, dry bulb temperature or ambient water vapor pressure.

2.3 Preclinical Findings

"Myopathic Changes in Diaphragm of Rats Fed Pyridostigmine Bromide Subchronically" Bowman, P.D., Schuschereba, S.T., Johnson, T.W., Woo, F.J., McKinney, L., Wheeler, C.R., Frost, D., and Korte, D.W., Fundam Appl Toxicol 1989 Jul;13(1):110-7

To determine if alterations in muscle morphology occur after subchronic oral administration of pyridostigmine bromide, rats were fed 90 mg/kg continuously in meal and examined at 1, 2, 4, 7, and 15 days. Within the first day, cholinesterase activity was reduced by 87% and remained inhibited by 74-91% for the entire course of the feeding. Light microscopy demonstrated that by the first day approximately 1 in 100 myofibers was shrunken and contained centralized nuclei. Electron microscopic examination showed that while presynaptic areas of neuromuscular junctions were relatively unaffected by this dose, postsynaptic areas invariably showed maximal changes. Ultrastructural alterations included disruption of myofilaments, mitochondrial changes consistent with accumulation of calcium, and nuclear alterations. These effects appeared not to be cumulative and were greatly diminished by 15 days even under constant drug administration and inhibition of cholinesterase activity. We conclude that subchronic feeding of pyridostigmine bromide induces primarily myopathic rather than neurogenic changes in the diaphragm and that some mechanism of accommodation may be activated that minimizes continued muscle injury.

2.4 Manufacturing Changes

Since the last annual report was submitted, there have been no manufacturing changes.

3.0 GENERAL INVESTIGATIONAL PLAN

Since the last annual report was submitted, there have been no changes in the general investigational plan.

4.0 REVISED INVESTIGATOR'S BROCHURE

Since the last annual report was submitted, there have been no changes in the investigator's brochure.

5.0 UNREPORTED SIGNIFICANT CHANGES IN PHASE I PROTOCOLS

Since the last annual report was submitted, there have been no significant changes in phase 1 protocols.

6.0 FOREIGN MARKET INFORMATION

The FDA Freedom of Information office was queried for any adverse drug reactions that might have been reported for pyridostigmine bromide as the result of studies outside of DOD control. The information provided by the FDA-FOI office is that no reports of adverse drug reactions have been submitted since the last annual report was submitted.

7.0 LOG OF OUTSTANDING BUSINESS WITH THE FDA

There is no outstanding business with the FDA.

DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

REPLY TO ATTENTION OF

February 14, 1990

Human Use Review and
Regulatory Affairs Office

SUBJECT: IND 23509 - Pyridostigmine Bromide
(Serial No. 012)

CENTER FOR
REC'D
FEB 1 6 1990
HFN-120
DRUGS AND BIOLOGICS

Director
Division of Neuropharmacological
Drug Products (HFN-120)
Office of Drug Review I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir:

Enclosed in triplicate is an additional clinical study entitled "Effect of Chronic Pyridostigmine Administration During Rest and Exercise at Acute Altitude" to be conducted by Margaret A. Kolka, Ph.D., under this IND.

Although Dr. Kolka is listed as the principal investigator, the test article will be administered under the supervision of the medical monitor, Captain James E. Cook, Medical Corps. Completed and signed FDA Forms 1572 and curricula vitae for Drs. Kolka and Cook were submitted with our letter of December 6, 1989.

This study was approved by the U.S. Army Research Institute of Environmental Medicine Human Use Review Committee on October 25, 1989 and by The Surgeon General's Human Subjects Research Review Board on December 13, 1989. Copies of those approvals are enclosed. Recommended revisions have been incorporated.

If you have any questions concerning this submission, please contact Ms. Marty Myers at (301) 663-2165.

Sincerely,

Gregory P. Berazuk
Lieutenant Colonel, Medical
Service Corps
Chief, Human Use Review and
Regulatory Affairs Office

1

Effect of Chronic Pyridostigmine Administration during Rest and Exercise at Acute Altitude

Recently, we have shown decreased skin blood flow and reduced heat exchange at rest and during exercise at terresterial elevations of 8500 (2591 m) and 15000 (4572 m) feet compared to sea level responses (1,2,3). Both thermoregulatory effectors, sweat glands and vasomotor elements are depressed at moderate and high altitude, as their response is attenuated during increasing body temperature during exercise. At altitude, individuals increase water loss through the skin and from respiration compared to similar activities at sea level (4,5). Thus, individuals become dehydrated during altitude exposure. The issues of water loss, temperature regulation, and fluid volume redistribution at altitude have been well defined by our institute (6).

Deployment of soldiers may occur at 2591 m (8500 ft) and above in many areas of the world with the possibility of these soldiers requiring chronic pyridostigmine pre-treatment. Therefore, the combined effects of altitude, exercise and carbamate (pyridostigmine) administration should be evaluated. Since pyridostigmine given over the course of a number of days may result in subtle dehydration in these soldiers, combined with the fact that acute altitude exposure increases both respiratory water loss and water loss through the skin, soldiers rapidly deployed to a high terresterial location may be at risk for increased heat storage due to dehydration. Long term exposure to altitude is associated with water loss and dehydration, however this protocol will only characterize acute, less than 1 hour, exposure to 3048 m (10000 ft). The effects of altitude on heat loss mechanisms are apparent during acute exposure, thus necessary data can be obtained without subjecting the subjects to the risks of prolonged altitude exposure.

Pyridostigmine is a synthetic analogue of physostigmine, which is the prototype of this class of drugs. Physostigmine is the principle alkaloid in the colabar bean and was first studied in the 1850's (13,14,15). The mechanism of action involves a reversible bond limiting cholinesterase activity (16). Under normal conditions, oral pyridostigmine produces physiologic responses expected from cholinergic stimulation. These responses may include miosis, stimulation of gastrointestinal motility and secretion, stimulation of salivary and eccrine sweat glands, slight bradycardia and hypotension (13,14,15). Pyridostigmine produces fever side effects, has a longer duration of action and has a greater margin of safety that physostigmine (13,14,17). Pyridostigmine contains a quarternary ammonium group and the resulting polarity does not allow penetration through biological membranes. As a result, oral doses are approximately 30 times greater that i.v. doses (18). Peak plasma levels are reached 1.5 to 2.5 hours after an oral dose and 95% of the drug is eliminated 8 to 10 hours after ingestion (19). Pyridostigmine is widely used for its effect at the neuromuscular junction in patients with myasthenia gravis resulting in increased muscular strength (20,21). Some of these patients receive up to 6000 mg per day, however most patients are adequately maintained at 200 to 1400 mg per day (22). Pyridostigmine is also used to reverse the neuromuscular blockade induced by curariform drugs. For this purpose it is administered i.v. in a dose equivilent to an oral dose of 250 to 500 mg (17,23).

Pyridostigmine ingestion is associated with decreased blood flow to the skin, (7), unchanged plasma volume responses during exercise (7), and increased respiratory and insensible water loss (13). These responses are similar to those seen during acute altitude exposure, thus the combined effects of sustained pyridostigmine treatment and acute altitude (less than 1 hour) exposure need to be addressed to evaluate the possibility of progressive dehydration during the three day drug regimen.

Exposure to environmental temperature extremes or increasing deep body temperature during exercise is associated with increased sweat gland secretion and vasodilation to maintain core temperature as heat is transferred away from the body core to the surface and subsequently to the environment. The sweat glands are innervated primarily by cholinergic fibers, although sweating can be induced through adrenergic stimulation (8). Skin and muscle blood flow are believed to have cholinergic components as well (9,10,11,12). Thus, any change in effector stimulation (sweat glands or vasomotor elements) which may result from increased cholinergic activity may affect heat dissipation via changing sensible heat flux and/or evaporative heat loss. We propose to evaluate heat exchange at rest and during exercise at sea level and during acute altitude exposure (10000 ft, 3048 m) in soldiers chronically (72 hours, 30 mg t.i.d.) treated with pyridostigmine. A partitional calorimetric (heat balance) study will be conducted during steady-state rest and during moderate exercise at both sea level and during acute hypobaria. Skin diffusion, active sweating, respiratory water loss, and skin blood flow will be characterized. These experiments should provide basic required knowledge regarding hydration status in soldiers exposed to altitude and carbamate therapy. We hypothesize that the combination of chronic pyridostigmine treatment and acute altitude deployment (rapid ascent in the hypobaric chamber) might lead to exaggerated water loss and increased heat storage. If these data indicate further study, chronic altitude exposure in combination with chronic pyridostigmine administration will be proposed.

Military Relevance

Under current U.S. Army doctrine, soldiers will be issued a blister pack containing 21 pyridostigmine bromide tablets to be administered as one 30 mg tablet t.i.d. for 7 days, if their deployment subjects them to a risk of nerve agent exposure. Additionally, soldiers may be deployed at elevations above 8500 feet, an altitude associated with altered heat loss. In this

protocol, we want to characterize possible thermoregulatory issues which accompany the chronic administration of pyridostigmine associated with acute altitude exposure to assess if water requirements or clothing systems might need re-evaluation or adjustment. Specifically, increased water loss and collection of water in clothing layers will decrease the insulative capacity of clothing in a cool environment, cooling requirements in chemical protective clothing may have to be adjusted due to increased water on the skin or in the boundary layer; and soldiers may have to be instructed to increase water intake when taking pyridostigmine whether or not they are exposed to altitude. Soldiers will be evaluated throughout 3 days of drug therapy for any adverse reactions to the pyridostigmine administration.

Methods

Six healthy subjects will be recruited from the NATICK test subject pool and/or from civilian or military personnel assigned to USARIEM. All tests will be conducted at an ambient temperature of 33°C, at an ambient water vapor pressure of 10 torr (1.3 kPa). Two tests (one after pyridostigmine and one control) will be run at sea level, and three tests (two after pyridostigmine and one control) will be run at 3048m (10000 feet, 520 torr) on each subject. All testing will take place at USARIEM and each subject will complete all five tests and all preliminary measurements in ten working days.

EXPERIMENT DESIGN

Control (CON)

Sea level (770 torr)
3048 meters (520 torr)

Pyridostigmine (PYR)

3048 meters (520 torr), 2 hours after first 30 mg tablet
3048 meters (520 torr), 26 hours after first 30 mg tablet
Sea level (770 torr), 74 hours after first 30 mg tablet, which is two hours after the last 30 mg tablet

The order of CON and PYR series will be balanced with three subjects tested first in CON and three first in PYR. Within the CON experiments, sea level and 3048 m will be balanced, with 3 subjects tested first at sea level and 3 tested first during acute altitude. These experiments will be separated by 48 h. The order of PYR tests will be constant as described above. The first PYR test at 3048 m will provide information regarding acute PYR ingestion and acute hypobaria. The second hypobaric exposure will provide information regarding sustained PYR and acute altitude. We do not anticipate any residual effects of the ambient temperature from the first PYR to the second PYR. The sea level exposure will occur 48 h after the second altitude exposure and will provide information regarding sustained PYR treatment, without the influence of hypobaria. All altitude exposures will be less than one hour.

The saturated water vapor pressure at the mean skin temperature at sea level in this environment is approximately 37 torr (4.9 kPa). Thus, based on our earlier findings, increased evaporation of sweat will occur at reduced barometric pressure. During all tests, subjects will be instrumented with an esophageal catheter containing a thermocouple for the measurement of core temperature. The use of esophageal temperature in these studies is critical as this site is the only one routinely used which responds very quickly and closely mimics changes in blood temperature. We routinely observe a rapid increase in esophageal temperature at the beginning of exercise and use this increase to evaluate changes in sudomotor and vasomotor responses which may be affected by pyridostigmine and exposure to hypobaria. Skin surface temperature (thermocouples) will be measured from eight sites (head, chest, back, upperarm, forearm, hand, thigh and calf) and a weighted mean skin temperature will be calculated based on the thermosensitivity and area weighting of the eight sites (24). Local sweating will be measured from the chest with a small dew-point sensor taped to the skin (25). This sensor will be ventilated with ambient air from the chamber at a flow rate of 600 $ml \cdot min^{-1}$ which will not artificially dry the skin under the capsule, but will allow sufficient evaporation.

Forearm blood flow will be estimated by venous occlusion plethysmography (26). Briefly, the forearm will be suspended at the wrist with a sling anchored at two points,

thereby minimizing movement artifact as the arm and strain gauge will move in translation with the torso. Blood flow from the hand will not be measured as the wrist cuff will be inflated to exceed systolic pressure. The measurement of FBF will include flow through the skin, muscle, adipose tissue and bone. Cutaneous perfusion of the skin (skin blood flow, SkBF) of the forearm and of the chest will be estimated by laser doppler velociometry. This system uses a 2 mW HeNe laser and fiber optic system to measure blood flow through the skin of the forearm and chest. The flow measurements represent a value which measured in mV is proportional to the quantity of moving red blood cells times the average velocity of the red blood cells within the sample volume of the capillary tissue measured. Laser probe and strain gauge (for FBF) placement will be identical for each experiment for each subject. Heart rate and mean arterial pressure will be measured by an auscultatory method. Heart rate will also be measured from the EKG.

After instrumentation as described above the chamber will be rapidly decompressed to reach the appropriate simulated altitude or remain at sea level depending on the experiment scheduled. Collection of baseline data (achievement of thermal balance) will begin upon reaching the simulated altitude (or at sea level as appropriate). The subject will then exercise for 30 minutes at 65 to 70% of his peak aerobic power while seated behind the pedals of the cycle ergometer. Exposure time at altitude will be less than 1 hour during any individual experiment. These tests will be done at 0800 hours (27). Drug administration will begin at 0600 hours and will continue at 8 hour intervals for 72 hours. Blood samples for cholinesterase activity will be taken by venipuncture (6 ml) immediately before the drug regimen begins and at 2, 26, 50 and 74 hours during pyridostigmine administration and at 0800 h on each CON day for a total of 7 samples (42 ml). Body weight will be measured daily at 0800 h. Exercise tests will be conducted at 2 hours, 26 hours and 74 hours after the

initiation of the drug regimen. Two subjects may be tested on the same day which would require the drug regimen to be altered by 2 hours.

Prior to actual testing, we will assess each individual's peak aerobic power while seated behind the pedals of a cycle ergometer at sea level and 10000 feet. The nature of the test will be continuously increasing ergometer resistance (~30 W) each two minutes until the subject voluntarily terminates the test. Confirmation of the peak aerobic power will be from a relatively stable (<150 $mL \cdot min^{-1}$) oxygen uptake with an increase in the ergometer resistance. This peak testing is essential to accurately assess the relative work intensity on all test days, and to ensure similar conditions for each test subject.

Minimizing risks to subjects

With the exception of the ingestion of pyridostigmine bromide, all of the procedures in this study fall within the framework, restrictions and safety limitations of the USARIEM Type Protocol for Human Research Studies in the areas of Thermal, Hypoxic and Operational Stress, Exercise, Nutrition and Military Performance.[1] Although these procedures are not considered harmful, there is the possibility that exercise (maximal and/or submaximal) may uncover or aggravate pre-existing heart problems. Some degree of tachycardia and hyperthermia is expected in all subjects during exercise and heat exposure. To assure adequate safety, heart rates, skin and esophageal temperatures will be measured in all test sessions. Subjects will be supervised at all times during exercise and heat exposure. Testing will be discontinued for any subject if the esophageal temperature reaches 39.1°C or if the heart rate

[1]Approved 8 March 1988. The type protocol provides information and explanations about conditions, standards and safeguards, in order to serve as an encompassing framework for specific in-house studies in its general subject area. It is to be used as a reference to facilitate the understanding and review of specific study protocols which conform to its provisions, and thus do not exceed the degree of risk, and safety limits herein stipulated (reference para 19, USAMRDC Reg 70-25, 27 April 1981).

exceeds 180 b·min$^{-1}$ for longer that 5 minutes except during the peak aerobic power tests when we expect heart rate to exceed this level. In addition, exercise will be terminated by achievement of any of the criteria established in the above Type Protocol. Localized discomfort, syncope or a hematoma at the site of needle puncture may occur as a result of the daily venipuncture. All blood samples will be taken by qualified personnel using sterile techniques. There is a risk of eye injury associated with looking into the light source of the laser during skin blood flow measurements, however, power to the laser is never turned on until the probe is firmly attached to the skin. Thus, this risk is small. To minimize risks associated with pyridostigmine, volunteers will be given medical examinations prior to acceptance as subjects. No one with a history of asthma; hepatic, renal, cardiovascular disturbances or hypersensitivity to pyridostigmine or related drugs will be included as a test subject. Toxic reaction to pyridostigmine is not common and is usually associated with chronically overdosed myasthenics. At high doses which approach the $LD_{50}$ in rats, damage to the muscle ultrastructure has been observed. These morphological changes have not been reported in humans. Toxic symptoms include nausea, vomiting, abdominal cramps, diarrhea, sweating and salivation. Atropine will be available to reverse the muscarinic side effects of pyridostigmine should they become unbearable.

Pyridostigmine treatment will consist of 30 mg orally, t.i.d. for up to 3 days. Blood samples (6 ml) will be drawn before initiation of the drug regimen by venipuncture at 24 hour intervals for red cell and/or whole blood cholinesterase determination. If red cell cholinesterase inhibition exceeds 70% at any time, drug administration will be discontinued. No blood will be drawn during exercise.

The risks associated with very acute hypobaric exposure are well described in the Type Protocol and include hypoxemia, retinal hemorrhage, and untoward effects of changes in gas

volumes entrapped in the body. The cummulative risks of acute altitude, short term moderate exercise and pyridostigmine ingestion are not known. However, the effects of exercise and altitude are known (1,2,3,6), and the effects of acute pyridostigmine administration in a similar thermal environment during exercise are known (7).

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DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
3109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

REPLY TO ATTENTION OF

December 6, 1989

Original IND AME

Human Use Review and
Regulatory Affairs Office

SUBJECT: IND 23509 - Pyridostigmine Bromide -
WR 270,710

Director
Division of Neuropharmacological
Drug Products (HFN-120)
Office of Drug Review I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir:

On October 20, 1989 we forwarded to you under Form FDA 1571, serial number 009, protocols for two additional clinical studies to be conducted under this IND.

We are now resubmitting those protocols under two separate Forms FDA 1571, serial numbers 010 and 011 and request that you rescind serial number 009.

Please note that since we submitted the protocol entitled "Effects of Pyridostigmine on Thermoregulatory, Metabolic and Cardiorespiratory Response to Cold Stress," a modification to the exclusion criteria has been approved by the U.S. Army Research Institute of Environmental Medicine Human Use Review Committee Chairman and the Acting Chairman, Human Subjects Research Review Board. Copies of those approvals are enclosed.

We regret any confusion caused by this request.

If you have any questions concerning this matter, please contact the undersigned at (301) 663-2165.

Sincerely,

DRUGS AND BIOLOGICS
HFN-120
RECEIVED
DEC 11 1989
FDA

Martha H. Myers

Martha H. Myers
Acting Chief
Human Use Review and
Regulatory Affairs Office

## EFFECTS OF PYRIDOSTIGMINE BROMIDE ADMINISTRATION ON THERMOREGULATORY, METABOLIC AND CARDIORESPIRATORY RESPONSES TO COLD STRESS

### ABSTRACT

When exposure to chemical warfare (CW) neurotoxic agents is anticipated, soldiers will be given a pretreatment of pyridostigmine bromide. This orally-active, reversible anti-cholinesterase agent is the drug of choice for protection from CW agent action due to its high degree of effectiveness and minimal side effects. The drug will be given in small repeated doses prior to exposure to CW agents to provide optimal protection; so situations could arise in which no exposure to CW agents would occur. In such a scenario, soldiers will have taken pyridostigmine yet will be required to tolerate environmental extremes, which may involve water exposure, and maintain performance levels to meet mission requirements even if no CW agent exposure occurs. Unfortunately, little is known about the soldier's ability to tolerate thermal extremes following pyridostigmine pretreatment. In therapeutic doses this drug can alter peripheral blood flow, sweat rate, and cardiac output. This study will examine the effects of acute pyridostigmine administration on select thermoregulatory, metabolic, and cardiorespiratory responses during rest in the cold. Prior to each experiment, subjects will ingest either one pyridostigmine bromide tablet (30 mg) or one placebo tablet (starch filler). Subjects will be exposed twice each for up to 180 minutes to cold air (5° C) and to cold water (20° C). A counter-balanced, single-blind design will be employed. During the resting cold exposures the subjects will be lying quietly in a comfortable position while exposed to the test environment. The following parameters will be measured: metabolic rate; shivering (by electromyography); cardiac output; arterial blood pressure; heat flow; muscle temperature; rectal temperature; mean skin temperature; body heat flow; thermal sensation; and red blood cell cholinesterase inhibition. The results obtained from these experiments should be important in the evaluation of, or further development of, doctrine on the determination of exposure to the cold following pyridostigmine treatment.

This protocol will be conducted under the Army's IND (#23509, 2 Feb 1987) "Use of Pyridostigmine as a Pretreatment Drug", and has been reviewed and approved for funding by USAMMDA.

## BACKGROUND

Acetylcholinesterase (ChE) plays a crucial role in terminating the action of the neurotransmitter acetylcholine (ACh) at synapses between cholinergic neurons and their effector organs. Agents which inhibit ChE cause ACh to accumulate at synaptic sites thus potentiating stimulation of the neurons and ultimately of their effector organs (32). Two general classes of anti-cholinesterase (anti-ChE) agents are recognized based on the characteristics of their ChE binding properties. "Reversible" anti-ChE agents, first described in the mid-nineteenth century (32), are a group of chemically related methylcarbamates represented by the prototypic drug physostigmine (eserine). Of more recent development are a group of highly toxic organophosphates. These "irreversible" agents were first employed as pesticides shortly before World War II (32), but because of their extreme toxicity and duration of action some (eg. soman and sarin) are now included in the neurotoxic chemical warfare (CW) arsenals of many nations (32).

Protection against irreversible organophosphate or CW agent poisoning can be provided by pretreatment with the reversible agents. Transient binding of reversible agents with ChE protects receptors from irreversible agent binding, slow dissociation of the complex provides enough ChE to maintain life until synthesis of ChE is resumed (17). Administration of reversible anti-ChE agents, in combination with atropine, has been shown to confer a considerable degree of protection against organophosphate and CW nerve agent poisoning in rodents (8,13). The protection afforded appears to be species dependent (10), with primates being highly responsive to carbamate prophylaxis (6). Further, McDonough and Modrow (19) have reported that, when given in protective doses, pyridostigmine treatment does not appear to produce behavioral performance decrement on operant tasks in either rodents or primates.

Of the physostigmine derivatives and analogues (reversible anti-ChE agents) pyridostigmine appears to display satisfactory efficacy, easier regulation and produces fewer, less severe side effects than other drugs of this class (11). For this reason the drug has been selected, by the U.S. Army and some NATO nations, for use as a pretreatment

drug when CW agent use is anticipated. While this drug has been used for many years as a therapeutic agent in the treatment of neuromuscular disorders little has been reported concerning its effects on healthy humans during exposure to environmental extremes.

Pyridostigmine is an orally-active, reversible ChE inhibitor belonging to the methylcarbamate family (24). The drug is a synthetic analogue of the naturally occurring alkaloid physostigmine (eserine). Both substances reversibly inhibit ChE activity and subsequently increase nerve impulse transmission in cholinergic neurons and their effector organs. By nature of their action, the drugs can produce somatic symptoms of cholinergic stimulation (24). In larger therapeutic doses ($300^{+}$ $mg{\cdot}day^{-1}$), pyridostigmine can: enhance gastric motility, stimulate gastric acid secretion, and augment motor activity of the small and large bowel; increase the activity of sweat, salivary and pancreatic acinar glands; facilitate neural transmission at the neuromuscular junction; cause bronchiolar constriction; increase peristalsis in the ureters; produce bradycardia, with a consequent decrease in cardiac output; and, even at low doses, stimulate respiratory and other subcortical centers (32). It is the action of increasing transmission across neuromuscular junctions which makes the drug efficacious for use in the treatment of myasthenia gravis, a neuromuscular disorder.

Pyridostigmine possesses a quaternary ammonium group which greatly increases the polarity of the drug. The increased polarity makes oral administration considerably less effective (~3% activity) than equivalent parenterally administered doses. The polarity also prevents its crossing the blood-brain barrier to a significant degree, thus reducing the possibility of a direct central effect (32). Peak plasma levels are not reached until approximately 90 to 120 minutes after oral administration of the drug (2). With a half-life of approximately 1.8 hours (2), 98% of the drug is eliminated within 10 hours of administration. The major route of elimination is renal, accounting for 75% of pyridostigmine clearance (4).

Adverse reactions to pyridostigmine are usually associated with overdoses. The side effects seen with overdoses are generally of two types, muscarinic and nicotinic (24).

Among the muscarinic reactions are: nausea, vomiting, diarrhea, miosis, blurred vision and diaphoresis. The side effects are usually successfully counteracted with atropine treatment (24). Nicotinic reactions can include: fasciculation, muscle cramps and weakness (24).

Both acute and chronic high doses of injected pyridostigmine have been reported to produce ultrastructural damage in rodent skeletal muscle (5,7), however, the reversibility of the damage was not studied. This is believed to be the result of the accumulation of ChE and of ion retention at the motor end plates which causes a disruption of postjunctional folds and sarcoplasmic reticular membrane (20). Wecker et. al. (37) have reported dose-dependent skeletal muscle fiber necrosis following injection of paraoxon, an anti-ChE agent. In doses high enough to produce fasciculation and tremor, paraoxon produced myopathy in rodent hemidiaphragm, but these effects were attenuated by pretreatment with physostigmine or neostigmine. Ultrastructural damage to skeletal muscle apparently has not been described in humans, even though very high doses (> 1400 $mg \cdot day^{-1}$) are occasionally used in the treatment of myasthenia gravis (33).

## Cold Exposure

During exposure to thermoneutral or hot environments, metabolic heat is transferred from the body core to the skin and then to the environment, a process which enables body core temperature to be maintained within narrow limits (34). The heat loss mechanisms of increased cutaneous blood flow and sweating provide protection against overheating (26). In cold environments, on the other hand, the physiological problem is to minimize heat loss and/or increase metabolic heat production, so that a substantial decrease in body core temperature can be prevented (34).

Immersion in cool or cold water constitutes a substantial thermal challenge to the maintenance of core temperature in that heat is lost from the body at a rate approximately two to four times faster than in air (29). During cold water immersion, compared to air exposure, there is a greater and more rapid lowering of core temperature and a more uniform skin temperature equaling that of the water (34). Thus, water is a convenient

medium for generating hypothermia and for studying many of the thermoregulatory and metabolic responses to cold. Additionally, during cold water immersion, individuals can be made hypothermic with little or no risk of peripheral tissue injury as opposed to cold air exposure (34).

During exposure to the cold, the body's insulative shell can provide protection against body core heat loss in both cold water and cold air (22). This protective shell has been subdivided into two components: the superficial shell, consisting of skin and subcutaneous fat, and the subcutaneous muscle shell (22). A part of the insulation provided by the subcutaneous shell is proportional to the thickness of the skin and of the subcutaneous fat layer (30,35). While the thickness and composition of these elements are subject to change over time they will remain constant during acute cold exposures. This stability implies that the segments of the shell provide a constant, or static, insulative protection during acute exposure. On the other hand, there is also a dynamic insulative capacity to the superficial and subcutaneous muscle shell which is determined by cutaneous and muscle blood flow, respectively (40). During cold exposure, the insulative capacity of the superficial and subcutaneous muscle shell can be increased by sympathetically-induced vasoconstriction (34). Further, in cooled muscle, perfusion may be reduced, increasing the insulative protection of the subcutaneous muscle shell (36). These combined responses have the effect of increasing the overall insulative capacity of the superficial shell if the individual is at rest.

During rest in the cold, there is an environmental "critical temperature" below which individuals increase resting metabolism to maintain core temperature (25). This increase is accomplished via shivering thermogenesis in water and in air (34). For most individuals this critical temperature, in water, is between 30° C and 34° C (25,30) and in air between 27° C and 29° C (1). Below the critical temperature, elevated thermogenesis is proportional to decreases in the environmental temperature, both in air and water (30). Smith and Hanna (30) have reported a high, negative correlation (r=-0.94) between skinfold thickness and critical temperature in water but only a modest correlation (r=-0.49) in air. Thus, at rest it appears that greater subcutaneous adiposity provides greater superficial shell

insulation in both air and water, but the insulation is less effective in water, where the need is greater.

At rest, subjects show distinct cardiovascular and respiratory responses to acute cold exposure. Subjects show increased cardiac output, which appears to result predominantly from increases in stroke volume (21,23). This increase in cardiac output can be as much as 30-40%, probably resulting from peripheral vasoconstriction and venoconstriction, both of which can produce increased central blood volume (23). Subjects also show increased mean arterial blood pressure resulting from increases in both systolic and diastolic pressures (21). Additionally, there appears to be an isotonic decrease in plasma volume during cold exposure (~12% in air and ~16% in water) as a result of isosmotic hemoconcentration (39). Muza et. al. (21) have shown that at rest, minute ventilation increases proportionally to the metabolic requirements for maintaining body temperature in the cold.

The literature is relatively devoid of studies examining the effects of anti-ChE agents on organisms exposed to cold environments. Marton et. al. (16) chronically exposed rats to malathion, an organophosphate anti-ChE agent with relatively low toxicity to mammals. Malathion-exposed rats and control rats were then exposed to a cold (1.5° C) air environment until death to measure survival time. Exposed rats had significantly shorter survival times ($\bar{X}$ = 60% of controls) than did control animals. The authors hypothesized that the reduced survival times resulted from the inability of malathion-treated animals to produce heat at a rate high enough to maintain core temperature. An additional possibility is that there were changes in the insulative capacity of the superficial and subcutaneous muscle shell of the exposed animals induced by the anti-ChE agent, however this is speculative. In this case, metabolic heat may have been produced but was not sufficiently retained by the animals to maintain core temperature. It has also been reported that hibernating (i.e., lowered body temperature) hamsters are more susceptible to poisoning with sarin, a highly toxic organophosphate anti-ChE agent, than are non-hibernating (i.e. normal body temperature) hamsters (27). This finding suggests there may be negative physiological consequences of treatment with anti-ChE agents when body core temperature and/or metabolism is lower.

It is difficult to extrapolate from these models to predict human metabolic and thermoregulatory responses to the cold. Data are available, however, on human responses to pyridostigmine during exposure to the heat (15,31). Recently in our laboratory, human subjects were studied during rest and exercise in comfortable, warm temperatures ($T_A$=37° C) following pyridostigmine (30 mg, p.o.) treatment. Subjects showed significant reductions in heart rate (~10 bpm) at rest and during exercise (15). Resting cutaneous perfusion, measured by laser doppler flowmetry on the forearm, was 32% lower at rest (15) and 50% to 54% (15,31) lower during exercise when compared to control (no drug) conditions. Additionally, mean skin temperatures were significantly lower, both at rest and during exercise, following pyridostigmine treatment (15). Despite reduced cutaneous perfusion, Kolka and Stephenson (15) report that there were no changes in total blood flow in inactive arm muscles, measured by venous occlusion plethysmography, either at rest or during exercise. This finding suggests that there was an increase in muscle blood flow, at least to resting muscle, following pyridostigmine ingestion.

Pyridostigmine-induced alterations in cutaneous perfusion and muscle blood flow would change the insulative capacity of the superficial and subcutaneous muscle shell. The increase in muscle blood flow, especially to inactive muscles during cold exposure, would increase heat loss and could cause greater or more rapid hypothermia during cold exposure. At present, the data are insufficient to thoroughly predict the problems encountered in thermoregulation during exposure to the cold following pyridostigmine treatment.

## STATEMENT OF THE PROBLEM

In the dosage dictated by current U.S. Army doctrine, there is only a small probability that pyridostigmine will produce side effects noted for the drug. However, the drug may have more pervasive and profound actions when the treated individual is thermally challenged by cold exposure.

The widespread cholinergic effects of pyridostigmine suggest the potential for multiple effects on thermoregulatory and metabolic responses during cold exposure.

Pyridostigmine increases sweat gland activity and ureter peristalsis which may place greater fluid balance demands on the soldier. The demands could be further enhanced during thermal stress, such as in the cold, where cold-induced diuresis may increase fluid intake requirements. Pyridostigmine-induced bradycardia (15,31) could augment the bradycardia seen during cold water immersion (21) to compromise cardiac output and/or alter regional blood flow.

With the reduction in blood flow normally seen in cooled muscle (40) the insulative capacity of the superficial and subcutaneous muscle shell is increased in both air and water. However, if blood flow to inactive muscles is increased following pyridostigmine treatment (15,31), the insulative capacity of the subcutaneous muscle shell could decrease and heat loss to the environment would increase. In pyridostigmine-treated individuals this would increase the likelihood of hypothermia and of frostbite or other tissue injuries during cold air exposure. Further, if blood flow to inactive limbs is increased and cardiac output reduced, there would necessarily be differences from the normal distribution of blood flow to other parts of the body.

In summary, little is known about the effects of pyridostigmine on humans during exposure to thermal extremes or during water immersion. Many of the known effects of pyridostigmine on the cardiorespiratory and thermoregulatory systems could interact with the effects of cold exposure and/or immersion to degrade normal physiological compensatory mechanisms. This study will examine the effects of acute pyridostigmine administration on select thermoregulatory, metabolic and cardiorespiratory responses during exposure to cold air and to cold water immersion. It is hypothesized that pyridostigmine treatment will decrease the superficial and subcutaneous muscle shell insulation and result in greater and/or more rapid body heat loss to the environment.



83-530 95 – 11

## DESCRIPTION OF THE STUDY

### SUBJECTS

Eight healthy males between the ages of 18 and 35 will serve as subjects in this study. They will be selected from the male Army personnel stationed at, or temporarily assigned to, Natick. Selected individuals will be screened for histories of pulmonary disease, neuromuscular disorder, hypersensitivity to pyridostigmine or related compounds, current hepatic or renal dysfunction, or contraindications to cold water immersion. Any subject presenting a positive history for any of the above will be excluded from participation. Additionally, only subjects between 10% and 16% body fat will be used in order to reduce inter-subject variability in subcutaneous adipose insulation.

### PROTOCOL

Body Composition. All subjects will have percent body fat estimated by hydrostatic weighing (9) with simultaneous residual volume determination by nitrogen washout. Body density will be determined and percent body fat estimated using the Siri equation (28). Additionally, fifteen-site skinfold measurements will be performed to estimate insulation differences.

Experimental Treatments. Each subject will engage in four experiments: (1) following pyridostigmine ingestion and lying immersed to the neck in 20° C water, (2) following placebo ingestion and immersed to the neck in 20° C water, (3) following pyridostigmine ingestion and lying in 5° C air and (4) following placebo ingestion and lying in 5° C air. Subjects will be exposed to the environmental conditions for up to 180 minutes during each experiment. These experiments will be conducted employing a single-blinded counterbalanced design.

Subjects will report for testing following at least a three hour fast and will ingest either pyridostigmine (one 30 mg. tablet, p.o.; supplied by WRAIR) or a placebo (one

tablet, p.o.; supplied by WRAIR) 1.75 hours prior to the scheduled initiation of testing. This timing should allow attainment of peak plasma levels of the drug at a time near cold exposure (2). The composition of the placebo is identical to that of the pyridostigmine tablet except starch replaces the pyridostigmine. Subjects will be monitored continuously from the time of ingestion until it is judged medically safe for release. Each experiment will be separated by a minimum of 48 hours to allow complete elimination of the drug (2). All subjects will be tested at the same time of day throughout the experiment. Provision for meals will be made for subjects with inflexible meal schedules, and no subject will have more than one mealtime per day altered by the test schedule.

The same initial setup and subject instrumentation will be employed for all experiments. Subjects will be clad only in swimming shorts during the exposure periods. Prior to each test, the subject will be instrumented for ECG with recording electrodes attached to the subject's chest in a modified V-5 configuration, and during the water immersion experiments the electrodes will be covered with a transparent water-resistant cover (Tegaderm®). Core body temperature will be measured by both rectal and esophageal thermistors. To measure rectal temperature ($T_{re}$), a flexible thermistor will be inserted, by the subject, into the rectum to a point ~10 cm beyond the anal sphincter. A flexible, small diameter probe for measurement of esophageal temperature ($T_{es}$) will be inserted, by the subject, into the esophagus to heart level. A four-site skin temperature thermistor harness will be attached to the subject for measurement of mean skin temperature ($\bar{T}_{sk}$) and heat flow disks attached for the measurement of heat flows. Recording electrodes will be attached to the skin overlying the bellies of the pectoralis major and the vastus lateralis muscles for the recording of electromyographic activity (EMG) in the muscles. Additionally, a copper-constantin thermistor will be inserted into the belly of the contralateral vastus lateralis muscle to a depth of approximately 25 mm for the measurement of muscle temperature in order to examine transients in muscle temperature during exposure.

A flexible non-reactive catheter will be inserted into an arm vein by an experienced technician using aseptic techniques. The catheter will be covered with a transparent

dressing leaving the stopcock free for access during blood collection. Heparinized saline will be used to maintain patency of the catheter throughout the experiment. During the water immersion experiments, the catheterized arm will be suspended out of the water to maintain asepsis.

Following instrumentation and before taking the tablet, a 3.5 ml blood sample will be drawn to determine baseline red blood cell cholinesterase inhibition. The subject will then ingest the tablet. The initiation of exposure to the test environment will begin 1.75 hours following ingestion of the tablet. Prior to entering the test environment, the subject will lie quietly for 20 minutes, covered in blankets, at room temperature to insure stabilization of plasma volume. At the end of this period a 3.5 ml blood sample will be drawn from the catheter, following a 3.0 ml flush, for subsequent determination of: 1) hematocrit (microhematocrit method) and hemoglobin (Coulter Hemoglobinometer) and 2) red cell ChE inhibition (Technicon, Technicon Instrument Corporation). The blood will be stored briefly in an ice bath for subsequent analysis. In the water immersion experiments, the subject will lie quietly in air until the second resting blood collection has been completed and will be lowered into the pool of stirred water.

Six times during the test and once at the cessation, a 3.5 ml blood sample will be drawn from the catheter. All blood samples will be stored in an ice bath for subsequent analyses as described above. A maximum of 84.5 ml of blood will be drawn during each experiment, or 338 ml maximum for the entire protocol. Additionally, blood pressure will be measured by auscultation and EMG recorded on analog audio tape periodically during exposure. ECG and body core and muscle temperature will be recorded minute-by-minute and esophageal temperature and heat flow measured continuously to record muscle and body core temperature transients. Using both esophageal and rectal temperatures will allow better understanding of the relation between temperature transients (esophageal) deep body (rectal) temperature. In that the rectum is an underperfused area (26), $T_{RE}$ may be the better measure of deep body temperature. $T_{ES}$, on the other hand, better reflects blood temperature, both from peripheral perfusion and deep sources (26) and thus affect receptor responses.

$\dot{V}_E$, $\dot{V}O_2$, and $\dot{V}CO_2$ will be measured by open-circuit spirometry (Sensormedic Horizon MMC) for three consecutive minutes at 15 minute intervals during the tests. Cardiac output ($\dot{Q}$) will also be measured by $CO_2$ rebreathing (14) using an automated system (Sensormedic Horizon MMC) following the metabolic measurements. Also, during the test subjects will rate their thermal perceptions using a scale of thermal sensation (enclosure 1).

## STATISTICS

Eight subjects should be sufficient to discern differences between the pyridostigmine and placebo treatment. Kolka and Stephenson (15) were able to demonstrate significant effects in blood flow and thermoregulation in four males in the heat. A repeated measures analysis of variance will be used to statistically compare the responses obtained during the test conditions at drug and no-drug conditions at rest and during drug and no-drug conditions at each water temperature. Post hoc analyses, using the Newman-Kuels test, will be conducted on those variables found to be significantly different. A significance level of 0.05 will be used for all statistical tests.

