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Human experiments using military service members have been an integral part of the U.S. chemical weapons program since its beginnings, resulting in tens of thousands of "soldier volunteers" having been exposed in experiments to a wide range of chemical agents, from World War 1 to about 1975. By the end of World War 2, nearly 60,000 U.S. service members had been used as human subjects, primarily with mustard agent and Lewisite (NAS 1993).

Additional concerns have focused on more recent experiments involving thousands of U.S. service members at U.S. military facilities, primarily at U.S. Army Laboratories at Edgewood Arsenal, Maryland, from 1955 to 1975. There are increasing concerns among veterans about possible long-term health effects among these subjects, and the U.S. Department of Veterans Affairs (VA) has announced a commitment to contact those involved with information about relevant health issues. Potential long-term health consequences is a key issue, but the desire to get to the truth about these events for participants and to the world is also an important concern. The history of chemical agent testing using "soldier volunteers," with a focus on experiments conducted at military facilities at Edgewood/Aberdeen, Maryland and related locations, are the focus of this review.

The U.S. VA, with support and cooperation from the U.S. Department of Defense (DoD), has made significant efforts to identify participants in the Edgewood/Aberdeen experiments (as well as earlier testing), notify them of their involvement, offer them access to VA health care, and to evaluate potential long-term health consequences. However, these efforts are significantly hampered by the lack of adequate records on subject identity, and the magnitude and identity of the agents they were exposed to. Complicating any evaluation, many subjects were used in multiple experiments involving exposure to a range of different agents. Finally, poor record keeping and the passage of decades have made it difficult to locate veterans of these experiments today. To help address these problems in the future, study protocols and institutional review board approvals of human subjects research involving military personnel should require careful documentation of experimental exposures and of the identity of experimental subjects.

HISTORY OF U.S. CHEMICAL WARFARE AGENT HUMAN EXPERIMENTS.

The United States has maintained an active biological and chemical warfare program since World War 1. Part of this program involved the large-scale testing, manufacture and stockpiling of chemical warfare agents and munitions. By the early 1990s, the US chemical weapon stockpile included an estimated 25,000 tons of chemical warfare agents, including organophosphorus (OP) nerve agents such as sarin and VX, and vesicant (blister) agents including mustard and Lewisite. Today, virtually everyone agrees that this stockpile is obsolete, and federal law and international agreements require that it be destroyed.

A significant part of this program involved experimentation using U.S. service member "soldier volunteers," which ended only in 1975. Many experiments were intended to enhance defensive capabilities, such as improved protective clothing and respiratory masks. Others attempted to evaluate the impact of chemical warfare agents upon the operational readiness of military personnel in the event of a combat exposure. Some tests evaluated the effectiveness of incapacitating and "brainwashing" agents such as cannabinoids and LSD. Human subjects were

part of this program from the beginning. However, the experimental program's scope, including the number of service members involved and the chemical warfare agents tested, has changed greatly over time.

Although these experiments were originally conducted in secret, today a great deal of information about them is available in the open literature. Sources include relevant Congressional hearings and media accounts. Some of the most detailed information is in reports from the National Research Council/National Academy of Sciences, commissioned by VA and DoD, which focus on long-term health consequences as well as wide ranging historical details about these experiments.

Although no longer secret, the history of these experiments, including how participants may have been affected, is not widely known. This review describes these events to help health care providers respond to clinical needs of affected patients. Perhaps more importantly, it may help providers appreciate the reality of this story, and support meaningful discussions with patients about their current concerns.

Finally, VA's and DoD's strong commitment to notify affected veterans and offer access to optimal health care has been hampered by the lack of relevant military records and related problems locating veterans who were involved in events that took place decades ago. During the height of the Cold War researchers probably gave little thought of future interest in identifying and tracking down subjects to evaluate potential long-term health consequences and for outreach purposes. To address these problems in the future, study protocols and institutional review board approvals of human subjects research involving military personnel should require careful documentation of experimental exposures and of the identity of experimental subjects.

Early Experiments Through World-War 2. The chemical warfare agent sulfur mustard (or just "mustard agent") caused nearly 400,000 casualties during World War 1 -- more than from any other chemical agent used during that conflict (NAS 1993). In World War 2, Germany used mustard agent against Polish citizens in 1939, and in response, the United States developed its own chemical warfare program. From relatively small beginnings, the U.S. chemical warfare program expanded. During this period, U.S. military planners concluded that animal studies were not an adequate substitute for human studies, and in 1942 U.S. chemical weapons program managers were given authority to recruit and use volunteer subjects (NAS 1993).

By the end of World War 2, over 60,000 U.S. service members had been used as human subjects in the U.S. chemical warfare defense research program (NAS 1993). At least 4,000 subjects participated in mostly classified experiments involving exposures to hazardous concentrations of mustard agents or Lewisite, in gas chambers or field exercises over contaminated ground areas. Research focused primarily on developing better weapons and improved protection methods. Subjects were exposed often to acutely toxic levels of agents via small drops applied to the arm or to clothing, or in gas chambers, sometimes without protective clothing (NAS 1993). In some experiments, subjects were repeatedly placed in gas chambers and exposed to mustard agent or Lewisite vapor sufficient to cause erythema (skin reddening) (NAS 1993). Finally, field tests involved contamination of large or small areas of land with sulfur mustard or Lewisite – human subjects were used in field tests to test protective clothing (NAS 1993).

Gas chamber experiments evaluated the effectiveness of protective clothing including gas masks. Subjects exposed in chambers for 1 to 4 hours were evaluated twenty-four hours later for

erythema as evidence of protective clothing failure (NAS 1993). Subjects often repeated this procedure every day or every other day until they developed moderate to intense erythema (NAS 1993). Most test subjects experienced intense, widespread erythema, especially in moist areas of skin folds, such as behind the knees and under the arms, in large areas of the chest and shoulders, and on their arms and legs (NAS 1993). Some experiments apparently involved less protected subjects who were reported to have experienced severe burns to the genital areas, including cases of crusted lesions to the scrotum (NAS 1993).

Documented injuries among subjects with various exposure routes was initially "quite high" -- one study of accidental injuries identified over 1,000 cases of acute mustard agent toxicity resulting in eye, ear, nose and throat symptoms occurred at Edgewood Arsenal over a 2-year period (NAS 1993). Nevertheless, the NAS and NRC reported that they had no studies of long-term health effects in this population to evaluate for their review (NAS 1993).

Accidents with Chemical Warfare Agents. Large scale chemical warfare preparations during this period involved numerous military and civilian personnel. By the end of the second World War, the U.S. had produced more than 87,000 tons of sulfur mustard, 20,000 tons of Lewisite, and 100 tons of nitrogen mustard, at Edgewood Arsenal, MD, Huntsville Arsenal, AL, Pine Bluff Arsenal, AR, and Rocky Mountain Arsenal, CO (NAS 1993). Tens of thousands of military and civilian workers were involved in production of these agents. Accidental exposures occurred when service members trained or otherwise came into contact with chemical weapons.

Similarly, a German bombing attack in December 1943 on U.S. ships loaded with mustard agent in the Italian harbor of Bari, Italy, released mustard agent into the air and water, which caused thousands of injuries and hundreds of deaths among U.S. service members and others in the area. Over 600 victims were treated from the harbor area alone, of which 83 died (NAS 1993). Close to 1,000 civilians from the town also died. Ironically, this was the only incident involving military use of mustard agent (or Lewisite) during World War 2 (NAS 1993).

Post World-War 2 – Edgewood/Aberdeen Experiments. The close of World War 2 led to a reduced interest in human experimentation with mustard and Lewisite (NAS 1993). However, by the 1950s, DoD again became interested in human testing – this time with a focus upon newer potential more effective chemical warfare agents, including the organophosphorus (OP) military nerve agents, nerve agent antidotes, incapacitating agents such as tear gas, and psychoactive agents such as LSD, PCP and synthetic cannabinoid (derived from marijuana) analogs (NAS 1993, NRC 1982). Renewed interest led to renewed human testing, although on a much smaller scale.

From the 1955 to 1975, approximately 6,720 soldiers took part in experiments involving exposure to more than 250 different chemicals administered by various routes at U.S. Army Laboratories (formerly Army Chemical Center) at Edgewood Arsenal, Maryland (NRC 1982, NRC 1984, NAS 1993). Some experiments involved exposures to placebos or common agents such as caffeine and alcohol. Related testing also occurred at other military facilities during this period, and other agencies, including the CIA and the Special Operations Division of the Department of the Army, also reportedly were involved in these studies (NAS 1993).

The more than 250 agents tested represented about half a dozen pharmacological agent classes, including common approved pharmaceutical agents (Table 1), anticholinesterase nerve agents (e.g. sarin and common OP and carbamate pesticides), glycolate anticholinergic agents (e.g.,

nerve agent antidotes atropine, scopolamine, and BZ), nerve agent reactivators (e.g., the common OP antidote 2-PAM and related compounds), psychoactive compounds (e.g., LSD and PCP), cannabinoids (related to the active ingredient of marijuana), and irritants (e.g., tear gases) (Tables 2 - 4). Table 5 shows the agent class and median year for the Edgewood/Aberdeen experiments.

Many tests were designed to evaluate acute (i.e., immediate) human toxic effects (NRC 1982). Anticholinesterase and anticholinergic agents were administered to approximately 3,200 subjects, or "almost half of some 6,700 subjects were exposed at Edgewood" (NRC 1984). The NRC evaluated potential long-term health effects among 750 subjects exposed to four cholinesterase reactivators (i.e., anticholinesterase antidotes such as 2-PAM), 260 subjects exposed to phencyclidine (PCP or "Angel Dust") or to 10 cannibinoid psychochemicals, and 1,500 subjects exposed to irritants and vesicants including CN, CS, other "tear gas" type irritants, and mustard agent. Anticholinesterases and anticholinergic agents were also purposefully tested in combination, since members of each are used as treatment for overexposure to the other (NRC1982). These agent classes were tested on most of the remaining volunteer subjects involved in the Edgewood/Aberdeen tests (NRC 1984).

