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IS MILITARY RESEARCH HAZARDOUS TO VETERANS' HEALTH? LESSONS SPANNING HALF A CENTURY

A STAFF REPORT PREPARED FOR THE

COMMITTEE ON VETERANS' AFFAIRS

UNITED STATES SENATE

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FOREWORD

U.S. Senate,
Committee on Veterans' Affairs,
Washington, DC, December 8, 1994.

During the last few years, the public has become aware of several examples where U.S. Government researchers intentionally exposed Americans to potentially dangerous substances without their knowledge or consent. The Senate Committee on Veterans' Affairs, which I have been privileged to chair from 1993-94, has conducted a comprehensive analysis of the extent to which veterans participated in such research while they were serving in the U.S. military. This resulted in two hearings, on May 6, 1994, and August 5, 1994.

This report, written by the majority staff of the Committee, is the result of that comprehensive investigation, and is intended to provide information for future deliberations by the Congress. The findings and conclusions contained in this report are those of the majority staff and do not necessarily reflect the views of the members of the Committee on Veterans' Affairs.

This report would not have been possible without the dedication and expertise of Dr. Patricia Olson, who, as a Congressional Science Fellow, worked tirelessly on this investigation and report, and the keen intelligence, energy, and commitment of Dr. Diana Zuckerman, who directed this effort.

JOHN D. ROCKEFELLER IV, *Chairman.*

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IS MILITARY RESEARCH HAZARDOUS TO VETERANS' HEALTH? LESSONS SPANNING HALF A CENTURY

I. INTRODUCTION

During the last 50 years, hundreds of thousands of military personnel have been involved in human experimentation and other intentional exposures conducted by the Department of Defense (DOD), often without a servicemember's knowledge or consent. In some cases, soldiers who consented to serve as human subjects found themselves participating in experiments quite different from those described at the time they volunteered. For example, thousands of World War II veterans who originally volunteered to "test summer clothing" in exchange for extra leave time, found themselves in gas chambers testing the effects of mustard gas and lewisite.[1] Additionally, soldiers were sometimes ordered by commanding officers to "volunteer" to participate in research or face dire consequences. For example, several Persian Gulf War veterans interviewed by Committee staff reported that they were ordered to take experimental vaccines during Operation Desert Shield or face prison.[2]

The *goals* of many of the military experiments and exposures were very appropriate. For example, some experiments were intended to provide important information about how to protect U.S. troops from nuclear, biological, and chemical weapons or other dangerous substances during wartime. In the Persian Gulf War, U.S. troops were intentionally exposed to an investigational vaccine that was intended to protect them against biological warfare, and they were given pyridostigmine bromide pills in an experimental protocol intended to protect them against chemical warfare.

However, some of the studies that have been conducted had more questionable motives. For example, the Department of Defense (DOD) conducted numerous "man-break" tests, exposing soldiers to chemical weapons in order to determine the exposure level that would cause a casualty, i.e., "break a man."[3] Similarly, hundreds of soldiers were subjected to hallucinogens in experimental programs conducted by the

[1]Veterans at Risk: The Health Effects of Mustard Gas and Lewisite, Pechura, C.M. & Rall, D.P. (Eds.) Institute of Medicine, National Academy Press, Washington, DC, 1993, p. 65.

[2]In a survey of 150 Persian Gulf War veterans conducted by Committee staff, 15 of 17 military personnel receiving botulinum toxoid in the Gulf war were told they could not refuse the vaccination; 54 of 73 military personnel receiving pyridostigmine were told they could not refuse the drug.

[3]Veterans at Risk, op. cit., p. 36.

DOD in participation with, or sponsored by, the CIA.[4,5] These servicemembers often unwittingly participated as human subjects in tests for drugs intended for mind-control or behavior modification, often without their knowledge or consent. Although the ultimate goal of those experiments was to provide information that would help U.S. military and intelligence efforts, most Americans would agree that the use of soldiers as unwitting guinea pigs in experiments that were designed to harm them, at least temporarily, is not ethical.

Whether the goals of these experiments and exposures were worthy or not, these experiences put hundred of thousands of U.S. servicemembers at risk, and may have caused lasting harm to many individuals.

Every year, thousands of experiments utilizing human subjects are still being conducted by, or on behalf of, the DOD. Many of these ongoing experiments have very appropriate goals, such as obtaining information for preventing, diagnosing, and treating various diseases and disabilities acquired during military service. Although military personnel are the logical choice as human subjects for such research, it is questionable whether the military hierarchy allows for individuals in subordinate positions of power to refuse to participate in military experiments. It is also questionable whether those who participated as human subjects in military research were given adequate information to fully understand the potential benefits and risks of the experiments. Moreover, the evidence suggests that they have not been adequately monitored for adverse health effects after the experimental protocols end.

Veterans who become ill or disabled due to military service are eligible to receive priority access to medical care at VA medical facilities and to receive monthly compensation checks. In order to qualify, they must demonstrate that their illness or disability was associated with their military service. Veterans who did not know that they were exposed to dangerous substances while they were in the military, therefore, would not apply for or receive the medical care or compensation that they are entitled to. Moreover, even if they know about the exposure, it would be difficult or impossible to prove if the military has not kept adequate records. It is therefore crucial that the VA learn as much as possible about the potential exposures, and that the DOD assume responsibility for providing such information to veterans and to the VA.

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[4]Testimony of Deanne Siemer, general counsel, Department of Defense, hearing before the Subcommittee on Health and Scientific Research, Committee on Human Resources, U.S. Senate, "Human Drug Testing by the CIA, 1977," September 20-21, 1977, pp. 157-168.

[5]Testimony of Sidney Gottlieb, M.D., former CIA agent, hearing before the Subcommittee on Health and Scientific Research, Committee on Human Resources, U.S. Senate, "Human Drug Testing by the CIA, 1977," September 20-21, 1977, pp. 169-217.

II. BACKGROUND

A. CODES, DECLARATIONS, AND LAWS GOVERNING HUMAN EXPERIMENTATION

The Nuremberg Code is a 10-point declaration governing human experimentation, developed by the Allies after World War II in response to inhumane experiments conducted by Nazi scientists and physicians. The Code states that voluntary and informed consent is absolutely essential from all human subjects who participate in research, whether during war or peace. The Code states:

> The person involved should have the legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health and person which may possibly come from his participation in the experiments.[6]

There is no provision in the Nuremberg Code that allows a country to waive informed consent for military personnel or veterans who serve as human subjects in experiments during wartime or in experiments that are conducted because of threat of war. However, the DOD has recently argued that wartime experimental requirements differ from peacetime requirements for informed consent. According to the Pentagon, "In all peacetime applications, we believe strongly in informed consent and its ethical foundations.....But military combat is different."[7] The DOD argued that informed consent should be waived for investigational drugs that could possibly save a soldier's life, avoid endangerment of the other personnel in his unit, and accomplish the combat mission.

More than a decade after the development of the Nuremberg Code, the World Medical Association prepared recommendations as a guide to doctors using human subjects in biomedical research. As a result, in 1964 the Eighteenth World Medical Assembly met in Helsinki, Finland, and adopted recommendations to be used as an ethical code by all medical doctors conducting biomedical research with human subjects. This code, referred to as the Declaration of Helsinki, was

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[6]The Nuremberg Code, from Trials of War Criminals before the Nuremberg Military Tribunals, U.S. Government Printing Office, Washington, DC, 1948.

[7]55 Federal Register 52,814-52,817 (December 21, 1990), "Informed Consent for Human Drugs and Biologics: Determinations that Informed Consent is Not Feasible."

revised in 1975, 1983, and 1989.[8] It differs from the Nuremberg Code in certain important respects. The Declaration of Helsinki distinguishes between clinical (therapeutic) and nonclinical (nontherapeutic) biomedical research, and addresses "proxy consent" for human subjects who are legally incompetent, such as children or adults with severe physical or mental disabilities.[9] Proxy consent for legally competent military personnel who participate in military research is *not* considered appropriate under the Nuremberg Code or the Declaration of Helsinki.

On June 18, 1991, the Federal Government announced that 16 U.S. governmental agencies would abide by a set of regulations, referred to as the "Common Rule," designed to protect human subjects who participate in federally funded research.[10] The provisions of the "Common Rule," first promulgated for the Department of Health and Human Services (DHHS) in 1974, described how federally funded research involving human subjects shall be conducted. However, local Institutional Review Boards (IRB's) may revise or exclude some or all consent elements if the research exposes subjects to no more than "minimal risk," meaning "that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[11] IRB's vary greatly in their interpretation of the risks of daily life.

There are three provisions governing research funded by DHHS that are intended to protect vulnerable populations, such as pregnant women and fetuses, prisoners, and children.[12] There are no special Federal regulations to protect military personnel when they participate as human subjects in federally funded research, despite logical questions about whether military personnel can truly "volunteer" in response to a request from a superior officer.

Current law prevents the Department of Defense from using Federal funds for research involving the use of human experimental subjects, unless the subject gives informed consent in advance. This law applies regardless of whether the research is intended to benefit the subject.[13]

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[8]Declaration of Helsinki, in European and Nordic Regulations and Guidelines for Good Clinical Practice, Pharmaco Dynamics Research, Inc., July 1990.

The Declaration of Helsinki was amended at the Twenty-Ninth World Medical Assembly held in Tokyo, Japan, in 1975, the Thirty-Fifth World Medical Assembly held in Venice, Italy, in 1983, and the Forty-First World Medical Assembly held in Hong Kong in 1989.

[9]Declaration of Helsinki, World Medical Association, in Biomedical Ethics, Third Edition, Mappes, T.A. & Zembaty, J.S., McGraw-Hill, Inc., 1991, pp. 211-213.

[10]56 Federal Register 28,002-28,032 (June 18, 1991), "Federal Policy for the Protection of Human Subjects."

[11]"Research Involving Human Subjects," statement of Robyn Y. Nishimi, Ph.D., Office of Technology Assessment, hearing before the Subcommittee on Energy, Committee on Science, Space, and Technology, U.S. House of Representatives, "Human Radiation, Experimentation, and Gene Therapy," February 10, 1994.

[12]45 CFR §46 (Public Welfare), subparts B,C, and D, revised October 1, 1991.

[13]10 U.S.C. (Armed Forces) and 32 U.S.C. § 980 (National Guard) put limits on the use of humans as experimental subjects.

B. MUSTARD GAS AND LEWISITE

According to a report published by the Institute of Medicine (IOM) last year, approximately 60,000 military personnel were used as human subjects in the 1940's to test two chemical agents, mustard gas and lewisite. Most of these subjects were not informed of the nature of the experiments and never received medical followup after their participation in the research.[14] Additionally, some of these human subjects were threatened with imprisonment at Fort Leavenworth if they discussed these experiments with anyone, including their wives, parents, and family doctors.[15] For decades, the Pentagon denied that the research had taken place, resulting in decades of suffering for many veterans who became ill after the secret testing. According to the 1993 IOM report, such denial by the DOD continues: "This committee discovered that an atmosphere of secrecy still exists to some extent regarding the WWII testing programs. Although many documents pertaining to the WWII testing programs were declassified shortly after the war ended, others were not."[16]

Based on findings from the National Academy of Sciences, the Department of Veterans Affairs recently published a final rule to compensate veterans for disabilities or deaths resulting from the long-term effects of inservice exposure to mustard gas and other agents which blister the skin (these are called vesicants).[17] The final rule expands coverage to veterans exposed to mustard gas under battlefield conditions in World War I (WWI), those present at the German air raid on the harbor of Bari, Italy (WWII), and those engaged in manufacturing and handling vesicant agents during their military service. Thus, for the first time, VA will compensate certain veterans for illnesses which may have been caused by their exposure to vesicants over half a century ago.

C. SEVENTH-DAY ADVENTISTS

Many experiments that tested various biological agents on human subjects, referred to as Operation Whitecoat, were carried out at Fort Detrick, MD, in the 1950's. The human subjects originally consisted of volunteer enlisted men. However, after the enlisted men staged a sitdown strike to obtain more information about the dangers of the biological tests, Seventh-Day Adventists who were conscientious objectors were recruited for the studies.[18] Because these individuals did not believe in engaging in actual combat, they instead volunteered to be human subjects in military research projects that tested various infectious agents. At least 2,200 military personnel who were

[14]Veterans at Risk, op. cit., pp. 3-4, 6-8, 50-52, 224-226.

[15]Ibid., p. 65.

[16]Ibid., p. 7.

[17]59 Federal Register 41,497-42,500 (August 18, 1994), "Claims Based on Chronic Effects of Exposure to Vesicant Agents."

[18]Gene Wars, Military Control Over the New Genetic Technologies, Piller, C. & Yamamoto, K.R., Beech Tree Books, William Morrow, New York, 1988, pp 44-45, 53.

Seventh-Day Adventists volunteered for biological testing during the 1950's through the 1970's.[19]

Unlike most of the studies discussed in this report, Operation Whitecoat was truly voluntary. Leaders of the Seventh-Day Adventist Church described these human subjects as "conscientious participants," rather than "conscientious objectors," because they were willing to risk their lives by participating in research rather than by fighting a war.[20,21]

D. DUGWAY PROVING GROUND

Dugway Proving Ground is a military testing facility located approximately 80 miles from Salt Lake City. For several decades, Dugway has been the site of testing for various chemical and biological agents. From 1951 through 1969, hundreds, perhaps thousands of open-air tests using bacteria and viruses that cause disease in human, animals, and plants were conducted at Dugway.[22] For example, antigens produced by animals that had come in contact with Venezuelan equine encephalomyelitis (VEE), a disease usually found in horses, were later found in animals around Dugway. Prior to the identification of these substances in the Dugway vicinity, VEE had only been identified in the rat population in Florida. Such a finding suggested that VEE had been used in the open-air tests at Dugway or within laboratories, and transferred to the nearby animal population.[23]

In 1968, approximately 6,400 sheep died following the intentional release of a deadly nerve gas from a plane. According to a veterinarian who evaluated the sick and dying sheep, there was little doubt that the sheep had been poisoned with nerve gas.[24] The sheep and other animals in the area had depressed cholinesterase levels, suggesting organophosphate nerve poisoning. Initially, the Department of Defense denied any responsibility for the accident, stating that the sheep died from organophosphate pesticides sprayed on a nearby alfalfa field. However, the nerve agent VX was identified when the poisoned sheep were autopsied, which made it clear that the deaths were not caused by pesticides.[25] Eventually, the Department of Defense reimbursed the ranchers for their animals.

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[19]Ibid.

[20]Ibid.

[21]At least one Seventh-Day Adventist Church has held reunions of those human subjects who participated in Operation Whitecoat. (Phone interview by Committee staff with Dr. Frank Damazo, Frederick, MD, March 21, 1994.)

[22]Hearing before the Subcommittee on Conservation and Natural Resources, Committee on Government Operations, U.S. House of Representatives, "Environmental Dangers of Open-Air Testing of Lethal Chemicals," May 20-21, 1969.

[23]Ibid., pp. 6-7.

[24]Testimony of Dr. D.A. Osguthorpe, veterinarian and consultant to Utah State Department of Agriculture, hearing before the Subcommittee on Conservation and Natural Resources, Committee on Government Operations, U.S. House of Representatives, "Environmental Dangers of Open-Air Testing of Lethal Chemicals," May 20-21, 1969, pp 63-66.

[25]Ibid., pp. 64-65.

It is unknown how many people in the surrounding vicinity were also exposed to potentially harmful agents used in open-air tests at Dugway. In 1969, concerns were expressed at a congressional hearing about the possible public health implications of the VEE virus tested at Dugway.[26]

Due to previous problems with dangerous organisms and chemicals, Dugway has developed an active program of "simulant" testing. According to the Department of Defense, simulants are harmless organisms or chemicals which do not cause disease. However, during 45 years of open-air testing, the Army has stopped using a variety simulants when they realized they were not as safe as previously believed.[27]

E. RADIATION EXPOSURE

Atomic Veterans

From 1945 to 1962, the United States conducted numerous nuclear detonation tests: Crossroads (Bikini); Sandstone, Greenhouse, and Ivy (Eniwetok Atoll); Castle (Bikini Atoll); Pacific Ocean 400 miles southwest of San Diego; Redwing and Hardtack I (Eniwetok and Bikini Atolls); Argus (South Atlantic); and Dominic (Christmas Island, Johnston Island, 400 miles west of San Diego).[28] The main goal was to determine damage caused by the bombs; however, as a result, thousands of military personnel and civilians were exposed to radioactive fallout. Similar tests were conducted within the continental United States, including sites in New Mexico and Nevada.[29] Veterans who participated in activities that directly exposed them to radioactive fallout are referred to as "atomic veterans."