## MILITARY RELEVANCE

It is the extreme toxicity of organophosphates which has lead many nations to include them in their chemical warfare arsenals. Despite Geneva Convention proscriptions on first use of CW agents, the production and stockpiling of these agents continues worldwide. The U.S. and some NATO nations have selected pyridostigmine bromide as the pretreatment drug of choice to combat the effects of CW agents. The mission of the Military Ergonomics Division includes understanding how soldiers can be expected to perform mission-oriented tasks under the variety of conditions they may encounter. This is especially true for thermally challenging environments where, according to Hanson and Goldman (12), military personnel may spend as much as 30% of the day during tactical operations. The conditions in which soldiers must operate include cold and cold-wet

environments and may occur after the soldier has begun pretreatment with pyridostigmine in anticipation of a CW attack. As a part of military operations, soldiers in the higher latitudes and at higher elevations may be exposed to the cold for prolonged periods of time. They may also engage in missions which require cold weather fording of streams or river crossings during which clothing becomes saturated. Even in cool environments, intense activity in MOPP clothing can produce heavy sweating soaking the overgarment and increasing heat flow to the environment. It is important to understand the impact of pyridostigmine pretreatment on the thermoregulatory responses of soldiers exposed to cold weather.

This study is part of a comprehensive program which will answer questions about the soldier's ability to survive and perform mission-essential activities under such conditions. The results of these studies should be important in the evaluation and further development of Army doctrine on expectations of a soldier's ability to tolerate environmental extremes, to perform at optimal levels in those environments when they have undergone pyridostigmine pretreatment. The findings could also influence Army doctrine on clothing and other protective garment requirements during operations in thermal extremes.

This protocol will be conducted under the Army's IND (#23509, 2 Feb 1987) "Use of Pyridostigmine as a Pretreatment Drug".

## MEDICAL RISKS AND PRECAUTIONARY MEASURES

Pyridostigmine use is <u>not</u> covered in the USARIEM Type Protocol for Human Research Studies in the Areas of Thermal, Hypoxic and Operational Stress, Exercise, Nutrition and Military Performance (approved 8 March 89), but the drug will be administered only in a quantity approved by the Food and Drug Administration for investigational purposes. Other procedures proposed in the protocol conform to guidelines for human research as stated in the Type Protocol. Although there are no specific guidelines in the Type Protocol for testing following administration of pyridostigmine,

every effort will be made to insure the safety of the subjects during participation in this study. All subjects will be medically screened before participation to exclude those for whom these conditions may pose a greater hazard than for normal, healthy persons.

A designated medical officer will be present or readily available at all times during the experimental periods in accordance with the specifications in the Type Protocol. Test subject participation will be discontinued in accordance with the physiological limits described in the Type Protocol or if there is an adverse response to the drug administration. Appropriate emergency medications and medical equipment specified by the assigned medical monitor will be available at all times during testing. Before testing begins, subjects will be familiarized with all equipment and procedures to be used and will be fully informed of the nature of the study as well as the requirements for participation. Furthermore, each subject will read and sign a Voluntary Agreement Affidavit (DA FORM 5303-R, enclosure 2) and will be fully informed of the right to withdraw from the study at any time without prejudice.

It is unlikely that the procedures outlined in this protocol will present excessive danger to the subjects. During all experiments, staff members will be present and at least one will be stationed near the subject to assist should the need arise. Testing will be discontinued should the subject shows signs of unusual distress during the test.

Appropriate and timely electrical safety checks will be performed on all required equipment by the Instrumentation Branch prior to the initiation of testing. During water exposure the equipment used for data collection will be operated by low-voltage battery powered instruments with appropriate grounding.

The test to determine body density by hydrostatic weighing involves completely submerging the subject in warm (~35° C) water. There is a slight risk of water intake into the respiratory tract. This risk is reduced by having the subject wear a nose clip and breathing through a mouthpiece connected to a snorkel tube secured above the water line. Water can be taken into the mouth only in the event the mouthpiece is removed while the

subject is underwater or if tubing connections uncouple. An attendant will be in direct visual contact and communication with the subject and will be able to assist should the need arise. The water is changed and the tank properly disinfected routinely. Residual lung volume determination is performed during hydrostatic weighing while the subject is submerged. The subject is required to rebreathe from a spirometer filled with 100% $O_2$. Breathing is deep and rapid and may produce minor lightheadedness or syncope. This is not deemed harmful and resolves rapidly.

Cold water immersion may result in mild hypothermia. The specific risk during exposure depends on several factors such as adiposity, body surface area and the subject's physical fitness. To minimize risk, exposure will be terminated if the subject shows a rectal temperature $\leq$ 35.0° C or a rate of change $\geq$ 0.6° C in 5 minutes. Immersion will be performed so that the subject can breathe and communicate freely with technicians. Testing will be conducted in the USARIEM Underwater Support Facility where continuous physiological monitoring can be maintained.

Venous catheterization involves some risk to the subject. Localized discomfort, syncope and mild hematoma may occur but usually quickly resolve. By employing aseptic techniques and using non-reactive plastic indwelling catheters, the probability of a local inflammatory reaction and infection will be reduced. Thrombosis, embolism and infections are potential outcomes but the occurrence is rare. The catheterization site will be covered and suspended out of the water to facilitate asepsis.

Insertion of the flexible thermistor into the rectum for monitoring core body temperature can result in mechanical injury to the mucous membranes of the rectum. As a safeguard, subjects will be asked to insert the lubricated probe themselves to minimize the chance of mechanical injury. There is a remote risk of electrical shock in the event of a current leak through the probe, however, Instrumentation Branch will check the equipment prior to the initiation of the experiment as directed.

Recording body core temperatures with an esophageal probe can result in mechanical injury to mucous membranes if the probe is inserted incorrectly. There may be discomfort with esophageal probes and the probe can cause nose bleeding. Subjects will be instructed in the proper technique for insertion which should greatly reduce the chance of injury. If the subject is unable to insert the probe, he will be assisted by a trained technician.

Muscle temperature will be measured with a copper-constantin thermocouple made of a small gauge wire which is inserted into a 21-gauge hypodermic needle. The thermocouple-needle assembly is sterilized by Cidex immersion followed by sterile saline rinse and alcohol (isopropyl) wipe. A length of PE-90 tubing, which has been sterilized by soaking in 90% isopropyl alcohol for at least 12 h, is attached to the needle and encases the thermocouple wire. The tubing stabilizes and supports the fragile thermocouple wire. The needle assemble will be advanced approximately 25 mm and will remain in place during the course of the experiment. The risks accompanying muscle temperature measurement are similar to those of venous catherization. Insertion may produce mild hematoma and or infection at the entry site. Minor discomfort may be experienced during the insertion of the thermistor and during the duration of its emplacement. The mild bruising which can occur around the entry site usually resolves quickly and is considered a minimal risk. Infection should be absent or will be minimized by the use of aseptic procedures.

During measurement of cardiac output by $CO_2$ rebreathing, the subject rebreathes a mixture of $CO_2$ and $O_2$ through a mouthpiece from a 5 liter anaesthesia bag. The $CO_2$ concentration in the bag may vary from 5 to 20%, depending on the anticipated mixed venous $CO_2$ concentration. During rebreathing the subject may feel lightheaded, but this sensation is transient and terminates soon after cessation of rebreathing. The subject will be accompanied and observed closely be a technician, and rebreathing will not continue for more than 30 seconds.

Adverse reactions to pyridostigmine are uncommon and usually associated with overdose. The maximal dosage proposed in this protocol is one 30 mg tablet in 48 hours. The 48 hour elapsed time is sufficient to allow virtually complete elimination of the drug. Although individual reactions to the drug vary, the dose employed has been deemed safe for use in humans. Appropriate medical intervention and atropine for treatment of adverse reactions will be available at all times through the medical monitors. Additionally, subjects will be instructed to abstain from consumption of ethyl alcohol for 8 hours before and after pyridostigmine ingestion. This precaution is taken because both ethyl alcohol and pyridostigmine can act as hypotensive agents. Ethyl alcohol consumption is proscribed to avoid the potential of interaction between the two which could alter cardiorespiratory and/or thermoregulatory function on days when the drug is administered.

DRUG INTERACTIONS/CHRONIC ILLNESS

When a threat of exposure to nerve agent has been determined to exist, soldiers may be instructed by their commander to begin taking the pretreatment pyridostigmine (30 mg tablets) every 8 hours. If exposed to nerve agent, the soldier must immediately receive the antidote combination of atropine and pralidoxime by injection to increase the chances of survival. Needless to say, there may be many pyridostigmine-treated soldiers on the battlefield, even though exposure to nerve agent may never occur.

There may be some soldiers with preexisting medical conditions who sometimes require daily medication for adequate control, and yet they may be considered "worldwide deployable." Thus, there may be soldiers subject to a pyridostigmine-drug interaction or a pyridostigmine-medical condition interaction. A possibility of pyridostigmine-drug interaction is based on similar target sites or a resultant change in the pharmacokinetics of either drug. Since there is no significant plasma protein binding by pyridostigmine, this eliminates the consideration of interactions involving competition for these sites. Only 10-25% of pyridostigmine is metabolized, so interactions with biotransformation processes is also of little importance. No attempt will be made to cover potential pyridostigmine interactions with every common drug; however, a few caveats are pointed out with regard to some common chronic medical problems requiring daily medication.

Hypertension: One in six Americans have hypertension. This is a well-recognized medical problem and many successful pharmacologic approaches are used to control this condition. Currently, several classes of drugs are used in the treatment of hypertension: diuretics (thiazide, loop, potassium sparing), beta-blockers, alpha-blockers, alpha$_2$ agonists (primarily centrally acting), converting enzyme inhibitors, calcium channel blockers, and direct acting vasodilators. Of these, few interactions are anticipated.

Beta-blockers, however, may pose a problem. Beta$_1$-antagonists have negative chronotropic and inotropic effects on the heart. Pyridostigmine augments vagal effects on the heart, so additive effects on heart rate may occur, resulting in a further reduction in cardiac output and blood pressure. Non-selective beta blockers also block beta$_2$-receptors and can cause an increase in airway resistance. Bronchoconstriction is not a problem with pyridostigmine at the recommended dosage; however, it may become manifest in an individual who is also taking a non-selective beta blocker or in a previously undiagnosed individual with reactive airway disease.

It is not known if pyridostigmine would increase the incidence of syncope in patients taking alpha-blockers, alpha$_2$ agonists, converting enzyme inhibitors, calcium channel

blockers, or direct acting vasodilators; however, if volume depletion is added to this scenario, this might enhance the likelihood of seeing the additive effects of pyridostigmine with these drugs. Patients should be advised of the possibility of becoming lightheaded, especially if not properly hydrated. Initiation of pyridostigmine under medical supervision should be considered.

Asthma: A known asthmatic is not worldwide deployable. However, a desert environment and/or pyridostigmine may unmask a previously undiagnosed individual with hyperreactive airways.

Glaucoma: Anticholinesterase drugs are often used in the treatment of several forms of glaucoma, so pyridostigmine would not be a problem, but simply additive. Effects of either or both drugs may interfere with night vision. On the other hand, timolol (a non-selective beta blocker) is also used to reduce intraocular pressure, and as mentioned earlier, in combination with pyridostigmine may result in bronchoconstriction in an individual who also has hyperreactive airways.

Low "dibucaine number" or low plasma cholinesterase: Dibucaine is used as a diagnostic tool because it inhibits plasma (or "pseudo-" or "butyro-") cholinesterase to varying degrees. Dibucaine inhibits the normal (homozygote) enzyme by 70-85%, hence a dibucaine #80 indicates the presence of normal enzyme, and the incidence in the population is 96%. Dibucaine #50-65 (50-65% inhibition) is characteristic for the heterozygote with an incidence of about 4%. Dibucaine #16-25 signifies the abnormal homozygote and occurs at a frequency of about 0.03%.

A person with a low dibucaine number has plasma cholinesterase that is resistant to inhibition by dibucaine. Pyridostigmine inhibits normal plasma cholinesterase by about 35%, and although it isn't known exactly how much pyridostigmine inhibits the atypical enzyme in general, the atypical enzyme is also resistant to inhibition by carbamates. However, the purpose of pyridostigmine pretreatment is to protect "true" cholinesterase at the neuromuscular junction (and reflected in red blood cell cholinesterase activity). People with abnormal plasma cholinesterase generally have normal true cholinesterase, and therefore, should be offered the same protection from pyridostigmine.

The significance of a low dibucaine number is that the individual will have a prolonged response to selected drugs, e.g., succinylcholine and ester local anesthetics. This is because the individual has a low quality (not necessarily low quantity) plasma cholinesterase that is normally responsible for metabolizing and inactivating these drugs. Regardless of whether pyridostigmine has an effect on this abnormal plasma

cholinesterase, the individual will have a higher blood level and prolonged response to drugs which require plasma cholinesterases for bioinactivation.

Decreased levels of plasma cholinesterase (as much as 50%) are sometimes seen in people taking birth control pills or corticosteroids, but again, the clinical significance of this in soldiers taking pyridostigmine is not related to the efficacy of nerve agent pretreatment, but rather is confined to enhanced responses to drugs that depend on the enzyme for their metabolism (e.g., succinylcholine and ester local anesthetics).

Antimalarials: Depending on the region, drugs used for prophylaxis/suppression and treatment of malaria symptoms include chloroquine, primaquine, mefloquine, quinine, quinidine, Fansidar (pyrimethamine + sulfadoxine), doxycycline and tetracycline. These drugs act by interfering with parasite replication and protein synthesis; therefore, no mechanistic interactions with pyridostigmine are anticipated. However, there may be interactive side effects: Quinine and quinidine (and possibly mefloquine based on structural similarity) have a weak nondepolarizing blocking effect on skeletal muscle. This side effect would tend to be negated by pyridostigmine. With regard to quinidine's cardiac effects, concurrent pyridostigmine administration may make A-V block more attainable and hypotension accentuated. Another possible interaction between antimalarials and pyridostigmine is the possible additive effects on the gastrointestinal tract. Loose bowels is the most common complaint about both antimalarials and pyridostigmine, and together they may pose a simple inconvenience or possibly a genuine problem.

Gastrointestinal problems (reflux esophagitis, peptic ulcers) may be exacerbated by pyridostigmine.

Hyperthyroid patients may develop atrial fibrillation if administered pyridostigmine.

The enclosed report from Military Medicine provides further information on these topics and on the interactions of pyridostigmine and drugs used in anesthesia.

## VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 70-25, the proponent agency is OTSG

### PRIVACY ACT OF 1974

**Authority:** 10 USC 3013, 44 USC 3101, and 10 USC 1071-1087

**Principle Purpose:** To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purposes.

**Routine Uses:** The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs; adjudication of claims; and for the mandatory reporting of medical conditions as required by law. Information may be furnished to Federal, State and local agencies.

**Disclosure:** The furnishing of your SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in the investigational study.

### PART A(1) - VOLUNTEER AFFIDAVIT

**Volunteer Subjects in Approved Department of the Army Research Studies**

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____, SSN _____,

having full capacity to consent and having attained my _____ birthday, do hereby volunteer/give consent as legal representative for _____, to participate in _____

Effects of pyridostigmine bromide on thermoregulatory, metabolic and cardiorespiratory responses to cold stress

*(Research study)*

under the direction of CPT W. Keith Prusaczyk, Ph.D.

conducted at US Army Research Institute of Environmental Medicine, Natick, MA 01760-5007

*(Name of Institution)*

The implications of my voluntary participation/consent as legal representative; duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by CPT W. Keith Prusaczyk, Ph.D.

Contact telephone(s): 508-651-5142

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights/the rights of the person I represent on study-related injury, I may contact

Office of Chief Counsel

at US Army Natick Research, Development and Engineering Center (508)651-4322

*(Name, Address and Phone Number of Hospital (Include Area Code))*

I understand that I may at any time during the course of this study revoke my consent and withdraw/have the person I represent withdrawn from the study without further penalty or loss of benefits; however, I/the person I represent may be required (*military volunteer*) or requested (*Civilian volunteer*) to undergo certain examination if, in the opinion of the attending physician, such examinations are necessary for my/the person I represent's health and well-being. My/the person I represent's refusal to participate will involve no penalty or loss of benefits to which I am/the person I represent is otherwise entitled.

_____

### PART A (2) - ASSENT VOLUNTEER AFFIDAVIT *(MINOR CHILD)*

I, _____, SSN _____, having full capacity to consent and having attained my _____ birthday, do hereby volunteer for _____ to participate in _____

_____

*(Research Study)*

under the direction of _____

conducted at _____

*(Name of Institution)*

*(Continue on Reverse)*

**PART A(2) - ASSENT VOLUNTEER AFFIDAVIT** *(MINOR CHILD) (Cont'd.)*

The implications of my voluntary participation; the nature, duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by

CPT W. Keith Prusaczyk, Ph.D.

I have been given an opportunity to ask questions concerning the investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights I may contact

at

*(Name, Address, and Phone Number of Hospital (Include Area Code))*

I understand that I may at any time during the course of the study revoke my assent and withdraw from the study without further penalty or loss of benefits; however, I may be requested to undergo certain examination if, in the opinion of the attending physician, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

**PART B - TO BE COMPLETED BY INVESTIGATOR**

INSTRUCTIONS FOR ELEMENTS OF INFORMED CONSENT: *(Provide a detailed explanation in accordance with Appendix E, AR 40-38 or AR 70-25.)*

This study will examine the effects of a small dose (30mg) of pyridostigmine bromide, taken by mouth, on your physiological responses to rest in cold water (20° C or 68° F) and in cold air (5° C or 41° F). If exposure to chemical warfare nerve (CW) agents is expected, soldiers will begin taking small, repeated doses of pyridostigmine to counter the effects of exposure should it occur. After taking this drug, soldiers will still be expected to continue mission-oriented and mission-essential tasks despite the weather or climatic conditions. This study is part of a larger program which is designed to evaluate the soldier's ability to continue to perform duties following treatment with pyridostigmine under a variety of conditions.

Pyridostigmine is used by physicians in the treatment of some muscle disorders and to reverse the effects of certain drugs used during anesthesia. It has also been shown that it has the ability to significantly protect lab animals from the effects of CW nerve agent poisoning. The dose you will be taking is half that of the smallest commercially available tablet, so the dose will be well below therapeutic levels. You will be taking no more than one tablet over any two consecutive days to allow your body to eliminate all the drug before another tablet is given.

I do ☐ do not ☐ *(check one & initial)* consent to the inclusion of this form in my outpatient medical treatment record.

| SIGNATURE OF VOLUNTEER | DATE | SIGNATURE OF LEGAL GUARDIAN *(If volunteer is a minor)* |
|---|---|---|
| PERMANENT ADDRESS OF VOLUNTEER | TYPED NAME OF WITNESS | |
| | SIGNATURE OF WITNESS | DATE |

Precautions. The use of pyridostigmine in this study is considered investigational, i.e. the preparation is deemed experimental for the purposes of investigation in this study. There are possible side effects from taking pyridostigmine, but these are most commonly associated with large doses or hypersensitivity to the drug. You should tell the screening physician if you or anyone in your family has a proven or suspected hypersensitivity to the drug. Some of the side effects seen include slowing of the heart rate, abdominal discomfort and excess sweating. These symptoms usually last only as long as you continue to take the drug, or the drug remains in your system. By 12 hours after administration over 98% of the drug is eliminated from the system in an average individual.

For your own protection, you must tell the screening physician if you are taking any prescription or non-prescription drugs, or have taken any in the previous week. You must also reveal any history of lung problems (including eg. asthma), muscular problems, heart or circulatory problems or anything which may prevent you from exposure to the cold. You must not drink any alcoholic beverages for at least 8 hours before and 12 hours after taking the drug. This is for your protection as there may be some interactions between alcohol and pyridostigmine. Pyridostigmine can cause some blurring of your vision, so do not operate any motor vehicle for at least 12 hours after taking the drug. We will watch you closely from the time you take the drug until it is judged safe for you to leave laboratory. Also, we will have a medical monitor available should you feel the need, or should we determine there is a need, for medical treatment.

Body Composition. Before we begin the actual experimental testing, you will engage in a test to determine your body composition, also called a body-fat test. During this test you will be submerged in a tank of warm water while breathing air through a mouthpiece connected to a snorkel tube. While under water, you will have to blow as much air out of your lungs as possible and hold your breath for approximately 10 seconds. At no time will you be disconnected from a supply of oxygen. After you have been weighed under water, you will come to the surface and breathe 100% oxygen for about 20 to 30 seconds. We will also be taking measurements of your skinfold thicknesses as a second measure of your body composition. This procedure involves using a caliper device to measure your external skin and fat thickness. The procedure is routinely used and is deemed safe.

Experimental Protocol. You will report to the laboratory after a minimum three hour fast. Provision for meals will be made for subjects with inflexible meal schedules, and no subject will have more than one mealtime per day altered by the test schedule. During the experimental sessions you will only be required to remain lying quietly on a lounge chair. You will engage in four (4) tests, two in water and two in air, once each after taking the pyridostigmine and once after taking a placebo, a tablet with the same make-up as the pyridostigmine tablet but with the drug replaced by starch.

Before each test you will have a catheter, a small flexible needle for the collection of blood, inserted into one of your arm veins by an experienced technician. This is done so that we may collect blood samples many times without repeatedly inserting a needle. During each test we will draw about 2.9 fluid ounces of blood, or approximately 11.3 fluid

ounces over the course of the study. This amount of controlled blood loss should not harm you.

The test will require you to remain in the specified conditions until: your physiological responses exceed the specified limits for safety, you voluntarily end your exposure, or you complete 180 minutes of exposure. During the water tests you will be lying submerged to about shoulder level in a pool of stirred water at the temperature indicated above. The arm with the catheter in it will be supported out of the water. During the air tests you will be lying quietly on a lounge chair in the environmental temperature indicated above. During both tests you will be wearing only swimming trunks.

We will be measuring your body's heat flow using a small rectal probe and a harness which will allow us to attach small thermistors (very small wires) to the surface of your skin. You will also have small probes attached to your skin for measuring the electrical activity of your muscles. We will moniter your heart's electrical activity using small recording electrodes attached to your chest. To measure rapid changes in your body temperature you will have a small flexible probe inserted into your esophagus (gullet). To measure your muscle temperature, we will insert a small wire thermistor into your muscle using a small-gauge hypodermic needle.

Periodically during the test, we will measure your oxygen uptake using a system for measuring metabolic rate. You will breathe through a mouthpiece connected to the equipment by a tube. The mouthpiece will be in your mouth for only about four minutes during each of these collections. You will also be required to wear a noseclip during this procedure.

Following the metabolic rate measurements, we will measure your cardiac (or heart) output of blood. This is done by having you breathe a mixture of carbon dioxide and oxygen for about 15 seconds. During this procedure you will be wearing the mouthpiece and noseclip as before.

The expected duration of your participation will be approximately twenty-five (25) duty days although you will not be involved in actual testing all of these days. This schedule may be altered by unforseen circumstances, but every effort will be made to conclude data collection within this time.

Risks. During underwater weighing, there is some small possibility that water can get into the mouthpiece or the tubing and that you will breathe in some water, but keeping a firm grasp on the mouthpiece will greatly reduce the probability that this will occur and you will be connected to room air at all times.

The possible side effects of pyridostigmine were outlined above, but as indicated, these should be minimal in the dosage used in this study.

There is some danger of damage to the lining of your rectum on insertion of the rectal probe. The dangers and discomfort caused by the probe are minimized by allowing

you to insert the lubricated probe by yourself. Discomfort following insertion to a depth of approximately 4 inches should be minimal. Insertion of the esophageal probe may cause some brief discomfort and/or gagging, but this should gradually disappear. A small amount of anesthetic is applied to the sterile probe to reduce the discomfort. Careful instructions will be given so that when you insert the probe the chance of injury is reduced. If you are unable to insert the probe, you may be assisted by one of the technicians.

Insertion of the probe to measure muscle temperature is accomplished through a hypodermic needle and should involve no more discomfort than any hypodermic needle insertion. The probe will be inserted into the large muscle on the side of your leg. Insertion may result in infection, some bruising and/or irritation at the site of insertion but these symptoms usually disappear within a day or two. The chance of infection is reduced by the use of aseptic techniques and the procedure will be performed by an experienced technician.

Insertion of the venous catheter introduces a small chance of infection and/or bruising at the site. The possibility of infection is reduced by the use of aseptic technique performed by an experienced technician. There is a chance of bruising at the site of introduction, but this usually lasts only a day or two when it occurs.

When in the cold environments, you will likely become slightly hypothermic (your body temperature will be lowered). Body temperature will be monitored continuously and you will be required to end the exposure if your body temperature should drop too low (below 95.0°F) or too rapidly (faster than 1.0°F in 5 minutes). Although potentially uncomfortable, neither the air nor the water temperature is low enough to produce damage to the skin.

Breathing carbon dioxide in the concentrations used for measuring heart output may cause some dizziness, light-headedness and/or nausea. These symptoms usually quickly resolve when you resume breathing room air.

**Benefits.** The benefits you gain from this study are both direct and indirect. You will gain knowledge of your percent body fat as determined by the most accurate method currently in use. You will learn about your physiological responses to exposure to a cold environment. You will also be able to experience the effects of pyridostigmine pre-treatment, in which case you may be better prepared to continue mission-essential tasks, and perhaps increase your chances to survive in the event you are ever exposed to CW agents.

**Withdrawal and Confidentiality.** You may withdraw from this study at any time without fear of retaliation or discrimination. You will receive a copy of this informed consent for your records. You should keep this copy for future reference on your participation in this study. All data and medical information obtained about you will be considered privileged, that is held in confidence. You will not be identified in any public presentation of the results of this study. Complete confidentiality cannot be guaranteed, particularly for military subjects. The applicable regulation notes the possibility that U.S. Food and Drug

Administration (FDA) and/or USAMRDC (U.S. Army Medical Research and Development Command) officials may inspect records.

ATTACHMENT 1 (CONT)

**Effects of pyridostigmine bromide on human thermoregulation during cold water immersion.** Prusaczyk, W.K., Sawka, M.N. J. Appl. Physiol. 1991;71(2):432-437.

US Army Research Institute of Environmental Medicine, Natick, Massachusetts 10760-5007.

"This study examined the effects of an oral 30-mg dose of pyridostigmine bromide (PYR) on thermoregulatory and physiological responses of men undergoing cold stress. Six men were immersed in cold water (20 degrees C) for up to 180 min on two occasions, once each 2 h after ingestion of PYR and 2 h after ingestion of a placebo. With PRY, erythrocyte cholinesterase inhibition was 33 +/- 12% (SD) 110 min postingestion (10 min preimmersion) and 30 +/- 7% at termination of exposure (mean 117 min). Percent cholinesterase inhibition was significantly related to lean body mass (r = -0.91, P less than 0.01). Abdominal discomfort caused termination in three of six PYR experiments but in none of the control experiments (mean exposure time 142 min). During immersion, metabolic rate, ventilatory volume, and respiratory rate increased significantly (P less than 0.05) over preimmersion levels and metabolic rate increased with duration of immersion (P less than 0.01) in both treatment but did not differ between conditions. PYR had no significant effect on rectal temperature, mean body temperature, thermal sensations, heart rate, plasma cortisol, or change in plasma volume. It was concluded that a 30-mg dose of PYR does not increase an individual's susceptibility to hypothermia during cold water immersion; however, in combination with cold stress, PYR may result in marked abdominal cramping and limit cold tolerance."

**Modulation of the dose-dependent effects of atropine by low-dose pyridostigmine: quantification by spectral analysis of heart rate fluctuations in healthy human beings.** Izraeli, S., Alcalay, M., Benjamini, Y., Wallach, K.R., Tochner, Z., Akselrod, S. Pharmacol. Biochem. Behav. 1991:39;13-17.

Israel Defence Forces-Medical Corps, Tel-Aviv.

"The interaction between a low-dose cholinesterase inhibitor, pyridostigmine (PYR), and atropine was investigated by spectral analysis of heart rate fluctuations in eight healthy humans. Each subject was given increasing boluses of IV atropine during treatment with PYR (30 mg.3/day) or placebo. PYR attenuated the bimodal dose-dependent changes in the respiratory peak (which respresents the parasympathetic control) in response to atropine. We suggest that spectral analysis can be used for quantifying the complex dose-dependent cholinergic agonist-antagonist interactions, and may help to disclose an asymptomatic low-dose intoxication with acetylcholinesterase inhibitors."

ATTACHMENT 2

Preclinical Studies

**Myopathic alterations in extraocular muscle of rats subchronically fed pyridostigmine bromide.** Schuschereba, S.T., Bowman, P.D., Vargas, J.A., Johnson, T.W., Woo, F.J., McKinney, L. Toxicol. Pathol. 1990:18(3):387-95.

Letterman Army Institute of Research, Presidio of San Francisco, California.

"To determine whether alterations in extraocular muscle morphology occur after subchronic oral administration of pyridostigmine bromide, rats were continuously fed 90 mg/kg in meal and examined at 1, 2, 4, 7, and 15 days. Within the 1st day, blood acetylcholinesterase activity was reduced by 87% and remained inhibited by 74-91% during the study. Light microscopy demonstrated that by day 1 approximately 3% of the extraocular myofibers were shrunken and invaded by inflammatory cells. The most severe degenerative changes consisting of vacuoles and inflammatory cell infiltration occurred at day 1, with progressively less severe changes at days 2 and 4. At days 7 and 15, 1.3-4.5% of the myofibers still exhibited damage. Ultrastructurally, all presynaptic areas were normal but the postsynaptic areas of affected myofibers at days 1, 2, and 4 showed myofilament and Z-band dissolution, mitochondrial inclusions, subneural fold and T-tubule/sarcoplasmic reticulum vacuolization, and subneural fold depth reduction. By days 7 and 15, these changes were diminished in some cases, and in others alterations appeared similar to day 1. Apparently, subchronic feeding of pyridostigmine bromide induces myopathic rather than neurogenic changes in rat extraocular muscle, and the myopathy is different in these muscles than in the diaphragm from the same rats."

**Primary dermal irritation potential of physostigmine salicylate, physostigmine free-base, and pyridostigmine bromide in New Zealand white rabbits.** Magnuson, D.K., Zaucha, G.M., Clifford, C.B., Korte, D.W. Report; ISS LAIR-438, Toxicology Ser-254; Order No. AD-A217812, 1990, 34 pp.

Letterman Army Institute of Research, Presidio of San Francisco, California.

"Physostigmine salicylate is being considered by the US Army Medical Research and Development Command as a replacement for pyridostigmine bromide in treatment regimens which protect soldiers from nerve agent toxicity/lethality. The primary dermal irritation potentials of physostigmine salicylate, physostigmine free-base, and pyridostigmine bromide were determined in male rabbits by using a modified Draize method. Each test compound was applied to two sites on the backs of a group of rabbits for a 4-h period. Exposure sites were evaluated for erythema and edema at approximately 1, 24, 48, and 72 h after removal of the test material. No skin reactions attributable to physostigmine salicylate were detected at any time during the 14-28 day observation periods. One animal in group 1 treated with pyridostigmine exhibited very slight erythema in one of the two test compound quadrants. One animal in group 3 also exhibited slight erythema in one of the two quadrants after exposure to physostigmine free-base. Of the animals in

ATTACHMENT 2 (CONT)

group 4 that were exposed to all three test compounds, the only reaction observed occurred in one animal that exhibited very slight erythema at the pyridostigmine test site. Physostigmine salicylate, physostigmine free-base, and pyridostigmine bromide were nonirritants under conditions of this study."

**Comparison of anticholinesterases and their effects on acetylcholine-activated ion channels.** Wachtel, R.E. Anesthesiology 1990;72(3):496-503.

Veterans Administration Medical Center, Iowa City, Iowa.

"Single-channel recording techniques were used to examine interactions between anticholinesterases and ion channels activated by acetylcholine. Single-channel currents activated by 200 nM acetylcholine were recorded from cell-attached patches of BC3H1 mouse tumor cells grown in culture. Channels were recorded in the absence and presence of edrophonium (1-20 _M), neostigmine (2-20 _M), or pyridostigmine (10-200 _M). All 3 drugs shortened channel open time but did not alter single-channel current amplitude. The effects on channel open time were not secondary to inhibition of cholinesterase but appeared to involve direct interactions between the anticholinesterase drugs and acetylcholine-activated channels. Drug concentrations calculated to reduce the time constant of open time distributions by 50% were 3.8 _M edrophonium, 4.6 _M neostigmine, and 97 _M pyridostigmine. Channel open time was decreased by edrophonium at concentrations comparable to those occurring during reversal of neuromuscular block, but it was reduced by neostigmine and pyridostigmine only at levels higher than those encountered clinically. Differences in interactions between anticholinesterases and acetylcholine-activated channels at the end plate may account for some of the clinical differences between these drugs."

**Toxic interactions between repeated soman and chronic pyridostigmine in rodents.** Kerenyi, S.Z., Murphy, M.R., Hartgraves, S.L. Pharmacol. Biochem. Behav. 1990;37(2):267-71.

Radiation Biology Branch, USAF School of Aerospace Medicine, Brooks Air Force Base, Texas.

"These experiments examined the interactions of pyridostigmine, a reversible, peripherally acting anticholinesterase, with soman, an irreversible, peripherally and centrally acting anticholinesterase. Lethality, weight change, symptoms, and serum cholinesterase inhibition were determined following five daily injections of soman in rodents implanted with osmotic pumps containing two concentrations of pyridostigmine or vehicle. Concurrent exposure to both anticholinesterases had no effect on any measure at pyridostigmine-induced cholinesterase inhibition levels of 35% or 70% compared to controls. These results emphasize the safety of pyridostigmine as a pretreatment against organophosphate toxicity."

ATTACHMENT 2 (CONT)

**Acute effects of oral pyridostigmine bromide on conditioned operant performance in rats.** Shih, J.H., Liu, W.F., Lee, S.F., Lee, J.D., Ma, C., Lin, C.H. Pharmacol. Biochem. Behav. 1991;38(3):549-53.

Chemical Systems Division, CSIST, Lungtan.

"The present study was undertaken to evaluate the dose-response and time-course effects of acute oral administration of pyridostigmine over a broad dose range (3-40 mg/kg) on the lever pressing of rats maintained under a multiple fixed-ratio (FR-20) time-out schedule of reinforcement for water reward. The drug produced a dose-dependent biphasic response depression in the overall rate of FR responding. Low doses of pyridostigmine (.ltoreq.12 mg/kg) that caused no gross signs of toxicity only moderately decreased rates of responding, primarily due to a decrease in response rates. High doses of pyridostigmine (>24 mg/kg), which produced overt signs of peripheral cholinergic intoxication, markedly suppressed overall responding, primarily due to cessation of responding. The lowest ED of performance disruption was 6 mg/kg, and (.ltoreq.12 mg/kg) had an onset latency within 40-80 min and a duration of 20-80 min, whereas high doses (.gtoreq.24 mg/kg) had an onset latency of 20-40 min and a duration greater than 80 min. These results suggest the recommended human therapeutic or prophylactic regimen of 30-120 mg pyridostigmine, orally taken each 8 h, might adversely affect behavioral performance."

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Kerenyi, S.Z., Murphy, M.R., Hartgraves, S.L. Toxic interactions between repeated soman and chronic pyridostigmine in rodents. Pharmacol. Biochem. Behav. 1990;37(2):267-71.

Magnuson, D.K., Zaucha, G.M., Clifford, C.B., Korte, D.W. Primary dermal irritation potential of physostigmine salicylate, physostigmine free-base, and pyridostigmine bromide in New Zealand white rabbits. Report; ISS LAIR-438, Toxicology Ser-254; Order No. AD-A217812, 1990, 34 pp.

Magnuson, D.K., Zaucha, G.M., Clifford, C.B., Korte, D.W. Comparison of anticholinesterases and their effects on acetylcholine-activated ion channels. Anesthesiology 1990;72(3):496-503.

Prusaczyk, W.K., Sawka, M.N. Effects of pyridostigmine bromide on human thermoregulation during cold water immersion. J. Appl. Physiol. 1991;71(2):432-437.

Schuschereba, S.T., Bowman, P.D., Vargas, J.A., Johnson, T.W., Woo, F.J., McKinney, L. Myopathic alterations in extraocular muscle of rats subchronically fed pyridostigmine bromide. Toxicol. Pathol. 1990:18(3):387-95.

Shih, J.H., Liu, W.F., Lee, S.F., Lee, J.D., Ma, C., Lin, C.H. Acute effects of oral pyridostigmine bromide on conditioned operant performance in rats. Pharmacol. Biochem. Behav. 1991;38(3):549-53.

DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

REPLY TO ATTENTION OF

June 6, 1991

Human Use Review and
Regulatory Affairs Office

SUBJECT: IND 23509 - Pyridostigmine Bromide - WR 270,710 (Serial No. 026)

CENTER FOR
REC'D
JUN 07 1991
HFN-120
DRUGS AND BIOLOGICS

Director
Division of Neuropharmacological
Drug Products (HFD-120)
Office of Drug Review I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir:

Enclosed in triplicate is an additional clinical study entitled "Effects of Multiple Dose Pyridostigmine Administration on Thermoregulation During Exercise in Cold Air," to be conducted by Donald E. Roberts, Ph.D., under this IND. Although Dr. Roberts is the principal investigator, the test article will be administered under the supervision of the medical monitor, Captain James E. Cook, Medical Corps. A completed and signed Form FDA 1572 and curriculum vitae for Captain Cook are also enclosed.

This study was approved by the U.S. Army Research Institute of Environmental Medicine Human Use Review Committee on April 10, 1991 and by the Acting Chairman of The Surgeon General's Human Subjects Research Review Board on May 1, 1991. Copies of those approvals are enclosed. Recommended revisions have been incorporated.

If you have any questions concerning this submission, please contact Ms. Marty Myers at (301) 663-2165.

Sincerely,

Gregory P. Berezuk
Lieutenant Colonel, Medical
Service Corps
Chief, Human Use Review and
Regulatory Affairs Office

## VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 70-25; the proponent agency is OTSG

### PRIVACY ACT OF 1974

**Authority:** 10 USC 3012, 44 USC 3101, and 10 USC 1071-1087.

**Principle Purpose:** To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purposes.

**Routine Uses:** The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study, implementation of medical programs, adjudication of claims, and for the mandatory reporting of medical conditions as required by law. Information may be furnished to Federal, State and local agencies.

**Disclosure:** The furnishing of your SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

### PART A(1) - VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____, SSN _____,

having full capacity to consent and having attained my _____ birthday, do hereby volunteer/give consent as legal representative for _____, to participate in _____

Effects of Multiple-Dose Pyridostigmine Administratioo on Thermoregulation

During Exercise in Cold Air
(Research Study)

under the direction of Donald E. Roberts, Ph.D.

conducted at US Army Research Institute of Environmental Medicine, Natick, MA 01760-5007
(Name of Institution)

The implications of my voluntary participation/consent as legal representative; duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by Donald E. Roberts, Ph.D.

Contact telephone(s): (508) 651-4837

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights/the rights of the person I represent on study-related injury, I may contact

Office of Chief Counsel

at US Army Natick Research, Development and Engineering Center (508)651-4322
(Name, Address and Phone Number of Hospital (Include Area Code))

I understand that I may at any time during the course of this study revoke my consent and withdraw/have the person I represent withdrawn from the study without further penalty or loss of benefits; however, if the person I represent may be required (military volunteer) or requested (civilian volunteer) to undergo certain examination if, in the opinion of the attending physician, such examinations are necessary for my/the person I represent's health and well-being. If my/the person I represent's refusal to participate will involve no penalty or loss of benefits to which I am/the person I represent is otherwise entitled.

_____

### PART A (2) - ASSENT VOLUNTEER AFFIDAVIT (MINOR CHILD)

I, _____, SSN _____ having full

capacity to consent and having attained my _____ birthday, do hereby volunteer for _____

_____ to participate in _____

_____
(Research Study)

under the direction of _____

conducted at _____
(Name of Institution)

(Continue on Reverse)

PART A(2) - ASSENT VOLUNTEER AFFIDAVIT (MINOR CHILD) (Cont'd.)