Relevant to today's heightened concerns by veterans and their supports, congressional hearings into these experiments in 1974 and 1975 resulted in disclosures, eventual notification of some subjects as to the nature of their chemical exposures, and compensation of a few families of those who had died while serving as human subjects (NAS 1993).

Biological Agent Human Experiments. This review focuses on major events in the U.S. chemical warfare agent test program, and particularly on the Edgewood/Aberdeen experiments. However, similar experiments involving biological agents and human subjects were also carried out during this period. For example, beginning in 1954 and over the next 18 years, about 2,300 military draftees, most of them stationed at Ft. Detrick, MD, and primarily consisting of Seventh-Day Adventists, volunteered for Operation Whitecoat (Washington Post 2003). This involved about 153 tests from 1955 to 1973. Test subjects were reportedly exposed to a variety of biological agents including tularemia, Venezuelan equine encephalitis, and sand-fly fever (Washington Post 2003). These tests also involved human exposure to Q fever at Dugway Proving Ground, Utah, in 1955. Although many test subjects became ill from the exposures, apparently none of the "Whitecoat" volunteers were reported to have died as a result of these tests (Washington Post 2003). However, Army officials acknowledge that little is known about what happened to these test subjects over the long-term. Strikingly, all volunteers reportedly signed consent forms prior to testing (Washington Post 2003).

SHAD and Project 112 Tests. From 1963 through the early 1970s, DoD conducted tests known as "Project 112," with chemical and biological warfare agents as well as less hazardous simulants, to evaluate the effectiveness of various protective and detection measures on both land and at sea. Shipboard tests were dubbed "Shipboard Hazard and Defense," or simply "SHAD."

In 2000, responding to a request from Secretary of Veterans Affairs, DoD began declassifying and sharing information with VA about the medical aspects of these tests, and the identities of those involved. Since May 2002, using declassified information provided by DoD, VA has been notifying veterans who took part in the Project SHAD and Project 112 tests, and encouraging them to come to VA medical facilities if they have any related health concerns.

DoD has stated that the military personnel involved in these tests were not actually test subjects, but rather were only involved as test conductors Further, DoD offered the reassurance that procedures were taken during the tests to protect these test conductors from hazardous exposures, and that no veteran became ill during these experiments. Despite these assurances, there has been a perception by some that military personnel may have been in some cases the unwitting subjects of secret military experiments involving their deliberate exposure to hazardous agents.

Based on DoD's declassification efforts, today we know that a wide range of chemical and biological warfare agents, less hazardous simulants, and disinfectant agents were used in SHAD and Project 112. Tested biological warfare agents included *Coxiella burnetii, Francisella tularensis*, and Staphylococcal Enterotoxin B. Biological agent simulants were also tested as relatively non-toxic substitutes with similar physical properties as actual biowarfare agents. These included *Bacillus globigii* (BG), *E. coli*, *Serratia marcscens* and zinc cadmium sulfide. Although these biological agent simulants were considered to be safe at the time they were used, we understand today that they can be opportunistic pathogens under certain unusual circumstances – circumstances that are probably not relevant to most active duty personnel.

SHAD and Project 112 tests also involved most of the organophosphorus chemical warfare nerve agents in the U.S. arsenal at that time, including Sarin, VX, Tabun and Soman. The majority of tests involved chemical warfare agent simulants such as methylacetoacetate or sulfur dioxide, which had similar physical properties such as vapor pressure, but without the acute lethal toxicity of the actual chemical warfare agents.

DoD also used a number of common agents for sterilizing surfaces, presumably following experiments with biological agents. These included β-propiolactone, ethyl alcohol, Lysol, peracetic acid, potassium and sodium hydroxide, and sodium hypochlorite (common bleach).

Literature on long-term health effects from biological agents used in Project 112 indicates such effects are unlikely in the absence of observable health problems at the time of exposure (VA 2002). These infectious agents are not associated with latent infections in the absence of acute and symptomatic illness. Similarly, in general, the chemical agents used in project SHAD are most likely to have produced long-term health effects only if they caused clinically significant effects during or shortly after exposure. However, there are few good, long-term studies of the health effects of exposure to low levels of the agents used in these tests. Consequently, VA has contracted with the Institute of Medicine (IOM) to conduct a comprehensive study of potential long-term health effects among SHAD test conductors.

A GROWING AWARENESS

The secrecy under which these experiments took place continues to impact our ability to respond to the health concerns of affected veterans. Many subjects were told at the time of these experiments that they should never reveal what happened, and apparently most kept this secret for the next 4 decades or more (NAS 1993). During their investigations of World War 2 mustard and Lewisite experiments, the 1993 IOM committee complained that an "atmosphere of secrecy still exists to some extent regarding the World War Two testing program." "As a result, the committee often had great difficulty obtaining information." "The committee is certain that

other relevant information exists that was never obtained." "It is also clear that there may be many exposed veterans and workers who took an oath of secrecy . . . and remain true to that oath even today." Their burden was compounded by the secrecy oath taken by the veterans and that they generally kept for nearly 50 years (NAS 1993). Finally, these same veterans have endured the denials by government agencies that such tests and related activities ever occurred (NAS 1993).

Public attention inevitably increased when participants in World War 2 era experiments began to seek compensation from VA for health problems that they believed had been caused by the experimental exposures during the Cold War or before. These veterans faced significant hurdles in establishing such claims because typically little or no supporting documentation was available. Commonly, the periods spent as volunteers in the World War 2 mustard agent and Lewisite experiments were unaccounted for in official service records (NAS 1993). Compounding veterans' difficulties, there was little scientific or medical information on long-term health effects from these exposures – existing literature focused nearly exclusively upon short-term effects.

Mounting pressure from veterans, the media and Congress on VA to address veterans' health concerns led VA's Secretary in June 1991, to announce new guidelines for compensation of veterans who had been subjects in the World War 2 mustard and Lewisite experiments. Those guidelines loosened the normal restrictions requiring documentation of participation, and identified certain illnesses that VA acknowledged as long-term effects from exposure to mustard agent and Lewisite chemical warfare agents. These include asthma, chronic laryngitis, chronic bronchitis, emphysema, corneal opacities, chronic conjunctivitis and keratitits of the eye. The Secretary also requested the National Academy of Sciences Institute of Medicine (IOM) to review relevant scientific literature on human health effects from exposure to mustard and Lewisite during World War 2, which was published in 1993 (NAS 1993).

Call for Independent Evaluation. In the early 1980s, DoD requested the National Research Council (NRC) to evaluate long-term health effects to the 6,720 servicemen subjects in the Edgewood/Aberdeen experiments in Army Laboratories from 1955 to 1975. This resulted in a series of three reports entitled "Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents" (NRC 1982, 1984, 1985). These three reports included reviews of the medical and scientific literature on the possible long-term health effects from exposure to the agents involved, and an epidemiological study of participants of these experiments that had been conducted from 1958 to 1975. Overall, the NRC concluded that long-term health effects among subjects were probably minimal, but that gaps in scientific knowledge about such effects made conclusions necessarily tentative. Results of the epidemiological study were also generally negative. These evaluations of potential health effects among the more recent Edgewood/Aberdeen subjects complemented the 1993 VA-requested IOM study on health effects of earlier World War 2 participants in experiments involving mustard and Lewisite.

Comparing Past and Current Human Research Guidelines. Review of experiments conducted decades ago by DoD that involved exposure of human subjects to chemical warfare and other agents inevitably invites comparison with current standards regulating human subjects research. Inevitably, many of the research protocols used during those earlier periods fall short of today's standards for protecting human subjects. Judging past actions with today's better standards is a source of the anger and frustration felt by many veterans, which derives from the

realization that, by current standards, these individuals were treated like "human guinea pigs" in experiments that may now be judged by many as unethical.

According to the 1982 NRC report, the protocols used during the Edgewood, MD experiments from 1958 to 1975:

> ". . . emphasized that voluntary consent of each human subject was absolutely essential. It was also stated that, in all experiments involving volunteer subjects, the subjects would be thoroughly informed of all procedures and of what might be expected as a result of each test. Furthermore, each volunteer would be free to determine whether he desired to participate in a given experiment."

Furthermore,

> "The Nuremberg and Helsinki guidelines were regarded by the investigators and their supervisors as appropriate constraints in studies performed on volunteers, although this was not clearly articulated in official memoranda until the mid—1960s. The provision of accurate, informative explanations of what was planned and what might be expected was regarded as essential to the continuance of the program. Written Consents, Witnessed by medical staff members, were required from the outset and became more elaborate with time."

Nevertheless, the NRC report acknowledges that human subjects research standards have evolved over time:

> ". . .minutes of hearings conducted by the U.S. Senate Subcommittee on Health and Subcommittee on Administrative Practice and Procedure, September 10—12, 1975, stated that the consent information was inadequate by current standards."

Most of these veterans certainly still feel a strong sense of patriotism, that they made a sacrifice for the protection of their country. In return, the VA has the obligation to provide health care and benefits to these veterans for the injuries that they sustained as active duty service personnel who were harmed while defending their country.

WHAT AGENTS WERE TESTED?

The NRC committee noted the difficulties in evaluating results from experimental designs used in the Edgewood/Aberdeen studies that tested a wide range of agents, took place decades ago and spanned many years (NRC 1984). They reported a common experimental approach would began with low doses among "a few" volunteers to evaluate administration routes, particularly with agents previously tested only in animals. Subsequently, more subjects could be tested with estimated safe but pharmacologically active doses. Later studies would follow up interesting effects or possibly worrisome side effects. Finally, later studies often involved interventions with experimental antidotes or antagonists.