Data obtained on some military personnel who were exposed to radioactive fallout were collected after these men were unintentionally exposed. However, some atomic veterans believe they were used as guinea pigs to determine the effects of radiation from various distances, including those at ground zero, on human subjects. Their suspicions are supported by a 1951 document from the Joint Panel on the Medical Aspects of Atomic Warfare, Research and Development Board, Department of Defense, which identified general criteria for bomb test-related "experiments" and identified 29 "specific problems" as "legitimate basis for biomedical participation."[30]

[26]Testimony of Hon. Richard D. McCarthy, a Representative in Congress from the State of New York, hearing before the Subcommittee on Conservation and Natural Resources, Committee on Government Operations, U.S. House of Representatives, "Environmental Dangers of Open-Air Testing of Lethal Chemicals," May 20-21, 1969, pp 6-7.

[27]Cole, L.A., "Risk and biological defense program," *Physicians for Social Responsibility Quarterly*, Vol 2, No. 1, March 1992, pp. 40-50.

[28]Compilation of Local Fallout Data From Test Detonations 1945-1962, extracted From DASA 1251, Vol I-Oceanic U.S. Tests, Contract No. DNA 001-79-C-0081, May 1, 1979, sponsored by the Defense Nuclear Agency.

[29]Ibid.

[30]Secret document, Department of Defense, Research and Development Board, Committee on Medical Sciences, Joint Panel on the Medical Aspects of Atomic Warfare, 8th Meeting, Washington, DC, February 24, 1951.

The National Research Council's Committee on the Biological Effects of Ionizing Radiation (BEIR) have prepared a series of reports to advise the U.S. Government on the health consequences of radiation exposure.[31] The first of these reports was not published until the late 1980's, decades after military personnel were first exposed to ionizing radiation. For the last 13 years, the VA has provided free medical care to atomic veterans who have disorders they believe to be caused by ionizing radiation, even if there is no conclusive evidence of the cause.[32] In addition, the VA provides monthly compensation to veterans who were exposed to ionizing radiation during military service, who have illnesses that are believed to be associated with their exposure. The lists of compensable diseases have been revised as more research information has become available. For example, on October 11, 1994, the VA announced that tumors of the brain and central nervous system would be considered for disability compensation for veterans exposed to ionizing radiation.[33]

Radiation Releases at U.S. Nuclear Sites

In addition to detonation testing, radioactive releases were also intentionally conducted at U.S. nuclear sites in the years following World War II. According to the U.S. General Accounting Office (GAO), at least 12 planned radioactive releases occurred at three U.S. nuclear sites during 1948-1952. These tests were conducted at Oak Ridge, TN; Dugway, UT; and Los Alamos, NM.[34] Additionally, a planned release occurred at Hanford, WA, in December 1949, which has been referred to as the Green Run test. It is not known how many civilians and military personnel were exposed to fallout from these tests.

Other Exposures to Ionizing Radiation

In January 1994, the Clinton administration established a Human Radiation Interagency Working Group to coordinate a Government-wide effort to uncover the nature and extent of any Government-sponsored experiments on individuals involving intentional exposure to ionizing radiation. The working group represents the Administration's response to Secretary of Energy Hazel O'Leary's promise to comb Government files for information on hundreds of experiments conducted on people in the 1940's and 1950's.

To assist in identifying those people who may have been harmed by secret experiments utilizing ionizing radiation, the Clinton administration solicited complaints from possible victims by installing several telephone hotlines. As of September 1994, 86 percent of the

[31]"Health Effects of Exposure to Low Levels of Ionizing Radiation," BEIR V, National Research Council, National Academy Press, Washington, DC, 1990.

[32]Letter from Hon. Jesse Brown, Secretary of Veterans Affairs, to Sen. John D. Rockefeller IV, Chair, Senate Committee on Veterans' Affairs, May 31, 1994.

[33]News release, Office of Public Affairs, Department of Veterans Affairs, Washington, DC, October 11, 1994.

[34]"Nuclear Health and Safety, Examples of Post World War II Radiation Releases at U.S. Nuclear Sites," U.S. General Accounting Office, November 1993, GAO/RCED-94-51FS.

21,996 callers to the radiation hotline were veterans who believed they had participated in various radiation "experiments."[35]

A VA advisory committee has concluded that activities other than atomic weapons tests and occupation force activities resulted in the exposure of veterans to ionizing radiation during their military service prior to 1970.[36] The committee concluded that the records for many individuals who were exposed to such activities are inadequate or inaccessible. Additionally, the committee concluded that information pertinent to military exposures is not always adequate to evaluate the health risks.

F. HALLUCINOGENS

Working with the CIA, the Department of Defense gave hallucinogenic drugs to thousands of "volunteer" soldiers in the 1950's and 1960's. In addition to LSD, the Army also tested quinuclidinyl benzilate, a hallucinogen code-named BZ.[37] Many of these tests were conducted under the so-called MKULTRA program, established to counter perceived Soviet and Chinese advances in brainwashing techniques. Between 1953 and 1964, the program consisted of 149 projects involving drug testing and other studies on unwitting human subjects.[38]

One test subject was Lloyd B. Gamble, who enlisted in the U.S. Air Force in 1950. In 1957, he volunteered for a special program to test new military protective clothing. He was offered various incentives to participate in the program, including a liberal leave policy, family visitations, and superior living and recreational facilities. However, the greatest incentive to Mr. Gamble was the official recognition he would receive as a career-oriented noncommissioned officer, through letters of commendation and certification of participation in the program. During the 3 weeks of testing new clothing, he was given two or three water-size glasses of a liquid containing LSD to drink. Thereafter, Mr. Gamble developed erratic behavior and even attempted suicide. He did not learn that he had received LSD as a human subject until 18 years later, as a result of congressional hearings in 1975.[39] Even then, the Department of the Army initially denied that he had participated in the experiments, although an official DOD publicity photograph showed him as one of the valiant

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[35]Information from the Office of the Assistant Secretary for Congressional Affairs, Department of Veterans Affairs, received at the Senate Committee on Veterans' Affairs, September 21, 1994; in Committee files.

[36]Letter from Hon. Jesse Brown, Secretary of Veterans Affairs, to Sen. John D. Rockefeller IV, Chair, U.S. Senate Committee on Veterans' Affairs, May 26, 1994.

[37]Gene Wars, op. cit., pp 50-51.

[38]Statement of David Gries, Director, Center for the Study of Human Intelligence, CIA, hearing before the Subcommittee on Administrative Law and Governmental Relations, Committee on the Judiciary, U.S. House of Representatives, "Government-Sponsored Tests on Humans and Possible Compensation for People Harmed in the Tests," February 2, 1994.

[39]Summary of testimony, Lloyd B. Gamble, LSD test subject, hearing before the Subcommittee on Administrative Law and Governmental Relations, Committee on the Judiciary, U.S. House of Representatives, "Government-Sponsored Tests on Humans and Possible Compensation for People Harmed in the Tests," February 2, 1994.

servicemen volunteering for "a program that was in the highest national security interest."[40]

According to Sidney Gottlieb, a medical doctor and former CIA agent, MKULTRA was established to investigate whether and how an individual's behavior could be modified by covert means.[41] According to Dr. Gottlieb, the CIA believed that both the Soviet Union and Communist China might be using techniques of altering human behavior which were not understood by the United States. Dr. Gottlieb testified that "it was felt to be mandatory and of the utmost urgency for our intelligence organization to establish what was possible in this field on a high priority basis." Although many human subjects were not informed or protected, Dr. Gottlieb defended those actions by stating, "...harsh as it may seem in retrospect, it was felt that in an issue where national survival might be concerned, such a procedure and such a risk was a reasonable one to take."[42]

G. INVESTIGATIONAL DRUGS USED IN THE PERSIAN GULF WAR

Under the Food, Drug, and Cosmetics Act, all vaccines and medical products must be proven safe and effective by the Food and Drug Administration (FDA) in order to be sold and distributed in the United States. This law also applies to medical products used by the Department of Defense, even if given to U.S. troops who are stationed in other countries.

FDA also regulates medical products that are proven safe and effective for some uses or with specific doses, but not for other uses or other doses. If the product is only sold at certain doses and not others, its use at the non-approved dose would be considered investigational. If the product is legally available for sale at the same dosage, physicians can legally prescribe it; however, manufacturers can not advertise it for that purpose. Such "off label" use is also considered investigational. So, for example, a drug may be proven safe and effective to treat one kind of cancer, but be considered investigational to treat a different disease.

Under current law, an unapproved vaccine or investigational use of a drug could only be administered by the DOD under an Investigational New Drug (IND) procedure.[43] Under an IND, any individual who is given the investigational product must give informed consent, i.e., must be told of the potential risks and benefits of the product, orally and in writing, and choose freely whether or not to participate. In addition, the IND requires that the medical product be distributed under carefully controlled conditions where safety and effectiveness can be evaluated.

When the Department of Defense began preparations for Desert Shield and Desert Storm in 1990, officials were extremely concerned that Iraq would use chemical and biological weapons against the

[40]Ibid.

[41]Testimony of Sidney Gottlieb, M.D., former CIA agent, before the Subcommittee on Health and Scientific Research, Committee on Human Resources, U.S. Senate, "Human Drug Testing by the CIA, 1977," September 20-21, 1977, p. 169. Actual wording is "convert means," which we took to mean "covert means."

[42]Ibid., pp. 169-217.

[43]55 Federal Register 52,814-52,817 (December 21, 1990).

United States. Despite years of study and billions of dollars, the DOD lacked drugs and vaccines that were proven safe and effective to safeguard against anticipated chemical nerve agents and biological toxins. Therefore, DOD officials wanted to use a medication (pyridostigmine bromide) and vaccine (botulinum toxoid) that they believed might protect against chemical nerve agents and botulism. Because the safety and effectiveness of pyridostigmine bromide and botulinum toxoid had not been proven for their intended use, these products were considered investigational drugs.

Pyridostigmine bromide is a chemical which enhances the effectiveness of two drugs, atropine and 2-PAM, which are proven effective for the treatment of nerve agent poisoning.[44] Pyridostigmine is also a nerve agent itself. Nerve agents exert their biological effects by binding to, and inhibiting, the enzyme acetylcholinesterase (AChE) which normally shuts off the neurotransmitter, acetylcholine (ACh). When levels of ACh increase, nerve impulses and organ activity increase. When nerve and organ stimulation are excessive, death can result.

There are two major categories of nerve agents, carbamates and organophosphate (OP) compounds.[45] German scientists developed many of the OP compounds for warfare agents and pesticides in the 1930's and 1940's. Examples of warfare agents include tabun, sarin, soman, and VX. Many organophosphates *permanently* inhibit AChE. This permanent effect, which can only be reversed when new enzymes are synthesized, makes OP warfare agents extremely lethal.

Pyridostigmine bromide is a carbamate, rather than an OP compound.[46] Although it is a nerve agent, pyridostigmine has a *reversible* effect which can protect the AChE from permanently binding to OP compounds. When appropriate doses are selected, pyridostigmine theoretically should not cause nerve agent poisoning and should help protect against some lethal chemical warfare.

Efficacy. Pyridostigmine only works when taken in combination with other drugs and only if taken *before* exposure to nerve gas.[47] Two antidotes to nerve agents, atropine and pyridine-2-aldoxime methochloride (2-PAM), are reportedly enhanced if pyridostigmine has already been given. Atropine and 2-PAM were included in the nerve agent antidote kits (Mark I) which were issued to U.S. troops in the Persian Gulf.

In research studies, animals given pyridostigmine, atropine, and 2-PAM were more likely to survive exposure to one chemical nerve agent, soman, than those given only atropine and 2-PAM. However, pyridostigmine is unable to enter and protect the brain, so that animals exposed to soman can still suffer from convulsions despite the pyridostigmine pretreatment.[48] To protect against brain damage from ongoing seizure activity, valium may also be required following

[44]Sidell, F.R., "Clinical Considerations in Nerve Agent Intoxication," Chemical Warfare Agents, Somani, S.M. (Ed.), Academic Press, Inc., 1992, pp. 155-194.

[45]Ibid.

[46]Ibid.

[47]Ibid.

[48]Ibid.

exposure to a warfare nerve agent. Similarly, pyridostigmine may offer little protection against the damage caused by nerve agents in the spinal cord.[49]

Safety. Pyridostigmine bromide is approved by the FDA for treating myasthenia gravis, a neurological disease characterized by extreme weakness. This disease occurs when individuals develop antibodies that prevent ACh from causing muscle impulses at the neuromuscular junction. Therefore, treatment with relative high doses of pyridostigmine increases ACh to levels that are able to overcome the "block" created by the antibodies. An analogy might be that of a fishing pond. The two ways to increase the number of fish caught are to increase the number of fishing poles or to increase the number of fish in the pond.

FDA and DOD officials claimed they were confident of the safety of pyridostigmine as an antidote enhancer for chemical warfare protection because it would be used at a much lower dose[50] in combat than normally used for treating patients with myasthenia gravis. However, normal patients and those with myasthenia gravis may not respond similarly to the same dose of pyridostigmine bromide. Whereas the dosage of pyridostigmine bromide for patients with myasthenia gravis may reach 120 mg every three hours,[51] the dose for U.S. troops was only 30 mg every 8 hours. A good analogy is the use of insulin for diabetes mellitus; very high doses of insulin are sometimes necessary to treat diabetics, but similar doses could be fatal for non-diabetic individuals.

Some scientists also question whether pyridostigmine is completely safe even for treating patients with myasthenia gravis. The proportion of patients with myasthenia gravis that recover after surgical treatment (thymectomy) has decreased since pyridostigmine therapy was introduced several decades ago.[52] Experts speculate that whereas the problems caused by myasthenia gravis can be corrected by surgery, pyridostigmine may cause immune damage to the neuromuscular junction that cannot be corrected by surgery. Since the symptoms of pyridostigmine damage would be similar to the symptoms of myasthenia gravis, any damage from the pyridostigmine would be extremely difficult if not impossible to diagnose.

In addition to its use for myasthenia gravis, pyridostigmine bromide has been approved by FDA for use with surgical patients; it is administered after surgery to reverse the effect of anesthesia, which are neuromuscular blocking agents. The dose is relatively small (15 mg) and not repeated. This treatment does not provide relevant information about the safety of repeated use of pyridostigmine by

[49]Das Gupta, S., Bass, K.N., Warnick, J.E. "Interaction of reversible and irreversible cholinesterase inhibitors on the monosynaptic reflex in neonatal rats," *Toxicology and Applied Pharmacology*, Vol. 99, 1989, pp. 28-36.

[50]55 Federal Register 52,814-52,817 (December 21, 1990).

[51]Drachman, D.B. "Medical Progress, review article: Myasthenia gravis," *New England Journal of Medicine*, Vol. 330, No. 25, June 23, 1994, pp. 1797-1810.

[52]Scadding, G.K., Havard, C.W.H., Lange, M.J., & Domb, I. "The long term experience of thymectomy for myasthenia gravis," *Journal of Neurology, Neurosurgery, and Psychiatry*, Vol. 48, 1985, pp. 401-406.

healthy individuals, since the dosage is small and the patients have received neuromuscular blocking agents.

The bromide that is included in pyridostigmine bromide pills is known to sometimes cause problems referred to as "bromide intoxication" when used for the treatment of myasthenia gravis.[53] Bromide intoxication may cause confusion, irritability, tremor, memory loss, psychotic behavior, ataxia, stupor, and coma. Some patients with bromide intoxication have a skin disorder of the face and hands resembling acne. A 60 mg tablet of the commercially available pyridostigmine bromide contains 18.4 mg bromide (30.6 percent).[54,55]

FDA has not approved pyridostigmine bromide for repeated use in healthy individuals as an antidote enhancer or for any other reason. Since it would be unethical to expose individuals to potentially lethal chemical weapons in order to evaluate the *efficacy* of pyridostigmine, this use has only been studied on animals. The product is therefore an investigational drug when used as an antidote enhancer for treating nerve gas poisoning.