The implications of my voluntary participation; the nature, duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by

_____

I have been given an opportunity to ask questions concerning the investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights I may contact

_____

at _____

(Name, Address, and Phone Number of Hospital Graduate Area Contact)

I understand that I may at any time during the course of this study revoke my assent and withdraw from the study without further penalty or loss of benefits; however, I may be requested to undergo certain examination if, in the opinion of the attending physician, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

_____

PART B - TO BE COMPLETED BY INVESTIGATOR

INSTRUCTIONS FOR ELEMENTS OF INFORMED CONSENT: *(Provide a detailed explanation in accordance with Appendix E, AR 40-38 or AR 70-25.)*

Pyridostigmine has been fielded by the US Army as a pretreatment drug against nerve gas. However, the effects of pyridostigmine on exercise and cold exposure are not well understood. This study will examine the effect of multiple-dose pyridostigmine administration (30 mg three times daily) on your ability to stay warm and effectively use food sources during low intensity work in a cold environment (40° F). The results of this study will help determine doctrine concerning the use of troops treated with pyridostigmine.

If you have a history of asthma, you should not volunteer for this study. For your own safety, you must tell the principal investigator or the medical monitor if you are taking any prescription or non-prescription medicines during the tests or during the ten days before tests begin. You must abstain from the consumption of alcoholic beverages before and during the pyridostigmine administration. You will undergo medical screening before beginning the study to help ensure that you have no medical abnormalities that might increase your risk of participating in this study.

This study will be divided into four parts: the first ten days will not involve pyridostigmine treatment and will be devoted to collection of control data; the next 7 days will involve pyridostigmine administration and collection of data. You will be required to take one pill (either pyridostigmine or placebo e.g. a tablet with no

I do ☐ do not ☐ *(check one & initial)* consent to the inclusion of this form in my outpatient medical treatment record.

| SIGNATURE OF VOLUNTEER | DATE | SIGNATURE OF LEGAL GUARDIAN *(If volunteer is a minor)* |
|---|---|---|
| PERMANENT ADDRESS OF VOLUNTEER | TYPED NAME OF WITNESS | |
| | SIGNATURE OF WITNESS | DATE |

active ingredients) 3 times daily with at least 8 hours between pills. You will report to the lab before breakfast on the days when you take pills. You will consume one pill and be given two more pills for that day. You will be given a time when those pills should be taken and you will phone the USARIEM CQ to vertify the time that you took the pill. If you fail to call on time, an NCO will be sent to find you. On the days that you are not working in the chamber, you will be allowed to have breakfast. On the days when you are in the chamber, we will provide a source of carbohydrate and you will then be allowed to eat after the trial is finished. The next 7 days will not involve testing or drug adminstration. During this time, you will not have any restrictions except to abstain from alcohol for 24 hours before you start the second phase. You will then repeat the 7 days of drug adminstration with the drug not taken in the first phase. The schedule will be arranged for each phase so that the only weekend involvement will be taking pills and drawing blood. This will require you to report to the lab before breakfast as mentioned above. The duration of your participation for this study is approximately 2 hours per day on two days during the pretest, approximately 2 hours per day for 8 days (non-exercise trial days) during the two phases and approximately 7 hours per day for 8 days during the exercise trials during the two phases. This time commitment will be over a five to six week period.

During the first 10 days, you will undergo tests to determine your body composition. You will be submerged in a tank of warm water while breathing air through a mouthpiece (nose closed off) connected to a snorkel tube. You will be asked to blow out as much air as possible and to hold your breath for approximately 10 seconds. At no time will you be disconnected from a supply of air. We will also use a caliper device to measure your skin and fat thickness. We will measure your body's capacity for exercise ($\dot{V}O_2max$) by determining its ability to consume and use oxygen. You will exercise by running on a treadmill and gradually increasing exercise intensity. At each increasing step, we will measure your oxygen uptake by having you breathe through a rubber mouthpiece and plastic breathing valve similar to scuba diving equipment. You will continue to exercise to the point of your maximal ability or until you feel you cannot continue. Each day of the study, we will obtain a nude body weight before breakfast to monitor hydration status.

You will engage in 8 exercise-cold trials which will involve 2 work intensities (25% and 50% of $\dot{V}O_2max$) with each being repeated 2 times each phase (after 2 days of drug use and after 7 days of drug use). Each exercise trial will involve walking on a treadmill in an environmental chamber (40° F) for 3 hours (5 minutes rest each hour). You will exercise while wearing shorts, tee-shirt and sneakers. Before each exercise trial you will be instrumented for heart activity (3 chest electrodes), skin temperature (small wires attached to your skin), and core temperature (a flexible probe (1/8 inch in diameter), which you insert approximately 4 inches into your rectum). On the exercise-cold trial days, we will

insert a venous catheter, a needle attached to a thin, flexible plastic tube, into an arm vein, where it will remain throughout that day's experiment. Prior to the start of exercise and once during each hour of exercise, we will draw a 13 ml (slightly less that 1/2 ounce) blood sample from the catheter for a total of 1 3/4 ounce each day. On non-exercise days during the pill administration, we will use a small bore needle to draw a single 3 ml (1/10 ounce) blood sample from a vein in your arm. The total amount of blood that will be withdrawn for this study is 15 ounces (approximately 1 pint).

Periodically during the exercise-cold trials, we will measure your oxygen uptake using a system (mouthpiece and valve) for collection of expired air. During the rest periods, we will weigh you and provide fluid for rehydration as needed.

The risks in this study include the risks associated with inserting a venous catheter, a venipuncture, with underwater weighing, with exercise in a cold environment, with taking pyridostigmine, and a small risk of electrical shock. The risks from inserting a venous catheter or venipuncture include pain, a small risk of hematoma (similar to a bruise), and infection. We will follow sterile procedures to minimize the risk of infection. You may accidentally inhale water during underwater weighing, but we have minimized the likelihood that this will happen by having you breathe through a snorkel. Exercise may uncover or worsen pre-existing heart problems, especially impaired blood flow to the heart muscle and irregular beats. There is a risk of falling on the treadmill which is minimized by the low intensity and the presence of technicians to help you. Risks associated with cold exposure include the possibility of freezing injury to skin and hypothermia. We will monitor rectal temperature, skin temperature, and heart rate continuously during exercise and cold exposure and if any skin temperature reaches 40° F, your core temperature reaches 95° F or exceeds 102.5° F or if heart rate is above 180 beats per minute for 5 consecutive minutes or if you appear or feel faint, sick or unable to continue, exercise will be stopped. At least one staff member will be watching you and ready to assist you if necessary. The side effects of taking pyridostigmine include slowing of your heart, abdominal discomfort, excess sweating, skin rash, excessive salivation and pupillary constriction. These symptoms disappear when the drug is discontinued.

Pyridostigmine has been used in medical practice for many years to treat myasthenia gravis (a rare muscle disorder), but the Food and Drug Administration regards its use for the present study as investigational. We do not expect any ill effects from your taking pyridostigmine, but medical coverage will be maintained during drug administration and all testing. Antidotes to pyridostigmine are available, which you may be given according to the medical monitor's judgement if you have major side effects from the drug. There is also a chance of your developing a skin rash from the bromide which this form of pyridostigmine contains. There is a possibility of electrical shock from malfunction of the

equipment. We have minimized the risk by having the instrumentation laboratory inspect all equipment. The rectal probe may be uncomfortable to insert, and the sensation of having it in place may be unpleasant. However, the sensations associated with the probe tend to lessen over time.

The benefits you gain from this study are both direct and indirect. You will gain knowledge of your percent body fat as determined by the most accurate method currently in use. You will learn about your physiological responses to exposure to cold air environment. You will also be able to experience the effects of pyridostigmine pretreatment, in which case you may be better prepared to continue mission-oriented tasks, and perhaps increase your chances to survive in the event you are ever exposed to CW agents.

If you volunteer and are selected for this study, we hope that you will complete the tasks described and remain in the study until the end of the project. However, you are free to withdraw from the study at any time and for any reason, without prejudice. We will give you a detailed oral description of the study as well as this written description and give you a chance to ask questions. You should sign this document only after you have read and understood it. All data and medical information obtained about you as an individual will be considered privileged and held in confidence; you will not be identified in any presentation of the results. Complete confidentiality cannot be promised, particularly to subjects who are military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities, and applicable regulation notes the possibility that the Food and Drug Administration and USAMRDC officials inspect the records. You will be given a copy of this form for your records.

# APPENDIX 9.—FOOD AND DRUG ADMINISTRATION AND DEPARTMENT OF DEFENSE NEGOTIATIONS

SGRD-UMP 30 August 1990

MEMORANDUM FOR RECORD

SUBJECT: Proceedings of Meeting Between FDA and DOD Regarding Operation Desert Shield

1. The purpose of the meeting was to review issues pertaining to the regulatory approach to deploy necessary medical products currently in IND status in Support of Operation Desert Shield. The meeting began at 1315 hours. Those in attendance from the FDA included Associate Commissioner Nightingale, Chief Counsel Porter, Center for Drugs Director Dr. Peck, Deputy Director for Drug Review I Dr. Botstein, Ms. Witt (General Counsel), Ms. Lorraine (General Counsel), Center for Biologics Deputy Director Dr. Elaine Esber, Deputy Dir Assoc Commissioner Mr. Duncan, Director Drug Evaluation II Dr. Bilstad, Ms. Wion (General Counsel), Mr. Hoeting - Office of Compliance, Mr. Geyer (General Counsel), and several other distinguished FDA personnel. Those from the Department of Defense were Lt Col Lehmann, LTC Berezuk, Dr. Clawson, Dr. Brandt, and Mr. Winchester.

2. Discussion was oriented to the unusual circumstances and military medical needs of Defense in support of Operation Desert Shield. Attention was focused primarily on the issue of informed consent. Other topics of discussion included investigational labeling, other sections of the IND regulations, and the FDA-DOD Memorandum of Understanding.

a. FDA expressed some concern about liability and the need to comply with the regulations. Mr. Winchester reviewed the Feres Doctrine and cited a case of applicability of the Doctrine to a Federal Agency other than Defense.

b. Investigational framework. Dr. Peck pointed out the need to establish an appropriate investigational framework to collect observational data and evaluate the military medical products in question. It was recognized that data collection could not occur during military conflict. However, medical personnel can be apprised of what to look for to facilitate retrospective analyses. He suggested that labeling the diazepam autoinjector, "For military Use and Evaluation Only" might facilitate this process. Similar labeling could be applied to all soldier carried medical items with investigational status.

c. It was pointed out that use of the export regulation obviates the applicability of the IND regulations.

d. Ms. Porter pointed out that the investigational status of the nonapproved products cannot be abandoned altogether.

3. The attached worksheet was used as a guide to address CFRs of concern to Defense. The following are those concerns and a brief synopsis of the discussion:

a. 21 CFR 312.6 - Labeling of an Investigational New Drug. Defense cannot comply with the requirement to label service member carried investigational medical products, "Caution: New Drug - Limited by Federal (or United States) Law to Investigational Use". Labeling such as "FOR MILITARY USE ONLY" is acceptable for service member carried items. Like informed consent, "investigational" labeling itself could undermine the soldier's confidence in the treatment or possibly result in nonuse of the treatment altogether. In addition, such labeling may undermine and damage the soldier's confidence in the chain of command, and adversely impact on morale and discipline. Immediate relief from the requirement for investigational labeling by waiver or by issuance of a new regulation is requested.

DISCUSSION. This is a problem only for soldier carried items. Labeling as, "FOR MILITARY USE AND EVALUATION ONLY" appeared to be an acceptable compromise. Investigational products handled only by health care providers could still be labeled as required in the CFR. The FDA Chief Counsel believes that the labeling requirement can be waived under the existing regulations, however, further internal consultation is required.

b. 21 CFR 312.7 - Promotion and Charging for Investigational Drugs. Defense needs to be able to buy investigational medical products from manufacturers to meet Defense needs. Such purchases cannot be considered "commercialization". Would the fact that a manufacturer and holder of an IND sells the investigational product to Defense for a profit violate this regulation? Clarification is requested.

DISCUSSION. Commercialization would occur only if the medical product were to be sold to the soldier, an event that will not occur.

c. 21 CFR 312.32 - IND Safety Reports. In armed conflict and in circumstances of potential armed conflict, for deployed or deployable units, Defense cannot comply with the requirement to submit safety reports of adverse experience no later than three working days after receipt of the information, nor can Defense comply with the requirement to submit a written report of the adverse experience within ten working days. Defense can submit safety reports as soon as military circumstances permit and the information becomes available. Modification of this FDA requirement for submission of safety reports by waiver or by issuance of a new regulation is requested.

DISCUSSION: It is agreed that the reporting time requirements

cannot be met. Filing of safety reports as expeditiously as the military situation permits is acceptable. Under the existing regulations, the appropriate Center Director and the Sponsor can agree on the time of reporting. A waiver is not required, and an amendment to the regulation is not required.

d. 21 CFR 312.33 - Annual Reports. Defense can submit annual reports.

e. 21 CFR 312.40 - General Requirements for Use of an Investigational New Drug in a Clinical Investigation. The reference to 21 CFR 50, the requirement for informed consent, cannot be complied with in armed conflict and in circumstances of potential armed conflict for deployed and deployable units. Immediate relief from the requirement of informed consent by waiver or by issuance of a new regulation is requested. Defense can comply with the requirements for IRBs referenced in 21 CFR 56.

DISCUSSION: The informed consent issue is addressed below.

f. 21 CFR 312.50 - General Responsibilities of Sponsors. Sponsors for investigational medical products needed by Defense may be the military department surgeons general or other sponsors such as commercial pharmaceutical, biologics, or medical device manufacturers. The wording in the new regulation needs to take this into consideration.

DISCUSSION: Commercial sponsors have no reason to deny Defense permission to cross reference INDs thereby allowing Defense to sponsor the IND.

g. 21 CFR 312.53 - Selecting Investigators and Monitors. In armed conflict and in circumstances of potential armed conflict for deployed and deployable units, Defense cannot comply with these requirements. The concept of an investigator, and investigator responsibilities in these circumstances is incompatible with the operational realities of applied military medicine. The control of the investigational inventory and supplies as stated in existing FDA regulations cannot be fully accomplished. Access to the investigational products will be controlled by Defense personnel. The distribution and use of investigational products will be controlled and monitored in the same manner as other medical supplies. Relief from or modification of these regulatory requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: FDA indicated that Defense should do "the best we can" to control inventory in a combat environment. A waiver or revision of the regulation is not required.

h. 21 CFR 312.55 - Informing investigators. In armed

conflict or in circumstances of potential armed conflict for deployed and deployable units, Defense may not be able to comply with requirements for an investigator brochure. There may not be an investigator, or there may not be an investigator at the time the investigational medical products are used. Information on safety and use of investigational medical products will be provided to medical and paramedical personnel, and to individual service members for investigational products intended for self administration. New information regarding safety and efficacy will be provided to the appropriate personnel. Relief from or modification of these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: FDA agreed that this requirement is met if pertinent information is provided in any form (technical reports, field manuals, updated information, etc) to military medical personnel such as field physicians. Waiver or revision of the regulation is not required.

i. 21 CFR 312.57 - Recordkeeping and Record Retention. In armed conflict or in circumstances of potential armed conflict for deployed and deployable units, Defense cannot comply with requirements to record the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment. The total quantity of investigational product used in these circumstances will be recorded in accordance with normal military medical inventory procedures. The retention of such records will be in accordance with standard military regulations. Relief from or modification of these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: FDA requested and Defense agreed to provide a copy of military regulations governing handling and control of distribution of scheduled substances like morphine, and the procedure for controlling atropine autoinjectors, in a field environment. This issue remains open.

j. 21 CFR 312.59 - Disposition of Unused Supply of Investigational Drug. Given the chaotic nature of armed conflict, Defense cannot assure the return of all unused supplies of an investigational medical product distributed in support of service members in armed conflict or potential armed conflict. Relief from these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION. See above discussion under paragraph i. This issue remains open.

k. 21 CFR 312.60 - General Responsibilities of Investigators. In instances where investigational medical products are distributed in support of service members in armed

conflict or in potential armed conflict, Defense cannot comply with requirements that the investigator will conduct the investigation according to the signed investigator statement, or the investigational plan; or the obtaining of informed consent from each subject to whom the investigational medical product is administered. This is because the concept of an investigator may not feasible in armed conflict or in circumstances of potential armed conflict for deployed and deployable units. The prohibitive nature of informed consent under these circumstances has been discussed. Relief from these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION. An investigational plan that is acceptable to Defense should be submitted with the IND (ie, for a retrospective survey). Informed consent is a separate issue discussed below. Dr. Peck stated his concern that some form of an investigator should be contemplated for retrospective data collection. For example, an investigator who is remote from the battle theatre can be appointed who is responsible for obtaining, organizing and evaluating retrospectively collected data. It was recognized that investigator activities traditionally associated with an investigational medical product study are not possible under conditions of military conflict.

l. 21 CFR 312.61 - Control of the Investigational Drug. In circumstances of armed conflict or in potential armed conflict, Defense cannot comply since investigators and subinvestigators may not directly supervise the administration of the investigational medical product. Relief from these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: FDA Chief Counsel stated that drug administration responsibilities of investigators and subinvestigators need to be addressed by FDA further. This issue is open.

m. 21 CFR 312.62 - Investigator Recordkeeping and Record Retention. In armed conflict and in circumstances of potential armed conflict for deployed or deployable units, Defense cannot comply with requirements for recording disposition of the drug, case histories, and requirements for record retention since placement of an on-scene investigator may not be possible in these circumstances. Relief from these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: The FDA and Defense agreed that some level of recordkeeping, case histories, etc, can be accomplished in a hospital setting (by way of medical charts for example), but not in a field setting. Waiver or revision of the regulation is not required.

n. 21 CFR 312.64 - Investigator Reports. Though the concept

of an investigator may not be feasible in armed conflict and in circumstances of potential armed conflict for deployed and deployable units, Defense will attempt to collect and provide information on safety and efficacy for investigational medical products used in these circumstances. Retrospective information collection is likely to be most feasible. Relief from or modification of these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: Investigator reports will depend on the type of investigator and investigation as described above. Waiver or revision of the regulation is not required.

o. 21 CFR 312.66 - Assurance of IRB Review. Defense will obtain IRB review and approval and will report to the IRB all changes in the information collection activity and unanticipated problems involving the use of the investigational medical product.

p. 21 CFR 312.68 - Inspection of Investigators Records and Reports. Regardless of whether or not an investigator is involved, FDA will have access to Sponsor and DOD records and reports associated with the use of investigational medical products. FDA access to classified documents will require the appropriate security clearance.

312.69 - Handling of Controlled Substances. Investigational controlled substances deployed with a deployed unit, in armed conflict and in circumstances of potential armed conflict, will be handled in accordance with existing Defense regulations for securing substances subject to the Controlled Substances Act. Relief from or modification of these FDA requirements by waiver or by issuance of a new regulation is requested.

DISCUSSION: See paragraph i above.

4. IND products for deployment by Defense will be considered on a case-by-case basis by FDA.

5. FDA raised the question of who resolves the impasse if FDA decides that it is inappropriate to deploy a particular investigational product that Defense wants to deploy? This question is not addressed in the FDA-DOD Memorandum of Understanding, and it was not resolved during this meeting.

6. Options summarized by Chief Counsel Margaret Porter, FDA, for resolving the informed consent issue.

a. For products in investigational status exported from US and used overseas, and not used in the US:

(1) The export licensing requirement cited in 21 CFR

312.110 is the quickest and most feasible approach. The IND regulations are not applicable under this export licensing provision - ie informed consent and investigational labeling are not required.

(2) In addition, the FDA will conduct a safety review for each product under consideration.

(3) In addition, as provided by the FDA-DOD MOU, the FDA will review available data to determine if use in an expanded military population is appropriate.

b. For investigational medical products used in the US, such as vaccines, amendment of the informed consent regulations, 21 CFR Part 50, signed by Secretary HHS, will be necessary. Coordination through OMB may be required. This overall process will take weeks. Since time does not permit publication of a notice of proposed rulemaking for public comment, a public announcement before finalizing the amendment will be necessary. Drafting of an amendment to the regulation is underway at FDA.

7. Since administration of appropriate medical products under IND is expected to be necessary both inside the US and overseas, both options outlined by Chief Counsel Porter appear to be necessary.

8. Diazepam Autoinjector regulatory approach. Deploying the diazepam autoinjector in support of Operation Desert Shield is a primary objective. The diazepam autoinjector will be produced overseas and is expected to be delivered overseas in about four weeks in support of Operation Desert Shield. In this circumstance the export licensing regulation is not applicable. An FDA safety review, and an FDA determination if use in an expanded military population is appropriate will suffice for deploying the diazepam autoinjector in support of Operation Desert Shield. Informed consent will not be required.

9. FDA and DOD recognize the urgency of the situation. Considerabe progress was made during the meeting. Further discussions, interactions, and meetings will continue. Ms. Lorraine and Lt Col Lehmann will continue to be the points of contact for the FDA and Defense, respectively.

Encl

CRAIG R. LEHMANN
Lt Col, USAF, BSC
Medical Chemical Defense
Product Manager
Pharmaceutical Systems

MEMORANDUM

DATE : September 7, 1990

FROM : Richard Klein and Ann Graham

SUBJ : September 7th meeting between FDA and DoD

TO : Stuart Nightingale

The following were in attendance at the meeting:

Department of Defense

| | |
|---|---|
| Craig Lehmann | U.S. Army Medical R & D Command |
| Ronald Clawson | U.S. Army Medical R & D Command |
| Gregory Berezuk | U.S Army Human Use and Regulatory Affairs |
| George Sisson | Command Judge Advocator, Army Medical R & D |
| Walt Brandt | Army Biologics |

FDA

Stuart Nightingale
Margaret Porter
Catherine Lorraine
William Lampkin
Carl Peck
Jim Bilstad
Ann Sutton
Karen Goldenthal
Robert Temple
Paula Botstein
Bill Damaska
Robert Sheridan
Ann Graham
Richard Klein
Linda Carter
Bonnie Lee
Ron Wilson
Ann Witt

- DoD will submit to FDA for review the training doctrine currently being developed for each product
- DoD will submit updated information on each product on an ad hoc basis, but at least once a week.
- FDA and DoD agreed to find a common interpretation of 10 USC 980 and 21 CFR 312 allowing DoD to comply with their statute and FDA regulations simultaneously.

- OHA will track the status of all DoD products being used for unique military purposes.

- DoD agreed to revise their protocols to expand post exposure observations in battlefield observations.

- Margaret Porter agreed to review and revise draft informed consent regulation, and bring it to the direct attention of the Commissioner.

- DoD still insists on a safety review under the terms of the MOU.

- Under the DoD directive the Secretary of Military Departments can dictate the use of unapproved FDA regulated products. DoD's current position is that this is not their primary choice at this time.

- DoD indicated that they want FDA review and agency assurance that the drugs are safe, as well as that their use is appropriate.

- OHA agreed to play a clearinghouse role for FDA, tracking drugs and medical devices.

- OHA and OGC will follow-up with George Sisson concerning the status of skin creme product.

IND 3723 December 29, 1990
Pentavalent Botulinum Toxoid
US Army

Memorandum of Teleconference

FDA Participants: Dr. Janet Woodcock
Dr. Karen Goldenthal
Mr. Roger Eastep

DOD Participants: MAJ Mike Balady
COL Harry Dangerfield
COL Williams
LTC Kelly McKee
LTC Berezuk

We called MAJ Balady to ask questions that had come up during the review of the IND. When we called, MAJ Balady was in a meeting regarding the IND with the other officers listed above, so we held a teleconference via speaker phones at both ends.

Our questions (or recommendations) and the responses were:

1. Are the female vaccinees going to be asked if they are pregnant?

   Yes.

2. Will there be a dose modification for subsequent inoculations if a vaccinee has a reaction to the initial dose?

   A dose modification had not been planned, but it would be considered.

3. Adverse reactions perhaps should be reported by the vaccinees whenever they occur, not just within the number of days listed in the protocol.

   This would be considered.

4. Will the information on the product be given in written form to each vaccinee, or only verbally?

   Verbally at a minimum.

5. Reactigenicity information for the individual lots, apparently had already been submitted to the IND, was requested again because of the Division's file access problems.

   The information would be faxed to the Division.

6. Would DOD be willing to provide product samples for any

additional testing that FDA may decide would appropriate?

Yes.

7. What lots are currently in use, and is DOD preparing additional lots?

The current lots are A2, B1 and B2, which were made from the same bulk toxoid. It is planned that additional lots will be made from the existing bulk material, and also that more toxoid will need to be made. Dr. Woodcock offered CBER's assistance in doing safety and sterility testing of the additional lots. She also agreed to provide CBER assistance in preparing manufacturing facilities for validation.

The DOD participants asked questions about FDA questions on the Patient Information Sheets and who will administer the vaccinations, but since those questions apparently had come from Dr. Nightingale's office, they were referred to Ms. Graham.

Roger Eastep
Deputy Director, DBIND, HFB-230

cc: Dr. Woodcock
Dr. Goldenthal

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Bethesda MD 20892

MEMORANDUM

DATE: December 31, 1990

FROM: Ann Sutton, M.A.,
Vaccines and Allergenics Branch/DBIND

THROUGH: Karen Goldenthal, M.D., M.D.
Chief, Vaccines and Allergenics Branch/DBIND

THROUGH: Jerome Donlon, M.D., Ph.D.,
Director, Office of Product Review/CBER

SUBJECT: Pentavalent Botulinum Toxoid Vaccine
IND 3723 - Sponsored by the Department of the Army
(Cross-reference: IND 161 - Sponsored by the CDC)

TO: Gerald V. Quinnan, Jr., M.D.,
Acting Director, Center for Biologics Evaluation and Research

This memo is a follow-up to update some information in the memo of December 28, 1990.

1. A meeting of the Informed Consent Waiver Committee was held on December 31, 1990 in the Parklawn Bldg. The minutes of that meeting will be prepared by the staff of Stuart Nightingale, M.D., Associate Commissioner for Health Affairs. At that meeting representatives of DoD asserted that in some instances it may be necessary to vaccinate pregnant women who are in the military theater of operation. The consensus of FDA attendees at that meeting was that DoD's position was reasonable. The final information sheet which will be read to vaccinees does contain a statement concerning the unknown effect of this vaccine on a fetus.

2. Some questions about the release specifications for the guinea pig potency test and antitoxin titers for botulinum toxoid vaccine were raised during an internal CBER meeting on Dec. 31, 1990. These questions and issues had been previously addressed by Dr. Charles Hatheway of the CDC (Section letter in IND 161, supp. 29, 1978). His comments and related data are summarized as follows:

   i. All 3 lots met the specifications for antitoxin response and survival after challenge for toxin types A and D.

ii. The immune response in guinea pigs to type C was strong but did not meet the 0.4 u/ml antitoxin specification. However, in view of the fact that 100% of these immunized guinea pigs (a total of 30 animals tested for 3 lots) survived an intraperitoneal challenge with $10^5$ mouse $LD_{50}$ of the type C toxin and all of the unimmunized control animals (a total of 6) challenged with the type C toxin died, Dr. Hatheway asserted that the specification for type C antitoxin response was set too high.

iii. The type B antitoxin response in guinea pigs met the predetermined specification in the lot A2 test and was below specifications for lots B1 and B2. However, 80-100% of these immunized animals per lot survived the challenge experiments indicating considerable vaccine potency. All unimmunized controls died.

iv. The type E antitoxin response in guinea pigs was relatively weak for all 3 lots. However, 30-70% of immunized guinea pigs/lot survived challenge with E toxin whereas no unimmunized guinea pigs survived indicating that at least some protection against type E toxin was conferred by all 3 lots.

Also, the E component of the pentavalent botulinum toxoid vaccine is immunogenic in humans as evaluated by neutralizing titers after 3 doses and is assessed routinely in subjects scheduled for boosters (see previous memo dated Dec. 28, 1990).

cc: Dr. Anthony
Dr. Habig

Revised Information Sheet 1/2/91

INFORMATION ABOUT BOTULINUM VACCINE

You are being given a vaccine called botulinum toxoid because you are considered at risk of exposure to botulism. Botulism can cause serious paralysis or death. It is caused by toxins that interfere with the normal transmission of nerve signals. Botulism can arise from; (a) contaminated food and water, (b) contaminated wounds, or (c) a biological warfare attack. Symptoms of botulism can begin as early as three hours or as late as several days after exposure to the toxin. Symptoms include blurred vision, generalized weakness, difficulty in swallowing and talking. Treatment after exposure is primarily supportive and there is an antitoxin/antidote which may be beneficial. Your primary protection against botulinum toxin is the use of your chemical protective mask and overgarment. Vaccination with botulinum toxoid is expected to provide additional protection for individuals exposed to the toxin. However, no vaccine is 100% effective. No other vaccine is available which can give you this protection.

This is an investigational (not yet licensed) vaccine that has been safely given to over 3000 laboratory workers and scientists over the past 25 years. It will be administered as a series of three injections under the supervision of qualified medical personnel.

About 92% of people who are vaccinated report no significant side effects beyond the local pain experienced at the time the vaccine is given. However, like other vaccines you have been given, this one may have some side effects. Side effects occur in 4% to 8% of people. When they occur, they are usually at the site of injection and include pain, tenderness, swelling, redness and/or itching. All these are common symptoms with the typhoid vaccine you have already received. The number of these local reactions tends to increase after the first injection. Rarely an individual may develop a small lump at the injection site which lasts for several days to weeks before going away. Local reactions that can interfere with performance of your duties are very uncommon. Generalized reactions may include fever, tiredness, headache and/or muscle pain and occur in less than 1% of people. Rarely (less than 1 in 1000 injections) an individual may be unable to perform duties for a day or two. As with any vaccination, a very rare, unexpected, potentially severe, side effect not previously observed could occur. If you are pregnant it is not known if this vaccine will harm your unborn baby. However, most vaccines do not harm an unborn baby when given to the mother.

If a reaction that worries you occurs after you leave the area where the vaccine was given you should report to sick call.

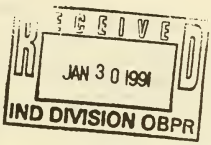
You may be one of a group to receive a postcard in the next few weeks asking for information on your experiences with this vaccine.



FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM




DATE: January 25, 1991

TO: BBIND 3723

FROM: Lawrence A. D'Hoostelaere Chief, QA & AT, DPQC, HFB-222

SUBJECT: General Safety Testing of Botulinum Toxoid

Botulinum Toxoid Adsorbed Pentavalent (Types A, B, C, D, E) Lot No. A2 was placed on General Safety Test January 14, 1991. Two mice weighing 19-22 grams were injected intraperitoneally with 0.5 mls each, and two guinea pigs weighing 350-370 grams were injected intraperitoneally with 5.0 mls each. The animals were observed over a seven day period. All animals lived throughout the observation time. The immediate reactions observed could not be distinguished from adjuvant induced responses. At the end of the test period all animals weighed the same or more than at the time of injection. Under 21 CFR 610.11 (d) the applied research sample lot no. A2 would pass the general safety test.

☐ ADVERSE REACTION ☒ MANUFACTURING DATA
☐ CLINICAL PROTOCOL ☐ OTHER (INCLUDES NEW INVEST., SITE)
☐ CLINICAL DATA ☐ PROGRESS REPORTS
☐ ENTITY CHANGE (SPONSOR, ADDRESS) ☐ RESPONSE TO LETTER /PHONE
☐ LOT PROTOCOL ☐ WITHDRAWAL REQUEST - ☐ REQUEST FOR INACTIVATION

IND/SUPPLEMENT #: 3723/1
ROUTED TO: DBP DATE 11-19-90
CMTS. INIT. AS

☐ I HAVE NO COMMENT DATE: _____ _____ Reviewer Signature
☐ MEMO ATTACHED IN DUPLICATE DATE: _____ _____ Reviewer Signature
☐ MEMO TO FOLLOW IN DUPLICATE DATE: _____ _____ Reviewer Signature
☒ SEE COMMENTS BELOW DATE: 11/20/90 Arnold Sutton Reviewer Signature

COMMENTS: Lots to be used: A-2, B-1, B-2. B-1, B-2 differ from A-2 in amt of formaldehyde, i.e., a greater amount. Little or no previous human use data for the latter two lots is obvious in IND 161. The sponsor should find such data, if it exists.

**RECORD OF TELEPHONE CONVERSATION**

**IND:** 161 **Date:** September 1, 1990

**Product:** Botulinum Toxoid, Pentavalent, Vaccine.

**Initiated by:** Dr. Walt Brandt

**Telephone No.:** 301-663-7564 (-7567)

**Firm Name:** USAMRIID, Fort Detrick

**Person with whom conversation was held:** Ann Sutton, BIND

He reviewed the CDC recommended immunization schedule and found that the schedule the Army is using is the same. He has contacted the CDC and offered to write and update for the information guide/ investigators' brochure. I said the most important elements to update would be the reactogenicity profile (CDC has this information) and immunogenicity data (Army has the most, and the most current, data).

161b.tel
cc: Dr. Woodcock
Dr. Scribner
Dr. Habig
Dr. Goldenthal

DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

REPLY TO ATTENTION OF

December 31, 1990

Human Use Review and
Regulatory Affairs Office

SUBJECT: IND 23,509 - Pyridostigmine Bromide 30mg Tablets (Serial No. 022)

CENTER FOR
REC'D
JAN 0 2 1991
HFN-120
DOCS AND ENCLOSURES

Division of Neuropharmacological
Drug Products (HFN-120)
Office of Drug Review I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir:

Enclosed in triplicate is a request from the Assistant Secretary of Defense (Health Affairs) to the Commissioner of Food and Drugs for a determination that obtaining informed consent is not feasible for the subject investigational drug. This request is made under the provisions of 21 CFR 50.23(d)(1) as published in the Federal Register of December 21, 1990. This regulation requires such a request be submitted as an amendment to the IND.

If you have questions concerning this submission, please contact the undersigned at (301) 663-2165.

Sincerely,

Gregory P. Berezuk
Lieutenant Colonel, Medical
Service Corps
Chief, Human Use Review and
Regulatory Affairs Office

Enclosure

Copy Furnished:

U.S. Army Medical Materiel Development Activity,
ATTN: SGRD-UMP

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
**INVESTIGATIONAL NEW DRUG APPLICATION (IND)**
*(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)*

*Form Approved: OMB No. 0910-0014. Expiration Date: March 31, 1990. See OMB Statement on Reverse.*

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Office of The Surgeon General, Department of the Army

2. DATE OF SUBMISSION
28 December 1990

3. ADDRESS *(Number, Street, City, State and Zip Code)*
Office of The Surgeon General, Department of the Army
ATTN: SGRD-HR (Human Use Review and Regulatory Affairs)
Fort Detrick, Frederick, MD 21702-5012

4. TELEPHONE NUMBER *(Include Area Code)*
(301) 663-2165

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Pyridostigmine Bromide - 3-Hydrox-1-methylpyridinum bromide dimethylcarbamate; Pyridinium, 3[dimethylamino)-carbonyl]

6. IND NUMBER *(If previously assigned)*
23,509

7. INDICATION(S) *(Covered by this submission)*
Pretreatment of organophosphate poisoning in the management of nerve agent exposure

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.

10. *IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.*

SERIAL NUMBER: 0 2 2

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☒ OTHER See Cover Letter *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(c) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP

DDR RECEIPT STAMP
REC'D
JAN 0 2 1991
HFN-120

IND NUMBER ASSIGNED:

DIVISION ASSIGNMENT:

FORM FDA 1571 (10/89) PREVIOUS EDITIONS ARE OBSOLETE.

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D. C. 20301-1200

HEALTH AFFAIRS

David A. Kessler, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Doctor Kessler:

Under the provisions of 21 CFR 50.23(d)(1) (as published in the Federal Register of December 21, 1990), I request a determination that obtaining informed consent is not feasible for pyridostigmine bromide 30mg tablets, IND 23,509, because of military combat exigencies in Operation Desert Shield. This determination would apply to the use of this drug by American military personnel at risk of attack with chemical weapons involving organophosphorous nerve agents.

As summarized in enclosure 1 and supported by documentation in the IND file, available evidence supports the safety and effectiveness of pyridostigmine pretreatment, in conjunction with other drugs as treatments, for this purpose. If threatened with these chemical weapons, the interests of individual service personnel and the overall needs of the military service will require that pyridostigmine be used by all threatened personnel. No satisfactory alternative regimen involving investigational or approved drug products is available to deal with these life-threatening weapons. Under these circumstances, withholding pyridostigmine from any threatened individual would be contrary to that individual's best interests. The recommendation for use of pyridostigmine without informed consent has been concurred in by a duly constituted institutional review board, enclosure 2.

Your prompt attention to this request is appreciated. A copy of this request is being filed as an amendment to IND 23,509. Should you need further information concerning this request, please contact

Lieutenant Colonel Gregory P. Berezuk, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, Maryland, 21702-5012, telephone (301) 663-2165.

Sincerely,

Enrique Mendez, Jr., M.D.

Enclosures

Copies Furnished:

Division of Neuropharmacological
Drug Products (HFN-120)
Office of Drug Review I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Office of Health Affairs (HFY-1)
ATTN: Dr. Nightingale
Room 14-95
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

JUSTIFICATION FOR WAIVER OF INFORMED CONSENT
FOR AN INVESTIGATIONAL DRUG
BECAUSE OF MILITARY COMBAT EXIGENCIES

1. IND.

**Pyridostigmine Bromide**, 30 mg tablets -- IND #23,509. The protocol under which this product is to be used is titled "Observations of Pyridostigmine Use as a Nerve Agent Pretreatment During Operation Desert Shield" (submitted with amendment 020 to this IND).

2. Intended use.

Pyridostigmine bromide, 30 mg tablets, is intended as a pretreatment, in conjunction with atropine and pralidoxime chloride, to help prevent or ameliorate the effects of chemical weapon attack involving organophosphorus nerve agents in Operation Desert Shield. It would be self-administered by American service members at risk of imminent attack with chemical weapons at such time as intelligence would indicate the likelihood of such an attack.

3. Safety of the drug.

The decades long use of pyridostigmine in this country for the treatment of myasthenia gravis testifies to its safety. It should be noted that the 90 mg daily dose of pyridostigmine (30 mg every eight hours) is only 15% of the average 600 mg daily dose routinely used in the treatment of myasthenia gravis. The only adverse effects noted in our studies were one incident of loss of consciousness 18 hours following discontinuation of an intravenous administration of nine (9) mg of Mestinon® (probably non-drug related) and one incident of moderate to severe hip flexor muscle cramps following a two hour cold ($10^{\circ}$) exposure and 30 mg or pyridostigmine, oral (probably drug related). Both cases were submitted to the Food and Drug Administration as an Adverse Reaction Report. Less severe abdominal cramping has also been observed when subjects have been exposed to cold.

4. Effectiveness of the drug.

The effectiveness of pyridostigmine has not been tested in humans, in this country, because of the unacceptability of exposing them to organophosphorus nerve agents (there are two classified studies which were conducted by a foreign country which can be made available upon request to reviewers with an appropriate security clearance).

Studies in multiple animal species have attested to the efficacy of pyridostigmine use as a pretreatment. In a large, definitive study conducted in Rhesus monkeys (study report provided with amendment 020 to this IND), it was shown that

pyridostigmine, when administered in a dose which resulted in inhibition of red blood cell acetylcholinesterase by 20%-40%, increased the effectiveness of the atropine/pralidoxime treatment regimen more than 20 fold. Atropine and pralidoxime alone protected against the effects of 1.64 $LD_{50}$'s of soman (GD) whereas, with pyridostigmine pretreatment, the protective ratio was projected to be approximately 40 with respect to no treatment and 25 with respect to atropine and pralidoxime treatment. Other studies have shown that pyridostigmine, in conjunction with atropine and pralidoxime chloride, provides protection against 5 to 10 $LD_{50}$'s of soman whereas atropine and pralidoxime alone protect against 1.5-2 $LD_{50}$'s.

Pharmacokinetic studies conducted in human volunteers have shown that 30 mg of pyridostigmine, every eight hours, results in acetylcholinesterase levels which are inhibited by 20%-40% (report has not yet been prepared, however, a summary figure of the data is provided at attachment 1). These inhibition levels correspond to those levels in the monkey and other species which provide added protection above and beyond that provided by atropine and pralidoxime alone.