Although available records indicate that many Edgewood/Aberdeen subjects were exposed to a wide range of simple placebos and also common pharmaceutical agents (or sometimes their close relatives), placebo controls were not always used in these experiments. According to the 1984

NRC report, controls may not have been relevant given the research goals. The NRC committee concluded that the experiments conducted in the early 1960s were crude by today's standards because pharmacological research was only in its infancy. "Not until the mid-1960s was there a general consensus in a minimally acceptable design for studying psychochemicals, and even now there may be disagreement. The experimental design used in the experiments at Edgewood compares favorably with the pharmacologic research at other research centers" (NRC 1984).

Common Pharmaceutical Agents and Placebos. Table 1 lists many of the common pharmaceutical agents, their close relatives, and harmless agents used apparently as control exposures in the Edgewood/Aberdeen experiments.

Table 1. Common Pharmaceutical Agents, Close Analogs, and Simulant or Control Agents Used in the Edgwood/Aberdeen Experiments.[1]

Agent/Simulant Name	*Agent Class*
Antipyrine	Analgesic (PDR[2], Auralgan)
Atropine (methylnitrate, sulfate salts)	Anticholinergic (PDR, Lomotil)
Banthi (Banthine bromide, Methantheline bromide)	Anticholinergic (drug not available in the US)
Benzetimide	Anticholinergic
Dibutoline	Anticholinergic
Methscopolamine (bromide salt)	Anticholinergic (PDR)
Methylatropine	Anticholinergic
Scopolamine (hydrobromide)	Anticholinergic (PDR)
THA (Tetra Hydro Amino Acrodim) (Tacrine)	Anticholinergic (PDR)
5-HTP (5-Hydroxytryptophane)	Antidepressant
Regitine (Phentolamine)	Antihypertensive
Prolixin	Antipsychotic (PDR, as Fluphenazine)
Thorazine	Antipsychotic (PDR)
Adrenaline (epinephrine)	Bronchodilator (PDR)
Methacholine (mecholyl)	Cholinergic
Mylaxen (Hexafluronium bromide)	Cholinergic
Pilocarpine	Cholinergic (PDR)
Prostigmine (Neostigmine)	Cholinergic (PDR)
Succinylcholine	Cholinergic (PDR)
Urecholine	Cholinergic (PDR)
2-PAM Chloride	Cholinesterase Reactivator
Amyl Nitrate	Cyanide Antidote
Fluorescein	Dye
Indo-Cardio-Green Dye (Indocyanine Green)	Dye
Ammonium Chloride	Salt
Saline	Salt
Sodium Bicarbonate (NaHCO3)	Salt
Alcohol (ethanol)	Sedative

Table 1. Common Pharmaceutical Agents, Close Analogs, and Simulant or Control Agents Used in the Edgwood/Aberdeen Experiments.[1]	
Agent/Simulant Name	*Agent Class*
Amobarbital (Amytal)	Sedative
Chloral Hydrate	Sedative
Meprobamate	Sedative (PDR)
Nembutal	Sedative (PDR)
Secobarbital Sodium	Sedative
Seconal	Sedative
Valium (Diazepam)	Sedative (PDR)
Caffeine	Stimulant
Dexedrine	Stimulant (PDR)
Ritalin	Stimulant (PDR)
MDA (methylenedioxyamphetamine)	Stimulant, incapacitating agent
Niacinamide (Niacin, Vitamin B3)	Vitamin
Thiamine (HCl) (Vitamin B12)	Vitamin
[1]Data provided by Department of Defense, Health Affairs, Deployment Health Directorate, 2006. [2]PDR = listed in the Physicians Desk Reference, Medical Economics Company, Inc.	

Anticholinesterases. Table 2 lists 16 anticholinesterase agents that were tested on about 1,400 subjects in the Edgewood/Aberdeen tests. Subjects were exposed to OP, carbamate and other cholinesterase inhibiting compounds via by intravenous, vapor, oral percutaneous, intramuscular routes of exposure (NRC 1982). Case summaries were "brief and anecdotal," and there were no reports of neurologic or psychologic examinations (NRC 1982). Subjects reported showed a wide range of symptoms consistent with acute cholinergic toxicity, including dizziness, frontal headache, blurred vision, lethargy, nausea, stomach pain, vomiting, rhinorrhea, chest tightness, wheezing, fasciculations, sweating on hands and feet, and significantly decreased red blood cell cholinesterase levels (NRC 1982). Many subjects showed no signs or symptoms of toxicity Some were treated simultaneously with protective or reactivating agents, while others reportedly required standard antidotes including atropine as a medical response to severe poisoning symptoms (NRC 1982).

Anticholinergics. Table 3 lists 24 anticholinergic "glycolates" agents related to atropine, which were tested on about 1,800 subjects in the Edgewood/Aberdeen tests. Similarly, cholinesterase reactivators antidotes such as 2-PAM were tested on about 750 subjects. About 1,406 subjects were experimentally exposed to 16 anticholinergic agents at Edgewood/Aberdeen, via intravenous, vapor, oral percutaneous, intramuscular routes (NRC 1982). Complicating the interpretation of the health effects of these experiments, some subjects were simultaneously treated with protective or reactivating agent "antidotes." Moreover, the 1982 NRC reported that the available case summaries were "brief and anecdotal," and although some laboratory results were available, any reports of neurologic or psychologic examinations were absent (NRC 1982).

Cholinesterase Reactivators, Cannabinoids, Irritants and Blister Agents, Phencyclidine and LSD. Table 4 lists 4 cholinesterase reactivators, 11 cannabinoids, 9 irritants and vesicants and phencyclidine (PCP or "Angel Dust"), tested on about 3,500 Edgewood/Aberdeen subjects.

Irritants (which include lachrymatory riot control agents) and vesicants were tested on about 1,500 subjects, and included riot control agents CN, CS, chloropicrin (PS), Diphenylaminochlorarsine (DM, Adamsite), other ocular and respiratory irritants, and mustard agent (NRC 1984). For example, from 1958 to 1973 at least 1,366 human subjects underwent experimental exposure specifically to CS at Edgewood (NRC 1984). For 1,073 subjects, there was some type of aerosol CS exposure, 180 subjects had skin applications and 82 subjects had both skin applications and aerosol exposures, and 31 underwent CS application to their eyes. Most of these experiments involved tests of equipment of subjects' abilities to perform military tasks during exposure. Only 147 subjects were exposed to mustard or Lewisite (NRC 1982). Some experiments only involved one or two subjects. For example, from 1962 to 1972, a total of 123 irritant chemicals were tested on only two subjects each (NRC 1984). Those chemicals had been classified as irritants based upon preliminary animal studies. In these small-scale experiments, each subject was only exposed once using a wind tunnel.

Various psychochemicals including phencyclidine ("angel dust," PCP) and 11 related synthetic cannabinoids were tested on about 260 subjects (NRC 1984). Other experiments involved LSD with about 741 soldiers (NRC 1984).

Table 2. Anticholinesterase chemicals tested on 1,406 subjects at Edgwood/Aberdeen (NRC 1982). Common examples of this class include common OP and carbamate pesticides, and Pyridostigmine Bromide, commonly prescribed for myasthenia gravis patients.

Compond Tested	*CAS No.*[1]	*Class*	*No. Subjects Tested*
Sarin (GB)	107-44-8	OP	246
VX	5-782-69-9	OP	740
Tabun (GA)	77-81-6	OP	26
Cyclosarin (GF)	329-99-7	OP	21
Soman (GD)	96-64-0	OP	83
DFP	55-91-4	OP	11
EA 3148[2] (cyclopentyl S-2-diethylaminoethyl methylphosphonothiolate VX analog)		OP	32
Malathion (a common household OP insecticide)	121-75-5	OP	10
THA (Tacrine)	321-64-2	Anticholinesterase	15
Eserine (Physostigmine)	57-47-6 (free base)	Carbamate	138
Prostigmine (Neostigmine)	59-99-4	Carbamate	22
Hexafluorenium (Mylaxen)	317-52-2	Quat. ammonium AChE inhibitor	11

Pyridostigmine (salt)	155-97-5	Carbamate	27
Methacholine (Mecholyl chloride)	62-51-1	Cholinergic agonist	9
Urecholine	590-63-6	Cholinergic agonist	15

[1]CAS = Chemical Abstract Service numbers, which are unique unambiguous numerical designations for a specific compound. Not all compounds tested had CAS numbers.
[2]EA numbers are Edgewood Arsenal designations.

Table 3. Anticholinergic Glycolic Acid Esters tested on 1,752 subjects at Edgewood/Aberdeen (NRC 1982). Common examples of this class include atropine, a common antidote for poisoning with OP and other anticholinesterases, and scopolamine, prescribed as a mild sedative and anti motion sickness drug.

Compound Tested	*CAS No.[1]*	*No Subjects Tested*
BZ	13004-56-3 (hydrochloride)	292
EA 3443[2] (N-methyl-4-piperidyl cyclopentylphenylglycolate)	37830-21-0	101
EA 3580 (N-methyl-4-piperidyl cyclobutylphenylglycolate)	54390-94-2	130
Scopolamine	55-16-3 (hydrochloride)	534
Atropine	33952-38-4 (hydrochloride)	444
EA 3167 (3-Quinuclidinyl phenylcyclopentyldlycolate)	29125-55-1 (hydrochloride)	2
Ditran	8015-54-1	9
EA 4929 (benzetimide, dl-2-(1-benzyl-4-piperidyl)-2-phenylglutarimide)	14051-33-3	18
27349 (L-2-α-Tropinyl benzilate)	64520-33-8	50
226,086 (L-2-α-Tropinyl L-cyclopentylphenylglycolate)	64471-85-8	21
302,196 (N-Methyl-4-piperidyl cyclopentyl-(1-propynyl)-glycolate)	53034-67-6	52
301,060 (cis-2-Methyl-3-quinuclidinyl cyclopentaylphenylglycolate)	*	29
302,282 (1-Methyl-4-piperidyl phenyl-(3-methylbut-1-yn-3-enyl)-glycolate)	*	8

302,368 (3-Quinuclidinyl (1-hydroxycyclopentyl) phenylacetate)	*	5
302,537 (3-Quinuclidinyl cyclopentyl-(2-propenyl)-glycolate)	*	18
302,668 (4-(1-Methyl-1,2,3,6-tetrahydropyridyl)-Methyl-isolpropylphenyl glycolate)	*	39
Benactyzine	57-37-4	16
Methyl-Scopolamine	155-41-9	72
Atropine methyl nitrate	52-88-0	18
EA 3834 (N-Methyl-4-piperidyl isopropylphenyl-glycolate	*	144
TAB, BAT (Tropine benzilate)	3736-36-5	24
[1]CAS = Chemical Abstract Service numbers, which are unique unambiguous numerical designations for a specific compound. Not all compounds tested had CAS numbers. [2]EA numbers are Edgewood Arsenal designations. 6-Digit numbers are contractor's designations.		