Botulinum toxoid is an unapproved vaccine that is used to protect laboratory workers and others who are likely to be exposed to botulism. Botulism is caused by at least one of seven neurotoxins produced by the bacteria Clostridium botulinum. When home-canning of food was common, food poisoning was the most common cause of botulism in the United States; the bacteria in the food produces a toxin which is eaten. Today, the most common form of botulism occurs in infants, since the bacteria that produces the toxin can thrive in a baby's intestinal tract.

A botulism vaccine that is intended to protect against five of seven neurotoxins (called A,B,C,D,E) is produced by the Michigan Department of Health. This is called pentavalent toxoid. This vaccine is not a licensed product and must be distributed as an Investigational New Drug (IND).

Efficacy. Desert Shield began on August 8, 1990. Since the air war did not begin until January 16, 1991, and the ground war took place from February 24-27, 1991, the Pentagon had several months to review the possible use of investigational drugs and vaccines.

In December 1990, the FDA advised the Department of Defense that it would be unable to test the botulism vaccine for efficacy, presumably because of limited time before the onset of the war. The FDA agreed to test the vaccine for safety, but these tests were not completed until late January 1991. At a meeting of the Informed Consent Waiver Review Group (ICWRG) on December 31, 1990, a representative of FDA's Center for Biologics Evaluation and Research discussed the vaccine, explaining that the existing supply was nearly 20 years old and consisted of three lots, stored under continuous

[53]Wacks, I., Oster, J.R., Perez, G.O., & Kett, D.H. "Spurious hyperchloremia and hyperbicarbonatemia in a patient receiving pyridostigmine bromide therapy for myasthenia gravis," *American Journal of Kidney Diseases*, Vol. XVI, No. 1, July 1990, pp. 76-79.

[54]Ibid.

[55]Mestinon is the brand name for one form of pyridostigmine bromide available in the United States.

refrigeration.[56] Given the age of these vaccines, there were concerns about their safety.

The recommended schedule for immunization with the pentavalent vaccine includes a series of three initial injections at 0, 2, and 12 weeks, followed by a booster 12 months after the first injection. According to the Centers for Disease Control's Center for Infectious Diseases, subjects given the vaccine did not have detectable antitoxin titers after the first two shots in the initial series, which means that they were unlikely to be protected at week 2.[57] If for any reason only two immunizations can be given, at least 4 to 8 weeks should elapse between injections if most individuals are to be protected against the disease.[58]

Safety. The Michigan Department of Health reported that 4.2 percent of patients reported a sore arm or other local reactions to the initial series of three shots, and 12.1 percent had local reactions to the booster shots.[59] Almost 3 percent had systemic reactions, such as general malaise, after either the initial three shots or the booster shots. Because of the relatively large percentage of adverse reactions, new lots of the vaccine were manufactured in 1971. However, there is no evidence that the newer lots produced fewer adverse reactions than the older lots.

In her review of the DOD's application for use of botulinum toxoid in the Persian Gulf, an FDA reviewer pointed out that in 1973, the Centers for Disease Control had considered terminating the distribution of the vaccine because of the relatively large number of individuals who had negative reactions to it.[60] The FDA reviewer also pointed out that "there are no efficacy data in humans" and that the dose for humans was an estimate based on results from guinea pigs. In addition, potency testing had suggested that the vaccine would not be effective against two of the five botulism toxins.

According to the Michigan Department of Health, the effects of the botulism vaccine on pregnant women had not been studied prior to its use in the Persian Gulf War.

Anthrax vaccine is an FDA-approved vaccine that is considered safe and effective for individuals whose skin may come in contact with animal products such as hides, hair, or bones likely to contain the anthrax infection. It is also recommended for veterinarians and

[56]Minutes of meeting of the Informed Consent Waiver Review Group (ICWRG), Food and Drug Administration, December 31, 1990.

[57]Ellis, R.J. Immunobiologic agents and drugs available from the Centers for Disease Control: Descriptions, recommendations, adverse reactions, and serologic response. Third Edition. Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA, March 1982.

[58]Middlebrook, J.L. "Contributions of the U.S. Army to Botulinum Toxin Research," Botulinum and Tetanus Neurotoxins, Das Gupta, B.R., (Ed.), Plenum Press, New York, 1993, pp. 515-519.

[59]Informational material for the use of pentavalent (ABCDE) botulinum toxoid aluminum phosphate adsorbed, Protocol #392, Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services, May 1992.

[60]Review by Ann Sutton to the IND record, November 14, 1990; in Committee files.

others who are likely to touch infected animals.[61] However, the vaccine's effectiveness against *inhaled* anthrax is unknown. Unfortunately, when anthrax is used as a biological weapon, it is likely to be aerosolized and thus inhaled. Therefore, the efficacy of the vaccine against biological warfare is unknown.

It appears that there is only one relevant animal study which showed that anthrax vaccine apparently provided additional protection against relapse in monkeys exposed to inhalation anthrax and treated with antibiotics.[62] Although the results of this study suggest the vaccine might protect against anthrax that has been sprayed, it is not sufficient to prove that anthrax vaccine is safe and effective as used in the Persian Gulf. The vaccine should therefore be considered investigational when used as a protection against biological warfare.

The anthrax vaccine is given as three injections 2 weeks apart, followed by three additional injections given 6, 12, and 18 months after the initial injection. If immunity is to be maintained, subsequent booster injections of anthrax vaccine are recommended at 1-year intervals.[63] According to the Interagency Task Force on Persian Gulf War Illnesses, one dose provides some immunity in 85 percent of those individuals vaccinated.[64]

According to the Michigan Department of Public Health which manufactures anthrax vaccine, it is not known whether anthrax vaccine is safe for pregnant women or their offspring.

III. FINDINGS AND CONCLUSIONS

A. FOR AT LEAST 50 YEARS, DOD HAS KNOWINGLY EXPOSED MILITARY PERSONNEL TO POTENTIALLY DANGEROUS SUBSTANCES, OFTEN IN SECRET.

The U.S. General Accounting Office issued a report on September 28, 1994, which stated that between 1940 and 1974, DOD and other national security agencies studied hundreds of thousands of human subjects in tests and experiments involving hazardous substances.[65] GAO stated that some tests and experiments were conducted in secret. Medical research involving the testing of nerve agents, nerve agent antidotes, psychochemicals, and irritants was often classified. Additionally, some work conducted for DOD by contractors still remains classified today. For example, the Central Intelligence Agency (CIA) has not released the names of 15 of the approximately 80 organizations that conducted experiments under the MKULTRA

[61]Informational material for the use of anthrax vaccine adsorbed, Michigan Department of Public Health, U.S. License No. 99, 1978.

[62]Friedlander, A.M., Welkos, S.L., Pitt, M.L.M., et al. "Postexposure prophylaxis against experimental inhalation anthrax," *Journal of Infectious Diseases*, Vol. 167, 1993, pp. 1239-1242.

[63]Anthrax vaccine adsorbed, package insert, Michigan Department of Public Health, Lansing, MI, 1978.

[64]"Summary of the issues impacting upon the health of Persian Gulf War veterans," Version 1.1, March 3, 1994.

[65]"Human Experimentation, An Overview on Cold War Era Programs," U.S. General Accounting Office, September 28, 1994, GAO/T-NSIAD-94-266.

program, which gave psychochemical drugs to an undetermined number of people without their knowledge or consent. According to the GAO report, the CIA has not released this information because the organizations do not want to be identified.[66]

World War II Veterans

As recently as 1993, the Institute of Medicine of the National Academy of Sciences reported that an atmosphere of secrecy still existed regarding World War II testing of mustard gas and lewisite.[67] Although many documents pertaining to the World War II testing programs were declassified shortly after World War II ended, others remain "restricted" even today. In addition to the classified or restricted documents, World War II veterans who participated in the research were sworn to secrecy. These classified documents and promises of secrecy have impeded medical care for thousands of veterans during half of the last century.

For example, Rudolph R. Mills participated in gas chamber experiments as an 18-year-old in 1945, one year after he joined the U.S. Navy.[68] He was sworn to secrecy and did not learn until 46 years later that approximately 4,000 servicemen were human subjects in mustard gas experiments conducted from 1942 through 1945 by the Chemical Warfare Service. Although his health began to deteriorate even before his discharge from the Navy in 1946, he did not learn that mustard gas might be responsible for his physical problems until more than 40 years later.

At a May 6, 1994, hearing of the Senate Committee on Veterans' Affairs, entitled "Is Military Research Hazardous to Veterans' Health? Lessons from World War II, the Persian Gulf War, and Today," Mr. Mills testified, "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....No one ever told me that the mask became less effective against the gas with each use....We were sworn to secrecy....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....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 newspaper."[69]

John T. Harrison participated in Navy chemical tests in 1943 to get an extra week pass. He was also sworn to secrecy. According to written testimony submitted to the Senate Committee on Veterans' Affairs by Mr. Harrison, "[I] was never warned or told anything about the dangers of what [I] volunteered for....told never to reveal what [I] did or where [I] was; if anyone asked [I] was to say [I] was on rowing

[66]Ibid.

[67]Veterans at Risk, op. cit., pp. 7-8.

[68]Statement of Rudolph R. Mills, hearing before the Committee on Veterans' Affairs, U.S. Senate, "Is Military Research Hazardous to Veterans' Health? Lessons from World War II, the Persian Gulf War, and Today," May 6, 1994; hereinafter referred to as Hearing, May 6, 1994.

[69]Ibid.

maneuvers."[70] At the time of his discharge from the military, he could not even describe his exposures to a Navy doctor who was trying to determine the cause of his severe respiratory illnesses. Although Mr. Harrison has suffered from recurrent breathing problems and has greatly diminished pulmonary function, he has never received any compensation for his illness. According to the VA and DOD, his medical and services records have been lost, making it difficult to prove that his disability is service-connected.

Cold War Veterans

During the years immediately following World War II, military personnel were intentionally exposed to radiation during the testing of atomic bombs and during radioactive releases. While it is unclear how many of these servicemembers were intentionally exposed to what were known to be harmful levels of radiation, there is clear evidence that in some cases military personnel were ordered to locate themselves in areas of high radioactive fallout. They were given no choice in the matter, and they were not told of the potential risks of those exposures.

Similarly, military personnel were intentionally given hallucinogenic drugs to determine the effects of those drugs on humans. The servicemembers were not told that they would be given experimental drugs, they had no choice of whether or not to take them, and even after the unusual effects of the drugs were obvious to researchers, the unwitting human subjects were given no information about the known effects of the drugs. Even if the DOD did not know about the potential long-term effects of the drugs, that would not justify their failure to provide information to thousands of servicemembers about the known short-term effects of the drugs.

Persian Gulf War Veterans

Persian Gulf veterans were also given investigational vaccines and ordered not to tell anyone. In a Committee survey of 150 individuals who served in the military during the Persian Gulf War (see Appendix), many of those surveyed indicated they were ordered, under threat of Article 15 or court martial, to discuss their vaccinations with no one, not even with medical professionals needing the information to treat adverse reactions from the vaccine. Similarly, 86 percent of the military personnel who told the Committee that they were ordered to take pyridostigmine bromide reported that they received no information on what they were taking or the drug's potential risks. According to a DOD study published in the Journal of the American Medical Association, commanding officers and medical personnel were also inadequately informed about the investigational drugs; as a result, they were ill-prepared to recognize or treat military personnel who experienced side effects.[71]

[70]Hearing, May 6, 1994; John T. Harrison, written statement submitted for the record.

[71]Although the study was published in the *Journal of the American Medical Association*, these results were not reported in the published article. They are reported in an unpublished report, Survey #1, Food and Drug Administration IND 23,509, Operation Desert Storm/Shield, May 27, 1992.

B. DOD HAS REPEATEDLY FAILED TO COMPLY WITH REQUIRED ETHICAL STANDARDS WHEN USING HUMAN SUBJECTS IN MILITARY RESEARCH DURING WAR OR THREAT OF WAR.

The major principle of all research ethics involving human subjects, as described by the Nuremberg Code, the Declaration of Helsinki, and the "Common Rule" of the U.S. Government, states that the voluntary, competent, informed, and understanding consent of the subject is absolutely essential, whether during war or peace.[72]

These standards are more than 50 years old. For example, the Nuremberg Code was based on testimony of two U.S. physicians, Drs. Leo Alexander and Andrew Ivy, who served as expert medical witnesses for the Nazi crime prosecutors. The code was not the outcome of an attempt to frame a new code of ethics, but rather a description of criteria said to be widely accepted by the medical profession at the time.[73] Therefore, DOD research during the 1940's was clearly conducted in an era when researchers were well aware of ethical codes regarding the use of human subjects.

The Department of Defense has violated these well-established ethical principles each time soldiers are required to participate in military research or take investigational drugs or vaccines or are not adequately informed about the risks of the experiments.

World War II Veterans

Many individuals were recruited for various military experiments of mustard gas and lewisite under the guise of testing clothing, without being warned beforehand that they would be exposed to dangerous chemicals. Additionally, young servicemembers frequently reported that they were enticed to volunteer for experiments by being promised extra leave time from duty.

For example, in 1944, Nathan Schnurman was a 17-year-old sailor who was recruited to test Navy summer clothing, in exchange for a 3-day pass. Instead, he participated in the testing of gas masks and clothing while he was locked in a gas chamber and exposed to mustard gas and lewisite. Mr. Schnurman believes that he was not really a volunteer since the research was misrepresented. Additionally, Mr. Schnurman stated in written testimony submitted to the Committee that "many were denied the 3-day pass, and many went to their graves without revealing this story."[74] Perhaps most outrageous, Mr. Schnurman was not allowed to leave the gas chamber when he became violently ill. Mr. Schnurman testified before the Committee on the Judiciary of the U.S. House of Representatives that, "During my sixth exposure in the chamber, I determined something was wrong. I called to the corpsman, via an intercom, and informed him of my condition, and what was happening and requested I be released from the chamber, now. The reply, was `No' as they had not completed the experiment. I became very nauseous. Again, I requested to be released from the chamber. Again,

[72]The Nuremberg Code, op. cit.

[73]Annas, G.J. & Grodin, M.A. "The Nazi Doctors and the Nuremberg Code," Human Rights in Human Experimentation, Oxford University Press, 1992, p 152.

[74]Hearing, May 6, 1994; Nathan J. Schnurman, written statement submitted for the record.

permission was denied. Within seconds after the denial, I passed out in the chamber. What happened after that, I don't know. I may only assume, when I was removed from the chamber, it was presumed I was already dead."[75]

John William Allen enlisted in the U.S. Navy in 1945 at the age of 17. Immediately after boot camp, he volunteered to test summer uniforms so he could go home before shipping out. His test clothing consisted of one pair of pants, undershorts, a gas mask, and a shirt that had been used in previous experiments and was therefore impregnated with toxic chemicals. According to Mr. Allen, the actual testing consisted of determining the amount of sulfur mustard that would cause illness ("man-break" test), not the testing of summer uniforms. He was exposed several times to sulfur mustard and was removed from further exposure on May 5, 1945, when he passed out in the gas chamber. A physical examination on May 14, 1945, revealed many wounds as the result of exposure to mustard gas.

Mr. Allen stated in written testimony submitted to the Committee, "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 had it on my record and would have received medical treatment."[76]

Persian Gulf War Veterans

Almost 50 years after World War II veterans were exposed to unethical research, the Department of Defense again failed to comply with the well-established ethical requirement that all soldiers and civilians make an informed choice of whether or not to use investigational medical treatment.

1. Military personnel were not given the opportunity to refuse investigational drugs.

When the Department of Defense began preparations for Desert Shield and Desert Storm in 1990, officials were extremely concerned about the need to protect U.S. troops against chemical and biological weapons that were believed to have been developed by Iraq. However, the DOD lacked drugs and vaccines that were proven safe and effective to safeguard against expected weapons, such as soman and botulism.