The efficacy of pyridostigmine can never be validated in humans, in a controlled study. However, based on results observed in numerous animal models, it is our opinion that pyridostigmine will provide enhanced protection to service members who may be exposed to organophosphorus nerve agents. This opinion is further supported by the fact that the military of several other countries have also fielded pyridostigmine for this indication (United Kingdom, Federal Republic of Germany, The Netherlands, Belgium, Luxembourg, Canada, Israel, and Spain). And finally, The Medical Letter (32:831, p. 103-105, November 16, 1990) states that pretreatment with pyridostigmine "...greatly enhances the effectiveness of atropine and pralidoxime chloride against GD exposure..." (attachment 2).

5. Military combat exigency.

Should an attack with such weapons appear imminent, in order to accomplish the military mission, the preservation of the health of each individual service member and the safety of the unit threatened will require that pyridostigmine be used by all threatened personnel. This will be necessary without regard to what might be any individual's personal preference for no treatment or for some alternative treatment, should any individual have such a personal preference.

6. Consideration of alternatives.

No satisfactory alternative pretreatment product involving investigational or approved drugs exists.

7. Nature of the disease or condition involved.

Organophosphorus nerve agents act by inhibiting acetylcholinesterase at cholinergic receptor sites. This results in stimulation of both muscarinic and nicotinic receptors which could ultimately result in death.

8. Best interests of military personnel.

Under the circumstances presented, withholding pyridostigmine from any individual service member threatened with nerve agent attack would be contrary to the best interests of that individual.

9. Information to be provided to recipients of pyridostigmine.

Recipients of pyridostigmine bromide, 30 mg tablets, will be given substantial information regarding proper use of the drug and its risks and benefits. The pertinent section of FM 8-285, titled "Treatment of Chemical Agent Casualties and Conventional Military Chemical Injuries" is provided at attachment 3. In addition, United Stated Army Medical Research Institute of Chemical Defense Technical Memorandum 90-4, "Pyridostigmine", is being prepared for medical personnel, and should be available prior to the end of the year.

10. Institutional Review Board approval.

A duly constituted and designated IRB carefully considered and approved the use of pyridostigmine bromide, 30 mg tablets, without informed consent at its meeting of 17 October 1990. A copy of the pertinent portion of the minutes of the meeting is at enclosure 2.

11. Manufacturing Information.

Currently, the Department of Defense is procuring pyridostigmine, 30 mg, from two manufacturers, Duphar Pharmaceuticals and Hoffman LaRoche (UK). The pyridostigmine is being manufactured in The Netherlands and the United Kingdom respectively. A letter from Duphar (Reid-Rowell) allowing the DOD to reference their master files for chemistry and other relevant data is enclosed (attachment 4). An effort is underway to obtain a similar letter from Hoffman LaRoche; however, because of the holidays, it will probably not be available until early January.

Fig. 8 Std. 30mg Tab. q 8 h - Group 1, Days 5,6
Mean (± SD) Pyridostigmine Conc. (n=8)

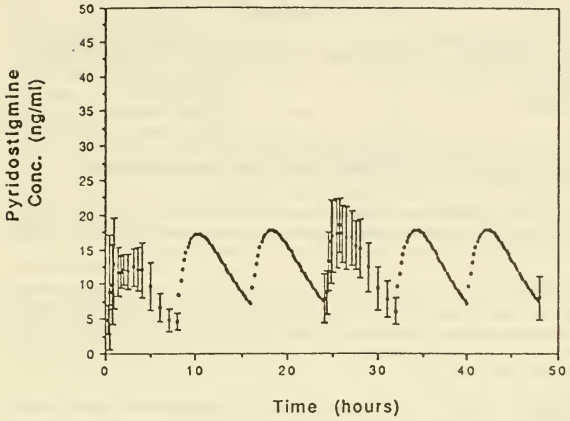
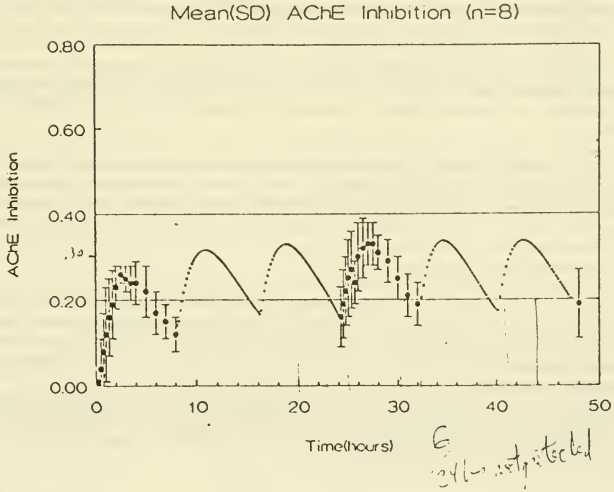



Fig 4. Std 30mg Tab q 8 h Gp 1, Days 5,6
Mean(SD) AChE Inhibition (n=8)



# The Medical Letter®

On Drugs and Therapeutics

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November 16, 1990



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Fluoxetine Interaction ... Page 106


## PREVENTION AND TREATMENT OF NERVE GAS POISONING

With the possibility that chemical weapons may be used against United States armed forces in the Persian Gulf, the military has taken steps to protect our troops against poison gas, particularly "nerve agents" (MA Dunn and FR Sidell, JAMA, 262 649, 1989).

**NERVE "GAS"** — At ambient temperatures, nerve agents considered likely to be used in chemical warfare — GA (tabun), GB (sarin), GD (soman), and VX — are liquids, not gases. GA, GB, and GD are volatile, but less so than water; at higher temperatures or when aerosolized by an explosion, they may be inhaled. VX is oily and less volatile. All of these agents can be absorbed through the skin.

**MECHANISM OF ACTION** — GA, GB, GD, and VX are organophosphates. Many insecticides are also organophosphates, but nerve agents are much more potent (DJ Rickett et al, Milit Med, 152:35, 1987). They act primarily by inhibiting acetylcholinesterase (AChE) at cholinergic receptor sites. As a result, the neurotransmitter acetylcholine (ACh) accumulates, causing hyperactivity at both muscarinic (most glands, involuntary or smooth muscle) and nicotinic receptors (skeletal muscle, pre-ganglionic fibers).

**CLINICAL EFFECTS** — Exposure to either a liquid or vaporized nerve agent can cause copious secretions from the nose, eyes, mouth, lungs, and intestines, in addition to muscle fasciculations and twitching. Miosis is prominent after vapor exposure, but may not occur with liquid.

**Liquid** – The initial effect of a small droplet on the skin may be unnoticed local sweating and fasciculations. The first systemic effects — nausea, vomiting, and diarrhea, followed by a feeling of uneasiness and sometimes muscle twitching — may not begin until as long as 18 hours after exposure. A larger exposure to liquid GA, GB, or GD, or even a small amount of VX, after a delay of one to 30 minutes, may cause sudden unconsciousness, convulsions and, within minutes, flaccid paralysis and apnea.

**Vapor** - Exposure to a small amount of vapor causes miosis, rhinorrhea, ocular pain, conjunctivitis, and dim or blurred vision within seconds. Bronchoconstriction and increased bronchial secretions cause symptoms varying from mild discomfort to severe dyspnea. With a larger exposure, one or two breaths may lead to loss of consciousness within seconds, followed by convulsions and, within minutes, flaccid paralysis and apnea.


EDITOR: Mark Abramowicz MD EDITORIAL BOARD Martin B Rosack MD PhD Consulting Editor Prescription Litho Lewis M Fraad MD Albert J Heyn Cornell Med Jules Hirsch MD Rockefeller Univ James D Kenney MD Yale Univ School of Med Fenton Schaffner MD Mt Sinai School of Med Neal H Steigbigel MD Albert Einstein Coll of Med ADVISORY BOARD Robert Byck MD Yale Univ School of Med Emil Frei III MD Harvard Med School Louis S Goodman MD Univ of Utah Coll of Med Philip D Hansten Pharm D Univ of Washington Mitch H Lepper MD Rush Med Coll Garland Leavy Pharm D State Univ of N Y at Buffalo Gerard L Mandell MD Univ of Virginia School of Med George B Neavy MD PhD Univ of Colorado School of Med Alan S Nies MD Univ of Colorado School of Med Richard I Ogilvie MD Univ of Toronto Faculty of Med Lewis D Vandam MD Tufts Univ Med School ASSOCIATE EDITOR Carol D M Hillman MS SENIOR EDITOR Donna Goodstein MANUSCRIPT EDITOR E J Perkins

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**TREATMENT** — Health workers should wear protective gear and be sure that the patient's skin is thoroughly decontaminated with hypochlorite (household bleach diluted 1:10) or soap and water, and plain water for the eyes. Military personnel carry moist "towelettes" impregnated with chloramine, hydroxide, and phenol.

**Atropine** - Atropine blocks the action of excess acetylcholine primarily at muscarinic sites, decreasing secretions, bronchoconstriction, and intestinal motility. The initial dose of the drug is 2 mg for mild dyspnea to 6 mg or more for severe dyspnea, hypoxia, or multisystem signs; it can be given intramuscularly (IM) or intravenously (IV). US military personnel in Saudi Arabia carry three automatic injectors, each containing 2 mg of atropine. Miosis is not affected by these doses, and skeletal muscle effects (nicotinic sites) alone are not an indication for higher doses. The drug can be given as often as every five minutes until secretions are minimal and ventilation is adequate; some patients require 15 to 20 mg in the first three hours after exposure. Atropine inhibits sweating, which could lead to hyperthermia in a hot environment such as Saudi Arabia.

**Pralidoxime Chloride** - Oximes like pralidoxime *(Protopam Chloride)* attach to and release the inhibiting agent from AChE. They act primarily at nicotinic sites to normalize skeletal muscle activity. Pralidoxime itself has little activity at muscarinic sites, but greatly enhances the effect of atropine. Most nerve agents can be effectively treated with pralidoxime for hours after exposure, but GD becomes refractory to the drug within a few minutes. The initial dose of pralidoxime is 1 gram, given IV over 20 to 30 minutes; this dose may be repeated at hourly intervals for one or two additional doses. Pralidoxime is also packaged in an automatic injector (600 mg/2 ml) for IM administration; US soldiers carry three of these for concurrent use with the three atropine injectors.

**Pretreatment with pyridostigmine** — The US military has also issued pyridostigmine bromide *(Mestinon)* tablets, used in treating myasthenia gravis, for pretreatment when a nerve agent attack is considered imminent. Pyridostigmine is a cholinesterase inhibitor with a relatively short half-life that occupies the active site of ACh and blocks the action of the nerve agent. In recommended dosage, pyridostigmine is non-toxic and greatly enhances the effectiveness of atropine and pralidoxime against GD exposure, but it is not effective if the other antidotes are not given.

**Anticonvulsants** - Experimental animals given pretreatment and the antidotes have survived large amounts of nerve agent without apnea, but with prolonged convulsive activity (CG McLeod, Jr. Fundam Appl Toxicol, 5:S10, 1985). Therefore, US soldiers will soon also carry an automatic injector containing 10 mg of diazepam (*Valium*; and others), to be given with the third dose of atropine -

**GAS MASKS** — How well gas masks work depends on their design, manufacture, storage, and fit, as well as the nerve agent used, the speed of the wind, and the individual's distance from the source of exposure. Masks that only fit over the nose and mouth are unlikely to be effective against nerve gas because the vapor can be absorbed through the conjunctiva. US government standard masks that cover the entire face have the adsorptive capacity to protect against many times the LCt50 (concentration and time of exposure that would be lethal for 50% of the population) of nerve gas, but some other masks may be less efficient. Any mask can lose protective capacity if it is crushed or stored in high humidity. The tightness of the masks' seal around the face is usually more of a limiting factor than the adsorptive capacity of the filter. beards and eyeglasses, among other variables, may interfere (GO Rogers et

al, *Evaluating Protective Actions for Chemical Agent Emergencies*, Oak Ridge:Oak Ridge National Laboratory, 1990, p 143).

**PROTECTIVE CLOTHING** — Liquid nerve agents penetrate ordinary clothing. Charcoal-lined Military Mission Oriented Protective Posture (MOPP) suits, worn with a mask under a hood offer a high degree of protection, but may severely limit movement, visual acuity and, in a desert climate, could cause heat stroke (JL Kobrick et al, Aviat Space Environ Med, 61:622, July 1990).

**CONCLUSION** — Nerve agents block acetylcholinesterase and cause both muscarinic and nicotinic overactivity. Moderate exposure causes copious secretions from the eyes, nose, mouth, bronchi, and intestines. A major exposure can cause loss of consciousness, convulsions, and apnea. Protective clothing, gas masks, pretreatment with pyridostigmine, and treatment with atropine, pralidoxime, and diazepam may be life-saving.

ROBERT O. PICK
COL, MS
PROJECT MANAGER
PHARMACEUTICAL SYSTEMS

ARMY FM 8-285
NAVY NAVMED P-5041
AIR FORCE AFM 160-11

FIELD MANUAL

# TREATMENT OF CHEMICAL AGENT CASUALTIES AND CONVENTIONAL MILITARY CHEMICAL INJURIES

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DEPARTMENTS OF THE ARMY, THE NAVY, AND THE AIR FORCE
FEBRUARY 1990

(or counteract) the muscarinic effects of the nerve agent and to maintain mild atropinization for as long as necessary.

*b. Management of Bronchial Secretions and Salivation.* Patients having excessive airway secretions and salivation (an indication for additional atropine) should be placed in the prone position, with the foot of the litter or bed elevated, if possible, to promote drainage. If airway obstruction is occurring, the collar should be loosened, the tongue pulled out, and the saliva and mucus cleared periodically from the mouth and pharynx by suction from a syringe and catheter. Then an oropharyngeal airway may be inserted and suction carried out intermittently, as needed, through and around the airway. If, despite concentrated efforts to carry out assisted ventilation, the upper airway remains obstructed and adequate exchange of air does not occur, deepening cyanosis ensues. Therefore, an endotracheal tube should then be inserted.

*c. Management of Convulsions.* Casualties poisoned severely enough to develop convulsions usually progress rapidly to unconsciousness and generalized muscular weakness or flaccid paralysis, at which point external evidences of convulsions cease. Seizures should be anticipated in all moderate to severe cases and expectantly treated with 10 mg diazepam preferably intravenously and repeated as necessary. Seizing is a prominent feature of GD poisoning. Diazepam should be administered until seizures are controlled.

*d. Treatment of Ocular Symptoms.* Ocular symptoms produced by local absorption of a nerve agent do not respond to the systemic administration of atropine. However, minimal pain relief may be obtained by the local instillation of atropine sulfate ophthalmic ointment (1%), repeated as needed at intervals of several hours for 1 to 3 days. If local ocular effects of a nerve agent are present, the size of the pupils cannot be used as an indicator of the systemic effects of the nerve agent or the atropine.

*e. Gastric Lavage.* If water or food contaminated with a dangerous amount of nerve agent has been ingested, colicky abdominal pains, substernal tightness, increased salivation, and perhaps vomiting will occur about 1/2 hour later. If ingestion has occurred, gastric lavage with water should be done.

*f. Removal of Liquid Nerve Agent.* Any liquid nerve agent on the skin or in the eyes should be removed immediately.

*g. Assisted Ventilation.* If respiration is severely impaired or if it ceases after administration of atropine, cyanosis will ensue and death will occur within minutes unless effective assisted ventilation is begun immediately and maintained until spontaneous respiration is resumed.

(1) *Using an oxygen-generating device.* Assisted ventilation with a positive pressure oxygen-generating device should be provided, as needed, using an endotracheal tube. Far forward in the field, a cricothyroidotomy is the most practical means of providing an airway for assisted ventilation, using a hand powered ventilator equipped with a filter. As soon as available, a mechanical ventilator should replace the hand powered ventilator.

(2) *Using a mechanical ventilator.* When a casualty reaches an installation where oxygen and a mechanical ventilator of the positive pressure type is available, these should be employed continuously until adequate spontaneous respiration is resumed. An endotracheal tube will be required in most cases.

## Section V. PYRIDOSTIGMINE PRETREATMENT FOR NERVE AGENTS

### 2-15. Purpose.

*a.* This section prescribes a nerve agent pyridostigmine pretreatment as an adjunct to the Nerve Agent Antidote Kit, Mark I. When used in conjunction with the Mark I (para 2-10 and app H), this pretreatment enhances the survivability of nerve agent poisoned casualties. This section also covers the aspects of individual, unit, and command responsibilities for the pretreatment regimen.

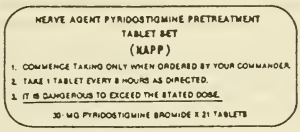
*b.* Benefits derived from the use of this pretreatment regimen are realized only in nerve agent poisoned casualties who have been treated with the Mark I at the time of nerve agent exposure, and who have taken their pretreatment medication within 8 hours prior to nerve agent exposure. This pretreatment medication, plus the nerve agent antidote (Mark I), reduces the severity of nerve agent poisoning, shortens the duration of treatment, and increases the survival rate of nerve agent poisoned casualties.

*c.* No detrimental effects are expected at the recommended dosages. Adverse effects are described in paragraph 2-20 below.

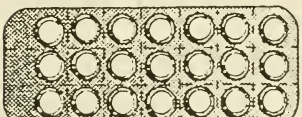
### 2-16. The Nerve Agent Pyridostigmine Pretreatment Tablet Set

*a.* The Nerve Agent Pyridostigmine Pretreatment Tablet Set (NAPP) (fig 2-2) contains the pretreatment medication to be taken within 8 hours prior to exposure to nerve agents at which time the Mark I is used. The NAPP consists of 30-mg pyr

dostigmine bromide tablets (21 total) which are packaged in a blister pack. Each blister pack (NAPP) contains enough tablets for 7 days (1 taken every 8 hours).




(A) SAMPLE OUTER WRAPPER.



(B) SAMPLE PYRIDOSTIGMINE BROMIDE TABLETS

*Figure 2-2. Nerve Agent Pyridostigmine Pretreatment Tablet Set.*

*b.* Service members are initially issued 1 NAPP when the chemical protective ensemble is expected to be opened for use. They are responsible for carrying the NAPP and safeguarding it against loss. Service members will secure the blister pack in the sleeve or breast pocket of the chemical protective ensemble (or in another part of the ensemble, as directed by local standing operating procedure (SOP)).

NOTE

In conjunction with the NAPP, service members should be issued an additional M258A1 Skin Decontaminating Kit (fig G-1) which will be carried on the load-bearing equipment suspenders.

*c.* Orders to start taking the NAPP will be issued by the proper authority within the chain of command.

*d.* Resupply will be provided by Combat, Combat Support, and Combat Service Support Units.

## 2-17. Effects of Pyridostigmine Bromide

*a.* Pyridostigmine bromide protects an enzyme (known as acetylcholinesterase) in the body from the action of nerve agents. Muscles function as a result of nerve impulses and the release of specific chemical substances. A chemical transmitter, acetylcholine, acts at the neuromuscular junction (where the nerve interfaces with the muscle) (fig 2-3). When a nerve impulse reaches the neuromuscular junction, acetylcholine (the chemical transmitter) is released, thereby causing the muscle to contract. The enzyme, acetylcholinesterase, stops

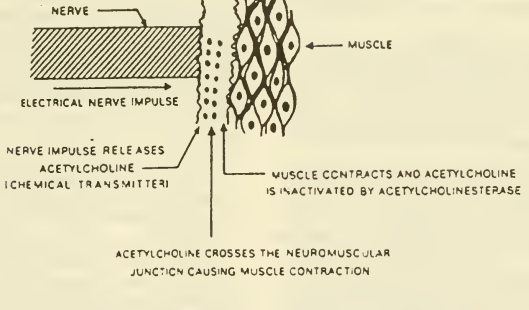



*Figure 2-3. Schematic neuromuscular junction (not to scale).*

the action of acetylcholine on the muscle after the muscle has contracted. Nerve agents block the acetylcholinesterase, thus there is an accumulation of excessive acetylcholine at the neuromuscular junction which results in nerve agent poisoning and its accompanying symptoms. Pyridostigmine protects acetylcholinesterase against nerve agents, thus preventing the accumulation of excessive acetylcholine when the Mark I is administered.

*b.* Pyridostigmine is not a "true" pretreatment. A true pretreatment would, by itself, provide some protection against chemical agents. Pyridostigmine is an *antidote enhancer*. Though NOT providing protection by itself, pyridostigmine significantly ENHANCES the efficacy of the Mark I within 1 to 3 hours after taking the first tablet. Maximal benefit develops with time and is reached when a tablet is taken every 8 hours.

## 2-18. Principles in the Use of the Nerve Agent Pyridostigmine Pretreatment Tablet Set

*a.* To be maximally effective, 1 pyridostigmine bromide tablet should be taken every 8 hours on a continuous basis prior to exposure to a nerve agent until all 21 tablets in the blister pack have been taken, or the individual has been directed to discontinue taking the medication. If pyridostigmine is to be continued, another blister pack of the medication must be issued. This regimen maintains an effective blood level of the medication. If a tablet is not taken every 8 hours, the beneficial effect of pyridostigmine as a pretreatment significantly diminishes after 8 hours from the last tablet.

*b.* The use of the pyridostigmine pretreatment medication does not change the administration of the Mark I.

NOTE

DO NOT ATTEMPT TO GIVE A NAPP TABLET TO A CASUALTY WITH NERVE AGENT SYMPTOMS.

*c.* At times a commander may have to make a decision to defer administration of the NAPP on schedule. Examples of this would be when service members—

(1) Have experienced sleep deprivation. The commander would have to decide whether the service members should be allowed to sleep or be awakened to take the pretreatment.

(2) Are in a contaminated environment. The commander would have to decide whether or not to delay administration of the medication until the unit is safely out of the contaminated area (para *d* below). In any case, the benefits versus the risks should be carefully weighed before a decision is reached.

*d.* When the order to take pyridostigmine has been given, it should be taken as directed (para 2-19). As long as the environment is contaminated, it is desirable to continue the pretreatment. The pretreatment should continue regardless of MOPP level since the protective posture could be breached at any time.

(1) HOWEVER, IF THE MISSION REQUIRES SERVICE MEMBERS TO REMAIN IN A CONTAMINATED ENVIRONMENT FOR EXTENDED PERIODS, COLLECTIVE PROTECTION OR REST AND RELIEF SHELTERS SHOULD BE PROVIDED SO THEY CAN REMOVE THEIR PROTECTIVE MASK AND TAKE THE TABLETS, OR THEY SHOULD BE RELOCATED TO AN UNCONTAMINATED AREA WHENEVER POSSIBLE.

(2) OR, IF THE SITUATION IS SUCH THAT TAKING THE TABLETS WHILE IN MOPP 4 WOULD BE HAZARDOUS; such as, WHEN IN A TOXIC CHEMICAL AEROSOL ENVIRONMENT OR AT NIGHT WITHOUT LIGHTING, THEN IT WOULD BE MORE APPROPRIATE TO DELAY TAKING THE MEDICATION FOR A FEW HOURS UNTIL THE TABLETS CAN BE TAKEN IN A LESS HAZARDOUS ENVIRONMENT.

(3) COMMAND GUIDELINES SHOULD BE DEVELOPED TO HANDLE THE PARTICULAR SITUATION.

*e.* The NAPP should not be taken during pregnancy.

## 2-19. Administration of Pyridostigmine Pretreatment in an Uncontaminated Environment

One 30-mg tablet is to be taken by mouth, with sufficient water to assist in swallowing the medication, every 8 hours as directed by your commander IF A DOSE IS MISSED, DO NOT MAKE IT UP DO NOT TAKE 2 TABLETS AT ONCE BE CAUSE OF A MISSED DOSE—MERELY START AGAIN WITH 1 TABLET EVERY 8 HOURS Taking 2 tablets at once could result in adverse side effects.

CAUTION

Taking more than 1 tablet at a time DOES NOT provide additional protection—in fact, IT MAY BE MORE HAZARDOUS IF THERE IS EXPOSURE TO A NERVE AGENT

*a.* When the order to take pyridostigmine pretreatment has been given, it should be taken directed, even though the protective mask is wor

*b.* During hours of darkness while in an uncontaminated environment, the NAPP will be administered using the above schedule.

## 2-20. Signs and Symptoms of Pyridostigmine Overdose and Allergic Reactions

Although no detrimental effects are expected at the recommended dosage, depending on the length of time and the amount of medication taken as well as individual physiologic variations, certain persons might experience adverse reactions from pyridostigmine.

a. Signs and symptoms of overdose and/or allergic reactions are—

(1) Abdominal cramps.

(2) Nausea.

(3) Diarrhea.

(4) Skin rash.

(5) Weakness, muscle cramps, and muscular twitching.

(6) Dimness of vision due to pinpointed pupils.

b. If any of the above signs/symptoms occur, the service member should consult unit medical personnel as soon as possible.

## 2-21. Emergency Treatment Administered by Medical Personnel for Pyridostigmine Adverse Side Effects, Allergic Reactions, and Overdose

Ordinarily, discontinuing pyridostigmine should be adequate to alleviate the signs and symptoms of adverse side effects, allergic reactions, and overdose. Pyridostigmine may persist in the blood for as long as 24 hours; however, after the blood level peaks in about 4 hours, the effects of the medication diminish gradually.

a. Emergency treatment for an overdose of pyridostigmine requires the administration of atropine in adequate doses to overcome the cholinergic crisis. Initially, the 2-mg atropine auto-injector found in the Mark I kit should be used. In most cases, this will be sufficient. Further administration of atropine may be necessary to control the cholinergic effects of pyridostigmine. If additional atropine is required, 2 mg should be administered by medical personnel every 15 to 20 minutes, thereby permitting the previous injection of atropine to exert its anticholinergic effect prior to the next injection.

b. Severe cases may require assisted ventilation because of weakness, but would be unusual when the pretreatment medication was administered every 8 hours as directed.

c. When stabilized the patient should be evacuated for further observation and treatment.

## 2-22. Responsibilities

a. The corps/division/wing commander will—

(1) Decide whether to begin, continue, or discontinue the NAPP medication based on threat. The intelligence officer or chemical officer and the surgeon act as advisors to the commander in making his decision if a chemical nerve agent threat exists (for example, the enemy having nerve agents in the combat zone or the probability of their use). After 3 days of self-administration of the medication by the service member, combat conditions should be reevaluated by the commander and his staff for a determination whether to continue the medication or not. However, orders to discontinue the pretreatment CAN and SHOULD be made at any time, depending on the situation. If the pretreatment is to be continued, then a second blister pack must be ordered while the service member completes the administration of the 7 days (21 tablets) and is issued the second pack on the 7th day. ADMINISTRATION OF THE MEDICATION BEYOND 21 DAYS IS NOT RECOMMENDED WITHOUT A THOROUGH EVALUATION OF THE SITUATION. However, the magnitude of the Threat may outweigh any possible adverse side effects and indicate continuance of the pretreatment.

(2) Train the service members that the NAPP must be faithfully taken as directed to enhance their survivability if they are exposed to a nerve agent. Service members must be trained to administer the NAPP during the day and at night, and while in MOPP 4 should these procedures become necessary.

(3) Issue appropriate unit SOPs for the retention and decontamination of the NAPP blister pack during personnel decontamination and overgarment exchange.

b. Combat, Combat Support, and Combat Service Support Units will—

(1) Obtain the NAPPs through medical supply channels.

(2) Maintain a quantity of the NAPPs commensurate with the basis of issue rate of 1 week's supply per service member. An additional week's supply of NAPPs will be maintained in the unit area. Authorized quantities will be commensurate with the latest doctrine and concept for use.

(3) Store the NAPPs for individual issue and immediate replacement as the end items are utilized, or as they exceed their labeled shelf life. The NAPPs should be stored refrigerated in temperatures ranging from 35 to 46 °F (2 to 8 °C). If the medication is removed from refrigeration for a total of 6 months, it should be assumed that it has lost its potency and should not be used.

(4) Issue the NAPPs to the service member at the time the chemical protective ensemble is expected to be opened for use.

c. Unit medical personnel will—

(1) Recognize the signs and symptoms of pyridostigmine overdose, allergic reactions, and side effects (para 2-20 above) for determining, on an individual basis, whether or not a service member is to continue the NAPP based on any adverse reaction to the medication.

(2) Advise the commander if any serious problems occur.

*d.* The individual service member will—

(1) Take the NAPPs as directed and in accordance with the provisions of paragraph 2-19 above.

(2) Secure the NAPP's against loss.

## Section VI. SUMMARY OF TREATMENT

### 2-23. Lifesaving Measures

*a.* Immediately mask the casualty.

*b.* Administer one set of the Mark I as a self-aid or three sets of the Mark I as a buddy aid measure as soon as symptoms are noted. Additional antidote may be given by Combat Lifesaver or medical personnel (such as the unit medical aidman) to maintain atropinization of the casualty.

*c.* Start assisted ventilation immediately for the paralyzed, nonbreathing casualty, and continue until spontaneous breathing is restored.

*d.* Administer diazepam intravenously to control convulsions.

*e.* Remove contaminated clothing and equipment, and then decontaminate skin surfaces.

*f.* Remove the patient from the contaminated area.

### 2-24. Prognosis

The effects of nerve agent poisoning may be prolonged. Recovery depends on many factors—one being the regeneration and protection of existing cholinesterase enzymes. This may take weeks to occur. In addition, there may be mental effects from nerve agents, as well as other residual effects. If exposure to many times the lethal dose has occurred or if treatment has been delayed too long, death will occur in most cases. This emphasizes the importance of prompt masking and prompt treatment.

DEPARTMENT OF THE ARMY
WALTER REED ARMY INSTITUTE OF RESEARCH
WALTER REED ARMY MEDICAL CENTER
WASHINGTON D.C. 20307-5100

IN REPLY REFER TO:

January 4, 1991

Div of Experimental Therapeutics

David A. Kessler, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Doctor Kessler:

It is my opinion that pyridostigmine 30 mg tablets should be provided to service members deployed in support of Operation Desert Shield. This product should be made available to service members deemed to be at risk of attack with chemical weapons. A military combat exigency exists, whereby the use of this product would be needed to facilitate the accomplishment of our military mission as well as preserve the health of the individual and the safety of others involved. I believe that withholding this potentially lifesaving treatment would be contrary to the best interests of those military personnel at risk because there is no other satisfactory alternative treatment available. Because there is no satisfactory alternative treatment, and the drug is potentially lifesaving, it should be given to those at risk without regard to what might be an individual's personal preference for treatment.

The IRB has reviewed this use of pyridostigmine and is of the consensus that it may be administered without obtaining informed consent under the conditions proposed.

Sincerely,

Brian G. Schuster, M.D., F.A.C.P.
Colonel, Medical Corps
Director
Division of Experimental Therapeutics

ORG. NO23606

DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

REPLY TO ATTENTION OF

January 8, 1991

Human Use Review and
Regulatory Affairs Office

SUBJECT: IND 23509 - Pyridostigmine Bromide - WR 270,710 (Serial No. 022)

CENTER FOR DRUGS AND BIOLOGICS
REC'D
JAN 14 1991
HFN-120

Director
Division of Neuropharmacological
Drug Products (HFN-120)
Office of Drug Review I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir:

The enclosed letter is provided in triplicate for insertion into the information submitted with our letter of December 31, 1990 (Serial No. 022).

Should you have any questions concerning this submission, please contact Ms. Marty Myers at (301) 663-2165.

Sincerely,

Gregory P. Berezuk
Lieutenant Colonel, Medical
Service Corps
Chief, Human Use Review and
Regulatory Affairs Office

Enclosure

Copy Furnished:

U.S. Army Medical Materiel Development Activity,
ATTN: SGRD-UMP

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

January 8, 1991

Enrique Mendez, Jr., M.D.
Assistant Secretary for Defense, Health Affairs
Department of Defense
Washington, DC 20301-1220

Dear Dr. Mendez:

I have received your request dated December 28, 1990, and submitted pursuant to 21 CFR 50.23(d) for a determination that obtaining informed consent is not feasible for the investigational agent pyridostigmine bromide 30 mg tablets.

In reviewing the justification for your request, I have considered the pertinent factors set forth in the regulation. Based upon your assessment of the military operation, I find that there is no available satisfactory alternative therapy for the prevention of the effects of exposure to organophosphorus nerve agents. Based on your agreement to provide and disseminate additional information to all military personnel concerning the risks and benefits of pyridostigmine, as stated in LTC Berezuk's January 8, 1991 letter to Dr. Stuart Nightingale, I concur with your assessment that informed consent is not feasible and that withholding treatment would be contrary to the best interests of military personnel.

Unless circumstances change, my determination expires one year from the date of this letter, or when the Department of Defense informs the Commissioner of Food and Drugs that the specific military operation creating the need for the investigational agent has ended, whichever is earlier.

Sincerely,

David A. Kessler, M.D.
Commissioner of Food and Drugs

DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH, VA 22041-3258

REPLY TO ATTENTION OF

January 17, 1991

Human Use Review and
Regulatory Affairs Office

SUBJECT: IND 23,509 - Pyridostigmine Bromide
(Serial No. 023)




Director
Division of Neuropharmacological
Drug Products (HFN-120)
Office of Drug Review I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir:

In your letter of December 11, 1990, in which you stated that "The Division has no objection to the DOD fielding [of] pyridostigmine...," you also discussed three additional requirements:

1. A revision of FM8-285 to delete any inferences that data on pyridostigmine were based on human experiences.

2. Submission of any data that support the effectiveness of the specific dosing regimen.

3. A document prepared for medical personnel which would be more detailed than the Field Manual.

The purpose of this amendment is to update you on the status of these requests. Most of this information has already been made available to you under other circumstances (i.e., Informed Consent meeting), however, this amendment will be the official submission under IND 23,509.

A letter is being prepared which will be sent to the proponent agency for FM8-285. This letter will strongly recommend that the appropriate changes to the FM be made and will detail the rationale for those changes. As was discussed at other meetings, this is a long term effort and could take several years to implement.

Two studies have recently been completed which measured red blood cell acetylcholinesterase during the course of the dosing regimen which was consistent with the doctrine in FM8-285. The first study, conducted at Johns Hopkins University, was entitled "Safety, Tolerance, Pharmacokinetics and Pharmacodynamics of Intravenous Pyridostigmine and Oral doses of Standard and Sustained-Release Pyridostigmine in Healthy Men and the Influence of Food on Oral Pyridostigmine Pharmacokinetics;" the second study, conducted by one of our laboratories, the U.S. Army Research Institute of Environmental Medicine (USARIEM), was entitled "Effects of Pyridostigmine Pretreatment on Physiological Responses to Heat and Moderate-To-Intense Exercise." Reports have not yet been prepared from either of these studies, however, some of the relevant figures have been extracted for your information. Enclosure 1 shows the acetylcholinesterase inhibition levels and pyridostigmine plasma concentrations over time from the Hopkins study; curves with error bars are actual data points, the rest of the curves were computer generated. Enclosure 2 shows the cholinesterase activity every 24 hours (eight hours after the previous dose and immediately prior to the next dose), while enclosure 3 shows the cholinesterase activity every 24 hours, two hours after dosing; these studies were conducted at USARIEM. Full copies of these reports will be provided upon receipt.

The third request was for a more detailed document on pyridostigmine for medical personnel. This manual has been prepared and is at enclosure 4.

If you have any questions concerning this matter, please contact Dr. Ronald Clawson at (301) 663-2051.

Sincerely,

Gregory P. Berezuk
Lieutenant Colonel, Medical Service Corps
Chief, Human Use Review and Regulatory Affairs Office

Enclosures

# U.S. Army Medical Research
# Institute of Chemical Defense




## Aberdeen Proving Ground
## Maryland

USAMRICD Technical Memorandum 90-4

DEPARTMENT OF THE ARMY
UNITED STATES ARMY MEDICAL RESEARCH INSTITUTE OF CHEMICAL DEFENSE
ABERDEEN PROVING GROUND, MARYLAND 21010-5425

REPLY TO ATTENTION OF

SGRD-UV-ZM (50) 29 November 1990

MEMORANDUM FOR SEE DISTRIBUTION

SUBJECT: USAMRICD Technical Memorandum 90-4, Clinical Notes on Chemical Casualty Care

1. This memorandum, the fourth in a series, is intended to provide technical information to health care professionals of the Army, Navy, Air Force and allied nations on the topic of chemical casualty care, in accordance with the postgraduate medical education mission of the Institute. The information is doctrinally consistent and assumes a working knowledge of the tri-service field manual "Treatment of Chemical Agent Casualties and Conventional Military Chemical Injuries," Army FM 8-285, Navy NAVMED P-5041, Air Force AFM 160-11, dated February 1990.

2. Unlimited reproduction and distribution of this memorandum is authorized. Readers are requested to submit topics and questions of general interest for future memoranda of this series. The point of contact for this Institute for instructional assistance and support is the undersigned at DSN 584-3393/2230/3276, Area Code (301) 671-3393/2230/3276.

FOR THE COMMANDER:

Frederick R. Sidell

FREDERICK R. SIDELL, M.D.
Acting Chief, Chemical Casualty
Care Office

DISTRIBUTION:

HQDA, ATTN: (DASG-PSZ), 5109 LEESBURG PIKE, FALLS CHURCH, VA 22041
HQ, USAF/SGHR, BOLLING AFB, WASHINGTON, DC 20332
NAVY DEPARTMENT, ATTN: CHIEF, BUREAU OF MEDICINE AND SURGERY
CODE 02B, WASHINGTON, DC 20372-5120
USCENTCOM CCSG, MACDILL AFB, FL 33608
COMMANDANT, AHS, ATTN: (HSHA-DTD), FT. SAM HOUSTON, TX 78234-6100

USAMRICD TECHNICAL MEMORANDUM 90-4

## PYRIDOSTIGMINE

### GENERAL

Pyridostigmine has been fielded in the military as a "pretreatment" for nerve agent poisoning. As a result, military physicians and other health care providers are often asked questions for which answers are not readily available in standard publications. Some commonly asked questions are: How does a cholinesterase inhibitor "pretreat" for nerve agent intoxication? How much benefit does it provide? What are the combined effects of the carbamate and a nerve agent? What will it do to normal people? Will it cause problems with military performance? What will it do to people with chronic illnesses or a tendency toward certain disease states? What will it do to those who take certain medications regularly? Should the need arise, what interaction might there be between pyridostigmine and drugs that might be used during anesthesia?

The purpose of this memorandum is to present the available data relevant to each of these questions.

### BACKGROUND AND EFFICACY

Pyridostigmine used alone does nothing for a person poisoned by a nerve agent. It does not reduce the effects, it is not an antidote, and in animal studies, it does not significantly change the $LD_{50}$ of the agent; however, when given before poisoning by a nerve agent and when the nerve agent challenge is followed by administration of the current antidotes (atropine and 2-PAMCl), therapy is more effective than it is without the pretreatment with pyridostigmine, i.e., the $LD_{50}$ is raised.

The effectiveness of a carbamate (e.g., pyridostigmine) as a "pretreatment" for nerve agent poisoning because a carbamate attaches to the same active site on the enzyme acetylcholinesterase (carbamylation) as does a nerve agent, and as long as the carbamate is on that site, the nerve agent cannot bind to the enzyme. After a nerve agent attaches, or binds, the agent-enzyme bond is "irreversible" and the enzyme can be replaced only by de novo synthesis. In contrast, the attachment of the carbamate is "reversible," and within minutes to hours (depending on which carbamate) the carbamate spontaneously leaves, or is hydrolyzed from the enzyme ("decarbamylation") leaving the enzyme able to function normally. Thus, the attachment of a carbamate provides temporary "protection" of the enzyme from the nerve agent.