Table 4. Reactivators, Cannabinoids, Phencyclidine, and Irritants and Vesicants Tested on 3,500 Subjects at Edgewood/Aberdeen (NRC 1984). Common examples of reactivators include 2-PAM, commonly prescribed for OP poisoning. The irritants include commonly used "tear gas" and "riot control" agents.

Compound	*CAS No.*[1]	*No Subjects Tested*
Reactivators		
2-PAM	51-15-0	607
P2S (methyl methanesulfonate salt of 2-PAM)	154-92-2	95
Toxogonin	114-90-9	41
TMB-4	3613-81-9 (hydrochloride)	32
Cannabinoids (11 analogs)	(various)	259
Phencylidine (PCP or "Angel Dust"	956-90-1	29
Irritants and Vesicants		
H Mustard	505-60-2	152
DM (Adamsite)	578-94-9	67
CS (o-Chlorobenzylidene malononitrile)	2698-41-1	1,372
CN (Chloroacetophenone)	532-27-4	99

CR (Dibenz [b,f][1,4]oxazepine)	257-07-8	97
CHT (1-Methoxy-1,3,5-cycloheptatriene)	1728-32-1	16
PS (Chloropicrin)	76-06-2	138
CA (Bromobenzyl cyanide)	5798-79-8	13
Nonanoyl Morpholide	5299-64-9	32
[1]CAS = Chemical Abstract Service numbers, which are unique unambiguous numerical designations for a specific compound.		

Table 5. Chemical Class and Median Year of Tests on 6,720 Subjects at Edgwood/Aberdeen (NRC 1982).

Chemical Class	*Median Year Tested*
Approved Drugs	1971
Innocuous Chemicals and Controls	1971
Anticholinergics	1968
Cholinergic Reactivators	1968
Irritants	1967
Cannabinoids	1965
Anticholinesterases	1962
LSD Derivatives	1959

ACUTE EFFECTS REPORTED FOR EDGEWOOD/ABERDEEN SUBJECTS.

The 1982 and 1984 NRC committees charge to evaluating possible long-term health effects from Edgewood/Aberdeen experiments began with an evaluation of immediate, short-term acute (i.e., showing immediate signs and symptoms following exposure) health effects reported for experimental subjects.

Anticholinergics. Anticholinergics include the military OP nerve agents such as sarin and VX, which along with OP pesticides inhibit acetylcholinesterases, leading to a toxic accumulation of the neurotransmitter acetylcholine. According to the NRC review, experimental subjects reportedly showed a wide range of symptoms consistent with acute cholinergic toxicity, including dizziness, frontal headache, blurred vision, lethargy, nausea, stomach pain, vomiting, rhinorrhea, chest tightness, wheezing, fasciculations, sweating on hands and feet, and significantly decreased red blood cell cholinesterase levels (NRC 1982). Consistent with the wide range of doses tested many subjects showed no evidence of acute toxicity. However, some subjects experienced severe clinical acute cholinergic poisoning symptoms and required treatment with conventional antidotes such as atropine (NRC 1982). The 1982 NRC review of experiments involving exposure to AChE inhibitors concluded that there was no firm evidence

that any of the anticholinergic test compounds surveyed produced long-term adverse human health effects in the doses used at Edgewood Arsenal. "On the basis of available data, in the judgment of the panel, it is unlikely that administration of these anticholinergic compounds will have long-term toxicity effects or delayed sequellae" (NRC 1982). However, the committee cautioned that "more intensive study is required to confirm this conclusion" (NRC 1982).

Reactivators. Reactivators are compounds intended to "reactivate" cholinesterases that have been inhibited by an OP nerve agent such as the military agent sarin, or commonly used OP pesticides. The commonly used nerve agent antidote 2-PAM is an example of this class. The 1984 NRC committee reported that medical records of subjects treated with these agents included test protocols, physicians' orders, nursing notes, clinical observations, symptom checklist, and laboratory and performance test results (NRC 1984). Reports of physicians' examinations were generally not included. Complicating the clinical interpretation, reactivators were often given following treatment with anticholinergics.

The most commonly reported effects among the Edgewood/Aberdeen subjects included dizziness, eye discomfort, blurred vision, diplopia, muscle pain (with intramuscular exposure), tingling sensations (with intravenous exposure), voiding difficulty, diarrhea, dry mouth, and lethargy (NRC 1984). In general, clinical responses to this relatively common class of reactivator compounds have been well characterized, and according to the 1984 review, "the manifestations experienced by subjects in these tests . . . were the moderate clinical effects that have been reported in the literature [and] in all but two instances, moderate effects disappeared within 24 hours" (NRC 1984).

Some more severe acute effects were also noted -- two subjects experienced severe acute effects, including one treated with P2S and soman who experienced significant chronic psychological effects, and a second treated with 2-PAM alone who experienced a grand mal seizure (NRC 1984). The committee concluded that "with the possible exception of those two cases, the records contained no evidence of delayed or persistent effects after administration of the cholinesterase reactivators. Such data cannot, however, address the issue of long-term effects or delayed sequelae" (NRC 1984).

PCP. PCP "phencyclidine," is an illicit drug with a somewhat sinister reputation as the recreational hallucinogen "Angel Dust." According to the 1984 NRC review, charts in the clinical files of Edgewood/Aberdeen subjects treated with PCP varied from sketchy and incomplete notes and line-line summaries, to records that could "serve as models for research documents" (NRC 1984). They reported that effects reported in Edgewood/Aberdeen subjects were similar to those reported in clinical research from pharmaceutical companies evaluating PCP as an anesthetic agent, that is, the military tests "did not involve extraordinary doses" compared to those civilian experiments, although inhalation exposure was unique to the military trials (NRC 1984).

According to reviews of existing military records, the Edgewood/Aberdeen PCP treated subjects reported "feelings of unreality – dream-like states with perceptual size changes," with variable affect and mood changes (NRC 1984). Some subjects became talkative and uninhibited, while others became passive and withdrawn (NRC 1984). At higher doses, symptoms intensified and were accompanied by "visual disturbance, blurred vision, ataxia, limb paresthesias, and memory impairment," and subjects becoming non-communicative (NRC 1984). Strikingly, amnesia was reported among some subjects. At the largest doses tested, subjects experienced analgesia,

nausea and vomiting, and four experienced collapse and prostration or incapacitation without convulsions, with recovery over the next few hours (NRC 1984). In general, signs and symptoms disappeared within 6 to 8 hours although at the largest tested doses, symptoms persisted for 24 or 48 hours (NRC 1984). No clinically abnormal effects, including renal or hepatic toxicity, were noted in available records. Strikingly, despite the negative "street reputation" of this agent for causing aggression, no subjects were reported to have become overly assertive, hostile or unmanageable (NRC 1984).

Cannabinoids. Edgewood/Aberdeen subjects were exposed to the active ingredient of marijuana and a series of related synthetic "cannabinoids," by oral, intramuscular, and intravenous routes. According to the 1984 NRC review, signs and symptoms reported in available records for subjects exposed to these agents were "very similar to those later described over the last 15 years by many research laboratories working with cannabis and THC" (NRC 1984). Reported effects included fatigue, weakness, drowsiness, ataxia, feeling of giddiness, mild headache, occasional increased thirst, general slowing of motor activity, and postural hypotension especially at higher doses, occasionally with fainting on standing (NRC 1984).

At the largest doses, subjects often showed marked psychomotor retardation, sluggishness, difficulty in concentrating, and blurred vision for up to 48 hours after a single dose (NRC 1984). Cardiovascular effects included tachycardia and orthostatic hypotension in some subjects and at almost all doses tested (NRC 1984). Importantly, these effects disappeared in most subjects after 24 hours, although they persisted for several days in a few (NRC 1984). Finally, the 1984 NRC review reported a "lack of evidence of severe mental or emotional disturbances" even among subjects experiencing intense and persistent cardiovascular effects (NRC 1984).

LSD. According to a 1980 report by the US Army Medical Department, the US Army Chemical Corps and the US Army Intelligence Corps conducted human experiments with LSD from 1955 through 1967, involving at least 741 individuals (US Army 1980). These experiments were intended to test LSD as a chemical warfare agent and in response to "the rumored use of LSD or some similar agent by certain Soviet block nations, for the purpose of interrogation and behavioral control (brain washing)" (US Army 1980). The Army report contained little information about the acute (immediate) effects experienced by subjects of this study, except to document that most received pharmacologically relevant exposures.