Under the Food, Drug, and Cosmetics Act, all vaccines and medical products must be proven safe and effective by the Food and Drug Administration (FDA) in order to be sold and distributed in the United States, or used by U.S. troops. However, DOD officials were interested in using a botulinum toxoid, which is a vaccine to prevent botulism, that was *not* approved by FDA. They also wanted to use pyridostigmine bromide, a medication to protect U.S. troops against chemical nerve agents. Although approved by the FDA for treating patients with a neurological disorder called myasthenia gravis,

[75]Testimony of Nathan Schnurman, WWII veteran, mustard gas test subject, hearing before the Subcommittee on Administrative Law and Governmental Relations, Committee on the Judiciary, U.S. House of Representatives, "Government-Sponsored Tests on Humans and Possible Compensation for People Harmed in the Tests," February 2, 1994.

[76]Hearing, May 6, 1994; John William Allen, written statement submitted for the record.

pyridostigmine is not proven safe or effective for repeated use by *healthy* persons under any circumstances, and is normally unavailable in doses that would be likely to be safe for healthy individuals.[77]

Under current law, the unapproved vaccine and the investigational use of pyridostigmine for healthy individuals could only be administered under an Investigational New Drug (IND) procedure.[78] Under an IND, any individual who is given the investigational product must give informed consent, i.e., must be told of the potential risks and benefits of the product, orally and in writing, and choose freely whether or not to participate. In addition, the IND requires that the medical product be distributed under carefully controlled conditions where safety and effectiveness can be evaluated.

In August 1990, the DOD contacted FDA to review regulatory restrictions of DOD's plan to use pyridostigmine and botulinum toxoid for U.S. troops in the Persian Gulf. The major focus of the meeting was informed consent. The DOD sought a waiver of requirements for informed consent for the use of pyridostigmine bromide and botulinum toxoid, arguing that these investigational products had well-established uses and were safe. They also claimed that there were no reasonable alternatives. According to minutes of the meeting, "FDA expressed some concern about liability and the need to comply with the regulations," and FDA's Deputy Director for Drug Review "pointed out the need to establish an appropriate investigational framework to collect observational data and evaluate the military medical products in question."[79]

In summary, DOD informed FDA that they did not want to abide by informed consent regulations, and FDA officials pointed out that pyridostigmine and botulinum toxoid were investigational and that there are laws regulating how they can be used. DOD claimed that "under the DOD directive the Secretary of Military Departments [could] dictate the use of unapproved FDA regulated products" in the Persian Gulf, but "DOD's current position is that this not their primary choice at this time."[80]

The issue was debated by the two agencies for several months. Finally, at a meeting on December 31, 1990, an agreement was reached. According to minutes of that meeting, DOD officials agreed that the botulism vaccine would be administered by trained individuals with a health care background, and that information would be provided orally "at minimum, and in written form if feasible, to all personnel receiving the vaccine."[81] Officials from the DOD said that the feasibility of distributing an information sheet would depend on many factors, and would vary from location to

[77]Pyridostigmine is approved by the FDA at a one-time dosage of 15 mg to reverse the effects of certain drugs given during anesthesia.

[78]55 Federal Register 52,814-52,817 (December 21, 1990).

[79]Memorandum for Record, August 30, 1990, submitted by Craig R. Lehmann, Lt. Col., USAF, BSC; in Committee files.

[80]FDA memorandum from Richard Klein and Ann Graham to Stuart Nightingale, September 7, 1990; in Committee files.

[81]Draft of minutes, meeting between officials of DOD and FDA, December 31, 1990, provided by FDA to Committee; in Committee files.

location within the military theater of operation. DOD officials "reiterated that at least verbal [sic] information would be provided to each person receiving the vaccine."

The FDA Informed Consent Waiver Review Group recommended that pregnant women be excluded from receiving the vaccine and that information about the vaccine be "posted at places where vaccine is administered." However, DOD argued that pregnant women would be at greater risk from exposure to botulism toxins than to the vaccine, and FDA agreed that instead of excluding pregnant women, a statement would be added to the information sheet stating that, "If you are pregnant, it is not known if this vaccine will hurt the unborn baby, however, most vaccines do not."[82]

In their application for a waiver, DOD described the safeguards that would be in place regarding the distribution of the botulism vaccine. In addition to oral warnings regarding the vaccine, DOD promised that the soldiers would be observed for 30 minutes after receiving the vaccine, and if possible, they would also be checked again 48 hours later. In addition, DOD claimed that they would provide all three vaccine injections and stated that all three were necessary to provide protection.

FDA granted the waiver on a temporary basis, concurring that obtaining informed consent during wartime is not feasible in a specific military operation involving combat or the threat of combat.[83] On January 8, 1991, Dr. David Kessler, FDA Commissioner, wrote to the Assistant Secretary of Defense for Health Affairs regarding the waiver for informed consent for pyridostigmine. In his letter, Dr. Kessler agreed that since there was "no available satisfactory alternative therapy" for protection against organophosphorus nerve gas, he would "concur with your assessment that informed consent is not feasible." This agreement was apparently based on DOD officials' promise to "provide and disseminate additional information to all military personnel concerning the risks and benefits of pyridostigmine."[84]

Although FDA agreed to waive informed consent for both the pyridostigmine bromide and the botulism vaccine, the Assistant Secretary of Defense for Health Affairs notified Dr. Kessler on March 15, 1992, that "Central Command" had decided that the vaccine would be administered on a *voluntary* basis.[85] However, based on interviews with 150 Persian Gulf War veterans by Committee staff (Appendix), 88 percent of those who said they received a botulism vaccine were told they had no choice.

According to the DOD, all 696,562 U.S. troops in the Persian Gulf War were *issued* pyridostigmine bromide as a pretreatment for nerve agent poisoning, and officials estimate that approximately two-thirds *took* the drug for varying periods of time. Of 150 who were interviewed by Committee staff, 73 took pyridostigmine and 74

[82]Ibid.

[83]55 Federal Register 52,814-52,817 (December 21, 1990).

[84]Letter in Committee files.

[85]Letter from Enrique Mendez, Jr., M.D., to David Kessler, M.D., Commissioner, Food and Drug Administration, March 15, 1991; in Committee files.

percent of them were told they could not refuse to take it. Approximately 8,000 individuals received botulinum toxoid in the Persian Gulf. Given the high proportion who have reported that they had no choice, it appears that hundreds of thousands of U.S. troops were ordered to take an investigational drug or vaccine without having the opportunity to refuse.

2. Military personnel were not informed about the risks of the investigational drugs

Although DOD officials convinced FDA they need not offer choice, DOD had promised to provide extensive information about potential risks orally and in writing. In addition to being ordered to take an investigational product without informed consent, most Persian Gulf War military personnel surveyed claim they received no oral or written information about the drug or vaccine, despite the DOD promises to FDA to provide information about potential risks. These claims are supported by a survey conducted by the Department of Defense following the Persian Gulf War. Sixteen of 23 selected Persian Gulf War medical personnel surveyed by the DOD indicated that no information on the side effects of pyridostigmine bromide was provided to those who were ordered to take the drug.[86] These medical personnel were responsible for 8,366 military personnel during the Persian Gulf War.

There are two kinds of risks associated with lack of information. One is a lack of trust. In the survey conducted by Committee staff, 14 of 73 (19 percent) Persian Gulf War veterans who had been ordered to take pyridostigmine bromide indicated that they did not take all the pyridostigmine bromide they were ordered to take, fearful that the drug was responsible for the symptoms they experienced (Appendix). Because no one would answer their questions about the safety and efficacy of the pyridostigmine bromide, they feared they were receiving a potentially harmful drug. Therefore, if pyridostigmine bromide had been crucial for surviving nerve agent exposure, an unknown number of individuals would have lacked protection because they had received inadequate information about the drug.

The other risk is that even if serious side effects were rare, they could have been treated if medical personnel were able to diagnose the problem. For example, Carol Picou, a nurse who was stationed in the Gulf for 5 months, had obvious side effects from the pyridostigmine starting on the third day that she took it. These side effects included incontinence, drooling, and blurry vision, among others. The side effects became worse 1 hour after she took each pill. One day, she did not take the pill as scheduled, and the side effects stopped; unfortunately, her commanding officer ordered her to continue taking the pills, and watched to make sure she swallowed them. She was ordered to take the pills for 15 days. She now has many permanent medical problems, including incontinence, muscle

[86]Survey #1, Food and Drug Administration IND 23,509, Operation Desert Storm/Shield, May 27, 1992.

weakness, and memory loss, that might have been avoided had she been allowed to stop taking the pills.[87]

Similarly, Lt. Col. Neil Tetzlaff had immediate side effects when he started taking pyridostigmine bromide on the plane ride over to Saudi Arabia. His nausea and vomiting became so severe that he needed emergency surgery to repair a hole in his stomach. When he became ill, the military doctor told him to continue to take the pills, because the doctor apparently did not know that nausea and vomiting were known side effects. According to Tetzlaff's sworn testimony, the doctor acted as if the pyridostigmine was as safe as a cough drop.[88]

Civilians in the Gulf War

Numerous civilians have reported to Committee staff that they also were given investigational drugs during the Persian Gulf War without informed consent. For example, civilians who worked for DOD contractors and news media personnel were apparently instructed to take the pyridostigmine bromide tablets. They usually were not told it was experimental or that the pyridostigmine bromide was being administered in a regime that was not proven efficacious or safe, and received no information on potential side effects of the drug.

For example, according to journalists who covered the Gulf War, some were given the pills by the U.S. military. Several of these journalists experienced serious medical problems similar to Persian Gulf War veterans.[89] The Committee has also received letters from civilians who are suffering from "Gulf War syndrome" who report the widespread use of pyridostigmine by civilians working for DOD during the Gulf War.

Other Studies of Pyridostigmine

Following the Committee's May 6, 1994, hearing, several individuals who were in the Air Force during the 1980's contacted Committee staff to report they had also received pyridostigmine bromide without their consent.[90] They indicated that they did not volunteer for any research study, were ordered to take the pyridostigmine pills as part of a research project, and were ordered to report any side effects to the flight surgeons. One individual estimated that several hundred individuals in his squadron participated in the pyridostigmine studies, and reported that the studies were conducted over a period of at least 2 years.

The descriptions of these studies are disturbing because, if accurate, they indicate that even during peacetime, the Air Force totally ignored the requirements of informed consent that are a central provision of the Nuremberg Code, the Declaration of Helsinki,

[87]Response to Committee survey completed by Carol Picou, Persian Gulf War nurse; in Committee files.

[88]Hearing, May 6, 1994; statement of Neil Tetzlaff, Persian Gulf War veteran.

[89]Memoranda describing phone conversations with journalists are in Committee files.

[90]Letters, summaries of phone conversations, and supporting documents are in Committee files. These include an "Aircrew Symptoms Checklist on AF Form 1666 (TEST) FEB 86, which instructs the pilots to "[t]ake one (1) pyridostigmine bromide tablet (30 mg) every eight (8) hours over a 24 hour period."

and the "Common Rule" which had been in effect in at least some U.S. Government agencies at the time.

In addition to being unethical, these studies were reportedly unscientific; there were apparently no safeguards to ensure that the pilots took the pills or accurately reported the side effects. Many pilots who participated in these studies were on flight status; if they reported any side effects, they could lose their flight pay.[91] Obviously, this provided an incentive for them *not* to report any side effects, since they did not want to lose their flight pay. Similarly, those who experienced side effects had an incentive to stop taking the drug without notifying the researchers conducting the study. Moreover, pilots who contacted the Committee staff reported that many of their friends and colleagues did not take any of the pills at all, and many of those who did take at least one pill stopped taking them when they experienced headaches and other side effects. Despite the pressure to obey orders, many of the pilots apparently believed that they should not trust the Pentagon regarding the safety of these experimental pills.

One member of the air crew who was given pyridostigmine as part of these studies, Craig Crane, notified the Committee that he now has memory loss, joint pain, sensitivity to chemicals, and other symptoms that are commonly associated with Gulf War syndrome, although he is only 32 years old and did not serve in the Gulf War. He has left the Air Force because of his disabilities.[92]

C. DOD INCORRECTLY CLAIMS THAT SINCE THEIR GOAL WAS TREATMENT, THE USE OF INVESTIGATIONAL DRUGS IN THE PERSIAN GULF WAR WAS NOT RESEARCH.

Despite the fact that pyridostigmine was an investigational drug whose safety and effectiveness had not been proven to FDA, the DOD claims that its use in the Persian Gulf War was prevention and treatment, not research. For example, Dr. Edward Martin, Acting Principal Assistant Secretary of Defense for Health Affairs, stated at the Committee's hearing on May 6, 1994, that "..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."[93] Additionally, John M. Bachkosky, Deputy Director, Office of the Director of Defense Research and Engineering, wrote to Sen. Rockefeller on May 19, 1994, that "[botulinum toxoid and pyridostigmine bromide] were used

[91]One of the men has provided records of these studies to the Committee; although the records specify that all pilots participating in the study were removed from flight status and given informed consent about the risks of pyridostigmine, those records are not consistent with the descriptions of the study provided by the pilots who contacted the Committee. Moreover, the records themselves do not include an informed consent form or information about the risks of pyridostigmine.

[92]Letter and medical records of Craig Crane are in Committee files.

[93]Hearing, May 6, 1994; statement of Dr. Edward Martin, Acting Principal Assistant Secretary of Defense for Health Affairs.

for direct prevention and treatment and were not employed as part of any research effort."[94]

In a letter to Sen. Rockefeller dated November 17, 1994, DOD continues to claim that its use of pyridostigmine was not research. John Deutch, Deputy Secretary of Defense, wrote that, "Although pyridostigmine and botulinum toxoid were classified as investigational drugs as required by FDA regulations, they were not used for experimental purposes in [Operation Desert Storm] and the military personnel who received these products were not experimental subjects."[95] Mr. Deutch added that, "The fact that these drugs were used for treatment purposes, not research purposes, was clearly understood by all parties involved and specifically approved by the courts in litigation challenging the governments [sic] actions." Once again, it appears that the DOD confuses the goals of using these medical products with the process, which was clearly considered investigational by FDA.

Dr. Arthur Caplan, who at the time he testified was Director of the Center of Biomedical Ethics at the University of Minnesota, addressed that issue at the May 6 hearing. He explained that the fact that the goal is treatment and that DOD believed the benefits of the pills and vaccines would outweigh the risks "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."[96]

Since the end of the Persian Gulf War, DOD has repeatedly requested that the waiver of informed consent be made permanent, arguing that "to not finalize it provides an arguable defect under the Administrative Procedures Act and leaves both DOD and FDA open to greater liability."[97] To finalize the interim rule would grant unrestricted use of investigational drugs by military personnel, even though investigational status means that efficacy and safety have not been proven. FDA has not yet decided whether to concur with DOD's request.

D. DOD USED INVESTIGATIONAL DRUGS IN THE PERSIAN GULF WAR IN WAYS THAT WERE NOT EFFECTIVE.

The DOD persuaded FDA that informed consent should be waived for pyridostigmine bromide and botulism vaccine because these

[94]Letter from John M. Bachkosky, Deputy Director, Office of the Director of Defense Research and Engineering, U.S. Department of Defense, to Sen. John D. Rockefeller IV, Chair, Senate Committee on Veterans' Affairs, May 19, 1994.

[95]Letter from John Deutch, Deputy Secretary of Defense, to Sen. John D. Rockefeller IV, Chair, Senate Committee on Veterans' Affairs, November 17, 1994; in Committee files.

[96]Hearing, May 6, 1994; statement of Arthur Caplan, Ph.D. Dr. Caplan is now Director of the Center of Biomedical Ethics at the University of Pennsylvania.

[97]Minutes, Meeting (July 27, 1992) on Finalizing Interim Rule on Waiver of Informed Consent, signed July 28, 1992, by William H. Habig.

investigational products had been used safely in the past. However, based on documents provided to the Committee staff, it is doubtful that either of these products would have been effective as used in the Persian Gulf War.