One might expect that tying up, or inhibiting, the enzyme with a carbamate would cause the same effects as inhibiting the enzyme by a nerve agent. This is true if equieffective amounts of the two inhibitors are used, as a large amount of a carbamate will cause the same effects as nerve agent intoxication; however, it has been found that only a small percentage of functional acetylcholinesterase is necessary for normal or near normal functioning in organs (e.g., neuromuscular preparations) or organisms. If this small amount can be temporarily "protected," the efficacy of immediate, adequate therapy is greatly enhanced. In animal studies, carbamylation of about 30% of circulating acetylcholinesterase (red blood cell, or erythrocyte, cholinesterase) corresponds to a great increase in the effectiveness of the antidotes. This degree of inhibition can be produced in normal humans by an amount of pyridostigmine that causes negligible side effects or performance decrements.

One might further expect that if pyridostigmine inhibits part of the acetylcholinesterase, a smaller amount of nerve agent would be needed to produce toxicity. For reasons not well understood, this is not the case. The administration of pyridostigmine before a nerve agent challenge does not change the $LD_{50}$ from that of nerve agent alone. In limited studies using very small amounts of nerve agents, humans pretreated with pyridostigmine had the same or, in many cases, fewer effects than they did without the pretreatment; in no instance were the effects more severe.

Several studies indicate that a carbamate "protects" the active site on the enzyme. In in vitro studies, Koelle demonstrated that physostigmine (another carbamate) protected acetylcholinesterase against phosphorylation by the DFP (an organophosphorous inhibitor, similar to a nerve agent) (1). About the same time, Leopold and McDonald noted that DFP caused prolonged miosis in the eyes of humans. When DFP was administered after physostigmine, the time course of miosis was short, corresponding to that of physostigmine alone, suggesting that DFP did not attach to the receptor sites (2).

In a more recent study, the duration of neuromuscular blockade in intact animals was measured after the nerve agent soman administration in animals pretreated with pyridostigmine and in animals not pretreated. After soman alone (no pretreatment), the blockade was still complete (0% functional) at the termination of the study; in pyridostigmine pretreated animals, the blockade was briefly 0% at 10 minutes after the soman, but had returned to normal (100%) by 30 minutes after soman administration. In the latter instance, the time course of the blockade was that produced by pyridostigmine alone. As part of this study, soman was administered after a small amount of VX (a persistent nerve agent; the VX-enzyme bond is easily reactivatible by an oxime). A few minutes later oxime was administered, and the complete neuromuscular block returned to normal, indicating that the receptor sites had been

occupied by the pre-administered VX, which is easily removed from the enzyme by an oxime, rather than by soman, which is not removed (3). In both of these studies, the investigators noted a species difference. Primates were most sensitive to pretreatment and therapy, guinea pigs next, followed by rabbits and rats.

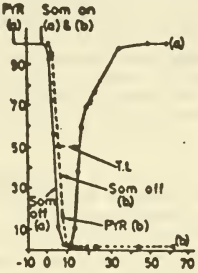



FIGURE. Rhesus monkey soleus muscle. Effectiveness of pyridostigmine pretreatment (100 ug/kg$^{-1}$, i.v.) in restoring soman depressed tetanus tension. (a) O--O, pyridostigmine (PYR) given 15 min before infusion of soman (14 ug/kg$^{-1}$, i.v.); (b) x -- x, PYR given 7 min after infusion of SOM (14 ug/kg$^{-1}$, i.v.). Som: Soman. T.t. tetanus tension recovery time. Ordinate: Tetanus tension (% of maximum). Abscissa: Time (min.)

Pyridostigmine given prior to soman considerably shortened the time of recovery of the soman induced neuromuscular blockade as measured by tetanus tension (curve (a); time course of pyridostigmine) compared to the recovery time when pyridostigmine is given after soman (curve (b); effects of soman (from reference 3).

The first use of a carbamate for "pretreatment" for lethal effects of an organophosphorus compound was in 1946 when Koster (4) reported that the administration of physostigmine before DFP protected cats against an otherwise lethal dose of DFP. Several years later, Wills (5) first used a carbamate as a "pretreatment" for a nerve agent. Atropine was unsuccessful therapy in sarin challenged rabbits (1/5

survived), but when physostigmine was given before the agent challenge and atropine therapy after agent challenge, all five animals survived.

Physostigmine has several drawbacks for field use. Its duration of activity is relatively short (an hour or less) which would necessitate frequent dosing and it causes side effects in man in the dose necessary for protection (physostigmine enters the CNS, and most of these side-effects are CNS related). In the early 1970s, pyridostigmine was found also to be effective. Because of its longer duration of activity dosing intervals are 8 hours; it also causes negligible side effects at the required doses (it does not readily cross the blood/brain barrier).

Efficacy was demonstrated by animal studies. As noted above, there was a species difference in response to pretreatment/therapy. Primates were the most responsive, followed by ginea pigs, rabbits, rats, and mice.

Pyridostigmine pretreatment was most beneficial in the pretreatment of animals challenged by soman (GD), an agent producing an agent-enzyme complex refractory to oxime reactivation. In three studies in guinea pigs challenged with soman and treated with atropine/2-PAMCl the PR's* were 3.4, 1.7, and 3.0; when pyridostigmine was given before agent challenge and the same therapy given after, the PR's were 6.4, 6.8, and 11.0. In two studies in rabbits, the addition of pyridostigmine pretreatment to the standard atropine/2-PAMCl therapy raised the PR's from 1.4 and 2.2 to 2.7 and 3.1. In rhesus monkeys, the PR in atropine/2-PAMCl treated animals was raised from 1.6 to over 40 by the addition of pyridostigmine pretreatment.

After tabun (GA) challenge, the PR's after atropine/2-PAMCl therapy were 2.4 in rabbits and 4.4 in guinea pigs; pyridostigmine pretreatment raised these to 3.9 and 12.2 respectively.

Standard therapy (atropine/2-PAMCl) given to sarin (GB) and VX challenged guinea pigs produces PR's of 30-50. Pyridostigmine pretreatment did not significantly change these (an observation reported over a decade ago (6)).

*The "protective ratio" (PR) is defined as the ratio of the $LD_{50}$ in a group of animals challenged with an agent and treated to the $LD_{50}$ of a group of animals challenged with an agent and not treated under the same experimental conditions. A PR of 1 would indicate the treatment is of no value. The more effective the treatment is, the higher the PR will be.

In several studies the effectiveness of atropine alone as therapy with and without pyridostigmine pretreatment was investigated, and this effectiveness was compared to that with the addition of an oxime. Generally oximes seem not to assist in the decarbamylation of the carbamate-enzyme complex (they usually are not useful in carbamate poisoning and in some cases may contribute to the toxicity of the carbamate). However, under the conditions of these studies, the addition of an oxime provided a small but definite benefit to the effectiveness of therapy. Harris, et al, suggested that under these circumstances the oxime may prevent recarbamylation of decarbamylated enzyme thereby interfering with the carbamate-enzyme equilibrium, or they may act directly by increasing the rate of decarbamylation of the cholinesterase (7,8).

The time course of the effectiveness of pyridostigmine was investigated in guinea pigs (6). The animals were pretreated with pyridostigmine and an oxime (both given i.m.), given soman after the stated time interval, and then treated with atropine and an oxime. Protective ratios for the times indicated were as follows:

| Interval Between Pyridostigmine and Soman | PR |
|---|---|
| 10 minutes | 3.4 |
| 30 minutes | 8.0 |
| 60 minutes | 12.5 |
| 2 hours | 6.0 |
| 3 hours | 4.7 |
| 4 hours | 3.2 |

SIDE EFFECTS

Over the past two decades, pyridostigmine (30 mg, in single doses are q.8h. for as long as 2 weeks) has been administered to thousands of military people in several countries. The incidence of side effects has been under 1%, and most were mild and involved the gastrointestinal tract (increased flatus, loose stools). If these effects are severe or prolonged, they might require therapy and they respond well to small amounts of atropine, e.g., one (1) mg i.m. or orally. It is possible that transient muscular fasciculations might also be seen due to the nicotinic effects of pyridostigmine.

Rarely, an individual might be sensitive to the bromide portion of the molecule and develop an erythematous rash.

## PHYSIOLOGICAL EFFECTS

In a large number of studies involving hundreds of subjects, pyridostigmine (doses of 30 or 60 mg given once or repeatedly) caused a decrease in heart rate of 5 bpm at rest and on exercise, and no effects on visual parameters including pupil size or "other physiological or blood parameters" (9). Several relevant recent studies are described below.

Five subjects exercised on a bicycle ergometer for 30 minutes (55% peak oxygen consumption) in an environmental chamber; the ambient temperature was 29° C (86°F) and the dew point temperature was 10° C. On one occasion, the subjects took 30 mg of pyridostigmine bromide orally 150 minutes before exercise and on another occasion they took no drug. After the drug, the esophageal temperature was higher ($p<0.01$), the whole body sweating rate was higher ($p<0.01$), the heart rate was lower ($p<0.01$), and the skin blood flow was lower ($p<0.05$). (10).

In a related study, 4 healthy males exercised for 30 minutes (bicycle ergometer; 58% peak oxygen consumption) on 3 occasions without taking pyridostigmine and on 3 occasions 150 minutes after taking 30 mg pyridostigmine orally. Ambient temperatures for these sessions were 22°C (69°F), 29°C (86°F), and 36°C (98°) and the relative humidity was 30%. The findings were similar to those noted above. Compared to the control (exercise alone), pyridostigmine administration and exercise at the higher temperatures caused a small but statistically significant decrease in heart rate, increase in the esophageal temperature, increase in sweating, and decrease in skin blood flow (by 40% at 29°C and by 50% at 36°C). The investigators noted that the decrease in skin blood flow created a less favorable temperature gradient for heat exchange between the skin and the environment, increasing heat storage. They suggested further that, in a chemical protective suit, heat loss by evaporation would be limited by the low water vapor pressure gradient between the skin and the immediate environment, and dry heat loss would become much more important in maintaining body temperature. In such an environment, pyridostigmine might adversely affect temperature regulation and an individual might be more susceptible to heat storage (11).

Seven males took pyridostigmine q.8h. for 4 days and exercised (55 minutes; 40% maximal oxygen consumption; 108°F and 30% r.h.) 2 hours after the first daily dose each day. They underwent the same experimental conditions taking a placebo tablet. There

were no differences between esophageal and skin temperatures, heart rates, and sweat rates between the drug and placebo trials. Skin blood flow was not reported. These findings (lack of differences in heart rates, temperatures, sweat rates between the drug and placebo groups) were in contrast to the differences found in the previous two studies. Although the ambient temperature was higher (108°F vs 98°F and 86°F, the workload was about 30% less (40% maximal oxygen consumption vs 58% and 55%). This suggests that workload, rather than temperature, may contribute more to potential heat storage (Kolka, M. A.; unpublished data). These data suggest that under conditions of moderate to a heavy workload at high temperatures (98°F - 108°F), heat storage with resulting illness may occur; however, the conditions of the third study, in which there were no changes, probably more accurately reflect most military operational scenarios.

Twelve males took pyridostigmine (30 mg q.8h., for four doses) and were subjected to altitudes of 8,000 feet and 13,000 feet, and rapid decompression from 8,000 to 23,000 feet in a simulator. No differences from a placebo trial were noted in $PAO_2$, $SaO_2$, $PACO_2$, heart rate, minute volume, forced expiratory volume, forced vital capacity, and forced expiratory flow (12).

## PERFORMANCE

In hundreds of subjects in studies conducted over the past two decades, pyridostigmine caused no changes in psychological tests for cognitive and psychomotor skills, memory, manual dexterity and vigilance, and driving tests by day and by night (9). Several studies are described below.

In a double-blind crossover study, 12 subjects underwent testing of sensory, motor, and cognitive functioning at ground level, 8,000 feet, and 13,000 feet after the fourth dose of pyridostigmine (30 mg, p.o., q.8 h.). After pyridostigmine, preferred hand tapping was decreased at 8,000 feet, nonpreferred hand tapping was decreased at 13,000 feet, and memory search recall (short-term memory) was decreased. Although statistically significant ($p<0.05$ in each case), these changes were felt to be operationally insignificant. The investigators concluded that overall performance was not functionally altered by the drug (13).

Twenty one C130 pilots flew a 1.5 hour C131H simulation flight after receiving pyridostigmine (30 mg) or a placebo in a double-blind crossover study. There were no differences noted between the conditions on measures of workload, fatigue, mood, and symptoms, nor were there any differences in overall performance (14).

DRUG INTERACTIONS/CHRONIC ILLNESS

When a threat of exposure to nerve agent has been determined to exist, soldiers may be instructed by their commander to begin taking the pretreatment pyridostigmine (30 mg tablets) every 8 hours. If exposed to nerve agent, the soldier must immediately receive the antidote combination of atropine and pralidoxime by injection to increase the chances of survival. Needless to say, there may be many pyridostigmine-treated soldiers on the battlefield, even though exposure to nerve agent may never occur.

There may be some soldiers with preexisting medical conditions who sometimes require daily medication for adequate control, and yet they may be considered "worldwide deployable." Thus, there may be soldiers subject to a pyridostigmine-drug interaction or a pyridostigmine-medical condition interaction. A possibility of pyridostigmine-drug interaction is based on similar target sites or a resultant change in the pharmacokinetics of either drug. Since there is no significant plasma protein binding by pyridostigmine, this eliminates the consideration of interactions involving competition for these sites. Only 10-25% of pyridostigmine is metabolized, so interactions with biotransformation processes is also of little importance. No attempt will be made to cover potential pyridostigmine interactions with every common drug; however, a few caveats are pointed out with regard to some common chronic medical problems requiring daily medication.

Hypertension: One in six Americans have hypertension. This is a well-recognized medical problem and many successful pharmacologic approaches are used to control this condition. Currently, several classes of drugs are used in the treatment of hypertension: diuretics (thiazide, loop, potassium sparing), beta-blockers, alpha-blockers, alpha$_2$ agonists (primarily centrally acting), converting enzyme inhibitors, calcium channel blockers, and direct acting vasodilators. Of these, few interactions are anticipated.

Beta-blockers, however, may pose a problem. Beta$_1$-antagonists have negative chronotropic and inotropic effects on the heart. Pyridostigmine augments vagal effects on the heart, so additive effects on heart rate may occur, resulting in a further reduction in cardiac output and blood pressure. Non-selective beta blockers also block beta$_2$-receptors and can cause an increase in airway resistance. Bronchoconstriction is not a problem with pyridostigmine at the recommended dosage; however, it may become manifest in an individual who is also taking a non-selective beta blocker or in a previously undiagnosed individual with reactive airway disease.

It is not known if pyridostigmine would increase the incidence of syncope in patients taking alpha-blockers, alpha$_2$ agonists, converting enzyme inhibitors, calcium channel

blockers, or direct acting vasodilators; however, if volume depletion is added to this scenario, this might enhance the likelihood of seeing the additive effects of pyridostigmine with these drugs. Patients should be advised of the possibility of becoming lightheaded, especially if not properly hydrated. Initiation of pyridostigmine under medical supervision should be considered.

Asthma: A known asthmatic is not worldwide deployable. However, a desert environment and/or pyridostigmine may unmask a previously undiagnosed individual with hyperreactive airways.

Glaucoma: Anticholinesterase drugs are often used in the treatment of several forms of glaucoma, so pyridostigmine would not be a problem, but simply additive. Effects of either or both drugs may interfere with night vision. On the other hand, timolol (a non-selective beta blocker) is also used to reduce intraocular pressure, and as mentioned earlier, in combination with pyridostigmine may result in bronchoconstriction in an individual who also has hyperreactive airways.

Low "dibucaine number" or low plasma cholinesterase: Dibucaine is used as a diagnostic tool because it inhibits plasma (or "pseudo-" or "butyro-") cholinesterase to varying degrees. Dibucaine inhibits the normal (homozygote) enzyme by 70-85%, hence a dibucaine #80 indicates the presence of normal enzyme, and the incidence in the population is 96%. Dibucaine #50-65 (50-65% inhibition) is characteristic for the heterozygote with an incidence of about 4%. Dibucaine #16-25 signifies the abnormal homozygote and occurs at a frequency of about 0.03%.

A person with a low dibucaine number has plasma cholinesterase that is resistant to inhibition by dibucaine. Pyridostigmine inhibits normal plasma cholinesterase by about 35%, and although it isn't known exactly how much pyridostigmine inhibits the atypical enzyme in general, the atypical enzyme is also resistant to inhibition by carbamates. However, the purpose of pyridostigmine pretreatment is to protect "true" cholinesterase at the neuromuscular junction (and reflected in red blood cell cholinesterase activity). People with abnormal plasma cholinesterase generally have normal true cholinesterase, and therefore, should be offered the same protection from pyridostigmine.

The significance of a low dibucaine number is that the individual will have a prolonged response to selected drugs, e.g., succinylcholine and ester local anesthetics. This is because the individual has a low quality (not necessarily low quantity) plasma cholinesterase that is normally responsible for metabolizing and inactivating these drugs. Regardless of whether pyridostigmine has an effect on this abnormal plasma

cholinesterase, the individual will have a higher blood level and prolonged response to drugs which require plasma cholinesterases for bioinactivation.

Decreased levels of plasma cholinesterase (as much as 50%) are sometimes seen in people taking birth control pills or corticosteroids, but again, the clinical significance of this in soldiers taking pyridostigmine is not related to the efficacy of nerve agent pretreatment, but rather is confined to enhanced responses to drugs that depend on the enzyme for their metabolism (e.g., succinylcholine and ester local anesthetics).

Antimalarials: Depending on the region, drugs used for prophylaxis/suppression and treatment of malaria symptoms include chloroquine, primaquine, mefloquine, quinine, quinidine, Fansidar (pyrimethamine + sulfadoxine), doxycycline and tetracycline. These drugs act by interfering with parasite replication and protein synthesis; therefore, no mechanistic interactions with pyridostigmine are anticipated. However, there may be interactive side effects: Quinine and quinidine (and possibly mefloquine based on structural similarity) have a weak nondepolarizing blocking effect on skeletal muscle. This side effect would tend to be negated by pyridostigmine. With regard to quinidine's cardiac effects, concurrent pyridostigmine administration may make A-V block more attainable and hypotension accentuated. Another possible interaction between antimalarials and pyridostigmine is the possible additive effects on the gastrointestinal tract. Loose bowels is the most common complaint about both antimalarials and pyridostigmine, and together they may pose a simple inconvenience or possibly a genuine problem.

Gastrointestinal problems (reflux esophagitis, peptic ulcers) may be exacerbated by pyridostigmine.

Hyperthyroid patients may develop atrial fibrillation if administered pyridostigmine.

The enclosed report from Military Medicine provides further information on these topics and on the interactions of pyridostigmine and drugs used in anesthesia.

## PHARMACOKINETICS

The pharmacokinetics of oral and intravenous pyridostigmine have been defined in healthy male volunteers and in patients with myathenia gravis(15-18). Pyridostigmine is highly water soluble and the tablet undergoes rapid dissolution. The drug (a quatenary ammonium compound) is a charged molecule, which probably contributes to its variable absorption. Pyridostigmine has a relatively short half-life and is primarily excreted unchanged in the urine. The mean pharmacokinetic parameters for pyridostigmine are summarized in Table 1.

Table 1. Pyridostigmine Pharmacokinetic Data(Ref. 15,17,18)

| | Mean | Std. Dev. |
|---|---|---|
| Total | | |
| Clearance(ml/min/kg) | 8.5 | 8.7 |
| Urinary Excretion(%) | 80-90% | 0.3 |
| Vol.Dist.(L/kg) | 1.1 | 0.3 |
| Half-life(h) | | |
| Intravenous | 1.9 | 0.2 |
| Oral | 3.7 | 1.0 |

## BIOAVAILABILITY

The bioavailability of pyridostigmine has been estimated to be between 14%(17) and 29.1%(15). There is a large intersubject variability in the extent of bioavailability. For example, in one study the mean bioavailability was 29.1% with a range of 14.7-51.1%(15).

## PHARMACODYNAMICS

### After Single Oral Dosing

There is considerable intersubject variation in the pharmacodynamic effect of pyridostigmine. After oral administration the peak erythrocyte acetylcholinesterase (RBC AChE) inhibition varied from 20 to 39% of the baseline enzyme activity and the period of inhibition exceeding 20% varied from 0.33 to 5.0 hours. The variation appears to be

due to interindividual differences in the amount of drug absorbed, in the rate of elimination of the drug, and in the sensitivity of the RBC AChE to inhibition by pyridostigmine.

After Multiple Dosing

Despite the varability in bioavailability of pyridostigmine and its pharmacodynamic effects following a single dose, relatively stable and predictable inhibition of RBC AChE is produced with multiple dosing. Figure 1 shows the mean RBC AChE inhibition in eight healthy male subjects following doses were given without any particular reference to meals. Using this regimen AChE inhibition was produced in the target range of 20 to 40%.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 17, 1991

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

SUBJECT: IND 23,509: Revisions to Field Manual

TO: File, IND 23,509

On December 11, 1990, the Division issued a letter to the Department of the Army, requiring, among other things, the revision of the following two statements in the Field Manual describing pyridostigmine pre-treatment for nerve agent induced injury:

1) When used in conjunction with the Mark I..., this pretreatment enhances the survivability of nerve agent poisoned casualties.

2) This pretreatment medication, plus the nerve agent antidote (Mark I), reduces the severity of nerve agent poisoning, shortens the duration of treatment, and increases the survival rate of nerve agent poisoned casualties.

The reason these statements were required to be changed was that they allowed the inference that they were based on human experience; in fact, the only evidence for these salutary effects was gained in studies in animals.

In a letter dated 4/4/91, the Army has proposed the following changes:

1) When used in conjunction with Mark I..., this pretreatment may enhance the survivability of nerve agent poisoned casualties.

2) This pretreatment medication, plus the nerve agent antidote (Mark I) may: reduce the severity of nerve agent poisoning, shorten the duration of treatment, and increase the survival rate of nerve agent poisoned casualties.

COMMENTS

The changes proposed are more accurate than the originals. That is, the originals stated as fact that the treatment was effective, whereas the revisions do imply that efficacy is not proven. However, our original objection was based on the fact that the statements about the efficacy of the treatment (whether proven or questionable) allowed the inference that they were based on human data. The statements as revised do not address our original concerns. Specifically, the reader of this manual cannot know that the statements about the (predicted) efficacy of the treatment are based, not on human data, but on animal studies. Any proposed treatment may work; the point is that, for this particular treatment, the belief that it may work is based on work done in animals. The absence of any statements to that effect will continue to allow the inference

that any statements about the efficacy, regardless of how less or more emphatic (may vs. will) are based on studies in humans.

RECOMMENDATIONS

I believe that the revised statements are inadequate, because they still allow the inference that (potential) efficacy is based on data derived from humans. They should be revised to include language that makes it explicitly clear that evidence to support even the potential for benefit in humans is derived from studies performed in animals.

Russell Katz, M.D.

cc:
HFD-120
HFD-120/Katz/Leber/Nighswander
rk 5/17/91
23509517.rev

DEPARTMENT OF THE ARMY
US ARMY MEDICAL MATERIEL DEVELOPMENT ACTIVITY
FORT DETRICK, FREDERICK, MARYLAND 21701-5009

REPLY TO
ATTENTION OF:

SGRD-UMB (70-1ff) 8 October 1991

MEMORANDUM FOR Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, Maryland 21702-5012

SUBJECT: BB-IND 3723, Botulism Pentavalent (ABCDE) Toxoid Reactogenicity

1. In accordance with BB-IND 3723 "Pentavalent (ABCDE) Botulinum Toxoid, Aluminum Phosphate Adsorbed," and agreement with the Division of Biologics, Food and Drug Administration, reactogenicity information concerning a subset of 121 individuals who received Pentavalent (ABCDE) Botulinum Toxoid Vaccine during Operation Desert Storm/Shield was collected. This information was collected by a retrospective postcard survey (enclosure 1 is a copy of the postcards distributed). The survey was given to individuals who received one or more doses of Pentavalent (ABCDE) Botulinum Toxoid and no other vaccines directed against biological warfare agents during their tour of duty in the Persian Gulf.

2. Postcards were sent to the Preventive Medicine Office, Camp Pendleton, California, and were disseminated by the Division medical personnel on 27 August 1991 to those persons who received Pentavalent (ABCDE) Botulinum Toxoid under protocol BB-IND 3723 during the period of 3 January 1991-2 March 1991. Almost all of these military personnel received two injections (116/121 or 95.86 percent) while 5/121 (4.14 percent) received one injection; none received a third injection.

3. One hundred and twenty-one responses were received for local and generalized reactions to Pentavalent (ABCDE) Botulinum Toxoid. Those individuals who did not respond to any of the categories listed under local reactions were listed as none in Table 1 (enclosure 2). Table 1 shows the local reactions to the Pentavalent Botulinum Toxoid. The reactogenicity data collected under BB-IND 3723 closely parallels previous U.S. Army experience with this vaccine. Eighty-four percent of the vaccinees reported either no local reactions (72.5 percent) or redness and swelling less than 6 inches in any dimension (11.66 percent). The one individual who listed his local reaction as incapacitating arm pain did not have a systemic reaction. Table 2 (enclosure 3) lists generalized or systemic reactions. No systemic reactions were reported by 118/121 (97.52 percent) of the respondents. Two of the three responses for generalized reactions (2/121)

SGRD-UMB
SUBJECT: BB-IND 3723, Botulism Pentavalent (ABCDE) Toxoid Reactogenicity

experienced mild systemic effects such as headache and muscle aches as a chief complaint. The rate of systemic reactogenicity of Pentavalent (ABCDE) Botulinum Toxoid during Desert Shield/Storm closely parallels the U.S. Army experience of 3.0 percent reactogenicity when this vaccine was administered to "at risk" laboratory personnel during the period 1970-78.

4. In accordance with the letter dated 15 March 1991 from Dr. Enrique Mendez, the Assistant Secretary of Defense to Dr. David Kessler, Commissioner of Food and Drugs concerning BB-IND 3723, the need to use this vaccine without informed consent has ended and no further subjects will be accrued under BB-IND 3723 using the Desert Shield protocol. However, we request that the Center for Biologics and Research Evaluation allow BB-IND 3723 to remain on active status so that studies conducted with new protocols under informed consent may be undertaken in the future. One of the proposed plans is to evaluate a more practical immunization schedule with this vaccine. It is also our intention to submit additional protection data collected in non-human primates and submit this data to the BB-IND 3723 file. If we plan to examine microencapsulated vaccine or other approaches that would modify the product, we will request inactivation of BB-IND 3723 and will prepare a new IND application.

5. The point of contact at this Activity is LTC Balady at extension 7661.

6. USAMMDA - Developing Quality Medical Products for Soldiers.

FOR THE COMMANDER:

Walter E. Brandt

3 Encls

WALTER E. BRANDT
Project Manager
Biological Systems Division




COMMANDER
U.S. Army Medical Materiel Development Activity
ATTN: SGRD-UMB
Building T-622
Fort Detrick,
Frederick, Maryland 21702-5009

Dear Servicemember,

You were among a group of persons who received Botulinum vaccine during Operation Desert Shield/Storm. We would appreciate your assistance in monitoring any side effects that you may have experienced within 48 hours after your vaccination.
Please check all boxes that apply.
Name_____
Number of Botulinum vaccinations_____
LOCAL REACTION

__ Redness &/or swelling less than 6 inches in any dimension.
__ Redness &/or swelling greater than 6 inches in any dimension.
__ Pain or swelling that limited but did not prevent your using your arm.
__ Incapacitating pain, swelling or tenderness that did not allow you to use your arm.
__ Other (Please describe). _____

GENERALIZED REACTIONS

__ None
__ Fever, fatigue, muscle aches, nausea, headaches that did not limit your activity.
___Fever, fatigue, muscle aches, nausea, headaches that did limit your activity.
___ Severe incapacitating reaction that resulted in quarters or hospitalization (Please describe).

01/08/91 16:48 ☎301 663 2982 BW USAMRDC 003

COUNTERMEASURES AGAINST CHEMICAL WARFARE AGENTS

Additional Information on Pyridostigmine

Your primary protection against chemical weapons is your chemical protective mask and battle dress overgarment (BDO). You have also been given some items to help you in case you are exposed to chemical warfare agents. These items are:

a. Two antidotes (Atropine and 2-PAM) which are components of your MARK I Nerve Agent Antidote Kit.

b. Pyridostigmine. Based on the results of studies in animals that were exposed to nerve agents, the Department of Defense has concluded that pyridostigmine, WHEN USED IN CONJUNCTION WITH ATROPINE AND 2-PAM, may be critical to your survival. Pyridostigmine, for military use, must be taken prior to exposure to nerve agents. Pyridostigmine can be effective only when used with the items in the MARK I Kit. Many years of use in humans for non-military purposes indicates that pyridostigmine is safe and free from debilitating side effects if used as recommended.

# APPENDIX 10.—DOCUMENTS REGARDING DR. MOSS' RESEARCH

JOHN D. ROCKEFELLER IV, WEST VIRGINIA, CHAIRMAN

DENNIS DECONCINI, ARIZONA
GEORGE J. MITCHELL, MAINE
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ARLEN SPECTER, PENNSYLVANIA
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JIM GOTTLIEB, CHIEF COUNSEL/STAFF DIRECTOR
JOHN H. MOSEMAN, MINORITY CHIEF COUNSEL/STAFF DIRECTOR

United States Senate
COMMITTEE ON VETERANS' AFFAIRS
WASHINGTON, DC 20510-6375

May 31, 1994

James I. Moss, Ph.D.
Agricultural Research Service
U.S. Department of Agriculture
P.O. Box 14565
Gainesville, Florida 32604

Dear Dr. Moss,

Thank you very much for your participation at the Committee's May 6 oversight hearing on military research, focusing on investigation compounds administered to Persian Gulf service members.

Unfortunately, we had limited time at the hearing to ask questions of the witnesses. Therefore, I am submitting the enclosed questions, and ask that you provide responses to these questions by June 15.

I look forward to working with you to ensure the best possible care for all our veterans.

If you have any questions, please contact Dr. Diana Zuckerman at (202) 224-9126.

Sincerely,

John D. Rockefeller IV
Chairman

Enclosure

**Posthearing Questions for**
**James Moss, Ph.D.**
**Agricultural Research Service**
**U.S. Department of Agriculture**

**from Senator John D. Rockefeller IV, Chair**
**Senate Committee on Veterans' Affairs**

1. It is my understanding that your data suggest that pyridostigmine enhances the mortality of insects exposed to pesticides. Based on your scientific knowledge, might a lower dose of pesticides and/or pyridostigmine result in increased illnesses rather than death?

2. It is my understanding that you have studied the toxicity of individual and combined chemicals on insects. Please describe the results you obtained when you tested chemicals that were used by the U.S. military in the Persian Gulf (i.e., pyridostigmine, DEET, and other carbamates and organophosphates on the Army list enclosed). Please summarize your data on insects and any other species. Please include dosage and mortality rates.

3. Based on published research, what are the mechanisms whereby insects and humans both could be adversely affected by a combination of pesticides and pyridostigmine?

4. The Department of Defense (DoD) maintains that pyridostigmine's adverse side effects are those associated with inhibition of acetylcholinesterase, which should be short-term and reversible. Do carbamates and organophosphates inhibit any other enzymes which could result in long-term effects? What other enzymes might pyridostigmine inhibit which could result in chronic illness?

5. Committee staff have talked to many scientists about the potential toxicities of various organophosphates and carbamates. Several scientists have discussed neuropathies associated with inhibition of neurotoxic esterase or neuropathy target esterase (NTE). Could the inhibition of NTE result in neurological or other symptoms or diseases (i.e., immune dysfunction, cancer) currently being reported by Persian Gulf War veterans? Are there other symptoms or diseases that might be expected, based on the effects that you have seen on insects? Please base your response on published research as well as your own scientific knowledge.

6. Please provide a copy of your research proposal to DoD and a brief description of the research that you believe is necessary to better understand whether Persian Gulf War soldiers who took pyridostigmine were likely to have been especially vulnerable to the toxic effects of pesticides or other environmental toxins.

Responses by J. I. Moss (USDA-ARS) to questions by J. D. Rockefeller, Chair, U. S. Senate Committee on Veteran's Affairs.

1. It is my understanding that your data suggest that pyridostigmine enhances the mortality of insects exposed to pesticides. Based on your scientific knowledge, might a lower dose of pesticides and/ or pyridostigmine result in increased illnesses rather than death?

1. Mortality versus non-lethal effects are a matter of dosage. With most drugs, toxins, or combinations of drugs, I would expect a range from sub-clinical effects (no gross symptoms) through obvious signs to acute mortality, all depending on the dose. In my research, data is collected using several doses to reveal dose-response relationships. Common cockroach symptoms of sublethal doses of most of the chemicals I have tested (and are referred to in these questions) are diarrhea and apparent neurological signs. It is quite possible that biochemical measurements would reveal changes from even lower doses. Although not guaranteed, biochemical interactions between the compounds at higher doses are likely to represent what occurs at lower doses. The inverse of this is also true. Something which causes illness at a given dose has a good chance of being acutely lethal at higher doses.

Responses by J. I. Moss (USDA-ARS) to questions by J. D. Rockefeller, Chair, U. S. Senate Committee on Veteran's Affairs.

2. It is my understanding that you have studied the toxicity of individual and combined chemicals on insects. Please describe the results you obtained when you tested chemicals that were used by the U.S. military in the Persian Gulf (i.e., pyridostigmine, DEET, and other carbamate and organophosphates on the Army list enclosed). Please summarize your data on insects and any other species. Please include dosage and mortality rates.

2. All of my data are from insect (German cockroach) assays. The measure of toxicity used here is the LD-50, which is the amount (in milligrams/kilogram) found to kill 50% of the test population. These numbers can then be used to examine relative potencies of compounds and the effects of other compounds on the potency of the test compound. If you know the mechanism of action of one compound and it interacts with another of unknown mode of action, inferences can be drawn about the unknown mode of action. When I tested mixtures of compounds, the LD-50 of a compound was found in the presence and absence of sub-lethal amounts of the other compound.

The numbers in the "Synergism Ratio" column are the change in the LD-50 resulting from sublethal "Synergist" doses. For example, DEET increased Bendiocarb toxicity one fold (no increase) and DEET increased pyridostigmine four fold. It therefore took one fourth as much pyridostigmine to kill the cockroaches in the presence of a sublethal dose of DEET. I have baseline data for toxicity of D-phenothrin, Diazinon, Lindane, and Methomyl, but I will not be able to look at interactions of these compounds before my employment expires this June.

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Table 1.
Toxicity of various compounds and combinations of compounds on German cockroaches.

| Drug | Dose Form | "Synergist" | Dose (mg/Kg) | LD-50 48 Hour (mg/Kg) | Synergism Ratio |
|---|---|---|---|---|---|
| Bendiocarb | t | None | 0 | 16 | 1 |
| Bendiocarb | t | DEET | 1,111 | 18 | 1 |
| Boric Acid | f | None | 0 | 363 | 1 |
| Boric Acid | f | DEF | 222 | 21 | 17 |
| Caffeine | f | None | 0 | 4,100 | 1 |
| Caffeine | f | Boric Acid | 2 | 333 | 12 |
| Chlorpyrifos | t | None | 0 | 4 | 1 |
| Chlorpyrifos | t | DEET | 1,111 | 4 | 1 |
| Chlorpyrifos | t | None | 0 | 5 | 1 |
| Chlorpyrifos | t | Pyridostigmine | 1 | 4 | 1 |
| D-phenothrin | t | None | 0 | 9 | |
| Chlordimeform | t | None | 0 | 1,134 | 1 |
| Chlordimeform | t | Theophylline | 11 | 483 | 2 |
| Chlordimeform | t | DFP | 22 | 405 | 3 |
| Chlordimeform | t | Boric Acid | 2 | 178 | 6 |
| Chlordimeform | t | PMSF | 2,222 | 88 | 13 |
| Chlordimeform | t | DEF | 1,111 | 47 | 24 |
| DEET | t | None | 0 | 5,957 | 1 |
| DEET | t | Theophylline | 11 | 2,467 | 2 |
| DEET | t | DEF | 1,111 | 2,028 | 3 |
| DEET | t | Permethrin | 1.3 | 1,498 | 4 |
| DEET | t | Chlordimeform | 222 | 790 | 8 |
| DEET | t | PMSF | 2,222 | 673 | 9 |
| DEET | t | Pyridostigmine | 2,222 | 611 | 10 |
| DEET | t | Permeth + PMSF | | 185 | 32 |
| DEF | t | None | 0 | 7,276 | 1 |
| DEF | t | Boric Acid | 0.02 | 1,777 | 4 |
| DEF | t | PMS | 2,222 | 515 | 14 |
| Diazinon | t | None | 0 | 7 | |
| Lindane | t | | 0 | 5 | 1 |
| Malathion | t | None | 0 | 59 | 1 |

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| | | | | | |
|---|---|---|---|---|---|
| Malathion | t | DEET | 1,111 | 39 | 2 |
| Malathion | t | Permethrin | 0 | 26 | 1 |
| Malathion | t | Permethrin | 1 | 10 | 3 |
| Methomyl | t | | 0 | 11 | 1 |
| Permethrin | t | None | 0 | 3 | 1 |
| Permethrin | t | DEF | 1,111 | 2 | 2 |
| Propoxur | t | None | 0 | 4 | 1 |
| Propoxur | t | Permethrin | 1 | 2 | 2 |
| Pyridostigmine | t | None | 0 | 7,594 | 1 |
| Pyridostigmine | t | DEET | 1,111 | 2,025 | 4 |
| Sevin | t | None | 0 | 17 | 1 |
| Sevin | t | DEET | 1,111 | 11 | 2 |
| Trichlorfon | t | None | 0 | 88 | 1 |
| Trichlorfon | t | Boric Acid | 2 | 41 | 2 |

t=topical f=in food (%)

LD-50: The amount of chemical that kills 50% of the test group. Synergism ratio: the LD-50 of the compound divided by the LD-50 of the compound plus a sublethal amount of the synergist.

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3. Based on published research, what are the mechanisms whereby insects and humans both could be adversely affected by a combination of pesticides and pyridostigmine?

3. I have not found documentation which directly addresses interactions of pyridostigmine and pesticides.

One Israeli report (post war) (1) indicated that symptoms reported as a result of pyridostigmine intake for nerve gas protection were not correlated to cholinesterase inhibition. This raises the question of how pyridostigmine is causing symptoms since its action is supposed to be exclusively by cholinesterase inhibition.

A non-cholinergic target for pyridostigmine, in addition to its cholinergic effects, increases the odds of interactions with other compounds. This is especially true for those insecticides which have anomalous actions and effects on biochemical systems in addition to the "known" target of the compounds. There are numerous examples of this with the conventional insecticides. Pyrethroids have demonstrated actions on several biochemical systems other than the "primary" target, the sodium channel (2). Some organophosphates, in addition to cholinesterase inhibition, inhibit neurotoxic esterase (NTE), and others (3). The cotton defoliant, DEF, not only inhibits cholinesterase but inhibits NTE, and some unidentified enzyme in cotton plants (thus the defoliation). Organochlorine insecticides are notorious for the number of biochemical targets responsible for their toxicity (4). Any of the "secondary" actions of any of these compounds could become "primary" if that action were synergised by another compound because the secondary effect might be selecetively increased while the expected effect might not change.

To summarize the answer, there are numerous mechanisms by which pyridostigmine could interact with insecticides and we do not know enough about the interactions of these compounds in people to allow their indiscriminate mixing.

The identity of DEET (insect repellant) effects on insects and mammals is difficult to assess because neither its repellant or toxic mode of action are understood. It is possible that the toxic actions on insects and vertebrates are the same because the toxicity to cockroaches and rodents are nearly the same on a weight basis (Table 2.). It remains to be seen if the other compounds increase DEET toxicity in vertebrates as they do in insects. One note of interest is that at the usual usage levels of DEET, it appears that the differences between the effective (repellant) dose and the toxic dose of DEET appear to be small as evidenced by reports if ill effects from DEET (5). Because of



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this, it is possible that normally safe use of DEET might be rendered toxic with even low levels of synergism by other compounds.