Irritants and Vesicants (Mustard Agents, Lewisite, CS, CN, CR, DM, CA, Chloropicrin, Nonanoyl Morpholide, CHT, and 123 Other Miscellaneous Irritants). Many of the Edgewood/Aberdeen experiments involved exposure to irritants such as riot control agents that produce intense lacrimation (tears) and respiratory distress, and to vesicants that produce reddening and blistering of the skin. Subjects involved in experimental exposures to irritants and vesicants at Edgewood from 1955 to 1965 were exposed to hundreds of different test compounds, via aerosol chamber and droplets applied directly to the skin. Some subjects sustained dermal injuries (NRC 1984). According to the 1984 NRC committee, subjects were generally at least partially protected with clothing and masks.

Mustard Agents, and Lewisite (chlorovinyldichloroarsine). In the period ending with World War 2, mustard agents and Lewisite "blister" vesicants agents were widely tested by the U.S. military using human subjects. By the time the war was over, "over 60,000 U.S. servicemen had been used as human subjects in this chemical defense research program" (NAS 1993). VA has recognized that some long-term health effects are associated with exposure to acutely toxic

levels of these two agents (VA 2005). After World War 2, the focus shifted to new types of chemical warfare agents. Nevertheless, experiments with mustard agents were conducted at U.S. Army Laboratories at Edgewood Arsenal, Maryland from 1955 to 1965. In those more recent experiments, subjects were typically removed from exposure after evidencing dermal erythema, noted on trunks, extremities, and backs of subjects (NRC 1984). Droplet exposure on skin also reportedly led to erythma and occasionally blisters at the application site. Some subjects experienced erythma without skin blistering, but others experienced blistering that occasionally required hospitalization with injuries that "might have been severe enough to cause permanent scarring" (NRC 1984). No subject was reported to have sustained ocular or respiratory tract injuries, perhaps because of protection used by subjects during experimentation (NRC 1984).

Effects reported among Edgewood/Aberdeen subjects are similar to more recent reports of effects from military exposure to mustard agents. For example, a report of Iraqi use of mustard agent against Iranian troops in 1984 documented health effects in more than 5,000 Iranian casualties. Affected individuals had first to third degree burns over 20 to 70 percent of the total skin surface. Eye exposure caused tearing, severe conjunctivitis, and temporary loss of vision. Corneal abrasion was nearly always present, and photophobia and blurred vision developed in some cases. Upper airway involvement due to chemical burning of the throat led to pharyngitis and tracheobronchitis. These effects were quite severe, and this group suffered approximately 15 percent mortality. Those who survived the initial symptoms later experienced various GI complaints, including nausea, vomiting, and diarrhea. After five to seven days, hematologic problems were the greatest health threat to survivors (Kadivar & Adams 1991).

CS (*o*-chlorobenzylidene malononitrile). The "tear gas" and riot control agent CS causes burning sensations of the eyes, intense lacrimation, coughing, conjunctivitis, erythemic eyelids and other symptoms of irritation of the eyes, skin and mucous membranes. From 1958 to 1973, at least 1,366 human subjects underwent experimental exposure to CS at Edgewood/Aberdeen, and 1,073 subjects were exposed to aerosol CS, 180 with dermal applications, 82 both dermal and aerosol, and 31 to the eye. Subjects were exposed via a gasmask or more often, in large wind tunnels (NRC 1984). Exposed subjects typically experienced short-term tears, nasal secretions and copious saliva flow that required "towels rather than handkerchiefs" (NRC 1984). Physical effects were reported to subside 5 to fifteen minutes after exposure stopped. CS applied to skin directly or as an aerosol produced erythma, vesicles and in some cases burns. "Hepatic dysfunction and urinary abnormalities" were seen in some subjects (NRC 1984). "A high percentage of subjects" reportedly developed allergic contact dermatitis after repeated exposure (NRC 1984). Thus, follow-up evaluations suggested that repeat CS exposure may cause allergic contact dermatitis in many subjects, and possibly idiosyncratic hepatitis or allergic pneumonitis in some persons (NRC 1984).

CN (chloroacetophenone). Subjects at Edgewood/Aberdeen were experimentally exposed to another "tear gas" agent CN from 1958 to 1972 as aerosols in chambers or skin application (NRC 1984). Aerosol exposed subjects showed transient effects that reportedly included lacrimation, blepharospasm, conjunctivitis, and rarely, palpebral edema, noropharyngeal irritation, rhinorrhea, and rarely dyspnea, headaches and dizziness (NRC 1984). Skin exposure produced local irritation and occasionally erythema at the exposure site, which lasted for 7 hours (NRC 1984). Laboratory tests for skin exposed individuals were normal, including urinalysis, complete blood count, blood urea nitrogen, alkaline phosphatase and serum glutamic oxalotransferase, 7 days after exposure (NRC 1984).

CR (dibenz[b,f][1,4]oxazepine. CR is another "tear gas" agent tested from 1963 to 1972 on subjects at Edgwood/Aberdeen, using aerosol (chamber) and dermal (patch) exposures. As with other "tear gas" type agents, transitory effects were reported as primarily respiratory and ocular (NRC 1984). Aerosol exposure universally lead to upper respiratory tract irritation among subjects with choking, and sometimes dyspnea. Dermal exposure produced stinging and erythmea at the exposure site, which resolved within 24 hours (NRC 1984). Laboratory analyses 7 days after exposure showed no abnormalities from the exposure (NRC 1984).

DM (diphenylaminochlorarsine). DM (Adamsite), another "tear gas" agent tested in 1958 and from 1966 to 1968 at Edgewood/Aberdeen, using aerosols in chambers. Predominant symptoms included burning sensations of respiratory tract, choking, dysphonia, dyspnea, coughing, sneezing, and nausea (NRC 1984). Less frequent effects included retching, anorexia, headache, dizziness, lacrimation, salivation, and increased urinary frequency. Laboratory results 7 days after the exposure showed no abnormalities due to the exposure (NRC 1984). "Although DM has greater acute toxicity to the respiratory tract than CS and CN, Edgewood subjects appeared to recover shortly after exposure" (NRC 1984).

CA (bromobenzyl cyanide). In 1966, Edgwood/Aberdeen subjects were experimentally treated with the "tear gas" agent CA in aerosol chambers. Reported effects were transient, and included ocular irritation, often accompanied by conjunctivitis, and upper respiratory tract irritation with rhinorrhea (NRC 1984). Blood and urine laboratory analysis 7 days after exposure for 12 subjects showed minimal leukocytosis (WBC 12,800) not seen prior to exposure (NRC 1984).

PS (chloropicrin). Chloropicrin, another "tear gas" agent, was tested from 1955 to 1971 at Edgewood/Aberdeen in chambers experiments. Subjects reportedly wore gas masks to test their function. Although records were incomplete, no acute effects were documented (NRC 1984).

Nonanoyl morpholide. Nonanoyl morpholide was another experimental "riot control" agent to which Edgewood/Aberdeen subjects were experimentally exposed in 1958 in chamber experiments (NRC 1984). Effects were reported as transient, mainly causing respiratory tract irritation, including rhinorrea, cough, substernal pain, and dyspnea (NRC 1984). Nausea was also commonly reported, and vomiting occurred if the subject had eaten before the test. Headaches sometimes occurred one hour after exposure, and for one subject the headache persisted for a week (NRC 1984). No laboratory analyses were available.

CHT (1-methyl-1,3,5-cycloheptatriene). Another experimental "riot control" agent CHT was tested on Edgewood/Aberdeen subjects in aerosol chambers during 1969 and 1970. Physical effects were described as transient, with "complete resolution by 15 minutes after leaving the chamber" (NRC 1984). The main effects were lacrimation leading to incapacitation from eye closure and blurred vision "lasting several minutes after the exposure" (NRC 1984). Dermal irritation and rhinorrhea also were reported among exposed subjects. Laboratory analysis 9 days later reported two subjects with slight increases in SGOT (31.5 and 44.5) – slightly less than double pre-exposure values (NRC 1984). However, SGOT was normal 1 month later. Other minor effects on laboratory results were also noted (NRC 1984).

123 Other Miscellaneous Irritant Chemicals. From 1962 to 1972, 123 other irritant "tear gas" like compounds were tested at Edgewood/Aberdeen, generally only on two subjects per compound (NRC 1984). Tested substances had been classified as irritants based on preliminary animal studies. Human experiments took place primarily in aerosol chambers, with exposures

lasting a minute or less, with subjects exposed only once (NRC 1984). Of the 123 tested chemicals, 64 caused slight or no effects, while 42 caused mainly ocular effects including eye irritation, lacrimation and conjunctivitis, and of those, 34 caused very mild effects (NRC 1984). Eight of these 42 compounds produced relatively more severe effects, including prolonged incapacitation associated with lacrimation and eye closing (NRC 1984). "The discomfort associated with the exposures was marked, but exposures were short and recovery appeared complete" (NRC 1984).

POTENTIAL LONG-TERM HEALTH EFFECTS AMONG EXPERIMENTAL SUBJECTS

Examination of the significant amount of literature on long-term health effects from exposure to the agents used in these military experiments can shed light on what health affects may be anticipated among the veterans who participated. Much of this literature is based on examination of veterans actually involved in these experiments – additional information comes from other groups who were exposed under a wide range of conditions, including actual combat, accidents or terrorist incidents.

Mustard Agent and Lewisite Experiments. Immediate signs and symptoms of acute mustard agent poisoning include severe irritation and tissue damage to eyes, skin, and respiratory and gastrointestinal (GI) tracts. Usually the onset of acute symptoms is delayed for some hours after exposure.

The 1993 IOM review of the long-term health effects from exposure to mustard agent concluded that several specific chronic diseases are causally associated with exposure to this agent. These include various respiratory cancers, skin cancer, chronic skin ulceration and scar formation, chronic respiratory disease including asthma, chronic bronchitis, emphysema, chronic eye diseases, and various psychological disorders including PTSD. The IOM committee also found suggestive evidence (weaker than the associations for the conditions just mentioned) that exposure to mustard agent was associated with leukemia. Finally, the IOM analyzed two studies that examined the link between mustard and reproductive dysfunction, but concluded that the database could not be used to make conclusions about human reproductive health effects (NAS 1993).