Pyridostigmine bromide, according to DOD, improves the survival of animals exposed to soman and treated with atropine and 2-PAM. However, pyridostigmine pretreatment makes individuals more vulnerable to other nerve agents, such as VX and sarin.[98] The DOD scientists who studied pyridostigmine and *sarin* therefore concluded that pyridostigmine should *only* be used when the chemical warfare threat is *soman*.[99]

The Pentagon, however, had no reason to believe that the Iraqis were more likely to use soman rather than sarin. According to a report by the Persian Gulf Veterans Coordinating Board, Iraq had several chemical weapons, including sarin.[100] Moreover, at a briefing for Senators and staff on November 10, 1993, Under Secretary of Defense John Deutch stated that the Czechoslovakian military detected low levels of *sarin* in the Saudi theater during the opening days of the air war against Iraq. This statement was also made by Joseph Corrivean, U.S. Army Foreign Science and Technology Center, on April 27, 1994, at a National Institutes of Health workshop on "The Persian Gulf Experience and Health."

Even if U.S. troops had been exposed to soman, it is unclear that the pyridostigmine would have provided adequate protection against nerve damage. When DOD began the second phase of research on pyridostigmine, it was noted that the atropine and 2-PAM did not seem to save the lives of animals that were exposed to soman. As a result, the dose of atropine was increased to 0.40 mg/kg, which according to FDA, increased the survival of Rhesus monkeys exposed to soman.[101] However, when the Department of Defense developed a treatment regimen for U.S. troops during the Persian Gulf War, it was based on the *inadequate* dose of atropine in the animal studies (0.096 mg/kg) rather than the higher, effective dose.[102] **Therefore, even if Persian Gulf soldiers had been exposed to soman, it is questionable if the pyridostigmine pretreatment would have provided any protection, since the dose of atropine was apparently inadequate.**

In response to posthearing questions about this dosage discrepancy from Sen. Rockefeller, the DOD stated "the dose of atropine in the Mark I kit was established based exclusively on safety, rather than

[98]Koplovitz, I., Harris, L.W., Anderson, D.R., Lennox, W.J., & Stewart, J.R. "Reduction by pyridostigmine pretreatment of the efficacy of atropine and 2-PAM treatment of sarin and VX poisoning in rodents," *Fundamental and Applied Toxicology*, Vol. 18, 1992, pp. 102-106.

[99]Sidell, F.R., op. cit.

[100]"Summary of the issues impacting upon the health of the Persian Gulf veterans," Version 1.1: March 3, 1994.

[101]The actual data from this study was not provided to our Committee, and apparently not provided to FDA either.

[102]IND Amendment, Reference to IND# 28480, March 28, 1988, Letter from Thomas H. Gray, Chief, Operational Unit Training Branch, Department of the Air Force, to Mr. David Banks, Consumer Safety Officer, FDA.

on efficacy, considerations."[103] This statement suggests that hundreds of thousands of servicemembers were put at risk by requiring them to take a drug with known risks (pyridostigmine bromide) in a situation where it might have done little good since the *atropine* dose in the Mark I kits, 6 mg, was inadequate. Based on the monkey data, a dose of 27 mg would have been required for a 150-pound man.[104] However, the side effects of only 2 mg of atropine in a normal young person (without nerve-agent exposure) include increased heart rate, decreased sweating, visual blurring, and others.[105] Apparently, DOD officials decided that the high dosage required for protection would impair performance, so they selected the much lower dosage, even though its effectiveness was questionable. Although results for monkeys may not be exactly comparable to those for humans, it seems unlikely that humans would respond dramatically differently. It is therefore likely that the dose of atropine in the Mark I kits was inadequate for efficacy, and even with this very low dose could have compromised the ability of servicemembers during war.[106]

Botulism vaccine was given too late to U.S. troops to be of any use had the Iraqis actually used biological warfare during Desert Storm. At a briefing on April 20, 1994, DOD officials informed Committee staff that botulism vaccine was not administered to most military personnel in the Persian Gulf until January 23, 1991, which was 7 days *after* the onset of the air war. Approximately 8,000 individuals received the vaccine, but most received only one or two inoculations. Because the war ended on February 27, 1991, before the third injection was scheduled to be given, it is unlikely that these soldiers were adequately immunized. Moreover, because of the severe shortage of the product, the remainder of those deployed received no inoculations, and hence no protection against botulism.

According to the Department of Veterans Affairs, 696,562 individuals participated in Operation Desert Shield/Desert Storm. **Therefore, 99 percent of the military personnel deployed would have received no protection due to the shortage of botulinum toxoid, and the remaining 1 percent were probably not protected because the vaccine distribution started too late.**

Additionally, in December 1990, the FDA advised the Department of Defense that it would be unable to test the botulism vaccine for efficacy, presumably because of limited time before the onset of the war.[107] Therefore, in addition to the limited supply of vaccine and late

[103]Answers from the Department of Defense to followup questions submitted by Sen. John D. Rockefeller IV, after the Committee's May 6, 1994, hearing. The answers were received by the Committee on September 19, 1994.

[104]A 150-pound man weighs 68 kg; 68 x 0.4 = 27 mg.

[105]Sidell, F.R., op. cit.

[106]The administration of additional atropine some hours after exposure to chemical weapons might have been helpful, but it is not clear how many soldiers would have been fortunate enough to receive medical treatment within hours of combat, or how effective that later treatment would have been.

[107]Minutes of Meeting of the Informed Consent Waiver Review Group (ICWRG), Food and Drug Administration, December 31, 1990.

onset of inoculations, efficacy of the existing supply was not determined prior to the onset of the war.

Anthrax vaccine was given to approximately 150,000 military personnel in the Persian Gulf. Anthrax vaccine is considered effective for protecting against anthrax exposure of the skin; however it is unclear whether it provides protection against inhaling aerosolized anthrax.[108] According to the Department of Defense, in biological warfare the anthrax would be sprayed, so the efficacy of the vaccine against aerosolized anthrax would have been the relevant test.[109] As stated earlier in this report, the DOD has only one study indicating that the vaccine might be useful against aerosolized anthrax, but there are no data on humans.

E. DOD DID NOT KNOW WHETHER PYRIDOSTIGMINE BROMIDE WOULD BE SAFE FOR USE BY U.S. TROOPS IN THE PERSIAN GULF WAR.

Committee staff reviewed all the clinical studies and related research regarding pyridostigmine on healthy individuals which DOD provided to FDA to support their IND and their NDA (new drug approval) application.[110] The number of human subjects in most studies was less than 35; several studies included as few as two or four individuals.

According to the materials that FDA provided to the Committee, virtually all the studies excluded women. The lack of studies on women is a problem, because dosage should be based on the weight of the person taking the drug, and because some scientists believe that pyridostigmine may affect men and women differently.[111,112] For example, women on birth control pills may have different levels of AChE than other women or men. Similarly, women in different stages of their reproductive cycle respond differently to pyridostigmine.[113] Since studies excluded women, there is no information on the potential long-term side effects of pyridostigmine on diseases unique to women (such as menstrual cycle irregularities or breast cancer).

Because of the DOD researchers' concerns about serious adverse reactions to pyridostigmine bromide, many of the studies screened the men to determine whether they were hypersensitive to pyridostigmine bromide before allowing their participation in the experiment. In some cases they used test doses; in other cases they asked questions regarding similar medications and sensitivity to bromide. In many of the studies, patients were excluded if they were taking any

[108]In a letter dated July 27, 1992, FDA asked whether an IND should be required to test the anthrax vaccine against aerosolized anthrax.

[109]Department of Defense briefing with staff of the Senate Committee on Veterans' Affairs, 414 Russell Senate Office Building, April 20, 1994.

[110]A list of many of these studies is in Appendix A.

[111]Barbarino, A., Corsello, S.M., Tofani, A., et al. "Sexual dimorphism of pyridostigmine potentiation of growth hormone (GH)-releasing hormone-induced GH release in humans," *Journal of Clinical Endocrinology and Metabolism*, Vol. 73, No. 1, 1991, pp. 75-78.

[112]O'Keane V. & Dinan, T.G. "Sex steroid priming effects on growth hormone response to pyridostigmine throughout the menstrual cycle," *Journal of Clinical Endocrinology and Metabolism*, Vol. 75, No. 1, 1992, pp. 11-14.

[113]Ibid.

medications, since adverse reactions could occur when pyridostigmine was administered with other drugs (i.e., propranolol, birth control medications, or anti-malarial drugs). In some studies, smokers were excluded; in many studies, participants were told not to drink any alcoholic beverages. Most research study participants were less than 35 years of age. In addition, individuals with abnormal blood pressure, asthma, glaucoma, low serum AChE levels, gastrointestinal disorders, urinary or intestinal blockage, or hyperthyroidism, were excluded from the studies.[114]

Despite these precautions, serious adverse reactions were reported for several of the studies. For example, in one study, pyridostigmine bromide was administered to a group of 28 active duty Air Force pilots.[115] One pilot experienced respiratory arrest 91 minutes after swallowing the third in a series of three 30-mg pyridostigmine tablets. This pilot had shown no sensitivity to the test dose of pyridostigmine prior to the study. In another study of 32 male subjects, one subject lost consciousness following vision problems and headache.[116] In other studies, abnormal liver tests, unusual electrocardiograms, gastrointestinal disturbances, and anemia were reported.[117,118,119]

Results also showed that pyridostigmine impaired performance, including tasks which require short-term memory, and prevented a number of test subjects from exercising in hot environments during the second or third day of treatment. A study of the impact of pyridostigmine on swimming in cold water had to be terminated when it was determined that its use caused severe cramps that could cause drowning.

Research published in 1978 on neostigmine, a "close relative" of pyridostigmine, found that the drug caused "profound physiological, electrophysiological, and electron microscopic disruption of nerve endings and muscles." Some of these changes increased in severity over time with continued treatment.[120] The author of that study believes this study has worrisome implications for pyridostigmine.

In August 1990, just before U.S. troops were sent to the Gulf, DOD scientists requested approval for a study of four men that would evaluate the effects of pyridostigmine on vision. This study was deemed urgent because of the situation in Kuwait, and it was approved quickly. It is important to note that this study, conducted just prior to the Gulf War, included extensive safety precautions, including giving medical exams to the men before giving the

[114]These instructions are consistent over time, and were included in many different studies between 1985-90. Copies are in Committee files.

[115]IND Amendment, 28 March 1988, IND 28,480.

[116]IND Annual Report, 1987-1988, IND 23,509.

[117]DAMD17-85-C-5133, Task Order 2, Kornhauser.

[118]*Israeli Journal of Medical Science*, Vol. 27, 1991, pp. 659-663.

[119]Keeler, J.R., Hurst, C.G., & Dunn, M.A. "Pyridostigmine used as a nerve agent pretreatment under wartime conditions," *Journal of the American Medical Association*, Vol. 266, No. 5, 1991, pp. 693-695.

[120]Letter from the author of the published research, Dr. Thomas Tiedt, to Sen. John D. Rockefeller IV, Chair, Senate Committee on Veterans' Affairs, June 8, 1994; in Committee files.

pyridostigmine. **The researchers indicated that pyridostigmine should *not* be given to individuals who had bronchial asthma, peptic ulcer, liver, kidney, heart disease, or hypersensitivity to pyridostigmine or related drugs**. They informed study volunteers that possible adverse side effects include nausea, vomiting, slow heart rate, sweating, diarrhea, abdominal cramps, increased salivation, increased bronchial secretions, and pupil constriction. They also warned of other side effects, including "weakness, muscle cramps, and muscle twitches" and explained that, **"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." (Emphasis added)[121] In addition, the Human Subjects Committee that reviewed this study considered whether the possibility of pyridostigmine causing death should be mentioned in the informed consent form; after some discussion, it was decided that such a warning was unnecessary since death was unlikely.

In contrast to the extensive precautions taken before giving pyridostigmine every 8 hours for 3 days to *four* volunteers, a few months later approximately 400,000 U.S. soldiers were ordered to take the same dosage of the drug for days, weeks, or months, none of whom had been screened for any of the diseases mentioned in the informed consent form given to the four men, none of whom were warned about the risks associated with the drug, and none of whom were given a choice of whether or not to take it. Additionally, approximately 28,000 of the 400,000 receiving the pyridostigmine were women, who were required to take an investigational drug that DOD had never tested on healthy women.[122]

The repeated claims by DOD and FDA at the Committee's May 6, 1994, hearing and at other times since the war that they were sure pyridostigmine was perfectly safe as used is not consistent with the concerns of DOD scientists regarding the potential serious adverse reactions and drug interactions while conducting research. It does not make sense that the researchers would establish such elaborate safeguards when giving the drug to four men, and then have none of those safeguards when giving the drug to more than 400,000 U.S. troops, none of whom had been tested for sensitivity to pyridostigmine, and most of whom were not screened for medical problems or medication use that could preclude the safe use of pyridostigmine. DOD researchers were aware of the shortcomings of their research. For example, in 1989 William K. Prusaczyk suggested, "Because of the existing incidence of asthma in soldiers in the U.S.

[121]Abbreviated Protocol, signed by Roger W. Wiley and Darcelle Delrie, and other documents regarding "The Effects of Pyridostigmine Bromide on Vision"; attached to a cover letter from Martha H. Myers, Acting Chief, Human Use Review and Regulatory Affairs Office, Department of the Army, August 15, 1990. Documents are in Committee files.

[122]There are several studies of the effects of a one-time dose of pyridostigmine on growth hormone in women, but the conditions of these studies, including fasting and use during one phase of the menstrual cycle, were not relevant to use of pyridostigmine in the Gulf War.

Army," the medical monitor believes that pyridostigmine should be studies on individuals who have asthma.[123]

F. WHEN U.S. TROOPS WERE SENT TO THE PERSIAN GULF IN 1994, DOD STILL DID NOT HAVE PROOF THAT PYRIDOSTIGMINE BROMIDE WAS SAFE FOR USE AS AN ANTIDOTE ENHANCER.

When U.S. troops were sent to the Persian Gulf in the fall of 1994 because of concern about Kuwait, the DOD considered the use of pyridostigmine to protect against chemical weapons. However, in the 3 years since the Persian Gulf War of 1991, the DOD had not conducted studies that proved the safety of pyridostigmine bromide for that use.

The safety of pyridostigmine was evaluated during and after the Persian Gulf War. In one study, approximately 37 percent of 213 soldiers reported at least one severe symptom 24 hours after beginning to take the 30-mg pyridostigmine tablets.[124] Additionally, the DOD conducted three surveys concerning the use of pyridostigmine in Operation Desert Shield/Storm which were reported in 1992.[125] These surveys indicated that side effects were frequently experienced by military personnel taking pyridostigmine bromide. One published article, based on reports from medical personnel providing care to 41,650 soldiers (6.5 percent women) who took pyridostigmine bromide in the Persian Gulf, found that over half experienced gastrointestinal disturbances.[126] Urinary urgency and frequency, headaches, nasal discharge, profuse sweating, and tingling of hands and feet were reported to occur in a range of 5 to 30 percent.[127] Several doctors who were interviewed for the study expressed concerns that the dose for women may have been too high.

In the 3 years that have elapsed since the Gulf War, the DOD has apparently not conducted research on the safety of pyridostigmine for healthy women. In early 1994, DOD submitted an NDA (new drug approval) application to FDA, urging that FDA determine that pyridostigmine bromide is safe and effective as an antidote enhancer. The studies provided in that application did not include women.

In the last few year, several studies have been published on the effects of pyridostigmine on growth hormones of women and men. In one study, three of the eight women who received one 120 mg dose of pyridostigmine bromide became so ill they had to be excluded from the study.[128] The entire study consisted of eight women and eight men who received pyridostigmine in single doses of 30, 60, or 120 mg. The women in the study experienced more severe and prolonged

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[123]to Protocol HURC #378," memorandum from William K. Prusaczyk, research physiologist, October 23, 1989; in Committee files.

[124]Sharabi, Y., Danon, Y., Berkenstadt, H., et al., "Survey of symptoms following intake of pyridostigmine during the Persian Gulf War," *Israeli Journal of Medical Science*, Vol. 27, 1991, pp. 656-658.

[125]Information amendment from the Department of the Army to FDA, IND 23509-pyridostigmine bromide-WR 270,710, May 27, 1992.

[126]Keeler, J.R., et al., op. cit.

[127]Ibid.