Table 2.

| Hypothetical: for a 70 kg insect. | Synergist | Dose (g) |
|---|---|---|
| DEET | None | 417 |
| DEET | pyridostigmine | 43 |
| DEET | eserine | 0.17 |

Everglades Study (NIOSH)

| DEET Use: | g/week | g/day |
|---|---|---|
| Mean | 14.6 | 2.085714 |
| Median | 2.6 | 0.371429 |

I have evidence of interactions of these compounds in insects and a central tenant of biochemistry is that of form and function are conserved. This includes cellular responses to chemicals. At the biochemical level, human cells are more likely than not to respond in chemicals in the same way. Examples to support this would fill volumes.

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4. The Department of Defense (DoD) maintains that pyridostigmine's adverse side effects are those associated with inhibition of acetylcholinesterase, which should be short-term and reversible. Do carbamate and organophosphates inhibit any other enzymes which could result in long-term effects? What other enzymes might pyridostigmine inhibit which could result in chronic illness?

4. The known target for pyridostigmine is acetylcholinesterase, the same enzyme the organophosphates (OP's) inhibit. Acetylcholinesterase is only one enzyme from a large family of enzymes (serine/threonine hydrolases) which have nearly identical mechanisms of action. This will be found in any general biochemistry text. These enzymes are digestive enzymes, phosphateses which regulate cell growth and development, proteolytic enzymes which regulate cell growth and development, and numerous others. Carbamates (such as pyridostigmine) and organophosphates (such as nerve gases) have the potential to inhibit any of these because the active site chemistry of the enzymes are the same as in cholinesterase and cholinesterase inhibition depends on that active site chemistry. The specificity is brought about mostly by the shape of the chemical and the enzyme. There are numerous research paper and textbook examples of inhibition of other enzymes by acetylcholinesterase inhibitors. One such enzyme is neurotoxic esterase (NTE), which is thought to be responsible for OP induced delayed neuropathy (OPIDN). OPIDN is caused by some OP insecticides (dichlorvos, leptophos, methamidophos, mipafox, trichlorfon, coumaphos, and dichlorvos), other OP's which inhibit cholinesterase (DFP, DEF, and TOCP) and nerve gases. NTE is also inhibited by Phenyl N-methyl N-benzyl carbamate (PMBC) and PMBC also causes acute cholinergic symptoms in addition to delayed neuropathy on prolonged exposure in hens. (6, 7, 8). One carbamate insecticide cholinesterase inhibitor (carbaryl {Sevin}) has been documented to cause delayed neurotoxicity in one human medical case (9).

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5. Committee staff have talked to many scientists about the potential toxicities of various organophosphates and carbamate. Several scientists have discussed neuropathies associated with inhibition of neurotoxic esterase or neuropathy target esterase (NTE). Could the inhibition of NTE result in neurological or other symptoms or diseases (i.e. immune disfunction, cancer) currently being reported by Persian Gulf War veterans? Are there other symptoms or diseases that might be expected, based on the effects you have seen on insects? Please base your response on published research as well as your own scientific knowledge.

5. In my opinion and that of some other researchers (not published), NTE may not be confined to the nervous system. One case (possibly more) of non-neuronal "NTE" enzyme inhibition has been shown to correlate with OPIDN (10). The predominance of published neurological symptoms by inhibition of NTE could be the result of the tendency of the nervous system to be more sensitive to stresses as it is with heat and anoxia. I used (in question #4) NTE and OPIDN as an example of non-cholinergic poisoning by cholinesterase inhibitors. I am not ruling out other enzyme targets. There are other potential targets for the OP's and carbamate. Because of this, the occurrence of non-neurological symptoms does not rule out OP's or carbamate as causative agents. There is therefore no reason to conclude that pyridostigmine acts only on acetylcholinesterase. If the pyridostigmine synergism by DEET I saw in cockroaches had been from cholinergic effects of pyridostigmine, I would also expect to have seen synergism with the insecticidal cholinesterase inhibitor bendiocarb. This did not occur (Table 1.).

Some of the subcellular effects of NTE inhibitors which have been observed are microtubule disruption and changes in the level of protein-phosphate bonds. Protein-phosphate bonds are regulated by phosphorylation (by kinases) and dephosphorylation (by phosphatases) in intracellular proteins. Protein phosphorylation and dephosphorylation regulate cell growth, division metabolic state, and oncogenes ("cancer genes"). I would expect to the greatest effects of disruption of such a system to be on nervous tissue and other tissues which tend to have growth demands and cycles made on the tissues. These tissues would be skin, digestive tract lining, gonads, liver, and glands such as the prostate, mammary and pancreas. In addition, one researcher (10) showed that lymphocyte "NTE" inhibition predicts OPIDN. White blood cells are important in immune function and defense against abnormal (cancer) cells.

The symptoms of Gulf War veterans I am aware of are consistent with exposure to high levels of tumor promoters such as phorbol esters and okadaic acid which effect kinases and

phosphatases. Some of these enzymes (especially the phosphatases) may also be serine hydrolases which are potential OP and carbamate targets. That raises the possibility that acetylcholinesterase inhibitors such as carbamate (pyridostigmine), and organophosphates (nerve gases, insecticides, and DEF) have a potential to be (with prolonged exposure) tumor promoters in addition to doing localized damage to these cells and tissues. Synergistic interactions with other compounds would make things worse.

One other note about pyridostigmine that may be of interest to the committee is that there are numerous publications which refer to its effect on growth hormone levels in vertebrates. The authors of these publications (for example #11) generally attribute these effects to indirect effects of cholinesterase inhibition. Even if this is the case, the results of sustained altered levels of growth hormone has the potential to cause problems beyond the cholinergic system.

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6. Please provide a copy of your research proposal to DoD and a brief description of the research that you believe is necessary to better understand whether Persian Gulf War soldiers who took pyridostigmine were likely to have been especially vulnerable to the toxic effects of pesticides or other environmental toxins.

6. Under normal circumstances, I would follow a conservative approach and stick with insects until more progress had occurred. I first would do what I could to pharmacologically localize possible causes for the chemical interactions that I have seen that lead to unexpected cockroach mortality. I would then study the direct effects of the suspect compounds on the implicated enzyme systems. Regardless of the implications for the Gulf War situation, this would have provided much useful toxicological information for insecticides and repellents. The results would have been the foundation for considering research on vertebrate toxicology of the interacting compounds. The toxic interaction of the compounds in insects is sufficient justification for examination of the effect in vertebrates, but I had hoped the insect work would have continued to lay the framework for the possible work on vertebrates. The insect assays yield information quickly and interesting results could have then been tested on vertebrates.

The lack of USDA support has forced me to seek DoD funding for vertebrate research before the insect work is done. Because of this, I have had to ask DoD for support with less information than either DoD or I would have liked. In addition, I have no institution from which to seek formal grant support. DoD has asked me for a full proposal, but neither they nor I can proceed unless I have an institutional affiliation and facility access. Because of this, I am in the process of seeking some kind of affiliation from the Veteran's Affairs Medical Center or University of Florida Pharmacology Department (Medical School) in Gainesville. This will be difficult because the insect work will be cut short and it will probably appear that there is some scientific weakness or other problem in my research because of the lack of USDA support.

My current plan is to treat rodents with compounds that enhance each other's toxicity (in cockroaches) and which are encountered by of humans. If interactions occur in toxicity assays, some of the other drugs used in my cockroach research will be tested. Given results similar to the cockroach work, I would then look at the same enzyme effects were looked at in the insect research. This will involve extra trial and error because the insect research stopped at this point. If the gross toxicological interactions occur in rodents as they do in cockroaches, I would seek cooperators who have expertise in

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chronic poisoning of the suspect organs. This would include histological and biochemical analysis in response to sublethal exposures. Behavioral assays would be appropriate at this stage also. I personally would concentrate on the biochemical work. If, during the research, I became aware of data that I thought might influence public health or military readiness I would attempt to inform those responsible.

Under normal circumstances, I would suggest research which would clearly demonstrate whether there is reason to be concerned about tumors or cancer. That could take several years to "prove". These are not normal circumstances in that we have a large population of possible exposures. Because of this, whether or not I get research funding or support, I have, and will continue to suggest that the Gulf War Veterans be at least checked for cancers which can be detected by screening tests.

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The insect repellent DEET and the structurally related herbicide

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diphenamid both cause ataxia associated with a spongiform myelinopathy largely confined to the cerebellar roof nuclei. This local myelinopathy was accompanied by the formation of neuronal cytoplasmic clefts and was produced by a single dose of 1 to 3 g/kg N,N -diethyl -m -toluamide (DEET). Our findings show close parallels with a number of human cases of DEET poisoning and indicate that other amides, like diphenamid, also pose a potential hazard.

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The use of highly concentrated DEET -containing insect repellents should be avoided to reduce the risk of toxicity in both children and adults. The consequences of DEET toxicity are variable and unpredictable.

Dorman -DC; Buck -WB; Trammel -HL; Jones -RD; Beasley -VR, Fenvalerate/N,N -diethyl -m -toluamide (Deet) toxicosis in two cats. J -Am -Vet -Med -Assoc. 1990 Jan 1; 196(1): 100 -2

Lipscomb -JW; Kramer -JE; Leikin -JB, Seizure following brief exposure to the insect repellent N,N -diethyl -m -toluamide. Ann -Emerg -Med. 1992 Mar; 21(3): 315 -7.
Avoidance of high - concentration DEET formulations in pediatric patients should be considered.

Mount -ME; Moller -G; Cook -J; Holstege -DM; Richardson -ER; Ardans -A, Clinical illness associated with a commercial tick and flea product in dogs and cats. Vet -Hum -Toxicol. 1991 Feb; 33(1): 19 -27.
Samples were obtained for DEET and fenvalerate analysis. Oral dosing of dogs and cats produced severe clinical illness at doses as low as 0.66% of a can (7 ounce spray can)/kg body weight. Serum DEET concentrations closely paralleled the clinical signs observed in the animals.

Oredsson -B; Palmborg -M; Kulling -P, [Mosquito repellents containing DEET can affect the central nervous system] (Karolinska sjukhuset.). Lakartidningen. 1990 Aug 8; 87(32 - 33): 2495 -6.

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Responses by J. I. Moss (USDA-ARS) to questions by J. D. Rockefeller, Chair, U. S. Senate Committee on Veteran's Affairs.

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Abou-Donia MB. Delayed neurotoxicity of phenylphosphonothioate esters. Science. 1979 Aug 17; 205(4407): 713-5. Administration of a single oral dose of five phenylphosphonothioate esters produced delayed neurotoxicity in hens; their potency was, in descending order, cyanofenphos, EPN, desbromoleptophos, leptophos, and EPBP (Seven). The results suggest that delayed neurotoxicity may be a general feature of phenylphosphonothioate insecticides.

Abou, Donia MB. Organophosphorus ester induced delayed neurotoxicity. Annu Rev Pharmacol Toxicol. 1981; 21: 511-48. In certain animals, including humans, exposure to some organophosphorus esters causes delayed neurotoxicity (OPIDN). The clinical condition becomes manifest after a delay period, first as ataxia, followed by paralysis. Lesions are characterized by degeneration of axons with subsequent secondary degeneration of myelin in the peripheral and central nervous systems. Recovery is only likely in mild cases, whereas more severe cases show symptoms of an upper motor neuron lesion in the lower limbs. The risk of use of these chemicals is related not only to human sensitivity to this syndrome, but also to the fact that in most

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disasters involving OPIDN, humans were the prime victims. Therefore, the neurotoxic action of a chemical is of great significance, since pesticides with this property are not recommended for use. Although OPIDN has been recognized for over a half a century, its mechanism of action is still unknown. It is believed, however, that the initial target in OPIDN is the phosphorylation of a neurotoxicity target protein in the nervous system.

Abou-Donia MB; Graham, DG; Abdo, KM; Komeil, AA. Delayed neurotoxic, late acute and cholinergic effects of S,S,S tributyl phosphorotrithioate (DEF): subchronic (90 days) administration in hens. Toxicology. 1979 Nov; 14(3): 229-43.

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We studied a patient who ingested 27 gm (500 mg/kg) of carbaryl (1-naphthyl N-methylcarbamate), a popular carbamate pesticide. After he recovered from acute cholinergic toxicity, acute weakness of arms and legs was accompanied by electrophysiologic findings consistent with axonal peripheral neuropathy. Recovery began at 1 week and continued for 9 months. A similar delayed neuropathy has been described with organophosphates but not with carbamate insecticides.

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On day 30, blood acetylcholinesterase (AChE), plasma butyrylcholinesterase (BuBhE) and lymphocyte NTE were markedly below the normal range but recovered slowly. Polyneuropathy symptoms began about 6 weeks after ingestion; the usual time is 3 to 4 weeks. NTE activity was 60 percent inhibited 4 weeks after the poisoning, and began to recover subsequently. The patient was reevaluated on day 62. Leg weakness had become more severe, gait was somewhat impaired, and tendon reflexes were absent.

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Together with muscular and nerve signs, all changes were consistent with a process of a mild distal axonopathy. The authors conclude that inhibition of lymphocytic NTE after OP intoxication correlates with delayed development of OP induced polyneuropathy.

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From Bob Chapin

Subject pyridostygmine and DEET

just got off the phone with Jim Moss at USDA who's been studying the synergism of DEET (an insecticide, the common mosquito repellent) and pyridostygmine or permethrin or caffeine/theophylline or nerve agents. Turns out that the lethality of DEET can be increased several fold (between, say, 4x and 20 x) by several of the above agents (there are some that increase its cockroach lethality by 2000-fold. TOCP also increases it, Somkuti !!). The main point is that there may be testicular toxicity here. I know that Schrader and I did a DEET study years ago that came up dry, but there may be a synergism here that could be having a public health effect.

Let me ask you guys the following: if you pursue the Gulf War sperm story, please ask questions about exposure to DEET and the above compounds. Try to get an idea of dosimetry (how much they were exposed to). If you see an exposure effect on spoims, then there may be some animal follow-up studies that need to be done. I don't care at all who does them, the point at first is to identify the effect and define the effective doses. Jim's been thinking a lot about mechanisms, and has some leads here. Let me get you guys together, I'll play whatever position is best for the project to move forward.

I'm out of the country until May 1. You all get talking and see if you can make something work

Bob

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JIM GOTTLIEB, MINORITY CHIEF COUNSEL/STAFF DIRECTOR

United States Senate

COMMITTEE ON VETERANS' AFFAIRS
WASHINGTON, DC 20510-6375

May 23, 1994

The Honorable Mike Espy
Secretary of Agriculture
U.S. Department of Agriculture
14th and Independence Avenue, SW
Washington, DC 20250

Dear Secretary Espy:

I want to thank you for arranging for Dr. James Moss of the USDA Agricultural Research Service in Gainesville to testify at our Committee's May 6 hearing on the potential dangers of pesticides and pyridostigmine use in the Persian Gulf. His testimony was invaluable to our deliberations.

Dr. Moss' research clearly indicates that the synergistic effect of pyridostigmine and pesticides could be causing many of the "mysterious symptoms" experienced by thousands of Persian Gulf War veterans. However, his research was conducted on insects, and it is therefore unclear whether the results are applicable to humans.

I would greatly appreciate your providing me with copies of any relevant research conducted by USDA on this issue, either on insects or animals. In addition, please let me know whether USDA has plans to support further research, by Dr. Moss or others.

I strongly believe that if our various Federal agencies work together on this issue, we can solve the mystery of the devastating illnesses experienced by many Gulf War veterans. In addition, Dr. Moss' research findings raise very important questions about the safety of commonly used pesticides, particularly when used in combination with other organophosphates or carbamates.

If you have any questions about this letter, please contact Dr. Diana Zuckerman of the Committee staff at 224-9126.

Sincerely,

John D. Rockefeller IV
Ranking Minority Member

ALAN K. SIMPSON, WYOMING, CHAIRMAN

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United States Senate

COMMITTEE ON VETERANS' AFFAIRS
WASHINGTON, DC 20510-6375

June 28, 1994

The Honorable Mike Espy
Secretary of Agriculture
U.S. Department of Agriculture
14th and Independence Avenue, SW
Washington, DC 20250

Dear Secretary Espy:

I am writing to request your assistance in safeguarding research data on pesticides and pyridostigmine coming from the laboratory of Dr. James Moss, a scientist at the Agricultural Research Service in Gainesville, Florida.

Dr. Moss, who testified at our Committee's May 6 hearing on the potential dangers of pesticide use in the Persian Gulf, will be leaving his position as a USDA research associate on June 30, 1994. Dr. Moss's preliminary findings are extremely important and I am requesting your assistance to ensure that his data are preserved and easily accessible.

I have not yet received a response to my May 23 letter to you, in which I asked about USDA's plans to support future research in this area. Since Dr. Moss' role at USDA has been terminated, it appears that USDA has no plans to support his research efforts in this area. Nevertheless, I remain hopeful that the Department will support similar research on the safety of these commonly used pesticides in the near future.

Meanwhile, I am writing to ask you to ensure that all Dr. Moss' raw data, laboratory books and logs, summarized data, and memoranda concerning these data, be preserved at USDA, and be made available for future scientific evaluation. I am enormously concerned about the potential enhancement of toxicity by combinations of organophosphates and carbamates. This is an issue of great importance for the health consequences of our men and women who served in the Persian Gulf War, and for future military personnel who will serve in similar conflicts.

Thank you in advance for your assistance. I look forward to hearing from you regarding this important research. If you have any questions about this request, please contact Dr. Diana Zuckerman of the committee staff at (202) 224-9126.

Sincerely,

John D. Rockefeller IV
Ranking Minority Member

cc Essex Finney, Ph.D.
Acting Administrator
Agricultural Research Service

DEPARTMENT OF AGRICULTURE
OFFICE OF THE SECRETARY
WASHINGTON, D.C. 20250

OCT 2 4 1994

Honorable John D. Rockefeller IV
Chairman, Committee on Veterans Affairs
United States Senate
414 Russell Senate Office Building
Washington, D.C. 20510-6375

Dear Mr. Chairman:

Thank you for your letters of May 23, 1994, and June 28, 1994, with respect to the testimony of Dr. James Moss before the Senate Committee on Veteran's Affairs on May 6, 1994, and his related research. I apologize for the delay in responding to your letters. I wanted to ensure that the Department fully responded to your inquiry and request.

We appreciate your comments about Dr. Moss' testimony on his observations of the potential dangers of pesticides and pyridostigmine use in the Persian Gulf. No one wants more than we do for a cause and cure to be found for the mysterious symptoms called Gulf War Syndrome afflicting many of our Gulf War veterans.

Dr. Moss, a Post-Doctoral employee at the Agricultural Research Service (ARS) Medical and Veterinary Entomology Laboratory, Gainesville, Florida, outside of his assigned research on cockroaches, made some observations on the synergism of the insect repellent DEET (N,N-diethyl-meta-toluamide) and pyridostigmine with other insecticides. In his testimony, Dr. Moss implied that DEET and pyridostigmine have the ability to synergize other insecticides and may have contributed to the Gulf War Syndrome. Since Dr. Moss' observations in this area have not been peer-reviewed or reproduced in other laboratories--his statements may be premature.

To answer your specific questions, it is not our intent to do follow-up research on this subject at this time. We do not have the toxicological expertise to conduct such confirmatory research which ultimately would require human subjects. Such work would more appropriately be done by the Environmental Protection Agency or the U.S. Army Environmental Hygiene Agency. To ensure they are aware of Dr. Moss' observations we will share copies of his data with them. We will forward a copy of our communication to them to you for your additional information.

We assure you that all of Dr. Moss' raw data, laboratory books and logs, summarized data and memoranda are secured at our laboratory in Gainesville, Florida. Since this is public information, we will make it available upon request.

Attached also is a review paper by Dr. Gary Mount which speaks to the subject of Dr. Moss' research and the synergism between insecticides as they affect cockroaches, which may be of interest to you.

We hope this information proves helpful as the search is made for causes of the Gulf War Syndrome. Thank you for contacting us on this issue.

Sincerely,

MIKE ESPY
Secretary

United States Department of Agriculture | Agricultural Research Service | South Atlantic Area Medical and Veterinary Entomology Research Laboratory | 1600 SW 23rd Drive P.O. Box 14565 Gainesville, Florida 32604

## Report on Toxicity of Deet, Permethrin, and Pyridostigmine to Cockroaches

Gary A. Mount, Medical and Veterinary Entomology Research Laboratory (MAVERL)
USDA-ARS, South Atlantic Area, Gainesville, FL, July 28, 1994

This report was requested by the Armed Forces Pest Management Board (AFPMB) in response to the testimony of Dr. Jim Moss, former MAVERL Research Associate, at a hearing on pyridostigmine, antidote enhancer for nerve agents, conducted by Senator John D. Rockefeller before his Veterans Affairs Committee. The request was also made because Dr. Moss's statements regarding synergism of pyridostigmine combined with deet and permethrin were reported in various newspapers. Deet was synthesized by ARS chemists at Beltsville in the 1950s and evaluated as an insect repellent by MAVERL and cooperators. Deet has been the primary active ingredient in most commercial insect repellents for the past four decades. Permethrin was developed by the National Research & Development Corporation, United Kingdom in the 1970s. Permethrin is a low-mammalian toxicity insecticide that was evaluated by MAVERL and cooperators in the 1980s as a clothing treatment for use by military personnel and the public. The newspaper articles based on Dr. Moss's statements have caused some concern about potential health risks of military personnel using combinations of these chemicals, particularly deet and pyridostigmine. Thus, the AFPMB needs this report to decide whether combinations of these chemicals should be recommended for further study. The following analysis is based on the raw data for these chemicals from the bound laboratory research notebooks left by Dr. Moss.

### Methods and Materials

The cockroaches used in these tests were 1-3-week-old adult males of the Orlando strain (insecticide-susceptible). They were reared according to our standard laboratory protocol. Ten cockroaches were placed in a petri dish and served as a test unit. Carbon dioxide was used to anesthetize the cockroaches during counting and topical application of chemicals.

Test chemicals were formulated by weighing the appropriate amount of technical-grade material and placing it into a one milliliter volumetric flask with acetone (stock solution). The pyridostigmine bromide used in these tests is subsequently identified as "PSB." Appropriate concentrations were prepared from the stock solution by serial dilution. Chemicals were applied topically in one microliter ($\mu$l) aliquots to the abdomen of each cockroach. Test units for pyridostigmine and permethrin were micrograms ($\mu$g) and deet was percent (percent was converted to $\mu$g for consistency). Chemicals were applied to the cockroaches with a 50$\mu$l Hamilton syringe attached to a calibrated Hamilton repeating dispenser. In tests with combinations of chemicals, the chemicals

were applied in a common solution. Acetone alone was applied to determine mortality of cockroaches not exposed to the chemicals. Mortality counts of the exposed cockroaches were made at 24 and 48 hours posttreatment. Only the 48-hour mortality counts were considered in this analysis because these counts represented maximum effect of the chemicals.

All tests with the chemicals considered in this report were executed from November 1993 to May 1994 except those for permethrin alone which were done in separate tests in 1992 against the same strain of cockroaches. The experimental design used to collect these data involved "paired tests" where a primary chemical and a combination of the primary chemical with a potential synergist(s) were compared in a single test on the same day.

Several steps were necessary to analyze the raw data The first step was to tabulate all numbers of cockroaches exposed and killed for each dose of each primary chemical or combination of primary chemical and candidate synergist(s). The number of cockroaches tested per dose ranged from 20-180 and the number of discriminating doses per chemical or combination of chemicals ranged from 3-10. With one exception, all data were omitted where mortality of cockroaches exposed to acetone solvent alone exceeded 20% (high check mortality is an indication that cockroaches were stressed by some factor(s) other than the target chemicals). The exception was the combination of deet and 100$\mu$g of PSB. This exception was made because these were the only data collected for this combination. These data were corrected by Abbott's formula for 37% check mortality during probit analysis. The second step of analysis was to sum percentage mortalities of each dose of each chemical tested singly corresponding to the same doses of chemicals tested in combination. Synergism is shown when the effect of two or more chemicals combined exceeds the sum effect of each chemical when applied singly.

The third step was to submit the dose-mortality data to probit analysis and compare lethal dose (LD) values for chemicals applied in combination to cockroaches in the same petri dishes to LD values for the same chemicals applied separately to cockroaches in different petri dishes (subsequently referred to as the "sum" method). The LD levels used in the analysis were 50% and 90% kill of the cockroach population. In some cases the mortality obtained at the highest dose tests was less than 90%. Thus, some extrapolation was necessary to estimate LD-90s with probit analysis. The probit analysis program automatically corrected for check mortality (average of 6%). The fourth and final step involved an alternative determination of the synergism ratio where the LD value for a chemical tested alone was divided by the LD value for a combination of chemicals that included the same primary chemical (subsequently referred to as the "primary" method). With this final step, I made a tentative assumption that the secondary chemical (candidate synergist) was tested in the combination at a sublethal dose and caused no mortality

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## Results and Discussion

The LD-50s and LD-90s for each of the chemicals tested alone and in various combinations are shown in Table 1. The average synergism ratios estimated by the sum method from three separate combinations of deet and pyridostigmine bromide (PSB) were 3.0 and 4.8 at the LD-50 and LD-90, respectively. Synergism ratios determined by the primary method for deet and PSB were 4.8 and 6.3 at the LD-50 and LD-90, respectively. The explanation for the higher estimates of synergism ratio obtained with the primary method is that 100$\mu$g PSB, 200$\mu$g PSB, and 50$\mu$g deet produced average mortalities of 5%, 26%, and 5%, respectively. These mortalities indicated that the assumption of sublethal doses for synergists was not completely valid Estimates of synergism ratio for the deet and permethrin combination obtained with the primary method were also slightly higher than with the sum method. Furthermore, the primary method also produced higher estimates of synergism ratio than the sum method when all three chemicals were combined.

One combination of chemicals (not shown in Table 1), 100$\mu$g of PSB and 0.06$\mu$g of permethrin, was tested only at these single doses. The mortalities for this combination tested singly and in combination were 10% and 29%, respectively. Thus, the tentative estimate of synergism ratio based on these results was 2.9.

The toxicity of the three chemicals tested alone is also shown in Table 1. Permethrin was about 4,000 and 5,000 times more toxic to German cockroaches than pyridostigmine and deet, respectively.

## Conclusions

The results of this study showed that statistically significant, but low levels of synergism were obtained with various combinations of permethrin, deet, and pyridostigmine bromide applied topically to German cockroaches. The overall average estimate (both sum and primary methods) of the synergism ratio for the deet and pyridostigmine combination was only 4.7. This ratio is low compared to the classic example of a synergism ratio of 100 or more achieved by combining piperonyl butoxide with natural pyrethrins. Thus, I concluded that pyridostigmine was not a potent synergist for deet and that deet was similarly not a potent synergist for pyridostigmine. I also concluded that permethrin was not a potent synergist for deet with an overall average synergism ratio of only 5.4. Permethrin and pyridostigmine combined were not demonstrated to be a potent synergist for deet with an overall average synergism ratio of only 3.3. No firm conclusion can be made regarding synergism with a combination of pyridostigmine and permethrin because data were insufficient to calculate LD values with probit analysis

The results of this study show that deet and pyridostigmine have extremely low levels of toxicity to German cockroaches when compared to permethrin. Even when combined, deet and pyridostigmine have extremely low levels of toxicity to German cockroaches.

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Table 1. The toxicity of permethrin, deet, and pyridostigmine bromide (PSB) to adult male German cockroaches when tested singly and combined.

| Chemical(s) | LD-50 LD-90 Singly[a] ($\mu$g) | LD-50 LD-90 Combined[a] ($\mu$g) | Sum Method Synergism Ratio[b] | Primary Method Synergism Ratio[c] |
|---|---|---|---|---|
| Permethrin | 0.14 (0.13-0.15)<br>0.20 (0.18-0.21) | | | |
| Deet | 280 (240-340)<br>1,000 (720-1,650) | | | |
| PSB | 338 (310-375)<br>791 (658-1,027) | | | |
| Deet + 100$\mu$g PSB | 150 (120-190)<br>380 (270-720) | 47 (33-56)[d]<br>92 (77-130)[d] | 3.2<br>4.1 | 6.0<br>11.0 |
| Deet + 200$\mu$g PSB | 130 (Infinite)<br>1,240 (Infinite) | 56 (5-82)[e]<br>220 (130->5,000) | 2.3<br>5.6 | 5.0<br>4.5 |
| PSB + 50$\mu$g Deet | 325 (197-3,826)<br>1,064 (410->5,000) | 97 (80-121)[d]<br>225 (162-539)[e] | 3.4<br>4.7 | 3.5<br>3.5 |
| Deet + 0.06$\mu$g Permethrin | 180 (120-330)<br>800 (400->5,000) | 61 (40-76)[d]<br>130 (100-200)[d] | 3.0<br>6.2 | 4.6<br>7.7 |
| Deet + 0.06$\mu$g Permethrin + 100$\mu$g PSB | 190 (150-230)<br>850 (580-1,640) | 51 (10-77)[d]<br>460 (220->5,000) | 3.7<br>1.8 | 5.5<br>2.2 |

[a] Confidence limits at 95% level of probability in parentheses.
[b] Ratio is LD value of sum mortality of two or three chemicals tested singly divided by LD value of chemicals combined.
[c] Ratio is LD value of the primary chemical (underlined) divided by the LD value of the chemicals combined.
[d] Significantly different from the LD value for the primary chemical alone and the LD value for the primary (underlined) and secondary chemicals tested singly.
[e] Significantly different from the LD value for the primary chemical

Senator J. D. Rockefeller
C/O Dr. Diana Zuckerman
Committee on Veterans Affairs
414 Russell Bldg.
U.S. Senate
Washington, D.C. 20510

7 November 1994

Dear Senator Rockefeller,

Dr. Diane Zuckerman, of the Veteran's Affairs Committee staff, recently asked for my comment on a report by Dr. Gary Mount (dated 28 July 1994), which was based on my data, and which discussed the toxicity of DEET, permethrin and pyridistigmine to cockroaches. This report was submitted to the Armed Forces Pest Management Board (AFPMB) at their request. I have not been approached for data analysis or interpretation of the data.

Most of the numbers are close enough to mine that no rebuttal is needed. Dr. Mount's alternate method of analysis method contributed little to the results and only served to slightly minimize the synergism ratios.

The one exception is that of the three compounds (DEET, permethrin and pyridistigmine) together. There is insufficient data to make conclusions about the mixture. I found that what appeared to be extreme synergism (>26,000 fold of DEET) was a product of dosing the cockroaches separately and knocking them out three times with carbon dioxide, plus the three chemicals. At the time I was specifically looking at the three, so I changed the protocol to mixing the three in one dose to remove the cumulative effects of the carbon dioxide. Carbon dioxide does not normally kill cockroaches in this type of multiple dosing. Had I continued this research, I would have explored this interaction of carbon dioxide and the other chemicals to produce some solid data. I think Dr. Mount should have considered the implications of "stress" induced by the carbon dioxide and its effects on the toxicity of the other chemicals, if he were concerned about health implications. (See Sharabi et al. 1991 below for support of this concept).

I also think Dr. Mount should have disclosed the extreme synergism (>2,000 fold) that is apparent from my data between DEET and eserine (physostigmine), a carbamate as is pyridostigmine. Eserine was actively tested as a nerve gas protectant by DOD and I presume DOD would want to have this knowledge as they continue chemical warfare defense research.

Toxicity of DEET plus other compounds on German cockroaches.

| Drug | Dose Form | Second Drug | Dose | 48 H LD-50 | Synergism Ratio |
|---|---|---|---|---|---|
| DEET | t% | None | | 27 | 1 |
| DEET | t% | Permethrin+Pyridostigmine | 0.06/100 | 0.001 | 26,805 |

Dr. Mount's apparent interpretation of the lack of importance of the "extremely low levels of toxicity" entirely misses the point with respect to potential of human health problems. Dr. Mount's "classic example of a synergism ratio of 100 or more" applies to levels which are seen as economically important in the development of insecticides. I presume that Dr. Mount's report was requested because of health concerns by the AFPMB and not for the purposes of insecticide development. If Dr. Mount had read the literature on DEET and pyridostigmine, he would have realized that both of these compounds are commonly used at levels which approach toxic levels as supported by published reports which document adverse effects of relatively small overdoses (much less than 100 fold) [see citations included]. Common sense dictates that even a two-fold increase in the toxicity of a compound of marginal safety is cause for concern. Even by Dr. Mount's most conservative calculations, most of the synergies were in excess of four-fold.

In conclusion, there is reason for concern and the real problem is whether these synergies occur in humans. The fact that DEET and another pyrethroid (fenvalerate - similar to permethrin) have been documented to injure and kill cats and that this formulation of DEET and fenvalerate was withdrawn, causes me to feel that there is in fact reason for concern about co-synergism of these compounds and I recommend that the AFPMB consult someone who will review the literature and understand it.

I am extremely disappointed that USDA officials have allowed this research to degenerate into a "good-guys bad-guys" debate and that health concerns appear to be secondary.

Sincerely,

James A. Moss

Examples of published reports which demonstrate that pyridostigmine need not be synergised 100 fold to pose a health hazard for cockroaches.

The first two are examples of unexpected results of pyridostigmine; the main points are that "typical effects were infrequent" and "No correlation was found between levels of cholinesterase and type or severity of complaints". It is clear that something other than the expected responses to pyridostigmine were present. The third is an example of a carbamate (which pyridostigmine is) causing long-term and possibly non-cholinergic poisoning.

Sharabi, Y; Danon Y.L.; Berkenstadt, H,; Almog, S.; Mimouni, Bloch A.; Zisman, A.; Dani, S.; Atsmon, J,. Survey of symptoms following intake of pyridostigmine during the Persian Gulf war. Isr J. Med. Sci. 1991 27 (11 -12): 656-8.
213 soldiers questionnaire. AChE inhibition compared between soldiers with and without complaints. The most frequent symptoms were nonspecific and included dry mouth, general malaise, fatigue and weakness. Typical effects, such as nausea, abdominal pain, frequent urination and rhinorrhea, were infrequent (anom, jim). No correlation was found between levels of cholinesterase and type or severity of complaints. Anxiety, which accompanies wartime, may have contributed to the appearance of significant symptoms. Further investigations concerning the effects of pyridostigmine ingestion under stressful conditions are warranted.
Israel Defense Forces Medical Corps, Petah Tikva.

Wacks -I; Oster JR; Perez -GO; Kett -DH
Spurious hyperchloremia and hyperbicarbonatemia in a patient receiving pyridostigmine bromide therapy for myasthenia gravis. Am -J - Kidney -Dis; VOL 16, ISS 1, 1990, P76 -9.
Medical Service, Veterans Administration Medical Center, Miami, FL 33125.

Dickoff, DJ; Gerber, O.; Turovsky, Z. Delayed neurotoxicity after ingestion of carbamate pesticide. Neurology. 1987 Jul; 37(7): 1229-31.
We studied a patient who ingested 27 gm (500 mg/kg) of carbaryl (1-naphthyl N-methylcarbamate), a popular carbamate pesticide. After he recovered from acute cholinergic toxicity, acute weakness of arms and legs was accompanied by electrophysiologic findings consistent with axonal peripheral neuropathy. Recovery began at 1 week and continued for 9 months. A similar delayed neuropathy has been described with organophosphates but not with carbamate insecticides.

Examples of published reports which demonstrate that DEET need not be synergised 100 fold to pose a health hazard for cockroaches.

Clem -JR; Havemann -DF; Raebel -MA, Insect repellent (N,N -diethyl -m -toluamide) cardiovascular toxicity in an adult. (Scott & White Hospital, Temple, TX 75608.). Ann - Pharmacother. 1993 Mar; 27(3): 289 -93
The use of highly concentrated DEET -containing insect repellents should be avoided to reduce the risk of toxicity in both children and adults. The consequences of DEET toxicity are variable and unpredictable.

Dorman -DC; Buck -WB; Trammel -HL; Jones -RD; Beasley -VR, Fenvalerate/N,N -diethyl -m -toluamide (Deet) toxicosis in two cats. J -Am -Vet -Med -Assoc. 1990 Jan 1; 196(1): 100 -2

Lipscomb -JW; Kramer -JE; Leikin -JB, Seizure following brief exposure to the insect repellent N,N -diethyl -m -toluamide. Ann -Emerg -Med. 1992 Mar; 21(3): 315 -7.
Avoidance of high - concentration DEET formulations in pediatric patients should be considered.

Mount -ME; Moller -G; Cook -J; Holstege -DM; Richardson -ER; Ardans -A, Clinical illness associated with a commercial tick and flea product in dogs and cats. Vet -Hum -Toxicol. 1991 Feb; 33(1): 19 -27.
Samples were obtained for DEET and fenvalerate analysis. Oral dosing of dogs and cats produced severe clinical illness at doses as low as 0.66% of a can (7 ounce spray can)/kg body weight. Serum DEET concentrations closely paralleled the clinical signs observed in the animals.

Oredsson -B; Palmborg -M; Kulling -P, [Mosquito repellents containing DEET can affect the central nervous system] (Karolinska sjukhuset.). Lakartidningen. 1990 Aug 8; 87(32 - 33): 2495 -6.

Schaefer -C; Peters -PW, Intrauterine diethyltoluamide exposure and fetal outcome. Reprod -Toxicol. 1992; 6(2): 175 -6. We report a 4 year old boy with mental retardation, impaired sensorimotor coordination, and craniofacial dysmorphology, whose mother applied DEET daily throughout her whole pregnancy in addition to the prophylactic use of chloroquine.

Verschoyle -RD; Brown -AW; Nolan -C; Ray -DE; Lister -T, A comparison of the acute toxicity, neuropathology, and electrophysiology of N,N -diethyl -m -toluamide and N,N -dimethyl -2,2 -diphenylacetamide in rats. (MRC Toxicology Unit, Carshalton, Surrey, United Kingdom.). Fundam -Appl - Toxicol. 1992 Jan; 18(1): 79 -88.
The insect repellent DEET and the structurally related herbicide

diphenamid both cause ataxia associated with a spongiform myelinopathy largely confined to the cerebellar roof nuclei. This local myelinopathy was accompanied by the formation of neuronal cytoplasmic clefts and was produced by a single dose of 1 to 3 g/kg N,N -diethyl -m -toluamide (DEET). Our findings show close parallels with a number of human cases of DEET poisoning and indicate that other amides, like diphenamid, also pose a potential hazard.

Wright -DM; Hardin -BD; Goad -PW; Chrislip -DW. Reproductive and developmental toxicity of N,N - diethyl -m - toluamide in rats. Fundam -Appl -Toxicol. 1992 Jul; 19(1): 33 -42.

# APPENDIX 11.—ADDITIONAL MATERIALS

## ATROPINE DOSES

4.2.4 Selection of 2-PAM and Atropine Doses

Phase 1 studies were conducted to determine the Rhesus monkey equivalents of expected human doses of atropine and 2-PAM to be used in the Phase 2 efficacy studies. Current doctrine for human therapy is successive administration of up to three autoinjectors, for a total dose of approximately 25.71 mg/kg of 2-PAM and 0.095 mg/kg of atropine (base).

For 2-PAM, Phase 1 studies indicated that a dose of 25.71 mg/kg in monkeys produced a maximum plasma concentration of approximately 28 µg/ml, in comparison to USAMRDC-supplied information that this same dose in humans produced a maximum plasma concentration of approximately 18 µg/ml. Clearance of plasma 2-PAM was approximately twice as rapid in the monkey than in humans. Considering the inter-human and inter-animal variability among both humans and Rhesus monkeys, these differences were considered to be slight, and a dose of 25.71 mg/kg of 2-PAM was considered appropriate for use in Phase 2 as the Rhesus monkey equivalent of 3 autoinjectors.

For atropine, the human pharmacokinetic data were not available to Battelle at the time of atropine dose selection, and USAMRDC (Sponsor) personnel selected the appropriate human-equivalent atropine dose. However, more recently-supplied data (see Table 4-18) indicate that the maximum concentration of atropine in serum following administration of 0.095 mg/kg to both humans (approximately 35 µg/ml) and monkeys (approximately 40 µg/ml) are very similar. As with 2-PAM, the clearance of atropine was approximately twice as rapid in the monkeys as in humans. Considering inter-animal and inter-human variability, these differences were considered to be slight. Therefore, a dose of 0.095 mg/kg of atropine (base) was deemed appropriate for use in Phase 2 as the Rhesus monkey equivalent of a human dose of 3 autoinjectors.