The 1993 review by the NAS concluded that it was clear that some veterans exposed to mustard and Lewisite in chemical warfare agent testing programs had consequently suffered serious and debilitating diseases for decades (NAS 1993). Lack of follow-up health assessments for mustard and Lewisite gas chamber and field military experiments severely limited assessment of long-term health consequences (IOM 1993). Similarly, NAS reviewers complained of the lack of epidemiological studies on chemical weapons production workers, chemical warfare munitions handlers and trainers, or chemical weapon combat casualties from World War 2 (NAS 1993). Nevertheless, records showed that many subjects of those World War 2 era experiments sustained dermal injuries severe enough to cause permanent scarring (NRC 1984).

Examples of actual combat use of mustard agents, including during World War 1 and the Iran-Iraq war, provides l useful insights into their health effects. Probably the largest military use of mustard was the 1980s Iran-Iraq war (NAS 1993). Iranian mustard agent casualties treated in European hospitals have well documented medical records. Those records describe mustard

agent casualties suffering from pulmonary, eye and skin lesions in a pattern similar to that reported for mustard agent casualties in World War 1, with 83 percent suffering skin lesions, 92 percent with eye problems, and 95 percent with pulmonary damage (NAS 1993).

The 1993 NAS medical literature review concluded that there was limited information associating exposure to mustard and Lewisite and specific long-term health effects (NAS 1993). They reported:

1. a *causal relationship* between exposure to mustard and Lewisite chemical warfare agents and the following health conditions:

- Respiratory cancers including;
    - Nasopharyngeal
    - Laryngeal
    - Lung
- Skin cancer
- Pigmentation abnormalities of the skin
- Chronic skin ulceration and scar formation
- Leukemia (typically acute non-lymphocytic type, nitrogen mustard)
- Chronic respiratory diseases
    - Asthma
    - Chronic bronchitis
    - Emphysema
    - Chronic obstructive pulmonary disease
    - Chronic laryngitis
- Recurrent corneal ulcerative disease (includes corneal opacities; acute severe injuries to eye from Lewisite will also persist)
- Delayed recurrent keratitis of the eye
- Chronic conjunctivitis
- Bone marrow depression and resulting immuno-suppression (an acute effect that may result in greater susceptibility to serious infections with secondary permanent damage to vital organ systems)
- Psychological disorders
    - Mood disorders
    - Anxiety disorders (including post-traumatic stress disorder)
    - Other traumatic stress disorder responses (These may result from traumatic or stressful features of the exposure experience, not a toxic effect of the agents themselves)

- Sexual dysfunction (scrotal and penile scarring may prevent ort inhibit normal sexual performance or activity)

2. a *suggested a causal relationship* between exposure and the following health conditions:

- Leukemia (acute non-lymphocytic type, sulfur mustard)
- Reproductive dysfunction (genotoxicity, mutagenicity, etc.; mustard agents)

3. *insufficient evidence found to demonstrate a causal relationship* between exposure and the following health conditions:

- Gastrointestinal diseases
- Hematologic diseases
- Neurological diseases
- Reproductive dysfunction (Lewisite)
- Cardiovascular diseases (except for those that may result from serious infections shortly following exposure – heart disease resulting from rheumatic fever, for example)

Epidemiological Studies of World War 2 Mustard and Lewisite Military Human Subjects. The NAS committee's call for high quality epidemiological research on veterans involved in mustard and Lewisite experiments was answered in 2000 when VA's Environmental Epidemiology Service reported a retrospective mortality study of 1,545 World War 2 Navy veterans experimentally exposed to mustard agent at Edgewood, MD. Mortality was compared to 2,663 similar Navy veterans who were not part of these experiments (Bullman & Kang 2000). This cohort was ideal for evaluating because all had been stationed at Bainbridge, Maryland, between 1943 and 1945, when these mustard and Lewisite exposure experiments had occurred. Long-term health issues had not been evaluated previously for this group.

The VA study reported finding no increased risk of any cause of death associated with mustard agent exposure, and no increased risk in cause-specific mortality associated with the level of mustard agent exposure among exposed veterans (Bullman & Kang 2000). In contrast, earlier studies of World War 1 veterans with combat exposure to mustard agent had reported an increased risk of death from lung cancers and respiratory related diseases. Studies of those earlier veterans reported that 10 years after their combat exposure, soldiers had residual disabilities including chronic bronchitis (usually associated with emphysema), bronchial asthma, chronic conjunctivitis, blepharitis, keratitis, and corneal opacities (NRC 1984). VA researchers speculated that the different findings might be because the Edgewood/Aberdeen veterans, in contrast to many World War I veterans, wore protective clothing and were exposed for relatively short periods to probably lower levels of agents (Bullman & Kang 2000).

Because of the large sample size available for this study, it had substantial statistical power, with a 95% power to detect a 2-fold or greater increase of risk of deaths due to respiratory cancers (Bullman & Kang 2000). Moreover, since exposures occurred over 40 years before this study was conducted, a long latency of effect should not have been missed.

Health Effects among Post World War 2 Edgewood/Aberdeen Subjects. NRC reviews carried out in the 1980s reported little evidence of health consequences among participants in military chemical warfare agent tests between 1955 to 1975. They evaluated long-term

morbidity and mortality for the 6,720 Edgewood/Aberdeen subjects exposed from 1955 to 1975 to 254 different chemicals, including common approved pharmaceutical agents, anticholinesterase nerve agents, glycolate incapacitating agents, atropine-related anticholinergic agents, LSD and related compounds, cannabinoids, and irritants (NRC 1985). Based upon available mortality data and toxicological data, test subjects surprisingly appeared to be healthier compared to era controls, and both groups were healthier than the general population (NRC 1984). However, the NRC committee pointed out that problems with available studies limited their ability to evaluate potential long-term health effects (NRC 1984).

Morbidity was evaluated through mailing a health survey sent to all living and locatable experimental subjects, and information gleaned from VA and Army hospitalization admissions data (NRC 1984). Eighty-two percent of subjects receiving a mailed health survey responded. VA hospital admissions data was examined for malignant neoplasms, mental disorders and diseases of the nervous system and sense organs. The long-term health effects of greatest concern included excess cancer risk, adverse mental, neurologic, hepatic and reproductive effects that might be associated with participation in the Edgewood/Aberdeen tests.

Devising an appropriate control group for this study was complicated because not only were subjects in the military, but they were apparently also subjected to further significant physical and psychological screening as a condition for being used in these studies (NRC 1985). Moreover, experiments involving actual chemical agents selectively used more fit subjects, leaving less fit subjects for controls (NRC 1985). Finally, experimental subjects were commonly used in multiple tests with exposure to multiple agents (NRC 1985). In practice, NRC researchers developed two internal comparison groups:

1) Subjects not exposed to any chemical warfare agents (1,058 subjects, including 907 apparently exposed to no agents, 93 exposed to 58-different FDA approved drugs, 17 exposed to common agents including caffeine and alcohol, 39 exposed to control substances such as water, saline, and sodium bicarbonate, and two subjects exposed to two of the above).

2) Subjects exposed to chemical warfare agents *other* than the agent being evaluated in a particular comparison. That is, a subject exposed only to LSD might be compared to subjects exposed to nerve agents.

Conclusions. NRC researchers were careful to document significant study limitations: "The experimental methods and the available comparison groups were such that only large effects were likely to be uncovered. The large standard errors, the initial differences between the exposed and the non-exposed groups, the possibility that more than one exposure might have led to the same adverse effect, and the self-reporting nature of the questionnaire study all would tend to obscure small differences" (NRC 1985).

Nevertheless, the study reported that Edgewood/Aberdeen subjects experimentally exposed to anticholinesterase and anticholinergic agents, cholinesterase reactivators or psychochemicals did not differ significantly from the two comparison groups in their mailed health survey responses (NRC 1985). Almost ninety percent reported no health problems related experimental exposures, and seventy-nine percent reported good to excellent health. Subjects tested with LSD at Edgewood reported an increased use of LSD compared to controls after the tests, but there "was no evidence of adverse health effects among these subjects" (NRC 1985). Subjects tested with irritants and vesicants, including those who had developed skin lesions from exposure to

mustard agent, reported no increased risk of "significant skin cancer" or other adverse health effects (NRC 1985). An apparent decrease in fertility among subjects exposed to anticholinergic agents in comparison with subjects tested with other agents disappeared after adjusting for age of subjects when tested such that "there was no difference between the observed fertility pattern of the men exposed to anticholinergic chemicals and that expected on the basis of men who were exposed to other chemicals" (NRC 1985).

Review of hospital admissions records for Army from 1958 to 1983, and VA from 1963 to 1981, showed a "barely statistically significant increase in admissions to VA hospitals for malignant neoplasms among men exposed to anticholinesterases and a statistically significant increase in admissions to VA hospitals and Army hospitals for nervous system and sense organ disorders among men exposed to LSD" (NRC 1985). However, the report noted that admission numbers were small, no dose relationships were observed, and, for subjects exposed to anticholinesterases, neoplasms occurred at various sites with no consistent pattern or correlation to a specific chemical (NRC 1985). In general, anticholinesterase compounds, including common pesticides and military nerve agents, are not considered carcinogens. Cardiovascular effects have been reported among individuals with acute (that is, immediate) anticholinergic poisoning, including poisoning from pesticides. However, such effects were not detected among the Edgewood/Aberdeen subjects (NRC 1985). Finally, admissions by experimental subjects to Army or VA hospitals for mental disorders did not appear to be significantly increased (NRC 1985).