[128]Barbarino, A., et al., op. cit.

symptoms than men, especially at the 120 mg dose, such as severe abdominal cramps, nausea, vomiting, asthenia, and muscle cramps. Three subjects who received 120 mg had vision impairment that lasted several hours.[129]

In addition, none of the studies of pyridostigmine evaluated the safety of pyridostigmine if taken over a period of weeks or months, as was done in the Gulf War. Moreover, none of the studies evaluated the long-term safety of pyridostigmine by providing followup information about men who had taken the drug years earlier.

Despite the Committee's hearing in May and numerous television news magazine reports and newspaper articles reporting our concerns about the safety of pyridostigmine, the DOD has apparently not yet conducted any studies that provide any more information than was previously available.[130] Several studies of pyridostigmine conducted by DOD under conditions of heat and/or exercise have been published, but they studied only four to seven young men. In one study of four men, one man became so fatigued on the third day that he was told to stop exercising; this problem was barely mentioned in the published study, and the implication for soldiers during wartime was not discussed.[131]

G. PYRIDOSTIGMINE MAY BE MORE DANGEROUS IN COMBINATION WITH PESTICIDES OR OTHER EXPOSURES.

In 1993, Dr. James Moss, a scientist at the U.S. Department of Agriculture, conducted research on cockroaches that could have important implications for Persian Gulf War veterans.[132] He found that when pyridostigmine was used in combination with a common insect repellent called DEET (diethyl-m-tolamide), the DEET became almost seven times as toxic as when it was used alone. Similarly, pyridostigmine became four times as toxic when used in combination with DEET.[133] DEET and many other insect repellents and pesticides were widely used in the Gulf War as protection against sand flies, scorpions, and other pests. If individuals who took pyridostigmine bromide became more vulnerable to pesticides, or those exposed to pesticides became more vulnerable to pyridostigmine bromide, this could explain the serious neurological symptoms experienced by so many Gulf War veterans.

[129]All the men and women in the study were between 19-25 years old, were free of other medications, and were fasting; the women were all in the luteal phase of their menstrual cycle.

[130]Although the DOD does plan to follow up on research on pyridostigmine and DEET conducted by Dr. James Moss (previously with the Agricultural Research Service, USDA) by conducting a study of rats, that research has not yet been initiated. Dr. Moss' research is described in the next section of this report.

[131]M.A. & Stephenson, L.A. "Cardiovascular and thermoregulatory responses to repeated anticholinesterase administration," *Journal of Thermal Biology*, Vol. 17, No. 6, pp. 333-337.

[132]Hearing, May 6, 1994; testimony of James Moss, Ph.D., researcher, Agricultural Research Service, U.S. Department of Agriculture, Gainesville, FL.

[133]Additional information about his results are provided in Dr. Moss' answers to Sen. Rockefeller's posthearing questions, included in the transcript of the Committee's May 6, 1994, hearing, and in documents provided by Dr. Moss which are in the Committee files.

The results were similar but not as alarming for permethrin, another insecticide that was used in the Gulf War. Permethrin was used in the military uniforms, impregnating the fabric before it was cut and sewn. In his cockroach studies, Dr. Moss found that DEET became twice as toxic when used with permethrin.

Dr. Moss also studied the combination of DEET and pyridostigmine with other toxic substances that were present in the Gulf War, such as lindane (a treatment for lice) and a wide range of insecticides. These substances also became more toxic when used at the same time than when used individually. Even caffeine was found to have a potential impact on the toxicity of other substances.

Dr. Moss believes his findings regarding cockroaches are likely to be relevant to humans; however, more research is needed to determine if humans would be similarly affected. Nevertheless, his findings are consistent with concerns that have been raised by military researchers, who have stated publicly that carbamates such as pyridostigmine must never be used *after* nerve agent exposure, presumably because the pyridostigmine could further decrease AChE from nerve agent poisoning. If military personnel were exposed to low levels of nerve agents due to bombing of nerve agent stockpiles as proposed by some,[134] as well as numerous pesticides procured by the Army,[135] and pyridostigmine bromide, it is likely that the combination could have been much more toxic than any of those substances would have been individually.

Dr. Moss' findings regarding pesticides are also consistent with a note in the Air Force records of Craig Crane, an Air Force crewman who participated in a pyridostigmine experiment in 1986. According to a description of the pyridostigmine study that was signed by medical personnel and included in Mr. Crane's records, "There is no sensitivity to pesticides or recent significant exposure." This medical notation suggests that Air Force medical personnel were concerned about a possible interaction between pyridostigmine and pesticides, and therefore avoided including men who had been exposed to pesticides.[136]

Dr. Moss testified about his findings at the Committee's May 6, 1994, hearing, despite efforts by USDA to prevent him from doing so. On June 31, 1994, his 3-year contract with USDA expired, and it was not renewed. Dr. Moss' repeated efforts to continue working at USDA were unsuccessful. Sen. Rockefeller wrote to Secretary Espy in May, June, and July to ask how USDA planned to continue Dr. Moss' research, but received no reply until after a CBS Evening News story on the subject on October 14, 1994. Secretary Espy then wrote to Sen. Rockefeller saying that the USDA had no plans to follow up on Dr.

[134]"U.S. Chemical and Biological Warfare-related Dual Use Exports to Iraq and Their Possible Impact of the Health Consequences of the Persian Gulf War," a report of Sen. Donald W. Riegle, Jr., Chair, and Sen. Alfonse M. D'Amato, ranking Republican member, U.S. Senate Committee on Banking, Housing, and Urban Affairs, May 25, 1994.

[135]List of pesticides procured during Desert Shield/Storm (acquired through the Federal supply system), information submitted to the Senate Committee on Veterans' Affairs, April 6, 1994, from the Department of the Army, Office of the Surgeon General.

[136]Hearing, May 6, 1994; document submitted for the record.

Moss' research, but would ensure that the data were provided to DOD.[137]

Although Dr. Moss made no accusations against USDA at the Committee hearing, he has subsequently expressed his views that he lost his job at USDA because of his research findings. He also now reports that his supervisor warned him that he should not discuss his research findings with anyone. Moreover, in an internal USDA memo dated December 30, 1993, Dr. Moss stated that he was advised to "keep quiet."[138] USDA and the Johnson Wax Company are the co-inventors of DEET, an ingredient in most commercially available insecticides, such as Raid.

H. THE SAFETY OF THE BOTULISM VACCINE WAS NOT ESTABLISHED PRIOR TO THE PERSIAN GULF WAR AND REMAINS UNCERTAIN.

At a meeting with DOD officials regarding informed consent in December 1990, the FDA agreed to test the botulinum toxoid (botulism vaccine) for safety.[139] A representative of FDA's Center for Biologics Evaluation and Research explained that the existing supply of the vaccine was nearly 20 years old and consisted of three lots, stored under constant refrigeration. There was concern that the vaccine would break down into toxic products due to prolonged storage. General safety testing was performed by the FDA on all of the lots of botulinum toxoid used in the Persian Gulf; however, the FDA did not complete these tests until January 24, 1991,[140] after the war had started.

While the results of FDA's general safety testing were encouraging, the problem with adverse reactions to the vaccine were not resolved. In her review of the DOD's application for use of the botulism vaccine in the Persian Gulf, an FDA reviewer pointed out that in 1973, the Centers for Disease Control had considered terminating its distribution because of adverse reactions.[141] New lots of the vaccine were manufactured in 1971, but research was not conducted to determine whether the newer lots produced fewer adverse reactions than the older lots.[142]

Since no records were kept for most of the Gulf War soldiers who received the vaccine, there is no new information about the safety of the botulism vaccine resulting from its use by U.S. troops. Therefore, its safety remains unknown.

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[137]Correspondence between Secretary Espy and Senator Rockefeller are in Committee files.

[138]Hearing, May 6, 1994; document submitted for the record by Craig Crane.

[139]Minutes of Meeting of the Informed Consent Waiver Review Group (ICWRG), Food and Drug Administration, December 31, 1990.

[140]BBIND 3723, Food and Drug Administration, memorandum from Lawrence A. D'Hoostelaere on "General safety testing of botulinum toxoid," March 2, 1994.

[141]Review by Ann Sutton, Vaccines and Allergenics, DBIND, Food and Drug Administration, to the IND record, November 14, 1990.

[142]Informational material for the use of pentavalent (ABCDE) botulinum toxoid aluminum phosphate adsorbed, U.S. Department of Health and Human Services, Centers for Disease Control, Atlanta, Georgia, Revised May 1982, protocol #392.

I. RECORDS OF ANTHRAX VACCINE ARE NOT SUITABLE TO EVALUATE SAFETY.

Although anthrax vaccine had been considered approved prior to the Persian Gulf War, it was rarely used. Therefore, its safety, particularly when given to thousands of soldiers in conjunction with other vaccines, is not well established. Anthrax vaccine should continue to be considered as a potential cause for undiagnosed illnesses in Persian Gulf military personnel because many of the support troops received anthrax vaccine, and because the DOD believes that the incidence of undiagnosed illnesses in support troops may be higher than that in combat troops.[143]

Unfortunately, medical records and shot records of individuals who served in the Persian Gulf frequently do not report the vaccines they received. In some cases, anthrax was recorded as "Vac-A." However, in many cases, veterans who believe they received anthrax vaccinations did not have them recorded in their medical records. According to testimony received at the Committee hearing on May 6, 1994, vaccines were recorded in separate vaccine records, for soldiers who had such records with them and insisted that the information be recorded.[144]

J. ARMY REGULATIONS EXEMPT INFORMED CONSENT FOR VOLUNTEERS IN SOME TYPES OF MILITARY STUDIES.

Army regulation (AR) 70-25 provides guidelines for the use of volunteers as subjects in military research. Section 3 describes three exemptions whereby military researchers are exempt from the provisions of these protective regulations (the following is a direct quote from the regulation):

a. Research and nonresearch programs, tasks, and tests which may involve inherent occupational hazards to health or exposure of personnel to potentially hazardous situations encountered as part of training or other normal duties, e.g., flight training, jump training, marksmanship training, ranger training, fire drills, gas drills, and handling of explosives.

b. That portion of human factors research which involves normal training or other military duties as part of an experiment, wherein disclosure of experimental conditions to participating personnel would reveal the artificial nature of such conditions and defeat the purpose of the investigation.

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[143]Briefing, Maj. Gen. Ron Blanck, Commanding General, Walter Reed Army Hospital, to Committee staff, 414 Russell Senate Office Building, Washington, DC, February 4, 1994.

[144]Hearing, May 6, 1994, testimony of the Rev. Dr. Barry Walker, Persian Gulf War veteran.

c. Ethical medical and clinical investigations involving the basic disease process or new treatment procedures conducted by the Army Medical Service for the benefit of patients.[145]

It is sometimes difficult to differentiate training from research. For example, military personnel at the U.S. Chemical School, Fort McClellan, AL, are currently exposed to nerve agent poisons as part of their training, so that they will learn how to cope with similar situations in combat. Soldiers who refuse to participate or do not complete live agent training are subject to reclassification in another military occupational specialty and cannot graduate.[146] To determine if the students used correct procedures during the training exercise, blood samples are obtained from some students before and after the procedure, and are analyzed for red blood cell cholinesterase to determine if the soldier was exposed to the nerve agents.

If the military collects data to determine how to better train individuals, the "training" is then defined as contributing information to generalizable knowledge, and is hence "research." For the optimal protection of U.S. troops, one would hope that training exercises are improved based on reliable information. However, during the testing of new training methods or equipment, exercises utilizing potentially dangerous substances, such as chemical weapons, should be considered research rather than training. Participants must be fully apprised of the nature of the experiments and have the opportunity to refuse without reprisal, in order to conform with the Nuremberg Code and other ethical standards.

K. DOD AND DVA HAVE REPEATEDLY FAILED TO PROVIDE INFORMATION AND MEDICAL FOLLOWUP TO THOSE WHO PARTICIPATE IN MILITARY RESEARCH OR ARE ORDERED TO TAKE INVESTIGATIONAL DRUGS.

A common theme voiced by military personnel who have participated in military research or training exercises over the last 50 years is the lack of information about the risks they faced and the lack of medical followup. World War II veterans frequently reported that they heard about the adverse health effects of mustard gas and lewisite from newspapers and television decades after they were exposed, not from the Department of Defense or Department of Veterans Affairs. Veterans and civilians who worked at the Dugway Proving Ground and were exposed to a variety of biological and chemical simulants began to question the association of poor health with work as they compared information among themselves, not because of information provided by military officials. Veterans who were inside atomic clouds from atomic testing heard nothing at all from their government after they returned home from duty. Similarly, soldiers who unknowingly participated in military research designed to test the effects of hallucinogens on human behavior were never

[145]Army Regulation 70-25, "Research and Development, Use of Volunteers as Subjects of Research," Department of the Army, Washington, DC, March 26, 1968.

[146]Letter from Sara E. Lister, Assistant Secretary of the Army, to Sen. John D. Rockefeller IV, Chair, Senate Committee on Veterans' Affairs, June 15, 1994.

given information to explain their hallucinations and suffered from severe psychological disorders as a result. Even today, most of those who served in the Persian Gulf indicate they have received no followup information about the investigational drugs they received.

It is the responsibility of DOD and VA to identify and keep track of veterans exposed to potentially dangerous substances so that they can receive medical care if needed. Even in situations where DOD believes an investigational drug is safe, such followup is necessary to establish with certainty whether exposures were safe, or whether they resulted in long-term side effects.

L. THE FEDERAL GOVERNMENT HAS FAILED TO SUPPORT SCIENTIFIC STUDIES THAT PROVIDE INFORMATION ABOUT THE REPRODUCTIVE PROBLEMS EXPERIENCED BY VETERANS WHO WERE INTENTIONALLY EXPOSED TO POTENTIALLY DANGEROUS SUBSTANCES.

In the last year, Gulf War veterans have reported that exposures during military service have resulted in miscarriages and birth defects, as well as excruciating pain during sexual intercourse. For example, at a Committee hearing on August 5, 1994, Kelli Albuck, the wife of a Gulf War veteran, described the miscarriage and pregnancy problems she had experienced since her husband returned from the Gulf War. She also described what she called "burning semen" or "shooting fire." Mrs. Albuck stated that many wives of Gulf War veterans complained that their husbands' semen caused a burning sensation, and in her case that the semen itself could cause a rash or blood blister on her husband's leg or her skin. Steve Miller, an Army nurse who also testified at that hearing, had no problems with burning semen, but his son was born with extensive birth defects, including having only one eye and one ear. The doctors told him that the combination of severe birth defects was very unusual and suggestive of a toxic exposure. Mr. Miller believes that his son's birth defects could be related to his use of investigational drugs or vaccines, perhaps in combination with pesticide exposures.

Similarly, many atomic veterans believe that infertility, miscarriages, stillbirths, and birth defects resulted from exposure to ionizing radiation.

Although these reports have received media attention for years, the VA and DOD have not conducted research on these questions, nor have they supported independent research. Finally, 50 years after veterans were intentionally exposed to ionizing radiation, the VA will be required by law to enter into a contract with the Institute of Medicine (IOM), or a similar independent agency, to evaluate whether it is feasible to support research on the reproductive problems associated with exposure to ionizing radiation. If the IOM determines that such research is feasible, the VA and the Congress will then determine whether such research should be funded.[147]

In November 1994, President Clinton signed a law that would require VA to conduct research on birth defects and miscarriages among Gulf War families. A preliminary study will be required, in

[147]The two provisions described in this section are part of Public Law 103-446, the Veterans' Benefits Improvement Act of 1994.

which information about these reproductive outcomes will be included in the Persian Gulf War Veterans' Health Registry. In addition, VA will be required to include semen analysis and other reproductive evaluations in a standard protocol used to evaluate Gulf War veterans with mysterious illnesses.

M. THE FEDERAL GOVERNMENT HAS ALSO FAILED TO SUPPORT SCIENTIFIC STUDIES THAT PROVIDE TIMELY INFORMATION FOR COMPENSATION DECISIONS REGARDING MILITARY PERSONNEL WHO WERE HARMED BY VARIOUS EXPOSURES.