The atropine and 2-PAM injections were given as divided doses--2/3 of the total dose 1 minute after GD dosing and the remaining 1/3 of the total dose 10 min later or at the onset of AChE signs. This regimen was used to simulate human therapy under field conditions, where 1 or 2 autoinjectors could be administered upon realization of GD exposure and the second or third if symptoms of intoxication occurred.

The atropine dose was later increased to 0.40 mg/kg; see Section 4.2.6 for details on this change.

4.2.5 Verification of GD Administration

Syringes containing GD were weighed pre-delivery (full) and post-delivery (empty) to quantitate the weight of dose formulation administered. The weight delivered was then converted to volume using the specific gravity of the formulated material, and the volume was converted to ug of GD using the labeled dose solution concentration (0.1-2.0 mg/ml). Documentation forms for dosing are shown in Appendix K-1. With four exceptions, all measured GD doses for the 136 monkeys used in Phase 2 were within approximately 90-110 percent of the targeted doses. These four exceptions (917T, 77 percent of the targeted dose; 48E, 88 percent of the targeted dose; 417D, 87 percent of the targeted dose; 936C, 75 percent of the targeted dose) were not considered to have affected the outcome of the study since they were all within approximately 75 percent of the targeted doses.

Data relating to the date of GD administration, the theoretical (targeted) GD dose, the delivered (actual) GD dose, survival, animal number, body weight, and percent of RBC AChE inhibition (pyridostigmine monkeys only) for the 136 animals that constituted Phase 2 are shown in Table 4-38. (The 18 monkeys that received atropine/2-PAM with or without pyridostigmine pretreatment on 7/29/86 and 7/31/86 were censored from this table, but they are shown in Appendices K-1 and K-2. Because of the lower atropine dose, they are not comparable to the animals in Table 4-38). These same data are shown in Appendix K-4 sorted by the date of GD exposure.

4.2.6 Results From the Initial Two Sets of Phase 2 and the Subsequent Change in Atropine Dose

Based on previous reports (see Appendix B), the 48 hr IM $LD_{50}$ of GD in Rhesus monkeys was expected to be approximately 7.7 ug/kg, and atropine/2-PAM therapy was expected to provide a protective ratio of slightly less than 2. The addition of pyridostigmine pretreatment was anticipated to provide a 2 to 5 fold protective ratio above that of the atropine/2-PAM.

(Table 4-37), attention was given to the atropine dose in terms of improving efficacy. Previous experimental studies in monkeys (see Appendix B) had used larger doses of atropine than the 0.095 mg/kg used in this study on 7/29/86 and 7/31/86. The 0.095 mg/kg dose was originally chosen because it produced similar maximum serum atropine concentrations in monkeys as did the current-doctrine dose of atropine (three autoinjectors) in humans. While it was assumed that pharmacokinetic (or at least maximum serum concentration) equivalency across species indicated pharmacologic equivalency as well, there is no documentation of such bioequivalency for atropine. In addition, clearance of serum atropine was more rapid in monkeys than in humans, suggesting a lessor period of pharmacological activity. Upon review of these data and other data sources (personal communication, D. Green, USAMMDA), USAMRDC personnel directed Battelle to increase the atropine dose to 0.40 mg/kg for subsequent experiments. Based on internal USAMRDC discussions of classified data, USAMRDC concluded that Rhesus monkeys may be pharmacologically less responsive than humans to equivalent doses (mg/kg) of atropine (personal communication, D. Green, USAMMDA). Therefore, USAMRDC considered the use of a higher atropine dose in the monkeys than the current doctrine human dose (3 autoinjectors) to be justified for the purposes of this study.

4.2.7 Clinical Signs of GD Intoxication

Each monkey was monitored for 48 hr after GD dosing for clinical signs of intoxication, in accordance with Study Specific SOP No. 22. No further observations were made beyond 48 hr. The individual animal clinical signs collection forms are shown in Appendix K-4.

GD intoxicated monkeys developed whole-body fasciculations, tremors, and hypersalivation rapidly after administration, often within a few minutes at the higher GD doses. This was especially true for the pyridostigmine-treated animals receiving GD doses in excess of 200 ug/kg. Localized fasciculations in the vicinity of the injection temporally site preceding whole-body fasciculations or tremors were common. Depending on the severity of the intoxication, prostration (loss of skeletal muscle tone) occurred within a few minutes of GD administration (especially for the pyridostigmine monkeys

# DOD INFORMS FDA THAT BOTULISM VACCINE WAS ADMINISTERED VOLUNTARILY

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D. C. 20301-1200

HEALTH AFFAIRS

1 5 MAR 1991

Honorable David A. Kessler, M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration
Department of Health and Human Services
Rockville, Maryland 20857

Dear Doctor Kessler:

Reference is made to your letters of December 31, 1990, and January 8, 1991, in which you determined, under 21 CFR 50.23(d), 55 Fed. Reg 52817, that obtaining informed consent was not feasible for the use of pentavalent botulinum toxoid vaccine and pyridostigmine bromide 30 mg tablets because of military combat exigencies in Operation Desert Shield.

As you know, my requests for these determinations were based on threatened combat circumstances regarding particular potential biological and chemical weapons agents. Following your determinations, appropriate authorities of the U.S. Central Command were given authorization to order the use of these two products without informed consent. Central Command has recently reported that the military command in the theater of operations decided to administer the vaccine on a voluntary basis. The pyridostigmine tablets were used without prior informed consent.

Under 21 CFR 50.23(d)(4), determinations that obtaining informed consent for the use of particular investigational new drugs is not feasible based on military combat exigencies expire at the end of one year, unless renewed, or "when DoD informs the Commissioner that the specific military operations creating the need for the use of the investigational new drug has ended." In view of the termination of hostilities, the Defense Department hereby provides notice that the military operation creating the need for the use of these two drug products without informed consent has ended. Therefore, as of this date, DoD considers these two determinations to be no longer in effect.

On behalf of the Secretary of Defense, please accept our thanks for the indispensable support of the FDA in assuring the best possible medical protection for our military forces in this Operation.

Sincerely,

Enrique Mendez, Jr., M.D.

# LETTER FROM R. JOHN VOGEL, UNDER SECRETARY FOR BENEFITS, TO CHAIRMAN ROCKEFELLER REGARDING RUDOLPH MILLS

THE UNDER SECRETARY OF VETERANS AFFAIRS FOR BENEFITS
WASHINGTON, D.C. 20420

June 9, 1994

The Honorable John D. Rockefeller, IV
Chairman
Committee on Veterans' Affairs
United States Senate
Washington, DC 20510-6375

Dear Mr. Chairman,

At the May 6, 1994, hearing on environmentally caused disabilities before your Committee, Mr. Rudolph R. Mills of Virginia testified concerning his exposure to mustard gas and his long and painful wait for action by VA on his claim for disability compensation.

The necessary final regulations will soon be published and available for use in the evaluation of disabilities suffered by our veterans who were subjected to such unconscionable treatment by their government. In the meantime, I asked that my staff carefully review Mr. Mills' records to determine what positive action we can take to help him. We have directed the Roanoke regional office to vacate an erroneous decision of October 8, 1992, and grant him disability compensation for laryngitis effective from July 31, 1992. The amount of retroactive disability compensation due him is $6,392.

We will again rate him for the far more disabling hemilaryngectomy as a result of carcinoma of the left larynx based on the final regulations.

I spoke with Mr. Mills today and told him of our actions. I apologized to him for the inordinate delay and conveyed your abiding interest in him and, indeed, in all veterans who, like him, have done so much for this nation.

Mr. Chairman, thanks for all you do for America's number one citizens: our veterans.

R. J. Vogel

# FINAL RULE ON MUSTARD GAS AND LEWISITE



**§ 1952.362 [Redesignated from § 1952.364]**

**§ 1952.364 [Reserved]**

4. Section 1952.364 ("Completion of developmental steps and certification") is redesignated as § 1952.362, and a new § 1952.364 is added and reserved.

**§ 1952.361 [Redesignated as § 1952.366]**

5. Section 1952.361 is redesignated as § 1952.366 and revised to read as follows:

**§ 1952.366 Where the plan may be inspected.**

A copy of the principal documents comprising the plan may be inspected and copied during normal business hours at the following locations: Office of State Programs, Occupational Safety and Health Administration, U.S. Department of Labor, 200 Constitution Avenue, N.W., Room N3700, Washington, D.C. 20210; Office of the Regional Administrator, Occupational Safety and Health Administration, U.S. Department of Labor, Room 602, 525 Griffin Street, Dallas, Texas 75202; and New Mexico Environment Department, Occupational Safety and Health Bureau, 1190 St. Francis Drive, Santa Fe, New Mexico 87502.

**§ 1952.381 [Redesignated from § 1952.383]**

6. Section 1952.383 is redesignated as § 1952.361 and a new § 1952.363 is added to read as follows:

**§ 1952.363 Compliance staffing benchmarks.**

Under the terms of the 1978 Court Order in *AFL–CIO* v. *Marshall*, compliance staffing levels ("benchmarks") necessary for a "fully effective" enforcement program were required for each State operating an approved State plan. In May 1992, New Mexico completed, in conjunction with OSHA, a reassessment of the staffing levels initially established in 1980 and proposed revised benchmarks of 7 safety and 3 health compliance officers. After opportunity for public comment and service on the AFL–CIO, the Assistant Secretary approved these revised staffing requirements on August 11, 1994.

[FR Doc. 94–20143 Filed 8–17–94; 8:45 am]
BILLING CODE 4510–25–M

## DEPARTMENT OF VETERANS AFFAIRS

**38 CFR Part 3**

**RIN 2900–AG29**

**Claims Based on Chronic Effects of Exposure to Mustard Gas or Lewisite**

**AGENCY:** Department of Veterans Affairs.

**ACTION:** Final rule.

**SUMMARY:** The Department of Veterans Affairs (VA) has amended its adjudication regulations concerning compensation for disabilities or deaths resulting from the chronic effects of in-service exposure to mustard gas and Lewisite. This regulation is based on a National Academy of Sciences (NAS) study of the long-term health effects of exposure to these vesicant (blistering) agents, commissioned by VA, which found a relationship between such exposure and the subsequent development of certain conditions. The intended effect of this amendment is to expand the list of conditions covered and apply the presumption to a broader group of veterans.

**EFFECTIVE DATE:** This amendment is effective January 6, 1993.

**FOR FURTHER INFORMATION CONTACT:** Donald England, Chief, Regulations Staff, Compensation and Pension Service, Veterans Benefits Administration, Department of Veterans Affairs, 810 Vermont Avenue NW., Washington, DC 20420, (202) 273–7210.

**SUPPLEMENTARY INFORMATION:** On July 31, 1992, VA published a final regulation (38 CFR 3.316) authorizing service connection in claims from veterans who underwent full-body exposure to mustard gas during field or chamber experiments to test protective clothing or equipment during World War II, and who subsequently develop chronic forms of laryngitis, bronchitis, emphysema, asthma, conjunctivitis, keratitis, or corneal opacities (See 57 FR 1699–1700 and 57 FR 33875–77). VA also contracted with NAS to conduct a review of the world medical and scientific literature, including that published in languages other than English, to determine the long-term health effects of exposure to mustard agents and Lewisite. After reviewing almost 2,000 medical and scientific papers, consulting with outside experts, and conducting public hearings, NAS issued its report, entitled "Veterans at Risk: The Health Effects of Mustard Gas and Lewisite", on January 8, 1993.

After reviewing the NAS report, VA published a proposal to amend 38 CFR 3.316 to expand compensation eligibility based on the long-term health effects of exposure to vesicant agents in the Federal Register of January 24, 1994 (59 FR 3532–34). Interested persons were invited to submit written comments, suggestions or objections concerning the proposal on or before March 25, 1994. We received nine comments: One from the American Legion, one from the Disabled American Veterans, and seven from concerned individuals.

One commenter stated that the proposed rule seems very confusing and is filled with terms that the normal citizen would not understand.

Based on this comment we have revised the heading of the regulation, substituting the phrase "mustard gas or Lewisite" for the term "vesicant agents," to make it easier for the average individual to identify the topic of the regulation from the table of contents. However, because the NAS study was based on a comprehensive review of scientific and medical literature that uses highly technical medical terms both for specific disabilities and for vesicant agents with different but similar chemical composition, we found it necessary to use the same terms in the regulation in order to accurately and precisely express the Secretary's decision. In simple terms, this amendment provides presumptive service connection for certain respiratory conditions, eye conditions and cancers based on full-body exposure to mustard gas and Lewisite.

Two commenter stated that the proposed regulation does not adequately provide for veterans who have one of the requisite conditions but cannot verify exposure to mustard gas or Lewisite because they lack access to government records. One of them suggested that service connection not be denied if their is no clear and convincing evidance of intercurrent cause.

VA does not concur. Generally, a presumption eases the burden of proof on a veteran by attaching certain consequences to the establishment of certain basic evidentiary facts. In the case of this regulation, establishment of certain basic evidentiary facts—full-body exposure to a vesicant agent during military service and the subsequent development of a specified disease—triggers the presumption that the disease is due to that exposure even where there is no medical evidence of an association between the veteran's disease and his or her military service.

The presumption does not work in reverse, however. A presumption that the presence of a condition indicates prior exposure to a specific substance

might be possible in the case of a condition associated exclusively or almost exclusively with a single cause. The only known cause of asbestosis or mesothelioma, for example, is exposure to asbestos. There is no basis for a presumption of in-service exposure to mustard gas or Lewisite based solely on the presence of any of the conditions specified in this regulation, however, because medical science recognizes other plausible causes for all of them.

Another commenter, a medical doctor and professor of medicine, pointed out that Lewisite contains arsenic and stated that exposure to arsenic is associated with increased malignancy in humans. He suggested, based upon his own clinical experience with a patient exposed to potassium arsenite, that service connection based on exposure to vesicant agents be established for chronic leukemia, primary cancers of the liver, bronchogenic cancer and skin cancers (based on exposure to Lewisite), accelerated atherosclerosis, and neurasthenia. To support this suggestion, he cited a published case study: Regelson W., Kim U., Ospina J., Holland J.F., 1968. Hemangioendothelial Sarcoma of Liver from Chronic Arsenic Intoxication by Fowler's Solution. *Cancer* 21: 514–522.

VA does not concur. The NAS report and recommendations which the Secretary relied upon were based upon a comprehensive literature review covering almost 2,000 medical and scientific papers including numerous epidemiological studies, industrial studies of workers in chemical factories, and studies of soldiers exposed to mustard gas in warfare. NAS found that there is so little literature of these types concerning the health risks associated with exposure to Lewisite that with few exceptions it is not possible to determine the relationship between Lewisite exposure and the onset of particular diseases. In essence, this commenter asks us to accept his medical judgment over that of a distinguished panel of experts in a wide range of specialties that had conducted an extensive literature search and review. In our judgment, the clinical experience of one person does not approach the probative weight of either the literature review conducted by NAS or the consensus opinion of the panel of specialists assembled by NAS. We also note that case studies, such as that submitted by the commenter, are anecdotal in nature and have no statistical significance. For these reasons, we find that the evidence is not sufficient to warrant presumptive service connection for the additional conditions recommended by this commenter.

Another commenter suggested that no claim based on verified mustard gas exposure be denied solely because there is insufficient data to establish a correlation between the claimed conditions and exposure to vesicant agents. Other commenters suggested that VA recognize additional conditions stating that veterans should not be penalized because of gaps in the medical literature.

VA does not concur. NAS found that there are few data to argue either for or against a casual relationship between exposure to vesicant agents and other conditions mentioned by the commenters, and recommended that VA conduct morbidity and mortality studies in order to resolve some of the remaining questions about the health risks associated with exposure to vesicant agents. The Veterans Health Administration is preparing to conduct morbidity and mortality studies as recommended by NAS. Should those studies indicate a relationship between exposure to vesicant agents and additional conditions, we will determine whether a regulatory presumption of service connection for those disabilities is warranted at that time.

Another commenter recommended that VA recognize additional conditions by applying VA's benefit of the doubt doctrine and resolving all doubt in favor of veterans exposed to mustard gas or Lewisite.

Again, we note that NAS found that there are few data to argue either for or against a casual relationship between exposure to vesicant agents and other conditions. VA regulations at 38 CFR 3.102 (See also 38 U.S.C. 5107(b)) define reasonable doubt as a doubt which exists because of an approximate balance of positive and negative evidence which does not satisfactorily prove or disprove the claim; a substantial doubt within the range of probability as distinguished from pure speculation or remote possibility. Although the primary purpose of the regulation is to resolve doubt in favor of a claimant when there is a balance of positive and negative evidence, it was never intended for use when there is insufficient evidence to support a conclusion one way or the other.

One commenter stated that even though VA indicated that the proposal represented a liberalization of the previous criteria, verified full-body exposure is, in fact, a higher standard and would place a greater burden of proof on veterans seeking benefits under this amendment.

The requirement for full-body exposure was included in the July 31, 1992, version of this regulation, and its retention does not place a greater burden of proof on those veterans seeking benefits under this regulation. We had proposed to add the word "verified," but that change was intended as a clarification and represented no substantive change in VA's position on the type of evidence required to establish entitlement to the presumption of service connection set forth in this regulation. To avoid creating the impression that we have imposed a greater burden of proof, however, we have deleted the term "verified" from the final regulation.

The regulation published on July 31, 1992, applied only to those veterans who experienced full-body exposure to mustard gas while participating in secret tests of protective equipment during World War II. This amendment expands that regulation to cover any full-body exposure to mustard gas or Lewisite during military service, and it now applies to veterans exposed under battlefield conditions in World War I, those present at the German air raid on the harbor of Bari, Italy, in World War II, those engaged in manufacturing and handling vesicant agents during their military service, etc. By expanding the number of conditions, vesicant agents, and veterans covered, this amendment clearly represents a significant liberalization of the previous criteria.

Since July 1992 both VA and the Department of Defense (DoD) have initiated projects which will make it easier for veterans to establish entitlement to benefits under this regulation. DoD is searching its records for exposure data on mustard gas and Lewisite testing, to include the names of exposed military personnel, test protocols, etc., and will share the information it discovers with VA. VA has instituted a project, under the direction of the Environmental Epidemiology Service of Veterans Health Administration (VHA), to consolidate information about mustard gas testing as it becomes known into a central source. VHA officials have visited several locations where testing is known to have been conducted and/or where records might be found. The information resulting from these visits is available to VA regional offices as they attempt to establish the exposures of veterans who have filed claims.

There is an additional protection for veterans elsewhere in VA's regulations. If a claim is disallowed because exposure cannot be established but new evidence establishing exposure later becomes available from service

department records. VA will reopen the claim and authorize benefits based on the date of the original claim. (See 38 CFR 3.400(q)(2)).

One commenter suggested that the regulation should apply to oral ingestion of vesicants; another suggested that exposure via drop or patch testing should also be covered. A third commenter, a medical doctor, agreed with VA that the presumption should apply only to full-body exposures.

As explained in the preamble to the proposed rule, the literature upon which the NAS report is besed covered animal studies and two types of human studies: (1) Industrial studies of workers in chemical factories which manufactured mustard gas; and (2) studies of soldiers exposed to mustard gas in warfare, primarily during World War I. The subjects of these studies were subjected to full-body exposure and NAS determined that the exposures of participants in chamber and field tests were equivalent to the full-body exposure of soldiers in World War I. Since the NAS report addressed only full-body exposures, in our judgment there is no basis for applying the presumption of service connection to those who received less extensive exposures.

Another commenter questioned why VA is restricting the presumption that acute nonlymphocytic leukemia is service-connected only to those veterans exposed to nitrogen mustard.

The NAS report found that the evidence indicated a causal relationship between the development of acute nonlymphocytic leukemia and exposure to nitrogen mustard only (See Table 12–1, Summary of Findings Regarding Specific Health Problems, Veterans at Risk: The Health Effects of Mustard Gas and Lewisite, NAS). Because of the use of nitrogen mustard in cancer chemotherapy, there is an extensive body of literature concerning the effects of nitrogen mustard in humans after systematic administration. This literature documents an increased incidence of acute nonlymphocytic leukemia in patients who were treated with nitrogen mustard as a chemotherapeutic agent. NAS noted, however, that as a therapeutic agent nitrogen mustard has a different systemic pharmacology than sulfur mustard, and that it is difficult to make quantitative extrapolations to the carcinogenicity of sulfur mustard or to which tumors sulfur mustard would be expected to produce. For those reasons, we have limited the presumption that acute nonlymphocytic leukemia is service connected to only those veterans exposed to nitrogen mustard.

Another commenter stated that the NAS report outlined and underscored a list of compelling ethical questions regarding the WWII tests of clothing and equipment that are now being ignored: why there was no formal long-term follow-up and medical monitoring in spite of clear evidence (as early as 1933) regarding delayed onsets of debilitating disease; why these subjects were treated so disrespectfully when they gave so much; and how many additional soldiers were physically harmed and morally abused from the end of World War II to 1975? The commenter decried the fact that these questions were not addressed by formal recommendations in the NAS report, although they caused the problems that have given rise to VA's efforts to expand compensation eligibility.

It is unquestionably beyond VA's ability to modify historical events by regulation; however, we believe that this regulation is an appropriate government response to these issues. VA recognizes that because the tests were secret and no follow-up examinations were conducted, veterans who took part in them are at a disadvantage when attempting to establish entitlement to compensation. This regulation addresses that situation by establishing a regulatory framework which recognizes that specific conditions are likely to result from exposure to vesicant agents and relieves veterans of the burden of submitting evidence to establish those associations in individual claims.

VA appreciates the comments submitted in response to the proposed rule which is now adopted with the corrections noted above, as corrected at 59 FR 10875, and with the following change to the effective date.

The proposed rule stated that the amendment would be effective on the date of publication of the final rule. In a letter of May 12, 1994, the Honorable John D. Rockefeller IV, Chairman of the Senate Committee on Veterans' Affairs, expressed his concern over the delay in publishing the final regulation as well as his belief that VA could establish an earlier effective date for the amendments. We share Senator Rockefeller's concern over the delay in the rulemaking process, and have therefore determined that it would be both appropriate and more equitable for this amendment to be effective January 6, 1993, the date of the decision to modify 38 CFR 3.316.

The Secretary hereby certifies that this regulatory amendment will not have a significant economic impact on a substantial number of small entities as they are defined in the Regulatory Flexibility Act (RFA), 5 U.S.C. 601–612. The reason for this certification is that this amendment would not directly affect any small entities. Only VA beneficiaries could be directly affected. Therefore, pursuant to 5 U.S.C. 605(h), this ameadment is exempt from the initial and final regulatory flexibility analysis requirements of sections 603 and 604. This regulatory action has been reviewed by the Office of Management and Budget under Executive Order 12866.

The Catalog of Federal Domestic Assistance program numbers are 64.109 and 64.110.

List of Subjects in 38 CFR Part 3

Administrative practice and procedure, Claims, Handicapped, Health care, Pensions, Veterans.

Approved: July 15, 1994.

**Jesse Brown,**

*Secretary of Veterans Affairs.*

For the reasons set out in the preamble, 38 CFR part 3 is amended as set forth below:

**PART 3—ADJUDICATION**

**Subpart A—Pension, Compensation, and Dependency and Indemnity Compensation**

1. The authority citation for part 3, subpart A, continues to read as follows:

Authority: 38 U.S.C. 501(a), unless otherwise noted.

2. Section 3.316 is revised to read as follows:

**§ 3.316 Claims based on chronic effects of exposure to mustard gas and Lewisite.**

(a) Except as provided in paragraph (b) of this section, exposure to the specified vesicant agents during active military service under the circumstances described below together with the subsequent development of any of the indicated conditions is sufficient to establish service connection for that condition:

(1) Full-body exposure to nitrogen or sulfur mustard during active military service together with the subsequent development of chronic conjunctivitis, keratitis, corneal opacities, scar formation, or the following cancers: Nasopharyngeal; laryngeal; lung (except mesothelíome); or squamous cell carcinoma of the skin.

(2) Full-body exposure to nitrogen or sulfur mustard or Lewisite during active military service together with the subsequent development of a chronic form of laryngitis, bronchitis, emphyseme, asthma or chronic obstructive pulmonary disease.

(3) Full-body exposure to nitrogen mustard during active military service together with the subsequent development of acute nonlymphocytic leukemia.

(b) Service connection will not be established under this section if the claimed condition is due to the veteran's own willful misconduct (See § 3.301(c)) or there is affirmative evidence that establishes a nonservice-related supervening condition or event as the cause of the claimed condition (See § 3.303).

[FR Doc. 94–20229 Filed 8–17–94; 8:45 am]

BILLING CODE 8320–01–M

## ENVIRONMENTAL PROTECTION AGENCY

### 40 CFR Part 52

[CO27–1–6754a; FRL–5012–6]

### Approval and Promulgation of Air Quality Implementation Plans; Colorado; New Source Review and Prevention of Significant Deterioration

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rulemaking.

SUMMARY: In this document, EPA is partially approving revisions to the State Implementation Plan (SIP) submitted by the Governor of Colorado on January 14, 1993. The submittal included revisions to the State's new source review (NSR) and prevention of significant deterioration (PSD) regulations, which were made to bring the State's regulations up-to-date with the amended Clean Air Act (Act) and the Federal regulations. EPA finds that the revised State rules meet the Federal nonattainment NSR permitting requirements of the Act for the State's carbon monoxide and ozone nonattainment areas. EPA also finds that the State regulations only partially meet the nonattainment NSR requirements of the Act for the State's PM–10 nonattainment areas because the State has not addressed the NSR requirements for new and modified major sources of PM–10 precursors in some of the State's PM–10 nonattainment areas. Last, EPA finds that the other revisions submitted are consistent with the amended Act and the Federal regulations in 40 CFR 51 and that the revisions correct previous EPA disapprovals promulgated in 40 CFR 52, Subpart G—Colorado.

DATES: This action will become effective on October 17, 1994 unless adverse or critical comments are received by September 19, 1994. If the effective date is delayed, timely notice will be published in the Federal Register.

ADDRESSES: Comments should be addressed to Vicki Stamper, 8ART-AP, U.S. Environmental Protection Agency, Region VIII, 999 18th Street, suite 500, Denver, Colorado 80202–2466. Copies of the State's submittal and other relevant information are available for inspection during normal business hours at the following locations: Air Programs Branch, U.S. Environmental Protection Agency, Region VIII, 999 18th Street, suite 500, Denver, Colorado 80202–2466; and Air Pollution Control Division, Colorado Department of Health, 4300 Cherry Creek Drive South, Denver, Colorado 80222–1530.

FOR FURTHER INFORMATION CONTACT: Vicki Stamper, (303) 293–1765.

SUPPLEMENTARY INFORMATION:

## I. Background

### *A. Nonattainment NSR Requirements of the Amended Act*

The air quality planning requirements for nonattainment NSR are set out in part D of title I of the Act. The EPA has issued a "General Preamble" describing EPA's preliminary views on how EPA intends to review SIPs and SIP revisions submitted under part D, including those State submittals containing nonattainment area NSR SIP requirements (see 57 FR 13498 (April 16, 1992) and 57 FR 18070 (April 28, 1992)). Because EPA is describing its interpretations here only in broad terms, the reader should refer to the General Preamble for a more detailed discussion of the interpretations of part D advanced in this notice and the supporting rationale. A brief discussion of the specific elements required in a State's NSR program is also included in Section II.B. of this notice.

EPA is currently developing rule revisions to implement the changes under the 1990 Clean Air Act Amendments in the NSR provisions of parts C and D of title I of the Act. The EPA anticipates that the proposed rule will be published for public comment in the fall of 1994. If EPA has not taken final action on States' NSR submittals by that time, EPA may generally refer to the proposed rule as the most authoritative guidance available regarding the approvability of the submittals. EPA expects to take final action to promulgate the rule revisions to implement the part C and D changes sometime during 1995. Upon promulgation of those revised regulations, EPA will review NSR SIPs to determine whether additional SIP revisions are necessary to satisfy the requirements of the rulemaking.

Prior to EPA approval of a State's NSR SIP submission, the State may continue permitting only in accordance with the new statutory requirements for permit applications completed after the relevant SIP submittal date. This policy was explained in transition guidance memoranda from John Seitz dated March 11, 1991 and September 3, 1992.

As explained in the March 11 memorandum, EPA does not believe Congress intended to mandate the more stringent title I NSR requirements during the time provided for SIP development. States were thus allowed to continue to issue permits consistent with requirements in their current NSR SIPs during that period, or to apply 40 CFR 51, Appendix S for newly designated areas that did not previously have NSR SIP requirements.

The September 3, 1992 memorandum also addressed the situation where States did not submit the part D NSR SIP revisions by the applicable statutory deadline. For permit applications complete by the SIP submittal deadline, States may issue final permits under the prior NSR rules, assuming certain conditions in the September 3 memorandum are met. However, for applications completed after the SIP submittal deadline, EPA will consider the source to be in compliance with the Act where the source obtains from the State a permit that is consistent with the substantive new NSR part D provisions in the amended Act. EPA believes this guidance continues to apply to permitting pending final action on Colorado's NSR SIP submittal.

### *B. Correction of Deficiencies in Colorado's NSR/PSD Regulations*

Aside from the new provisions of the amended Act, EPA has previously identified many deficiencies in the State's NSR and PSD permitting regulations. On June 28, 1985, EPA disapproved certain provisions in the State's NSR rules (see 50 FR 26734), and on February 13, 1987, EPA disapproved specific provisions in the State's PSD rules (see 52 FR 4622). In addition, after completing a thorough evaluation of the State's NSR and PSD regulations, EPA notified the State on February 17, 1988 of various other deficiencies in Regulation No. 3 and the Common Provisions Regulation.

On May 26, 1988, EPA issued a SIP call to the State due to the failure of many areas to attain the national ambient air quality standards (NAAQS) for ozone and carbon monoxide (CO). Pursuant to the SIP call, EPA required the State to correct all of the

## REFERENCE TO IND# 28,480

Chig N(WD)

DEPARTMENT OF THE AIR FORCE
AIR FORCE HUMAN RESOURCES LABORATORY (AFSC)
WILLIAMS AIR FORCE BASE, AZ 85224

IND AMENDMENT

N=28 3-6-88
1 serious

28 March 1988

Mr David Banks, Consumer Safety Officer
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
Rockville, Maryland 20857

Dear Mr Banks

REFERENCE TO IND# 28,480.

We wish to inform your office that the data collection phase of the study covered by the above IND # was completed on 25 March 1988. Henceforth, no further use will be made of pyridostigmine bromide (PB) by this Laboratory under the provisions of the foregoing IND authorization. Therefore, we ask that IND authorization be terminated.

In the course of the study, PB was administered to a group of 28 active duty Air Force pilots. One of the pilots in this group, as previously reported to your office by telephone and by letter, experienced a medical mishap after taking PB. This pilot was returned to active duty status two to three weeks after the medical mishap. No further medically significant event occurred within this group of pilots in the judgment of the flight surgeon who monitored the conduct of the study.

We would like to express our appreciation for your careful review of the procedures undertaken in the study and for your support of the effort.

Further, we anticipate the early completion of a report of the study that will be available through my office.

Thomas H. Gray
THOMAS H. GRAY
Chief, Operational Unit Training Branch



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DEPARTMENT OF THE AIR FORCE
AIR FORCE HUMAN RESOURCES LABORATORY (AFSC)
WILLIAMS AIR FORCE BASE, AZ 85240-6457

1.1

Orig. Reports copy. Mailed 9/21/87 JGA

Mr David Banks
Consumer Safety Officer
Office of Drug Research and Review
Division of Neuropharmacological Drug Products
Rockville, MD 20857

9 September 1987

Dear Mr Banks:

Reference is made to IND 28,480.

Dr Arthur Harriman was informed in August 1986, that the Notice of Claimed Investigational Exemption for a New Drug (IND) for pyridostigmine bromide, dated July 1986, had been approved.

In the notification, he was informed that a progress report was to be submitted no later than one year after the approval was granted.

This letter is respectfully submitted for the purpose of summarizing progress to date in the approved study.

At this point in the study, 11 active duty USAF pilots have been tested with the drug. An additional 16 pilots will be tested during the fall of 1987.

Data have been discarded for three of the pilots who volunteered to serve as subjects in the study. Data for two of these pilots could not be used because there was a breakdown in the data collection system. The third pilot in this group (1Lt [redacted]) experienced a medical mishap. A report was given by telephone to your office on the day of mishap (15 May 1987). This oral report was followed by a formal statement on the event which cleared my desk on 19 May 1987 for transmission to your office.

None of the other pilots in the study has experienced even the slightest of adverse reactions to the drug. Guesses by the pilots (two hours after dosing) as to whether they have swallowed a drug tablet or a placebo tablet show exactly 50% accuracy.

Sincerely,

Thomas H. Gray

THOMAS H. GRAY
Chief, Operational Unit Training Branch



AMENDMENT

DEPARTMENT OF THE AIR FORCE
AIR FORCE HUMAN RESOURCES LABORATORY (AFSC)
WILLIAMS AIR FORCE BASE, AZ 85224

22 MAY 1987

Mr David Banks
Consumer Safety Officer
Div of Neuropharmacological Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration/DHHS
Rockville, MD 20857

Dear Mr Banks

This letter is submitted in response to your request for a statement detailing the occurrence described to you by Dr Harriman in his phone call of 18 May 87.

The medical misadventure occurred while a volunteer A-10 pilot was being readied for participation in a study of the effects of pyridostigmine bromide (PB) upon simulated flight performance in the AFHRL A-10 flight simulator.

The pilot who was adversely affected by the drug is Lt [redacted], age 25, (SSAN [redacted]), who is a member of the 76 TFS, 23 TFW, England AFB, LA 71311. Lt [redacted] entered into a cholinergic crisis, as determined by Williams AFB flight surgeons, at 0831 hours on 15 May 1987. In its acute phase, the crisis lasted between three and four minutes. The crisis began 91 minutes after Lt [redacted] had swallowed the third in a series of three 30-mg PB tablets (Hoffmann-LaRoche). The tablets had been administered in a double blind procedure at 1500 hours (Thursday), 2300 hours (Thursday), and 0700 hours (Friday) under the supervision of a flight surgeon at the USAF Hospital, Williams AFB. At the time of the misadventure, Lt [redacted] was being readied for the second of two test sessions in the A-10 flight simulator.

Lt [redacted] arrived at Williams AFB on the evening of 10 May 87 and was screened for tolerance to PB at the USAF Hospital on the following morning. On the basis of the blood value determinations, he was admitted into the experiment. At 0600, 11 May 87, a baseline blood draw was taken. A flight surgeon then administered one 30-mg PB tablet to Lt [redacted] At 0800, a second blood draw was taken. Baseline blood values: Cholinesterase (CHE), 3437 U/L; hematocrit, 46.4. Values after PB intake: Cholinesterase, 3179 U/L; hematocrit, 44.1. Normal values (factory analysis for 88 normal young male subjects tested with a CHE kit like that used at Williams AFB): 2618 - 6971 U/L.

Lt [redacted] was scheduled for three practice sessions and for two test sessions in the A-10 flight simulator. He completed the three practice sessions on 11 and 12 May and the first test session on 13 May. Lt [redacted] received three placebo tablets over the 24 hours prior to the first test session. Lt [redacted] guessed, however, that he had received the drug when questioned just prior to the test session (90 minutes after taking the third of the three placebo tablets).

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Lt [redacted] reported to the experimenter in the A-10 simulator facility at 0800 on 15 May 87 for the second test session. He arrived one hour after taking the third tablet in the second series of three tablets. Procedures required for a double blind study continued in force. Temperature in the facility was 70 deg F, and relative humidity was 60%. Times for administration of the tablets were the same as those for the first series of tablets. After he arrived, inert sensors were attached to his upper torso so that physiological readings could be taken. Also, he was tested for grip strength (hand dynanometer), was questioned on whether he had been given the drug or the placebo and on reactions to the tablets. He completed a subject status questionnaire (attachment 1) and a symptom questionnaire (attachment 2).

An 11% decrease in grip strength was recorded. Despite this decrease, he answered, when questioned, that he had received the placebo, not the drug. Responses on the subject status questionnaire were satisfactory. Also, Lt [redacted] wrote (at 0830) at the end of the symptom questionnaire checklist that he had no symptoms.

At 0831, while Lt [redacted] was standing and sensors were being placed on his skin, his knees buckled, and, without a sound, he pitched toward the floor, face forward. The experimenter was able to break his fall. The experimenter is not medically trained, but it was his opinion that Lt [redacted] had undergone respiratory arrest - mouth open, no detectable movement of any sort. The experimenter determined that the tongue had not been swallowed and next notified the nearest person to call an ambulance. The experimenter then began artificial respiration. After about six breaths, he was satisfied that Lt [redacted] had begun to breathe on his own. At this time, Lt [redacted] began to return to consciousness and, as he did so, the experimenter noted that Lt [redacted] upper body musculature was rigid, as though in tonus. There then developed an episode of sweating that continued for a few minutes. At 0834, Lt [redacted] was alert. He insisted on getting to his feet and on being allowed to go to a toilet. The experimenter helped him to a nearby facility. Medical help arrived no later than 0836. After an interview with the paramedics, Lt [redacted] walked to a waiting ambulance and was taken to the emergency room of the USAF Hospital.

In the medical interview at the USAF Hospital emergency room, Lt [redacted] recalled the episode as one in which he first felt lightheaded, of wishing to sit down, and then of fainting. Even so, he later reported being aware that people nearby were going and coming, though there was no one other than the experimenter in the vicinity. When he became conscious, he discovered that he had lost bladder and bowel control.

On entering the emergency room, he was found to be oriented, alert, and with no complaints. Blood pressure was 120/70, and all other vital signs were normal. At 0940, his CHE level was 2312 U/L. The diagnosis by flight surgeons was that he had undergone a cholinergic crisis.

By midafternoon, the CHE level was above 2800. An EEG evaluation at this time was normal. Lt [redacted] was held for observation overnight and was released for return to England AFB just after 0930 on 16 May 87. The final medical determination sustained the early diagnosis that Lt [redacted] is a normal, healthy individual who experienced a cholinergic crisis.

A recommendation is being offered to reviewing authorities in the USAF in light of our awareness that all of the pilots who volunteer for this study will be tested for tolerance to PB before coming to Williams AFB. Possibly, a useful adjunct to the PB screening program would be to determine the values for baseline CHE in the blood and for CHE inactivation. Some cutoff values could then be decided upon by medical personnel. There may be some support for this idea in the small data base acquired to date in this study. Specifically, pilots, other than Lt [redacted] who have participated in the study to date have had nil side effects from PB. These five pilots showed baseline CHE values (U/L), together with % CHE inactivation values, that are much higher than those found for Lt [redacted] These values for the different pilots are as follows: 6447 (3.37%), 5913 (12.60%), 5807 (6.84), 5233 (15.67%), and 3963 (13.83%). The baseline CHE value for Lt [redacted] of 3437 U/L (7.51%), though the normal range, may have been too low to withstand PB challenge. Possibly, problems with use of pilots as subjects in this study can be avoided on the basis of the above information. For example, if pilots with CHE values below 4000 U/L were not allowed to participate, one PB tolerant pilot would have been excluded, but so would have been Lt [redacted]

Sincerely

Michael C Lane

MICHAEL C. LANE, Colonel, USAF
Chief, Operations Training Division

2 Atchs
1. Subject Status
2. Symptom Checklist

Barry N. Rosloff, Ph.D.
5/8/86

Review and Evaluation of Pharmacology and Toxicology for Marketed Drugs

IND # 28,480

Drug(s): Pyridostigmine Bromide

Date of Submission: _____ Date of Review: 8/8/86

Sponsor: Air Force Human Resources Laboratory, OTU
Williams AFB, AZ

Proposed indication, dosage, patient population, duration of trial:
Effects of pyridostigmine on pilot performance in an A-10 flight simulator
N = 20-30 male pilots. Dose = 30 mg p.o., taken once in hospital and once
1 hr. prior to flight simulator session.