LSD Effects. In the 1985 NRC evaluation, 317 out of 571 soldiers involved with LSD experiments at Edgewood/Aberdeen returned completed health survey questionnaires (NRC 1985). LSD exposed subjects did not differ from the comparison groups in total hospital admissions, admissions for malignant neoplasms, mental disorders, or current health status (NRC 1985). However, they did show an increased number of first admissions for nervous system and sense organ disorders (NRC 1985). No increase in suicide or epilepsy was found, although interestingly, subjects reported an increase in the use of controlled substances (NRC 1985).

According to an earlier 1980 report by the US Army Medical Department, the US Army Chemical Corps and the US Army Intelligence Corps conducted human experiments with LSD from 1955 through 1967, which involved at least 741 individuals (US Army 1980). These experiments were intended to test LSD as a chemical warfare agent and in response to "the rumored use of LSD or some similar agent by certain Soviet block nations for the purpose of interrogation and behavioral control (brain washing)" (US Army 1980). According to the Army Medical Department report, "with rare exceptions, all LSD-exposed subjects voluntarily participated in the chemical warfare testing and were informed ahead of time that they would be receiving a psychoactive agent." Moreover, "strict medical supervision was provided during the testing, and prior to the actual receipt of drugs, almost all subjects received some degree of psychological screening" (US Army 1980).

In 1978, the US Army Health Services Command initiated a follow-up health evaluation of subjects involved in these experiments with LSD. Evaluation was complicated because these experiments had occurred on average 19 years earlier, from 1955 to 1967. However, researchers had access to a "comprehensive" computerized roster of individuals "believed to have received LSD in Army chemical warfare projects between 1955 and 1967," with names of 741 individuals involved in LSD experiments between 1955 to 1967 (US Army 1980). Most of these tests took

place at Edgewood arsenal, but substantial numbers took place (in decreasing frequency) at Ft. McClellan, Ft. Benning, Ft. Bragg, and Dugway Proving Ground (US Army 1980).

Long term health effects were evaluated by inpatient health evaluations (220 subjects) at military facilities, including Walter Reed Army Medical Center, Letterman Army Medical Center, Presidio of San Francisco, and Dwight David Eisenhower Army Medical Center), or by a mailed brief "Health History Questionnaire" (100 subjects) for those declining medical examination, yielding an overall response rate of 43% among 320 subjects (US Army 1980). Their ages ranged from 30 to 72 years (average 45 years). All were male with at least two years military service, and most (261 or 81%) were married. Of the remaining 421 subjects, 55 were US Air Force personnel who were excluded from the evaluation, 24 (3.2%) were deceased, 193 (26%) could not be located, and 149 (20%) were located but declined to respond. Cause-of-death data were obtained for 21 of the 24 deceased subjects (US Army 1980).

A valid comparison group was problematic because the LSD subjects were clearly not a random sample of the Army population at the time. Many (117) were apparently involved in experiments with other agents, including glycolates such as Ditran and BZ, riot control agents, and alcohol (US Army 1980). Poor records made it impossible to verify that all 741 subjects had actually been exposed to LSD (records for 119 subjects listed "unknown" under administered agent). Records for 10 subjects listed them as "controls," but without any actual exposure data. Researchers decided that since all 741 subjects had been assigned to projects studying LSD, "it was assumed that they probably received LSD." Because of these limitations, matched controls were not used for this health follow up study, and formal statistical epidemiological analysis was not attempted because "such methodology is inappropriate and potentially misleading" (US Army 1980).

Conclusions. Seventy-six LSD subjects (24% of 320) reported one or more long-term adverse reactions to LSD exposure (Table 6) (US Army 1980). All complaints from subjects were reported as "adverse effects" even though these events had occurred on average 19 years earlier. Fifty subjects reported symptoms that met criteria commonly associated with LSD effects, including flashbacks, or spontaneous transient occurrences of experiences reminiscent of the symptoms originally evoked by LSD. Forty one (13%) stated that the adverse effects continued to the time of the survey. Nine reported post LSD depression. Some subjects also reported "possible" LSD effects including memory loss, blackouts, alcohol abuse, etc.

Table 6. Adverse effects reported by 320 LSD subjects (US Army 1980).

Reported Effect	**Frequency**
Flashbacks	27
Somatic complaints	18
Depression	12
Personality change	7
Anxiety	6
Nightmares	5

Dissociative episodes	5
Alcohol abuse	4
Paranoid ideation	4
Memory loss	4
Phobia	2
Episodic withdrawal	2
Drug abuse	2
Seizure disorder	1
Miscellaneous	1

Hearing loss was the most frequent medical finding among study participants (88 subjects, 28%), but was of a type most commonly associated with chronic noise exposure and LSD "is not known to be ototoxic" (US Army 1980). Alcohol abuse was reported in 27 subjects (8%) and attributed to LSD exposure by four. Twenty-seven subjects reported "flashbacks," with 11 stating their flashbacks persisted to the present time of the study (Table 6). Twelve subjects reported depression from their LSD exposure (Table 6), lasting from a few days to several years, with psychiatric intervention or hospitalization apparently required half those cases. Subjects reported a range of negative personality and other changes attributed to LSD exposure (Table 6), including social withdrawal, loss of interest in work, irritability and aggressiveness, anxiety, increased nightmares, paranoid ideation, non-specific memory loss, dissociative episodes, and use of other illicit drugs. Forty-one subjects reported "present problems," from LSD, in particular somatic complaints.

Overall, this group was reported to have "remarkably little disability,"and to show "marital stability, exceptional levels of education and employment, and no more medical or psychiatric illness than might have been expected for a random sample of the population" (US Army 1980). Some suffered significant "socioeconomic difficulty," including marital and family disruption resulting from reported personality changes, depression, alcohol abuse, etc, reported by seven subjects. At least five reported work-related difficulties and job instabilities that they attributed to LSD exposure. A total of 23 subjects "felt that symptoms related to prior LSD exposure had significantly compromised, at least temporarily, their socioeconomic adjustment."

Psychological Impact of Test Participation. Not surprisingly, the mere act of participation in experiments such as these can sometimes lead to long-term psychological effects. For example, the evaluation of veteran subjects of DoD's mustard agent experiments found significant rates of Post-traumatic Stress Disorder (PTSD) when compared to controls who did not participate in those experiments.

Researchers at VA's National Center for PTSD used structured interviews to assess PTSD and other psychosocial outcomes among twenty-four subjects of World War II mustard agent experiments (Schnurr et al., 2000). Ninety-two percent reported they had volunteered for the original mustard experiments. Ninety-six percent had participated in gas chamber exposure tests during the mustard agent tests. Twenty-two percent of the subjects reported that they understood the dangers involved, and sixty-seven percent were ordered to not discuss their participation with anyone.

Most of these experimental subjects (83 percent) reported experiencing physical symptoms at the

time of exposure to mustard agent. Examined nearly 5 decades later these same subjects were found to be less psychologically and physically healthy in comparison to men of similar age (Schnurr 1996). They were also found to suffer an unusually high PTSD prevalence of 17 percent. Lifetime estimates for full and sub-diagnostic PTSD were reported to be 17 and 33 percent, respectively (Schnurr 1996). Strikingly, the only mustard gas experience that predicted lifetime full or sub-diagnostic PTSD was the number of separate exposures to the gas (Schnurr 1996).

A related study evaluated PTSD among 363 veterans randomly selected from a VA list of veteran-subjects from military World War 2 mustard agent experiments. Investigators reported that 32% of these veterans suffered from full-PTSD, and 10% for partial-PTSD (Schnurr et al., 2000). Veterans with full PTSD reported poorer physical health and a higher likelihood of several chronic illnesses (Schnurr et al., 2000). Similar mental health effects have also been reported among survivors of the 1995 terrorist attack with the chemical warfare agent sarin against civilians in the Tokyo subway system (Ohbu et al., 1997; Okumura et al., 1996).

Recent Study on Long-Term Health Effects Among Edgewood/Aberdeen Subjects. A 2003 study provided follow-up health evaluations of 4,022 out of the 6,720 soldiers involved in the1955 to 1975 Edgewood/Aberdeen experiments (Page 2003). Of these, 256 had been exposed to sarin, 740 to VX, 571 to various psychochemicals including LSD, 1,366 to irritants including CS, and 147 to vesicants including mustard agent. As always, identifying comparable controls were a problem -- this study also relied upon internal controls including subjects exposed to none, one or multiple agents *other* than the agent under evaluation (Page 2003).

Conclusions. Only two statistically significant effects were detected (Page 2003). Subjects exposed *only* to OP nerve agents reported 1) *fewer* attention problems compared to subjects exposed to *other* agents, and 2) *greater* sleep disturbances compared to subjects exposed to *no* active agents. Neurological diseases including Parkinson's, and chronic multisymptom illnesses such as CFS and FM, were not significantly different from controls, and were generally very low among all groups (Page 2003). Interestingly, subjects reporting exposure to chemicals in civilian or military activities *other* than from the Edgewood/Aberdeen testing reported many statistically significant adverse neurological and psychological effects, regardless of their experimental exposure.

Evaluating SHAD Veterans. A January 2006 review of Project SHAD veterans examined VA health care utilization among 5,032 identified Project SHAD veterans (about 90% of DoD's estimated total for SHAD veterans) . Of these, 37.2% had been seen at least once at a VA medical facility between 1970 and 2005, which is comparable to other veteran groups over the same period of time. The most common diagnoses cover a wide range of health problems that are similar to those found in the general, middle to older aged U.S. population, and no particular health care problem stands out among SHAD veterans in this descriptive survey. Importantly, since May 1, 2002, when the Veterans Benefits Administration (VBA) began mailing letters to SHAD participants notifying them of potential chemical and biological exposures during these Cold War tests, 449 Project SHAD veterans have newly enrolled for the first time for VA health care. While this review was not a substitute for a well-designed epidemiological study, it does summarize the clinical experience of a group of SHAD veterans who have received medical care from VA.