For decades, military personnel who were injured from various exposures have been denied compensation until scientific evidence could support their claims for service-connected disabilities. Although 60,000 military subjects were involved as human subjects in testing programs involving mustard gas and lewisite over 50 years ago, the initiation of a study to review research regarding the long-term health consequences from these military experiments did not occur until 1991, and the results of the study were not published until 1993.[148]

Similarly, the use of Agent Orange and other herbicides in Vietnam has stimulated concern and controversy ever since the United States began the military herbicide program in 1961, but a comprehensive review and evaluation of available scientific and medical information regarding the health effects of herbicides and the contaminant dioxin was not conducted until it was authorized by Congress in 1991.[149] The Department of Veterans Affairs has recently announced new rules for awarding compensation for more Agent Orange-related diseases, three decades after military personnel were exposed to the defoliant in Vietnam.[150]

Reports of the National Research Council's Committee on the Biological Effects of Ionizing Radiation (BEIR), written to advise the U.S. Government on the health consequences of radiation exposure, frequently relied on mortality and morbidity experiences of exposed individuals, some of which took decades to accumulate.[151] Information is continuing to be gathered, which will be incorporated into future BEIR reports.

When investigational drugs and vaccines were given to thousands of military personnel during the Persian Gulf War, this provided an unprecedented opportunity to learn more about the safety of those products. Unfortunately, no effort was made to gather objective information, despite the fact that data gathering is required as part of the IND process for investigational drugs and vaccines.[152] Any research that is conducted years after the war is over will be less

[148]Veterans at Risk, op. cit.

[149]Veterans and Agent Orange, Health Effects of Herbicides Used in Vietnam, Institute of Medicine, National Academy Press, Washington, DC, 1993.

[150]News Release, Office of Public Affairs, Department of Veterans Affairs, Washington, DC, June 13, 1994.

[151]"Health Effects of Exposure to Low Levels of Ionizing Radiation," op. cit.

[152]Hearing, May 6, 1994; prepared statement of Robert J. Temple, M.D., Director, Office of Drug Evaluation, Center for Drug Evaluation and Research, Food and Drug Administration.

scientifically valid and much more expensive as a result of the lack of objective information gathered during the war about which servicemembers took which drugs or vaccines, and the adverse reactions that they experienced.

The Medical Follow-up Agency (MFUA) of the Institute of Medicine will take 3 years to issue its final report on whether there is a scientific basis for an epidemiological study on the health consequences of service in the Persian Gulf.[153] If the MFUA determines such a study or studies should be conducted, it will take several more years to gather the necessary data.

N. PARTICIPATION IN MILITARY RESEARCH IS RARELY INCLUDED IN MILITARY MEDICAL RECORDS, MAKING IT IMPOSSIBLE TO SUPPORT A VETERAN'S CLAIM FOR SERVICE-CONNECTED DISABILITIES FROM MILITARY RESEARCH.

Although hundreds of thousands of U.S. military personnel have been involved in military research, their medical records usually do not contain information about the studies they participated in, or the investigational drugs or vaccines they received.[154] There are currently no standardized guidelines imposed by either the DOD or VA to include a copy of the informed consent form or research proposal in the medical records of exposed human subjects.

Even if medical records contain relevant information regarding health consequences from various investigations, these medical records may be difficult to obtain. Of the 150 individuals who were interviewed for the Committee's survey, not all respondents had tried to obtain their medical records, but 28 (19 percent) indicated that part or all of their medical record were lost and 48 (32 percent) respondents indicated that their medical records were incomplete or inaccurate (Appendix). Some of those surveyed believed their records had been deliberately altered or contained inaccurate information.

The VA Office of Inspector General recently investigated the possible illegal removal of official documents from certain veterans' appeals files assigned to two Board of Veterans' Appeals attorneys.[155] It is unknown whether such intentional removal is a rare occurrence; clearly, any removal of medical information would make it difficult and perhaps impossible for a veteran to receive the medical care and compensation that he or she is entitled to.

In addition to any intentional removal of information, veterans' service medical records are difficult to find. According to the U.S. General Accounting Office, veterans' service medical records can

[153]Public Law 102-585, § 706, November 4, 1992, Agreement with National Academy of Sciences for Review of Health Consequences of Service during the Persian Gulf War.

[154]"It is likely that a great majority of ground personnel [in the Persian Gulf] received at least one dose and probably up to the full 21 tablets [of pyridostigmine] dispensed," National Institutes of Health Technology Assessment Workshop, "The Persian Gulf Experience and Health," final statement issued June 22, 1994, p. 10. The workshop was held April 27-29, 1994.

[155]News Release, Office of Public Affairs, Department of Veterans Affairs, July 20, 1994.

potentially be in thousands of locations.[156] The DOD has attempted to simplify the retrieval of medical records by modifying the route for medical records of individuals who have left the military. The simplified route was initiated for the Army in October 1992, for the Navy in February 1994, and for the Air Force and Marines in late 1994. Although the new procedures should simplify the process, the GAO concluded that the possibility of misplaced medical records remains because there are still thousands of locations where records could be found within the new system.

O. DOD HAS DEMONSTRATED A PATTERN OF MISREPRESENTING THE DANGER OF VARIOUS MILITARY EXPOSURES THAT CONTINUES TODAY.

According to Dr. Leonard Cole, professor at Rutgers University, the DOD has denied the possibility of harm from various exposures. However, in many instances the military belatedly recognized that some exposures may be causing disease and death.[157] Such denial, however, delays the availability of medical assistance to those harmed.

For example, the military has released chemicals and biological agents through outdoor "open air" tests for over four decades. Some of these supposedly safe chemicals and biological agents, referred to as simulants, were also released over populated areas and cities.[158] Although scientific evidence suggested that the tests may have caused illnesses to exposed citizens, the Army repeatedly claimed that these bacteria and chemicals were harmless until adverse health effects convinced them to change the simulants used. The death of Edward J. Nevin was associated with the release of one simulant, Serratia marcescens, over San Francisco in 1950.[159] A subsequent court trial revealed that on September 26 and 27, 1950, the Army sprayed Serratia marcescens from a boat off the coast of San Francisco.[160] On September 29, patients at the Stanford University Hospital in San Francisco began appearing with Serratia marcescens infections. Although the judge denied the validity of the plaintiffs' claims that the exposures were related to the death of Mr. Nevin, the trial raised frightening questions about the selection of simulants. Serratia marcescens is no longer used by the military as a simulant.

Dugway Proving Ground has been a site for "open air" testing of chemical and biological agents for decades. The purpose of the tests is to determine how the agents spread and survive, and their effect on people and the environment. Earl Davenport is a veteran who participated in tests at Dugway Proving Ground in Utah, first as a military employee and later as a civilian employee. He became ill in

[156]B-257173, GAO letter to Senator John D. Rockefeller IV, Chair, Senate Committee of Veterans' Affairs, on the location of veterans' service medical records, May 4, 1994.

[157]Hearing, May 6, 1994; testimony of Leonard A. Cole, Ph.D., professor, Rutgers University.

[158]Ibid.

[159]*San Francisco Chronicle,* December 22, 1976, page 1.

[160]Cole, L.A. Clouds of Secrecy, The Army's Germ Warfare Tests Over Populated Areas, Rowman and Littlefield, 1988, pp. 75-104.

1984 after being exposed to a chemical simulant called DMMP (dimethyl methylphosphate). He had been spraying the chemical into the path of a laser beam when a sudden change in wind blew the chemical all over his face and hair before he was able to put on a protective mask. Although he was "wheezing and coughing" the next day, and his symptoms lasted for weeks, the Dugway Army Hospital merely gave him cough medicine and antibiotics. The Dugway Safety Office assured him that the chemical was safe. However, by 1988, officials at Dugway had reevaluated the simulant's danger, and were becoming concerned that DMMP could cause cancer and kidney damage.[161] Mr. Davenport is currently attempting to obtain compensation for his illness from the Department of Labor, since his exposure occurred when he was employed at Dugway as a civilian.

In 1992, several military personnel from the Arizona National Guard experienced chemical burns during a summer training exercise at the Dugway Proving Grounds. According to two physicians, a daughter from one of the guardsmen also received chemical burns when she later handled her father's duffle bag. One of these doctors, Dr. Michael Vance, was contacted by military officials and encouraged to modify his written findings on the possible cause of the daughter's injury.[162] He refused.

According to scientists and doctors from the University of Utah, there is great concern over the potential health consequences not only for military personnel who work and train at Dugway, but also for civilians who live in a small town and on an Indian reservation near the Proving Grounds.

Moreover, physicians from the Utah Medical Society have complained about the lack of information provided to the medical community about the agents that are used in Dugway, despite repeated requests.[163]

According to Dr. Cole, the use of potentially harmful chemical and biological agents continues at Dugway even today. For example, he testified that the Army uses a simulant called Bacillus subtilis, "which is fairly harmless in many natural conditions, [but] 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."[164]

Dr. Cole also testified about the lack of informed consent at Dugway in recent months. For example, in November 1993, a test that was intended to evaluate whether chemical agents could penetrate protective clothing used informed consent forms that did not mention the chemicals.[165]

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[161]Hearing, May 6, 1994; testimony of Earl P. Davenport, veteran and former employee, Dugway Proving Ground.

[162]Memorandum of phone interview with Dr. Michael Vance, Good Samaritan Hospital, Phoenix, AZ, March 21, 1994; in Committee files.

[163]"UMA Seeks Health and Safety Controls at Dugway," *Bulletin of the Utah Medical Society*, May 1992, Vol. 40, No. 5, p. 1; "UMA Joins Lawsuit Against Army," *Bulletin of the Utah Medical Society*, June 1992, Vol. 40, No. 6, p. 1; in Committee files.

[164]Hearing, May 6, 1994; testimony of Dr. Cole.

[165]Ibid.

IV. STAFF RECOMMENDATIONS

A. FDA SHOULD DENY THE DEPARTMENT OF DEFENSE REQUEST FOR A "BLANKET WAIVER" TO USE INVESTIGATIONAL DRUGS WITHOUT INFORMED CONSENT IN CASE OF WAR OR THREAT OF WAR.

If investigational drugs are deemed necessary for protection or treatment, a waiver of informed consent should be sought only on a case-by-case basis. While the military might order individuals to take an investigational drug or use an investigational device if it is clearly safe and potentially efficacious, under no circumstances should the DOD fail to inform individuals about the known short-term and long-term risks prior to its administration.

In 1990, DOD applied to FDA for a waiver of informed consent, claiming they would provide warnings orally and in writing regarding the risks of pyridostigmine, even though they would not give soldiers the choice of whether or not to take it. According to reports from various sources, including DOD's own study, DOD did not fulfill its promise. In addition, DOD personnel apparently distributed these drugs to civilians without any warnings. These failures and broken promises should be sufficient to persuade FDA to reject the DOD request for a blanket waiver, and should be taken into consideration any time DOD applies for a waiver of informed consent. In addition, FDA should investigate these problems and work with DOD to prevent similar problems in the future.

In addition, third-party or "deferred" consent should not be considered unless the individual receiving the drug is physically or mentally incompetent to make an informed decision on his/her behalf. If the DOD fails to obtain the necessary waivers, or fails to adequately inform those receiving the investigational products, DOD should be required to provide a written explanation to the appropriate congressional committees.

B. FDA SHOULD REJECT IND AND NDA APPLICATIONS FROM DOD THAT DO NOT INCLUDE DATA ON WOMEN AND LONG-TERM FOLLOWUP DATA.

When DOD submits an IND (investigational new drug) application or NDA (new drug application) to FDA for any product that they plan to use, they should always be required to include women in their research, since it is likely that the product will be used by women. On the basis of that requirement, FDA should reject the currently pending NDA for pyridostigmine's use as an antidote enhancer, which was submitted to FDA in early 1994.

At a Senate briefing in November 1994, Dr. Ruth Merkatz, FDA's Associate Commissioner for Women's Health, stated that FDA will always require data on women in future drug approval applications, if the product under review is intended for use by women. However, Dr. Merkatz was not specific about whether this policy would apply to DOD.

In addition to data on women, it is increasingly clear that drugs can have long-term adverse reactions that are not immediately obvious. Given the responsibility of the Federal Government to

provide medical care to veterans who were harmed during military service, DOD and FDA need to ensure that the VA and the public are aware of any potential long-term adverse reactions of any medical products that are given to military personnel.

In the case of pyridostigmine, a drug that DOD wants to have the authority to use in future conflicts in the Persian Gulf and elsewhere, FDA should immediately urge DOD to conduct the kinds of research that is needed to prove its safety for future military use, including research on its potentially toxic effects when combined with insecticides and other chemical agents that are commonly used by military personnel.

C. CONGRESS SHOULD AUTHORIZE A CENTRALIZED DATABASE FOR ALL FEDERALLY FUNDED EXPERIMENTS THAT UTILIZE HUMAN SUBJECTS.

Currently, the U.S. Department of Agriculture maintains a database which can identify the number of research grants awarded for studying various species, such as beef and dairy cattle, poultry, sheep, swine, and others.[166] However, a database which identifies the types of human subjects does not exist.

Congress should authorize a database which would provide crucial information on federally funded research utilizing human subjects. Included in this database should be the amount of Federal dollars spent on various research efforts and the type of human subjects utilized, such as women, minorities, children, prisoners, military personnel, and others.

Annual reports from the data collected should be provided to Congress. Such information would enable legislators to understand better the use of human subjects in federally sponsored research.

D. CONGRESS SHOULD MANDATE ALL FEDERAL AGENCIES TO DECLASSIFY MOST DOCUMENTS ON RESEARCH INVOLVING HUMAN SUBJECTS.

Information involving human subjects in military research, which remains classified for purported reasons of national security, needs to be reevaluated and declassified whenever possible. All Federal agencies should scrutinize classified information and make information available which might benefit individuals who participated in such research.

E. CONGRESS SHOULD REESTABLISH A NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS, WITHOUT A TERM LIMIT, WHICH HAS THE AUTHORITY TO INVESTIGATE POTENTIAL VIOLATIONS OF HUMANS SUBJECTS' RIGHTS IN FEDERALLY FUNDED RESEARCH.

A National Commission should standardize Federal regulations (45 CFR 46), and consider adding military personnel as a vulnerable population. Policies for the conduct of research in war or for the purposes of national security should receive greater public debate. No

[166]Phone interview, Patrick Casula, Office of Grants and Program Systems, U.S. Department of Agriculture, October 12, 1994.

existing regulations governing military personnel should be finalized without such public dialogue.

Congress should provide authorization and appropriations for the National Commission, and require annual reports on potential violations of human subjects' rights. The administrative body of the Commission should consist of nine members, three appointed by the majority party in Congress, three appointed by the minority party in Congress, and three appointed by the executive branch.

F. THE DEPARTMENT OF VETERANS AFFAIRS AND THE DEPARTMENT OF DEFENSE SHOULD IMPLEMENT REGULAR SITE VISITS TO REVIEW THE PERFORMANCE OF INSTITUTIONAL REVIEW BOARDS.

DOD and VA authorized site visits should include an evaluation of military and VA research onsite, and a random sample review of actual research and medical records, interviews with human subjects, and signed consent forms to assure investigator compliance. A mechanism should be in place whereby human subjects can express concern over perceived or actual violations of the informed consent contract. This mechanism should allow human subjects to register complaints to a regulatory agency and the National Commission, rather than solely the investigator of the research project. All military personnel and veterans involved in research should receive a copy of the "Experimental Subject's Bill of Rights."[167]

G. THE FERES DOCTRINE SHOULD NOT BE APPLIED FOR MILITARY PERSONNEL WHO ARE HARMED BY INAPPROPRIATE HUMAN EXPERIMENTATION WHEN INFORMED CONSENT HAS NOT BEEN GIVEN.

The U.S. Supreme Court has interpreted the Feres Doctrine to mean that soldiers "injured in the course of activity incident to service" may not sue the Government for compensation.[168] However, when inappropriate experimentation has resulted in suffering for military personnel, this interpretation stands in violation of established ethical standards, including the Nuremberg Code, the Declaration of Helsinki, and the "Common Rule." Congress should not apply the Feres Doctrine for military personnel who are harmed by inappropriate experimentation when informed consent has not been given.

The U.S. Supreme Court mentioned the Nuremberg Code in *United States v. Stanley* in 1987. James Stanley, an Army serviceman, volunteered to test the effectiveness of protective clothing and equipment against chemical warfare in February 1958.[169] In the process, he unknowingly received LSD as part of an Army study to determine the effects of the drug on humans. Although Stanley suffered from periods of incoherence and memory loss for years, he

[167]"Summary of Findings and Recommendations, Review of the Office of Health and Environmental Research Program, Protection of Human Research Subjects," Subcommittee of the Health and Environmental Research Advisory Committee, U.S. Department of Energy, May 1994.