Is pharmacological rationale adequate? Explain. Pyridostigmine has been
suggested to be useful as a prophylactic measure against nerve gas
poisoning. Similar studies have been performed by the armed forces under
numerous related IND's

Are exclusion criteria (e.g. women of childbearing potential) adequate? If no, explain. Yes

Are there other factors that the investigator should consider in addition to the PRECAUTIONS, WARNINGS, and ADVERSE REACTIONS in the package insert?
No. Monitoring will include continuous digital ECG and [redacted]
respiration. Test dose will be given in hospital [redacted] prior to flight simulator
session. Antidote (atropine) will be available.

Other comments: See below

Recommendations: The study may proceed with the following recommendation:
The consent form compares the [redacted] proposed dose of 30 mg with the
much higher doses (mean 600 mg) that are given to myasthenia gravis patients,
implying a large margin of safety. However this is misleading since such
patients generally [redacted] are less sensitive to anticholinesterase agent. The
consent form should thus be appropriately modified.

cc:
HFD-120
HFD-120/JContrera
HFD-120/Reviewer

8/11/86

Barry N. Rosloff, Ph.D.
Signature

APPLICATION TO THE AFHRL/OT HUMAN USE COMMITTEE

1. PROJECT TITLE: Effects of Protective Drugs on Aircrew Flight Performance: Ground Support Aircraft

2. PROJECT NUMBER: 2729 12 01

3. PRINCIPAL INVESTIGATORS: Arthur E. Harriman, Ph.D. (AFHRL/OTU).

Robert R. Woodruff, M.C. (AFHRL/OTE).

4. ASSOCIATE INVESTIGATOR: Ronald A. Grattopp, Major, USAF (AFHRL/OTU).

5. MEDICAL MONITOR: Janet C. Green, M.D., Capt. USAF (USAF Hospital, Williams AFB).

6. STATISTICIAN: David Hubbard, Ph.D. (University of Dayton Research Institute).

7. LOCATION OF STUDY: Air Force Human Resources Laboratory, Williams Air Force Base, AZ 85240-6457

8. PLANNED TIME SPAN: 1 OCT 84 THROUGH 30 SEPT 87

THIS PROTOCOL HAS NOT BEEN SUBMITTED FOR APPROVAL TO ANY HUMAN USE COMMITTEE AT ANY OTHER FACILITY OR INSTITUTION

9. PROJECT OBJECTIVE: To determine if pyridostigmine bromide (pyrido), a candidate pretreatment agent in chemical warfare defense, deranges physiological functions and/or degrades performance of pilots given the task of executing a simulated mission in the AFHRL flight simulator.

10. BACKGROUND RELEVANCE: The AFHRL at Williams AFB has been tasked to evaluate the effects of pyrido on aircrew performance and physiology in a simulated military operational environment. Side effects of pyrido, as these effects may reduce the value of this compound as a pretreatment drug for aircrews, have not been determined previously. Tasking for this study of pyrido side effects has been funded by a Joint Working Group through the US Army-directed Triservice Program to evaluate the effects of chemical defense protective agents on military performance.

This evaluation is being conducted in support of the USAF Surgeon

General who has made the decision that our forces will be best protected in a chemical warfare environment if they are treated with pyrido before any exposure to chemical warfare nerve agents. Modern chemical warfare nerve agents are powerful compounds which interfere with normal functions of the nervous system as well as with other bodily operations. The most toxic of these agents belong to the organophosphate series of compounds which irreversibly inhibit acetylcholinesterase (AChE). In the normal course of events, release of acetylcholine (ACh) from presynaptic terminals triggers action potentials (nerve impulses) in postsynaptic nerve cells through the peripheral somatic nervous system, at all spinal nerve cell endings in the autonomic nervous system, and in many central nervous system circuits. Action of ACh is terminated, usually in less than one (1) msec, by the enzyme AChE which is released from various sites in the vicinity of cholinergic synapses. Pyrido, like the organophosphates, also binds to and inhibits AChE, but, unlike the organophosphate compounds, does so both incompletely and temporarily (reversibly). The mechanisms through which pyrido protects against organophosphate poisoning are not known. The primary functional consequence from pyrido administration, however, has been identified as failure of organophosphates to inhibit AChE in the presence of the pyrido molecule (1). In this manner, AChE remains effective in the regulation of ACh activity in cholinergic nerve circuits.

In overview, the results from the controlled clinical trials that have been conducted to date on pyrido effects among human subjects have been in support of the recommendation by the Surgeon General. Specifically, normal adult males who are given pyrido at the dosage now recommended by the Surgeon General (90 mg day in divided doses) for as many as five consecutive days do not exhibit significant drug side effects. Research data on effects of pyrido on normal female subjects have not been reported. Consequently, the possibility is open that there exist sex differences in pyrido side effects. Presumably, such side effects as may occur in some portion of subjects would not prevent the broad military use of pyrido for pretreatment against an anticipated exposure to a toxic nerve agent.

Pyrido, though administered to afford protection against organophosphate compounds, may also alter peripheral and, possibly, central nervous system functions. An ideal chemical warfare pretreatment drug would have no side effects, but, apparently, pyrido (as would be the case with any other drug) retreats from the ideal. In sum, the protective action of pyrido involves a dimension of benefit that must be weighed against the risks associated with degraded performance of military tasks. Several investigations have been conducted concerning the extent and the nature of these risks. The results of these study are summarized below.

A. Graham and Cook Study. Researchers at the Midwest Research Institute, under contract with the Air Force (2),

examined the effects of pyrido in the laboratory on performance by normal young adult males on a multiple-task battery. Pyrido, administered orally at the rate of 90 mg/day in divided doses, was given to experimental subjects for five consecutive days. This regimen was repeated after the subjects had been permitted a 7-day rest interval. Pyrido was found (1.)to produce reduced probability-monitoring in a vigilance task and (2.) to degrade performance in a dual task that required time-sharing between visual tracking and short-term memory recall.

B. Gall Study. Gall (3), in a summary of British studies that were performed over the preceding decade, reported that pyrido, given at the rate of 90 mg/day in divided doses, was tolerated well by a large group of normal young adult subjects during a five-day period. In contrast to the Midwest Research Institute study, results of the British work showed no changes in performance by the subjects on any psychological measure within an array of tests, whether cognition, memory, psychomotor skills, neuromuscular coordination, or vigilance were involved. Further, there were no changes among the subjects in the majority of measured physiological functions. The functions observed included elements of visual physiology and blood characteristics. The only exception to the overall finding that pyrido lacked physiological effect was the observations that some subjects experienced minor gastrointestinal problems (loose stools and\or increased flatus). These symptoms ended promptly when the drug was no longer administered.

C. Williams Study. Williams (4) substantially repeated the procedure used in the British studies and obtained comparable results. In this study, 24 male subjects, who were given pyrido at the rate of 90 mg/day in divided doses for five consecutive days, gave no indication that pyrido had any adverse effects to health.

Nonetheless, none of the reported investigations into pyrido have included systematic tests of aircrews in the performance of actual or simulated flight and military tasks. The only work which has been performed in this connection (5) was informal rather than systematic and suggestive rather than conclusive. In the study, the subjects were aircrew personnel who occupied the rear seat of F-4C aircraft during flight operations. Only minimal gastrointestinal distress was reported by several subjects among the 18 volunteer participants. Mission effectiveness was not compromised. For safety reasons, however, no front seat pilots were used in the study. Therefore, the significant concern which remains for aeromedical research and for the operational squadron is whether pilots who take pyrido may experience adverse effects that interfere with flying ability.

11. IMPACT STATEMENT: The possibility exists that USAF aircrews may be exposed to enemy chemical weapons in the event of any outbreak of hostilities. It is necessary, therefore, that these

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aircrews be provided with adequate defense against such attack. Efforts heretofore have been primarily to provide protective clothing and apparatus (e.g., air filtration systems) and postexposure (treatment) drugs (primarily atropine and 2-PAM). It now appears possible that protective chemicals, taken orally, can supplement the physical protection and the chemical treatment measures previously devised. Among these agents, pyrido appears to be the candidate substance of greatest promise because its protective effects are more enduring and its known side effects are generally less significant than is the case for related chemicals which could be put to the same use. The question of pyrido side effects, however, insofar as these implicate behavioral and physiological functions, has not been resolved. It is, of course, critically important that USAF pilots along with other personnel be given chemical protection from neural toxins by an agent that does not adversely affect execution of missions. If this study is not conducted, current and future guidelines which concern aircrew survivability and mission-effectiveness in a chemical warfare environment will be inadequate for use by the US DOD and by NATO allies. Furthermore, important information could be denied in consequence to commanders who have the responsibility of ordering administration of pyrido to military personnel.

12. EXPERIMENTAL PLAN:

A. Equipment/Facilities:

The subjects in the experiment will be tested in the AFHRL A-10 flight simulator at Williams AFB. Light valves will project a full-color flight scenario to the A-10 pilot during test sessions of 55-min duration. The scenario will be comprised four segments as follows: 1.) Take-off and climb (11 min); 2.) Air refueling (11 min); 3.) Air-ground strafing (11 min); 4.) Low level penetration and "Red Flag" target area attack (22 min). An extensive array of equipment, biobehavioral instrumentation, computers, and data collection subsystems will be used to support the study.

(1) A-10 flight simulator. This advanced flight simulator has been updated further through the addition of light valves and installation of a full-color scenario. The simulator, so equipped, provides veridical representation of threats, targets, and terrain.

(2) Biobehavioral recordings. A Honeywell SIMULTRACE VR-12 recorder will be used to provide continuous digital ECG, respiratory, thermal (skin surface), EMG, arousal (swallowing rates), and blood flow (ear lobe) recordings. Slow-speed strip chart recordings of the six physiological measures will be taken during the first three (3) 11-min segments in each of the two test sessions. High-speed recordings will be made of the responses by the subjects during both 22-min "Red Flag" segments. These recordings will be subjected to measurements which will

supplement the computer-generated analyses of the physiological data. The specific measures within in each of the six categories of physiological response are detailed in Section 12.D.(5) (below).

(3) Performance measurement system. The basic element in the performance measurement system is a Digital Electronics Corporation VAX. Software needed for acquisition of data on the VAX is currently being developed by a contractor.

(4) Medical aid station. Paramedical personnel will be present during all test sessions to provide medical supervision of the subjects. A medical aid station adjacent to the A-10 flight simulator will be equipped with a stowable cot, a supply of supplementary oxygen, a SparKit augumented with atropine, Di-Gel, blood pressure cuffs, and an Ambubag.

B. Subjects:

(1) Subjects and selection criteria. The subjects in the study will be male USAF personnel who are experienced A-10 pilots. No fewer than 20 subjects will be tested and, if possible, data will be gathered from as many as 30 A-10 pilots. All of the subjects will have passed a FAA Class II medical examination within the previous 12 months.

(2) Volunteer subjects. At the outset, and before they have left their home base, the prospective subjects will each be informed that participation in the experiment is to be undertaken on an entirely voluntary basis.

C. Duration. Each subject will participate in the study at Williams AFB over a 5-day period. All subjects will receive three (3) sessions of familiarization flight time and two (2) data collection sessions in the AFHRL A-10 flight simulator. Sessions in the simulator will take 55 min each, and no subject will undertake more than one simulator session per day.

D. Method:

(1). Screening. Presumably, by the time the subjects enter the study, they will have been screened - as part of a USAF testing program - for tolerance for pyrido. Whether or not the testing program has by then been put into effect, the prospective subjects will be screened by means of a questionnaire for potential hyperreactivity to pyrido. An affirmative response to any one of the items by a subject will serve to disqualify him from the study. The items will serve to eliminate from the study those subjects with any history of bronchial asthma, intestinal or urinary obstruction, peptic ulcer, hypotension, and a medical history of hypersensitivity either to cholinergic blocking agents (scopolamine, atropine) or to bromide compounds (6,7).

On arrival at Williams AFB, the prospective subjects

will be briefed on all aspects of the study by the principal investigator conjointly with medical personnel assigned to the project. Then, the prospective subjects be handed a consent form (Attachment 1). After the form has been read, the principal investigator and a physician assigned to the project will respond fully to any and all questions raised by the A-10 pilots. At this point, the pilots will have opportunity to sign and date the form. A witness will also sign and date the form, after he has determined that the subject has agreed out of his own volition to participate in the study, that the form has been understood and that all questions have been answered to the satisfaction of each subject.

As the next step, the subjects will check into the USAF Hospital at Williams AFB for assessment of each individual's response to pyrido. Medical personnel will obtain an initial venous blood sample from the different subjects to establish a baseline. A single 30-mg tablet of pyrido will then be ingested by each subject. One hour later, the first of four blood samples, obtained thereafter at hourly intervals, will be drawn from every subject. If a subject so requests, a "heparin lock" will be administered by the medical monitor to negate need for multiple draws. A new needle will be used for each sample, and the total volume of blood drawn from any subject will approximate 35 ml (7 ml/5 samples). No other blood will be drawn from any subject during the study.

Through the procedure of multiple blood samples, the time course for absorption rate of pyrido in the blood will be obtained and time of the peak AChE inhibition level for the various subjects may be estimated (8,9). A subject will be withdrawn from the study if the pyrido tablet reduces blood AChE by 40% or more qr, in the absence of such reduction, on the basis of the symptom picture. The symptom picture will be identified by use of a check list and evaluated by the medical monitor.

Before a subject has taken the pyrido tablet, as well as during the intervals between blood draws, his muscle strength and neuromuscular coordination, and simple reaction time will be be tested. The tested behaviors, like the other data, will be evaluated by the medical monitor who will then determine whether the subject should continue in the work or be dismissed from the study. In sum, no testing will be performed until the subjects have been cleared by the medical monitor for participation in the experiment.

(2). Design. The experiment to be conducted will be a double blind study of split-plot design in which there is counterbalanced presentation of the within groups treatment. The main features of the design are as follows:

a. The between-groups factor: Chemical defense ensembles (CDE gear).

b. The within-groups factor: Pyrido.

(3). A-10 Simulator Performance. Among the subjects, (20 or, possibly, as many as 30 pilots), 50 percent will wear CDE gear during all training and test sessions (experimental group), and the other 50 percent (control group) will not use CDE gear at any time during the study. All subjects will receive daily sessions of A-10 simulator training over a three-day period prior to being tested in the simulator once daily during each of the next two days. In the double blind procedure of the experiment, the subject will take a 30 mg tablet of pyrido one hour prior to one session in the simulator and a placebo before the other session.

(a) Flight scenario. The 55-minute scenario that is described in Section 12.A (above) will be the same in all of the training and test sessions.

(b) Physiological recordings. Every subject will be instrumented with small skin-surface electrodes just prior to each of the two test sessions. Leads from the electrodes will connect with amplifiers for physiological measures that are identified in in Section 12.A.(2)(above). The responses which will be monitored in each of the categories of measurement are as follows: (Swallowing) Number of swallows/min; (Respiration) Number of respiratory cycles/min and I-fraction [ I-fraction = inspiration (msec)/inspiration (msec) + expiration (msec) ]; (Skin temperature) Deflections [ up/down in deg C ] from base line (skin temperature of quiesent subject at start of session); (Ear pulse plethysmograph) Linear information on changes [ vasodilation and vasoconstriction ] in the peripheral vascular volume which occurs during each heart beat; (Electromyograph [EMG]) A notch filter will be set at 60 Hz, but all other EMG signals between 10 Hz and 150 Hz will be monitored; (Cardiac activity) The electrocardiogram (ECG) will be recorded only for the purpose of further providing for subject safety. All six (6) channels of data will be recorded at the rate of 100 Hz throughout both of the 55-min test sessions for each subject.

(c) Performance tasks. The scenario for the 55-min "mission" in the A-10 flight simulator will be comprised of the four segments described in Section 12.A. An overview of the activities taking place in each segment is presented in this section. More specific description of the performance measures taken in the different tasks is contained in Attachment II.

Segment 1: The pilot will take off from Nellis AFB and climb normally to 5000 ft MSL and level off. During both the climb and the level flight, weather (visibility) fluctuations and inflight emergencies (engine failure and imminent mid-air collision) will occur. At four (4) min into the flight, visibility will drop

from eighteen (18) nautical miles to one (1) nautical mile. At six (6) min into the flight, a C-130 "moving model" will approach from the A-10 on a collision course from the pilot's one o'clock position. At seven (7) min, visibility will change to twelve (12) nautical miles. At 9.5 min, visibility will change to five (5) nautical miles. At ten (10) min, one engine will fail, and full manual control will be required. At 11 min, visibility will fade to zero as the pilot "enters a cloud", and the flight simulator will "freeze".

Segment 2: The flight simulator will again be initialized at an altitude and airspeed that to be determined. The "aircraft" will emerge from the "cloud" referred to above with both engines operating normally and with 18-mile visibility. The point of emergence will occur near a rendevous with a KC-135 tanker "moving model". The pilot will adjust his flight parameters to match those of the tanker and will attempt "refuel". Whether or not the pilot is successful in the effort, at eleven (11) min into Segment 2 (22 min total elapsed time), visibility will fade to zero, and the simulator will "freeze".

Segment 3: Once again, the flight simulator will be initialized over the Nellis AFB strafing range. From the outset of this segment, the pilot will have the task of strafing targets like those found on a conventional gunnery range. After engaging in strafing for eleven (11) min (33 min total elapsed time), visibility will fade to zero, and the flight simulator will "freeze".

Segment 4: The flight simulator will be initialized for a low level penetration into a tactical target area. After briefing, the pilot will traverse a route of 30 nautical miles at 50 to 500 feet AGL and 350 KIAS through two navigation points to an initial position (IP). From the IP, the pilot will proceed, with the intention of destroying a main target, into a threat area. While in the threat area, the pilot will be frequently threatened by AAA's and by SAM's. If or when the main target has been destroyed, the pilot will either exit the area or loiter to attack targets of opportunity. The pilot may be "killed" by threats or by impact with the terrain. On any occasion of either event, the simulator again will be initialized for flight at the nearest safe point. When twenty-two (22) min in this exercise have passed, (55 min total elapsed time), the visibility will fade to zero, and the flight simulator will freeze. The mission will be concluded at that point.

(d) A subject status questionnaire and a sleep survey form will be completed by each subject prior to screening for tolerance to pyrido and before each of the two test sessions in the flight simulator. A symptoms checklist, a subjective assessment of workload, and a fatigue scale will be completed at the end of each of the test sessions (10). The pilots will be encouraged to report any physical symptoms or changes in mood state which occur after intake of pyrido. In addition, a Profile

of Mood States (POMS) will be completed before and after each of the two test sessions (11).

(2). Outline of procedure. The general procedure of the experiment is diagrammed below. The order of pyrido/placebo administration for ten (10) subjects in each of the two groups, as shown below, was determined by the Gellerman random order series. Although not shown, the order of testing the subjects on the between-groups factor (CDE gear) will also be set in accordance with a Gellerman order. If more than 20 subjects are obtained, both random order series will be extended.

Groups

| Experimental (CDE Gear Worn) | | | Control (CDE Gear Not Worn) | | |
|---|---|---|---|---|---|
| | Pyrido taken? | | | Pyrido taken? | |
| Subjects | Yes | No | Subjects | Yes | No |
| A | 1 | 2 | K | 1 | 2 |
| B | 2 | 1 | L | 2 | 1 |
| C | 2 | 1 | M | 2 | 1 |
| D | 2 | 1 | N | 2 | 1 |
| E | 1 | 2 | O | 1 | 2 |
| F | 1 | 2 | P | 1 | 2 |
| G | 2 | 1 | Q | 2 | 1 |
| H | 1 | 2 | R | 1 | 2 |
| I | 1 | 2 | S | 1 | 2 |
| J | 2 | 1 | T | 2 | 1 |

(3) Data analysis.

(a) Hardware. The basic data collection equipment for measurement of pilot performance consists of the following - an A-10 cockpit, colored light valves in a dodecahedron, an advanced simulator pilot trainer (ASPT), which has inputs to an advanced visual training system (AVTS), and a programmable intelligence collection system (PICS) interface with a Digital Electronics Corporation VAX 11-780 computer. The Honeywell VR-12 Simultrace biophysical recorder will be connected to the VAX via a junction box.

(b) Software. The two categories of measures described in Attachment II - common measures and segment specific measures - will be cast into univariate plots and frequency distributions. These data will be analyzed by means of various statistical packages and prepared as final displays and as archival data. The statistical packages which will be used to treat the data are as follows: BMDP, MINITAB, DATAPLOT, SPSS-X, and RUMMAGE.

(c) Blood data. The biochemical determinations of AChE and plasma pyrido levels will be analyzed by a method adapted from Ellman (12) and Lin (13).

(d) Ratings. The subjective ratings collected during critical phases of the work, as described above, will be analyzed by nonparametric statistical methods.

(4) Safety precautions.

(a) Medical. The screening procedures (questionnaire focusing on sensitivity to pyrido and use of blood sampling over time to determine fate of pyrido in the body) will be conducted by paramedical personnel under the supervision of medical personnel and will take place in the USAF hospital at Williams AFB. Thereafter, each subject will take but one more pyrido tablet which will be of the same dosage used in the screening. This dosage will be taken by each subject while he is in an AFHRL laboratory and in the immediate vicinity of a the medical station described in Section 12.A.(4) above. The station will be manned by paramedical personnel. Every subject will be instructed to report immediately to the paramedic on any adverse reactions to the pyrido tablet. In such event, a physician, who will be on call, also will be notified. In addition, the strip chart recordings will be monitored throughout both tests sessions, whether pyrido or the placebo has been administered.

(b) Flight simulator. There is no history of problems encountered by subjects operating the A-10 flight simulator. Nevertheless, in advance of the first practice session in the A-10 flight simulator, the AFHRL will provide each subject with a safety briefing on how safely to enter, to operate, and to leave the simulator. In connection with this briefing, all subjects will watch a videotape (prepared for this study) which demonstrates proper use of the simulator and means for coping with hazards that conceivably could be encountered by a subject while in this simulator.

13. MEDICAL RISK ANALYSIS:

A. Pyrido. The medical risks from participation in this study are slight. Pyridostigmine bromide is approved and marketed as Mestinon by Hoffmann-LaRoche, Inc. (14). The primary therapeutic indication for Mestinon is the treatment of myasthenia gravis for which the mean dosage is 600 mg day orally in divided doses. The dosage to be used in this study is 20 times smaller than the mean treatment dosage and will be given only twice - once during the screening test and again before one or the other of the two test sessions. Exposure of the subjects to this level of pyrido would be markedly below that for patients routinely treated with Mestinon.

B. Overdosage. Adverse reactions to pyrido are typically

attributable to an overdosage of the drug. As cited above, such reactions are not likely to develop among subjects in the present study because the doses are few (2) and small (30 mg each). Also, the close paramedical and medical supervision given to the subjects will limit both the severity and the duration of any adverse reactions, were these to occur. In cases where side effects do occur (as from overdosage), the symptoms include nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis (contracted pupils), diaphoresis (profuse perspiration), muscle cramps, fasciculations (muscle twitching), and weakness. In rare cases, a rash occurs from prolonged use of pyrido, but this reaction subsides promptly when the use of the drug is discontinued. In a recent study (15), normal subjects were observed for symptomatology after they were given doses of 60 mg orally as well as 2.0, 4.0, or 8.0 mg doses intravenously. The most common side effects noted among the subjects were those of fatigue, fasciculations, heavy eyelids, and gastric distress.

C. Cellular and biochemical changes. In two studies, Hudson et al (16,17) tested for ultrastructural cellular changes in rat diaphragms that were produced by pyrido administered by an infusion pump over a two-week period. Ultrastructural cellular changes were found at the junctions between nerve terminals and muscle fibers (end plates) under the electron microscope at doses low enough to cause only about 10 percent reduction in blood AChE level. More severe effects were seen with pyrido doses that evoked 70 percent reduction in blood AChE. Further, qualitatively similar changes were found in the rats within 24 h of pyrido injections that produced between 30 percent and 40 percent blood AChE inactivation. These effects, however, were substantially reversed after the first week. Other work, however, has shown still less effect of pyrido on rat tissue (18). Pyrido-induced inactivation of AChE by means of oral dosages produced reversible tissue changes after periods ranging from 14 to 56 days after administration of the drug ended. Further, the severity of the observed tissue changes was less than that reported by Hudson et al (16,17). Apparently, the significance of the ultrastructural changes seen in rats which have been given pyrido is not clear.

Currently, medical opinion holds that AChE inactivation in the blood of normal humans in the range of 20 to 40 percent may be safely produced in the interest of laboratory research. Neither the functional animal data nor the results of studies with human subjects contravene this medical judgment.

D. Briefings. Points raised in previous sections of this application are herewith repeated or supplemented as follows:

1. The subjects will learn that the drug screening and drug administration procedures have been designed to minimize risks to the participants while maximizing their relevance to the operational world. All participating pilots will be free from

idiosyncratic reactions to pyrido as administered in the dosage amount and in the manner approved in a comparable mass screening program supervised by the Surgeon General of the Air Force.

2. The volunteer pilots will be briefed on the following: potential side-effects from taking a 30-mg oral dose of pyrido, blood sampling procedures, physiological monitoring techniques, safety procedures in operation of the flight simulator, hazards attendant to use of the simulator, how to report symptoms, and how to initiate medical and paramedical contacts with these personnel who will be physically present in the study area for eight (8) h after a tablet has been taken - whether placebo or pyrido is involved.

3. The nature of the flight scenario, the research protocol, and the consent form will be thoroughly reviewed with every subject.

4. All subjects will be instructed not to consume alcohol during the the period of the study and not to engage in any strenuous exercise for eight (8) h after ingesting a tablet - whether placebo or pyrido.

"Effects of Atropine and Pyridostigmine on Exercising Monkeys." Avlonitou, E., and Elizondo, R.S., The FASEB Journal, V2(4): A521; 1988.

"A Comparison of Subacute and Acute Pyridostigmine Pretreatment Against Soman Intoxication." Talbot, B.G., Harris, L.W., Lennox, W.J. and Anderson, D.R., Proceedings of SAFMLS: 39; 1988.

"Effects of Soman of Pyridostigmine Bromide on Primate Equilibrium Performance and Serum Cholinesterase Activity". Blick, D.W., Brown, G.C., Murphy, M.R., Yochmowitz, M.G., Hartgraves S.L., and Fanton, J.W., USAFSAM-TR-87-20, October, 1987

"Mestinon (PYR) Induced Alterations in Rats: Impact of Fixation, Nifedipine and Body Weight." Bowers, W., Blaha, M., Moales, I., and Daum, P., The FASEB Journal V2(4); A825; 1988.

"90-Day Oral Dose Toxicity Study of Pyridostigmine in Dogs." Kluwe, W.M. and Page, J.G.,DAMD-17-84-C-4088, May, 1988.

2.3.2 Summary of the Major Preclinical Findings:

Pyridostigmine, administered to rats in drinking water for 1 week (300 mg/L), had no adverse effects on exercise endurance. However, pyridostigmine resulted in a significant ($p < .05$) inhibition (approximately 25 percent) of circulating cholinesterase when compared with rats receiving only tap water.

Pyridostigmine pretreatment in the primate (1.2 mg/kg for six administrations, or 1.2 mg/kg for the first, 1.8 mg/kg for the second, and 2.4 mg/kg for the third through the sixth administrations) and mouse (0.2 or 0.82 mg/kg) models, was shown to provide significant protection against organophosphate (soman) intoxication when combined with atropine/2-PAM therapy.

Well-trained rhesus monkeys were tested for their ability to perform a compensatory tracking task (Primate Equilibrium Platform, or PEP) under the influence of intramuscularly injected doses of pyridostigmine bromide (0.12, 0.24, 0.48, and 0.96 mg/kg). Only the highest dose produced a clear performance decrement. Performance, 30 to 60 min after the highest dose, was significantly worse than after any other dose. Performances following the other three doses did not differ significantly from each other or from performances following placebo injections. The $ED_{50}$ of pyridostigmine bromide required to produce a reliable decrement in PEP performance was 0.66 mg/kg.

The estimated reduction in serum cholinesterase (ChE) activity associated with the $ED_{50}$ was 77 percent, measured 30 min after exposure.

The effects of atropine (0.03 mg/kg) and pyridostigmine (five doses 0.4 mg/kg) on non-human primates are similar to those reported for man on exercise tolerance time.

Guinea pigs and rats were administered pyridostigmine orally (1.25 mg/kg every 6 hrs for 14 days). Rats were administered pyridostigmine orally (1.0 mg/kg every 12 hrs for 14 days) and via an implanted osmotic mini pump (5 mcl/hr for 14 days). After termination of pyridostigmine administration, the animals were challenged with soman. Acetylcholinesterase activity and the protective ratio (24 hr LD50 values of the treated/untreated groups) were determined. The protective ratio was similar within species when single, multiple or sustained pretreatment doses of pyridostigmine were given in combination with other compounds (atropine + 2-PAM). The authors concluded that the determining factor in pyridostigmine pretreatment efficacy is the inhibition of acetylcholinesterase by pyridostigmine and not the frequency of dosing.

Pyridostigmine bromide, 0.05 mg/kg, administered orally to beagle dogs every 8 hours for 90 days, resulted in no observed toxic effects. Beagle dogs administered 0.5 mg/kg every 8 hr for 90 days caused marked inhibition of erythrocyte (RBC) acetylcholinesterase (AChE) in both sexes and pronounced gastrointestinal (GI) distress in males. Dogs administered 2.0 mg/kg pyridostigmine bromide every 8 hr for 90 days caused profound RBC AChE inhibition and severe GI effects in both sexes. Beagle dogs administered 2 or 5 mg/kg pyridostigmine did not develop a tolerance to the drug.

The oral administration of 60 mg of pyridostigmine for three days every 8 hrs reduced plasma cholinesterase and erythrocyte acetylcholinesterase activities in swine, to levels found acceptable for man for protection against exposure to nerve agents. Chronic pyridostigmine administration for three days in swine increased hematocrit and tended to increase blood glucose levels. Acute reduction of AChE activity by pyridostigmine administration in euvolemic or hemorrhagic conscious swine failed to significantly alter biochemical and physiological parameters.

When superfused over an isolated slice of rat forebrain ($2.5 \times 10^{-7}$ M to $1 \times 10^{-4}$ M), pyridostigmine produced a direct postsynaptic membrane action on dorsolateral septal nuclei neurons. Data suggest a dose dependent effect of pyridostigmine on muscle ultrastructure with the threshold for presynaptic alterations being approximately 0.001 $LD_{50}$ (approximately 10 percent whole blood cholinesterase depression).

Lesions detected by electron microscopy were visible in rat diaphragm taken 1 hour after a dose of pyridostigmine (0.01 and 0.1 times the $LD_{50}$) but not in samples taken 28 and 56 days post-dose, suggesting the lesions were reversible. Rats orally administered 0-64 mg/kg/day of pyridostigmine bromide for 14 days showed some signs of developing tolerance to pyridostigmine bromide during the second week of dosing.

Rats were given ad libitum pyridostigmine 90 mg/kg (in the feed) for a maximum period of two weeks. Light microscopy analysis of diaphragm tissue harvested at 24, 48, and 96 hr and at 1 and 2 wks, demonstrated 1/50 myofibers shrunk and appeared dark with centralized nuclei. Presynaptic areas of neuromuscular junctions were relatively unaffected, but postsynaptic areas invariably showed maximal changes. These ultrastructural changes consisted of disruption of myofilaments, mitochondrial changes consistent with accumulation of calcium and nuclear alterations. These effects appeared not to be cumulative and were greatly diminished by 2 weeks. The authors concluded that subchronic feeding of pyridostigmine induces primarily myopathic rather than neurogenic changes in the diaphragm of rats.

2.4 Manufacturing Changes

Since the last annual report, there have been no manufacturing changes.

## 3.0 GENERAL INVESTIGATIONAL PLAN

There are plans to continue investigation of pyridostigmine under this IND. The study "Physiological and Biophysical Evaluation of Pyridostigmine Pre-Treatment in Different Environments" is planned with Margaret A Kolka, Ph.D. as the principal investigator. The purpose of the study is to determine the effects of a single pyridostigmine administration (30 mg orally) on various physiological and biophysical parameters of human temperature regulation, during rest and submaximal exercise, in multiple environmental conditions. The study will involve eight healthy male subjects. The protocol and a subsequent amendment to the protocol have been previously provided to the FDA.

## 4.0 REVISED INVESTIGATOR'S BROCHURE

Since the last annual report, there has been no change in the investigator's brochure.

## 5.0 UNREPORTED SIGNIFICANT CHANGES IN PHASE I PROTOCOLS

Since the last annual report, there have been no significant changes in phase 1 protocols.

## 6.0 FOREIGN MARKET INFORMATION

The FDA Freedom of Information office was queried for any adverse drug reactions that might have been reported for pyridostigmine bromide as the result of studies outside of DOD control. The information provided by the FDA-FOI office is that no reports of adverse drug reactions have been submitted since the last annual report submission.

## 7.0 LOG OF OUTSTANDING BUSINESS WITH THE FDA

There is no outstanding business with the FDA.

## DEPOSITION OF DR. SCHAUMBURG REGARDING AGENT ORANGE AND GULF WAR ILLNESSES, AND RELATED DOCUMENTS

1

APRIL 22, 94. A.M. SESSION.

THE COURT: WOULD YOU CALL YOUR NEXT WITNESSE, PLEASE.

MR. CONRAD: YES. AT THIS TIME, WE WOULD CALL DR. HERBERT SCHAUMBURG, WHO I BELIEVE IS ALREADY STANDING BESIDE THE WITNESS CHAIR.

THE COURT: OKAY. DR. SCHAUMBURG, WOULD YOU RAISE YOUR RIGHT HAND? (WITNESS SWORN).

THE COURT: AND, DOCTOR, YOU ARE MORE COMFORTABLE STANDING.

THE WITNESS: I AM.

THE COURT: YOU MAY STAND. PLEASE PROCEED.

MR. CONRAD:

Q DR. SCHAUMBURG, WOULD YOU STATE YOUR NAME FOR THE RECORD, PLEASE, SIR?

A HERBERT HOWARD SCHAUMBURG.

Q WERE YOU BORN AND RAISED HERE IN HOUSTON?

A YES, I WAS. UNTIL I WAS 18 YEARS OLD.

Q BACK IN THE LATE THIRTIES AND FORTIES, WE HAD A DISEASE PROBLEM HERE IN HOUSTON CALLED POLIO, DID WE NOT?

A YES.

Q AND YOU HAD THAT?

A I DID.

Q AND FOR THAT REASON, DO YOU PREFER TO STAND

[skip to pg 58]

Q YOU HAVE DONE FOR MOST OF THE MAJOR CHEMICAL COMPANY. IS THAT TRUE?
A AND DRUG COMPANIES.
Q YOU'VE DONE WORK ON BEHALF OF DOW?
A DOW.
Q YOU WERE INVOLVED IN THE AGENT ORANGE LITIGATION ON BEHALF OF DOW, WERE YOU NOT?
A YES.
Q AND IT WAS YOUR OPINION THAT AGENT ORANGE IS NOT NEUROTOXIC.
A IT'S NOT.
Q THAT'S YOUR OPINION.
A WELL, IT'S NOT.
Q WHAT ABOUT DIOXIN AND AGENT ORANGE? DO YOU HAVE AN OPINION WHETHER THAT IS NEUROTOXIC?
A DIOXIN CAUSES SKIN DISEASE AND LIVER DISEASE, BUT I THINK IT'S ALMOST CERTAINLY PROVEN NOW, DOES NOT EFFECT THE NERVOUS SYSTEM.
Q SO ALL OF THE VETERANS WHO HAVE MADE COMPLAINTS ABOUT PSYCHOLOGICAL AND PSYCHIATRIC CONSEQUENCES, YOU DISCOUNT THOSE COMPLAINTS AND ALL OF THE STUDIES THAT DO SUGGEST THAT THERE IS A NEUROTOXIC AFFECT OF EITHER THE 2,4 D OR 2,4,5 T IN THE DIOXIN?
A THE ANSWER IS YES. I DISCOUNT THE FACT THAT IT'S DUE TO THE TOXIC EFFECT, BUT I DON'T DISCOUNT THE

CLAIMS. THE CLAIMS WERE VERY REAL AND THESE MEN ARE PSYCHIATRICALLY IMPAIRED. BUT THAT'S -- THERE IS A REACTION TO THIS THING. IT'S THE SAME -- EXACTLY THE SAME PROBLEM IS THE PERSIAN GULF SYNDROME WHERE I'M GOING NEXT WEEK TO WORK FOR THE GOVERNMENT TO TRY TO STRAIGHTEN THAT OUT TO TRY TO FIGURE OUT WHAT'S REAL AND WHAT'S NOT REAL. PEOPLE FROM VIETNAM WHO WERE EXPOSED TO AGENT ORANGE HAS A REAL PSYCHIATRIC DISEASE. THEY HAVE A POST-TRAUMATIC STRESS DISORDER, AND IT CAN RUIN THEIR LIVES. BUT IT'S NOT A REAL -- IT'S NOT BECAUSE THE CHEMICAL HAS DAMAGED THEIR BRAINS, BUT THEY REALLY HAVE GROUNDS FOR, AS FAR AS I'M CONCERNED, FOR GETTING COMPENSATION.

Q THERE ARE AUTHORITIES, THOUGH, WHO DISAGREE WITH YOU WITH RESPECT TO THE NEUROTOXIC PROPERTIES OF AGENT ORANGE, ARE THERE NOT?

A I THINK THEY ARE FALLING -- THE NEW STUDY DR. SWEENEY'S STUDY IS IN, I THINK THAT --

Q I BELIEVE MY QUESTION WAS, ARE THERE AUTHORITIES WHO DISAGREE WITH YOU IN THAT RESPECT?

THE COURT: YOU MAY ANSWER THE QUESTION, IF YOU BELIEVE IT'S AN ACCURATE ANSWER.

A I'M SORRY. AGAIN, MR. REICH, I'M MORE ACCUSTOMED TO LECTURE HALL.

YES, THERE ARE PEOPLE WHO DISAGREE WITH ME.

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

HEALTH AFFAIRS

AUG 15 1994

Honorable John D. Rockefeller IV
Chairman, Committee on Veterans' Affairs
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

Thank you for your letter dated July 19, 1994, regarding the military use of pyridostigmine and the National Institutes of Health (NIH) Technology Assessment Workshop on the Persian Gulf Experience and Health.

Concerning the alleged financial conflicts of interest among DoD personnel who were involved in DoD sponsored research on pyridostigmine, and of those DoD individuals who were involved in the decision to issue pyridostigmine to military personnel in the Persian Gulf War, we would be pleased to look into these matters if you would provide to the Department specific allegations of improprieties.

With regard to the selection of panelists for the NIH workshop and copies of conflict of interest statements, the NIH Office of Medical Applications of Research was responsible for the planning and execution of the workshop. That office should be able to provide you with a description of the selection process and other desired documentation concerning this workshop. To facilitate this, I will forward your letter to the Director, NIH requesting that he address the concerns you have raised.

If I may be of further assistance in this important matter please contact me directly or members of my staff.

Sincerely,

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

cc:
Honorable Frank Murkowski,
Ranking Republican

COPY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

March 16, 1994

John Ferguson, M.D.
Director
Office of Medical Applications
of Research
National Institutes of Health
Federal Building, Room 618
Bethesda, Maryland 20892

Dear Dr. Ferguson:

At your request, I am writing to identify any real or apparent conflicts of interest related to my participation as a panel member in the upcoming NIH Technical Assessment Workshop on the Persian Gulf Experience and Health to be held on April 27-29. In this regard, please be advised that I am disclosing below any publications, public positions, or memberships as well as any personal financial interests (including equity positions, consulting agreements, or employment arrangements) related to the issues under discussion at the workshop.

✓ I have no financial interests or advocacy position related to the issues under discussion.

X My relevant financial interests are:

NONE

X My relevant publications, public positions, or memberships are:

NONE

Print name HERBERT H. SCHAUMBURG, M.D.

Signature

Date MARCH 29, 1994

COPY

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