The medical data obtained for just those SHAD veterans who receive health care from VA does

not allow for meaningful comparisons with other SHAD veterans who have not utilized VA health care or to military veterans who did not participate in Project SHAD. To obtain valid scientific data, VA contracted in October 2002, with the IOM to conduct a study to evaluate health risks among all Project SHAD veterans. That scientific study is scheduled for completion in late 2006.

Today, decades after the SHAD tests, no diagnostic test can accurately tell us which agents veterans were exposed to and if any health problems might be associated with such an exposure. The pending IOM study will evaluate whether SHAD veterans are experiencing greater morbidity or mortality than similar veterans who served during the same period. For today, accurate diagnoses are possible based on a patient's symptoms and pathologic findings, and treatment is the same regardless of etiology. That means high quality health care is available now for any SHAD veteran with a health problem who seeks care from the VA, even before the IOM study is completed.

LONG-TERM HEALTH EFFECTS IN OTHER POPULATIONS

From Military OP Nerve Agents. Sarin and VX are highly toxic chemical warfare nerve agents that are intended to be lethal to humans. In 1998, VA requested the IOM to review the entire medical and scientific literature on long-term health effects potentially related to sarin exposure. Although the IOM focused on sarin, their findings are applicable to related nerve agents, including VX. The IOM had access to an abundant scientific literature, published over more than five decades, including significant data from human experimentation, occupational and accidental exposures, laboratory animals, and from terrorist attacks including the 1994 and 1995 sarin attacks in Japan.

For organophosphorus (OP) nerve agents as a class, including military agents and related pesticides, four distinct health effects have been described, including 1) acute cholinergic toxicity, 2) organophosphate-induced delayed neuropathy (OPIDN), 3) subtle long-term neuropsychological and neurophysiological effects; and 4) a reversible muscular weakness known as "intermediate syndrome" (Brown and Brix, 1998).

Some effects described in this literature are subtle, often difficult to differentiate from health effects caused by other diseases or occupational exposures. These effects all have threshold exposure levels below which they are not likely to be clinically detectable. Therefore, meaningful prediction of clinical short- and long-term human health effects require data on exposure magnitude (Brown and Brix, 1998, IOM 2000).

The IOM committee similarly concluded that the threshold exposure for all long-term effects from OP nerve agent exposure are at least large enough to cause acute, immediate signs and symptoms of cholinergic poisoning. Long-term health effects reported for survivors of acutely toxic and even life threatening poisoning from OP agents are generally subtle, detectable in exposed populations but not individuals, and not reported in individuals experiencing only subclinical exposures (Brown 2006). Clinically observable long-term health effects are reported only in the aftermath of acute clinical poisoning; that is, such long-term effects are unlikely in the absence of evidence of acute signs and symptoms of poisoning (Brown 2006).

Two IOM committees (2000 and 2004) reached essentially identical conclusions about long-term

health effects from sarin for different exposure levels, as defined by the magnitude of initial acute poisoning signs and symptoms. They reviewed a number of human studies on sarin health effects, as well as a wide range of laboratory animal studies. They focused upon studies of four human populations exposed to sarin, including military volunteers in experiments conducted in the U.S. and U.K. several decades ago, which involved exposure to sarin and other chemical warfare agents, industrial workers involved in the manufacture of sarin, and victims of terrorist attacks in Matusumoto City and Tokyo, Japan, in 1994 and 1995. The 2000 IOM committee also reviewed the hypothesis that exposure to sub-clinical traces of sarin might produce a new, previously undescribed disease – a "Gulf War syndrome." The committee did not endorse this hypothesis, and in fact, their most important conclusion relative to Gulf War health effects was that there was "inadequate/insufficient evidence of an association" between exposure to sub-clinical levels of sarin and any subsequent long-term health effects.

Not surprisingly, considering the fact that these chemical agents are designed to kill or incapacitate, the committee also found "sufficient evidence of a causal relationship" between exposure to sarin and a dose-dependent acute cholinergic syndrome that is evident seconds to hours subsequent to sarin exposure and resolves in days to months (IOM 2000).

The IOM committee also reported "limited/suggestive evidence of an association" between exposure to sarin at doses sufficient to cause acute (that is, immediate) cholinergic signs and symptoms and subsequent long-term health effects, based primarily on studies of three groups of people exposed to sarin – 1) workers occupationally exposed to sarin in the 1950s and 1960s; 2) a terrorist attack on civilians in Matsumoto, Japan in 1994; and 3) a terrorist attack on civilians in Tokyo, Japan in 1995. As previously described, no Gulf War veteran was known to have experienced an exposure this high, which caused acute symptomatic illness.

The committee pointed out that the Japanese survivors of terrorist attacks obviously experienced a wide range of exposures, as well as the stress of the event itself. Some terrorist victims showed severe cholinergic poisoning that required hospitalization or even resulted in death, some showed milder signs and symptoms, and some were exposed at levels leading to no acute effects. Commonly reported long-term health consequences included increased risk of PTSD and reports of "fear of subways," are likely to have derived from the psychological stress of the terrorist attack rather than directly from cholinergic poisoning.

A 2004 IOM update on sarin health effects added about 250 peer-reviewed articles published *after* the earlier 2000 review, including 19 epidemiological studies of sarin health effects as well as a wide range of animal studies. These included all relevant studies from 1) U.S. military volunteers who had been experimentally exposed decades ago to non-lethal doses of sarin and other chemical warfare agents; 2) industrial workers with documented acute exposure to sarin; and 3) victims of the sarin terrorist attacks in Matsumoto City in 1994 and Tokyo in 1995.

The update supported the findings of the earlier IOM analysis, that: 1) There is sufficient evidence of a causal relationship between exposure to sarin and a dose-dependent acute cholinergic syndrome that is evident seconds to hours subsequent to sarin exposure and resolves in days to months; 2) There is limited/suggestive evidence of an association between exposure to sarin at doses sufficient to cause acute cholinergic signs and symptoms and a variety of subsequent long-term neurological effects; and 3) There is inadequate/insufficient evidence to determine whether an association does or does not exist between exposure to sarin and subsequent long-term cardiovascular effects (this last finding was not contained in the 2000

report).

From Cannabinoids. A 1999 NAS committee review of medical and scientific literature on marijuana health effects addresses potential long-term health effects from exposure to cannabinoids (NAS 1999). That committee identified a significant amount of literature on cannabinoid health effects from research conducted in the 1980s and 1990s. They concluded that cannabinoids have a "natural role in pain modulation, control of movement, and memory." They also found that animal research suggested a potential for cannabinoid dependence and withdrawal symptoms, although milder than that seen for benzodiazepines, opiates, cocaine or nicotine. A distinctive but mild and short-lived marijuana withdrawal syndrome includes restlessness, irritability, mild agitation, insomnia, sleep EEG disturbances, nausea, and cramping (NAS 1999).

Although euphoria is commonly the sought for reaction to smoking marijuana, transient (resolving in hours) adverse mood reactions including anxiety and paranoia and less often panic, depression, dysphoria, depersonalization, delusions, illusions and hallucinations can also occur (NAS 1999). They concluded that although marijuana is not a completely benign substance, "except for the harm associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications."

Long-term health effects from smoking marijuana are unclear. Immunological effects have been reported, but their clinical significance remain uncertain (NAS 1999). Addressing the suggestion that marijuana might produce lasting mood disorders or psychotic disorders, such as schizophrenia, the committee found that very high doses of marijuana have been reported to be associated with a gradual waning of the positive mood and social facilitating effects of the drug and an increase in irritability, social isolation, and paranoid thinking (NAS 1999). Other reports describe development of apathy, lowered motivation, and impaired education performance in heavy marijuana users who do not appear to be behaviorally impaired in other ways (NAS 1999). Similarly, there are clinical reports of marijuana-induced psychosis-like states lasting for a week or more, apparently through triggering a latent psychopathology.

Nevertheless, the committee concluded that there was little evidence that marijuana alone produces a psychosis that persists after the period of intoxication. Thus, although heavy marijuana use can precipitate schizophrenic episodes, there is less evidence that it can cause the underlying psychotic disorder. They concluded that individuals with schizophrenia or with a family history of schizophrenia are likely to be at greater risk for adverse psychiatric effects from cannabinoid use. Other studies have also shown subtle effects on cognitive tasks and psychomotor performance, but these studies are difficult to interpret, and it remains unclear if repeated use of marijuana at therapeutic doses produces any irreversible cognitive effects (NAS 1999).

Smoked or ingested marijuana can also cause cardiovascular effects including tachycardia, which can last three to five hours (NAS 1999). Cases have been reported of blood pressure increase while a subject is in a reclining position but decreases inordinately upon standing, resulting in postural hypotension (decreased blood pressure due to changing posture from a lying or sitting position to a standing position, which can cause dizziness and faintness. These cardiovascular changes "have not posed a health problem for young healthy users of marijuana," but they could present problems for older patients with coronary arterial or cerebrovascular diseases (NAS 1999).

Finally, the committee reported that there was "no conclusive evidence that marijuana causes cancer in humans, including cancers usually related to tobacco use." However, a range of studies suggest that the smoke of a marijuana cigarette may be an important risk factor for respiratory cancers (NAS 1999).

CONCLUSIONS

The US military personnel who participated in these Cold War experiments took great health risks in the service of their country. They deserve our respect and assistance for any health problems that were the result of toxic exposures during these military tests. Some of these exposures had the potential to cause substantial harm to the veterans' health, whereas some participants may not have been exposed to any toxic substance because they were used as controls in these experiments. Regardless, long-term psychological effects could have resulted just from participating in these experiments.

Unfortunately, the records are not complete enough to determine the exact nature of the exposure in many of these veterans. Each veteran therefore has to be cared for as an individual and given a thorough clinical evaluation to identify all outstanding health problems. Fortunately, high quality health care does not depend on identification of etiologic factors. This is true for much of modern health care. For example, cancer diagnosis and effective therapy does not depend on the identification of a specific etiology.

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