[168]Annas, G.J. & Grodin, M.A. "The Nazi Doctors and the Nuremberg Code," Human Rights in Human Experimentation, Oxford University Press, 1992, p. 209.

[169]Ibid., pp. 212-214.

only learned in 1975 that he had participated in the LSD study when the Army solicited his cooperation in a followup study. Having been denied compensation for injury by the Army, Stanley filed under the Federal Tort Claims Act. Justice Antonin Scalia wrote the opinion for the Court, split 5 to 4.[170] Justice Scalia wrote that permitting Stanley to sue the Army would disrupt the Army itself and "would call into question military discipline and decision-making." However, Justice Sandra Day O'Connor, writing for herself as one of the dissenting judges, stated that the Feres doctrine bar

> "surely cannot insulate defendants from liability for deliberate and calculated exposure of otherwise healthy military personnel to medical experimentation without their consent, outside of any combat, combat training, or military exigency..."[171]

Justice O'Connor also commented on the Nuremberg Code in her writing, stating that voluntary consent of the human subject is absolutely essential, even for the U.S. military. It was, after all, the U.S. military who played an instrumental role in the criminal prosecution of the Nazi officials who experimented with human beings during World War II.

[170]*United States v. Stanley*, 107 S. Ct. 3054 (1987), cited in "The Nazi Doctors and the Nuremberg Code," Human Rights in Human Experimentation, Annas, G.J. & Grodin, M.A., Oxford University Press, 1992, pp. 212-214.

[171]Ibid.

APPENDIX

Survey of 150 Persian Gulf War Veterans

Male respondents: 120 [80%]
Female respondents: 30 [20%]

Active duty servicemembers: 46 [31%]
Retired: 4 [3%]
Temporarily disabled retirement list: 2 [1%]

Active reservists: 46 [31%]

Veteran: 15 [10%]
Individual ready reserves: 10 [7%]
National Guard: 27 [18%]

Those ill since returning from Gulf: 136 [91%]
Those who had ill family members: 60 [40%]

Those who identified at least one investigational drug that they took: 75 [50%]

ANTHRAX—
Number of respondents who received anthrax: 68 [45%]
1 vaccination: 31 [46% of those who received anthrax]
2 vaccinations: 31 [46%]
3 vaccinations: 2 [3%]
Unknown number: 4 [6%]

Of those receiving anthrax vaccinations, those who:
received no oral or written information about the vaccine: 61 [90%]
were told they could not refuse it: 58 [85%]
described immediate side effects: 29 [43%]

Of the women receiving anthrax vaccination, those who received no warning on risk if pregnant: 12/16 [75%]

BOTULINUM TOXOID—

Number of respondents who received botulinum toxoid: 17
- **1 vaccination:** 10 [59% of those who received botulinum toxoid]
- **2 vaccinations:** 3 [18%]
- **Unknown number:** 4 [24%]

Of those receiving botulinum toxoid, those who:
- **received no oral or written information about the vaccine:** 13 [76%]
- **were told they could not refuse it:** 15 [88%]
- **described immediate side effects:** 6 [35%]

Of the women receiving botulinum toxoid, those who received no warning on risk if pregnant: 4/4 [100%]

PYRIDOSTIGMINE BROMIDE—

Number of respondents who took pyridostigmine bromide: 73 [49%]

Of those taking pyridostigmine bromide, those who:
- **received no oral or written information on side effects:** 63 [86%]
- **were told they could not refuse it:** 54 [74%]
- **described immediate side effects:** 38 [52%]
- **did not comply and take drugs when they were supposed to:** 14 [19%]

Of the women receiving pyridostigmine bromide, those who received no warning on risk if pregnant: 14/18 [78%]

OTHER SURVEY INFORMATION—

Number of respondents who received a vaccination but did not know what it was: 25 [17%]

Number of respondents who received a drug but did not know what it was: 28 [19%]

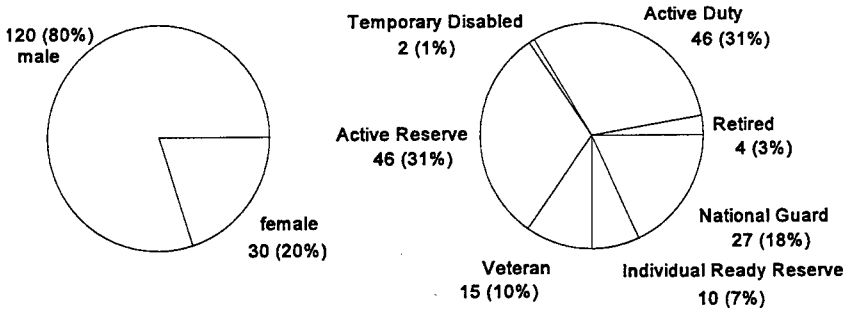
Number of respondents who have not received any information following the Persian Gulf War concerning investigational drugs from either VA or DOD: 128 [85%]

Concerning medical records:
- **Medical record is incomplete/inaccurate:** 48 [32%]
- **Medical record [part or all] is missing/lost:** 28 [19%]

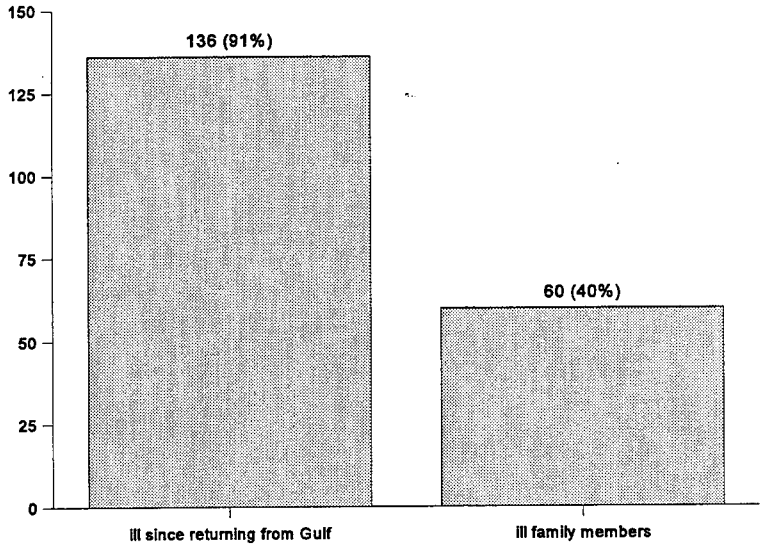
25 MOST COMMON SYMPTOMS REPORTED
[number of respondents reporting]

Fatigue	65
Skin problems	61
rashes	50
Memory loss	59
blackouts, forgets where they are	5
Joint pain	55
Headaches	52
Personality changes	44
Diarrhea	32
Muscle pain, weakness, spasms, tremors	29
Pain [back, shoulder, neck, etc]	28
Trouble with vision	24
Shortness of breath	22
Sleep disturbances	22
Hair loss	19
Numbness [hands, fingers, feet]	19
Dental problems/bleeding gums	18
Reproductive problems	18
Bleeding	16
Sores	14
Chest problems [pain]	12
Abdominal/stomach pain	12
Fever	10
Nausea/vomiting	10
Dizziness/staggering	10
Sinus, nasal discharge	9
Sensitivity to light, smell, noise	9
Children born with birth defects	7
Partners with reproductive problems	16

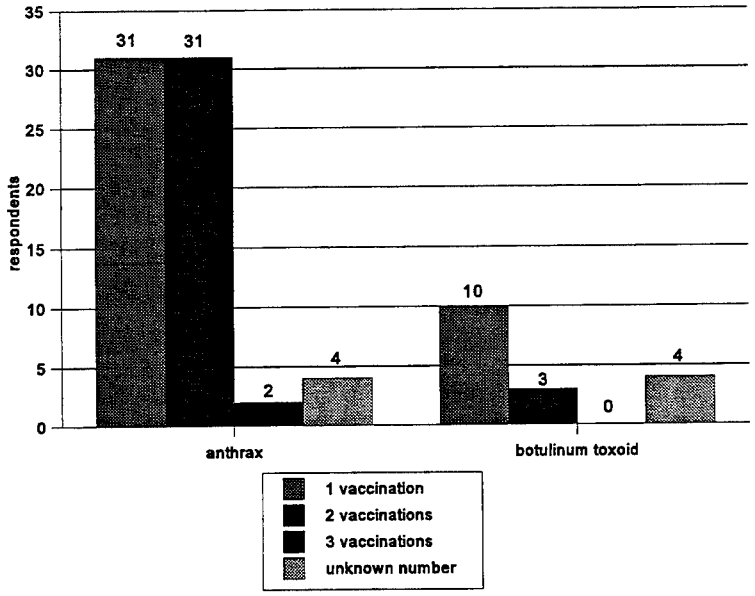
Profile of 150 Survey Respondents



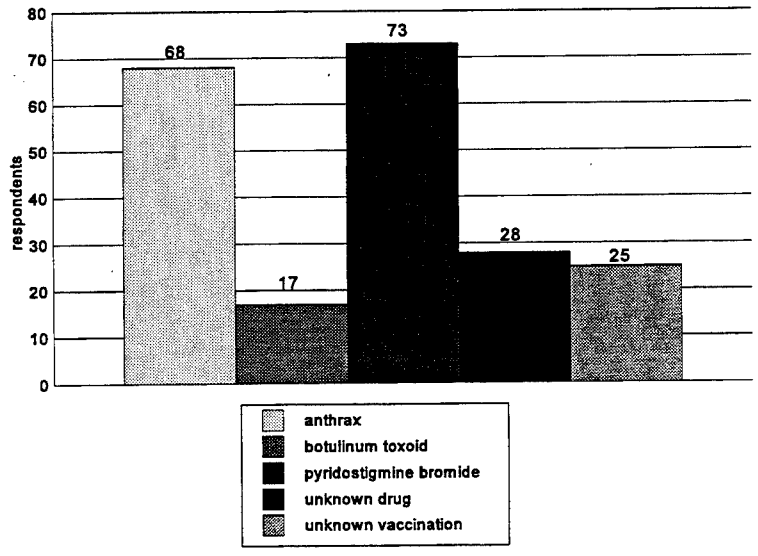
Survey of 150 Persian Gulf War Veterans



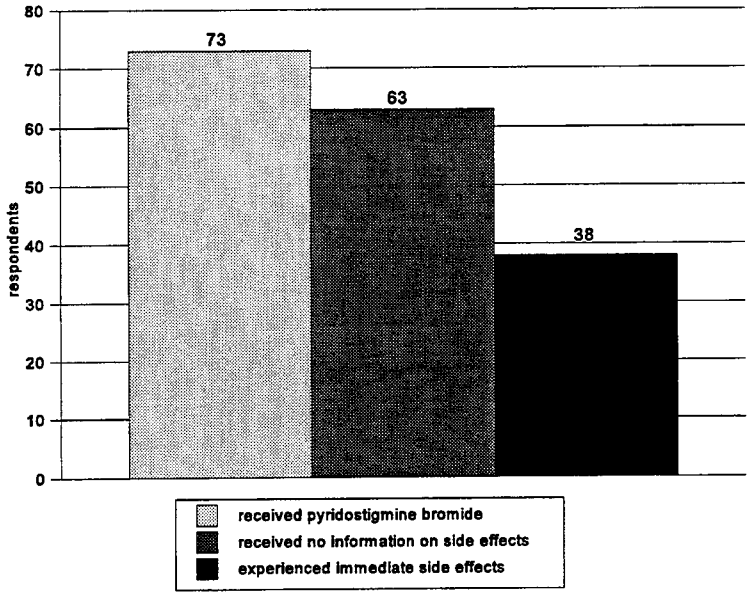
Respondents Receiving Vaccines



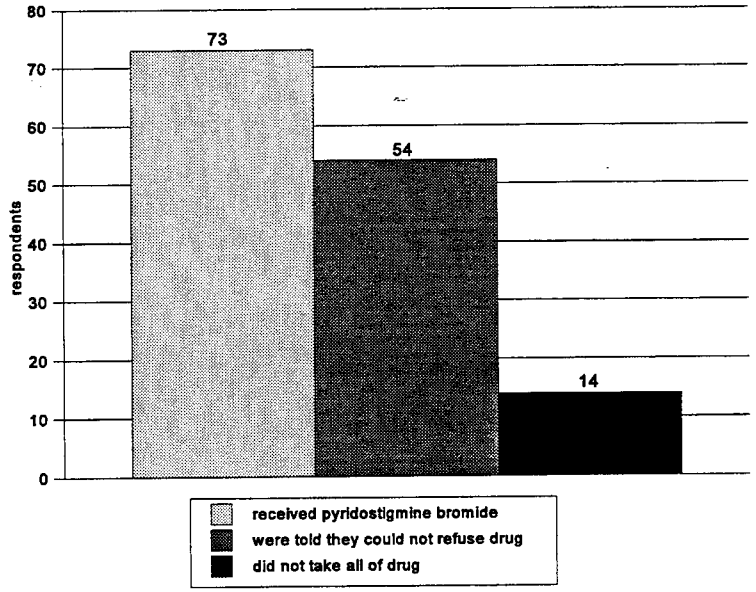
Respondents Receiving Investigational Drug or Vaccine



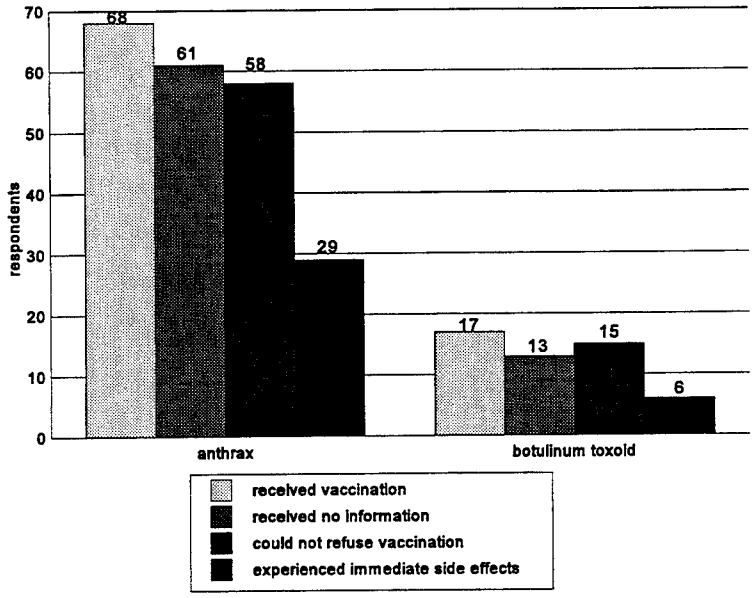
Pyridostigmine Bromide and Side Effects



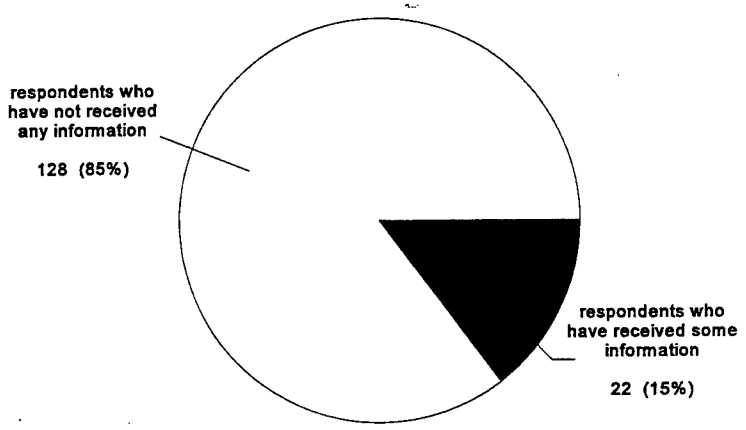
Pyridostigmine Bromide Taken by PGW Veterans



Vaccines Administered and Side Effects



Information from VA or DOD concerning investigational drugs, provided to PGW veterans



Medical Records of Veterans Surveyed