CHEMICAL WARFARE AGENT EXPERIMENTS AMONG U.S. SERVICE MEMBERS

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Military experiments using service member as subjects have been an integral part of the U.S. chemical weapons program, producing tens of thousands of "soldier volunteers" experimentally exposed 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 were experimentally exposed mainly to mustard agent and Lewisite (NAS 1993). From 1955 to 1975, thousands of U.S. service members were experimentally treated with a wide range of agents, primarily at U.S. Army Laboratories at Edgewood Arsenal, Maryland. Veteran and others have become increasingly concerned about long-term health effects potentially related to participation in these experiments. Even service members who were not experimental subjects but were involved only in carrying out military testing have expressed concerns about potentially related long-term health consequences, for example, tests evaluating ship vulnerability to attacks with chemical and biological agents conducted during the 1960s. Veterans and their supporters are also responding to a perception that participating veterans were the unwitting and unwilling subjects of secret military experimentation.

In response, VA with support from the U.S. Department of Defense (DoD) has made significant efforts to identify participants in the Edgewood/Aberdeen experiments conducted from 1955 to 1975 (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. Such efforts are significantly hampered by lack of military records on subject identity, and about the identity and magnitude of the agents they were exposed to. Many subjects were involved in multiple experiments with exposure to many different agents. These experiments were conducted decades in the past, further confounding modern efforts to piece together what happened. Today we appreciate that concerns about long-term health consequences among experimental subject are inevitable, earlier military researchers failed to anticipate this issue. 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.

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

The U.S. has had an active chemical warfare program since World War 1, with large-scale testing, manufacture and stockpiling of chemical agents and munitions. By the early 1990s, this stockpile included an estimated 25,000 tons of chemical warfare agents, including nerve agents such as sarin and VX, and vesicant (blister) agents including mustard and Lewisite. Today, this stockpile is considered obsolete, and federal law and international agreements require that it be destroyed.

A significant part of this program involved experimentation with 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 evaluated the impact on military personnel operational readiness, and the efficacy of new materials such as potential riot control agents. Other experiments evaluated the effectiveness of incapacitating and "brainwashing" agents such as cannabinoids and LSD. Human subjects were part of this program from the beginning, but the number of service members involved and the chemical warfare agents

tested has changed greatly over time. Although originally conducted in secret, today a great deal of information about them is available in the open literature.

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). German use of mustard agent against Polish citizens in 1939 led U.S. military planners to respond in kind. U.S. military planners ultimately 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).

Research focused primarily on improving weapons and means of protection. "Soldier volunteers" were exposed commonly to acutely toxic levels (i.e., levels resulting in immediate signs and symptoms of poisoning) 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). Field tests involved subjects passing through areas of land treated with sulfur mustard or Lewisite (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 experimental subjects using 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).

By the end of the World War 2, 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, and some accidents were inevitable these individuals trained or otherwise came into contact with these materials. 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 initially to reduced interest in human experimentation with mustard and Lewisite (NAS 1993). However, by the 1950s, DoD again saw a need for human experiments, although on a much

smaller scale, and with a focus on newer and potentially 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).

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). Many of these experiments were designed to evaluate acute human toxic effects (NRC 1982). Some 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). Congressional hearings about these experiments in 1974 and 1975 resulted in significant disclosures and the notification of some subjects about their participation, and compensation of a few families of subjects who had died during these experiments (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.

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). Subsequent attempts to evaluate potential long-term health effects uncovered limited information on 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 (NRC 1982).

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. The shipboard tests were called "Shipboard Hazard and Defense," or simply "SHAD." In 2000, responding to a request from Secretary of Veterans Affairs, DoD began declassifying and sharing what information was still available with VA about the medical aspects of these tests, and the identities of those involved. Unlike many such experiments before or since, Navy ship rosters have turned out to be an excellent source for determining who was actually involved in these tests, although data about individual exposures is more typically poor or non-existent. Since May 2002, using declassified information provided by DoD, VA has been notifying veterans who took part in these 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 to conduct a comprehensive study of potential long-term health effects among SHAD test conductors (VA 2002).

CALLS FOR INDEPENDENT EVALUATION

Public attention about these military human subjects experiments increased considerably when affected veterans began to seek compensation from VA for health problems they believed had been caused by their involvement. Veterans faced significant hurdles in establishing such claims because typically little or no supporting documentation was available. For example, generally the time spent as subjects 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.

Responding to mounting concerns about potential long-term health consequences from participation in military experiments, in 1980 DoD requested the National Research Council (NRC) to evaluate long-term health effects among the 6,720 servicemen subjects in the Edgewood/Aberdeen post-World War 2 experiments conducted in Army Laboratories from 1955 to 1975. This produced three reports titled "Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents" (NRC 1982, 1984, 1985), which reviewed the medical and scientific literature on the possible long-term health effects from exposure to the agents involved, and included an epidemiological study of experimental subjects. 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.

Similarly, in 1991, increasing concerns among veterans, Congress and the media led VA's Secretary to announce new guidelines for compensation of veterans experimentally exposed to mustard and Lewisite agents. Those guidelines loosened the normal restrictions requiring documentation of exposure, and identified certain illnesses that VA would presume to be associated with exposure to mustard agent and Lewisite, including 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 these agents, which was published in 1993 (NAS 1993).

COMPARING PAST AND CURRENT HUMAN RESEARCH GUIDELINES.

Review of US military experiments conducted decades ago that involved exposure of human subjects to chemical warfare and other agents inevitably invites comparison with current standards regulating human subjects research. Many of the research protocols used during those earlier periods fall short of today's standards for protecting human subjects, a comparison leading in part to the outrage expressed by some affected veterans today – the sense that they were treated as no more than "human guinea pigs."

Nevertheless, according to the 1982 NRC report, experimental 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 (NRC 1982)."

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 acknowledged 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."

Finally, nearly all veterans who talk about their participation in these experiments express a strong sense of patriotism and the belief that they made an important sacrifice for the protection of their country. In return, VA has the obligation to provide equitable health care and benefits for any injuries these veterans sustained while on active duty.

EXPERIMENTAL PROTOCOLS – WHAT DO WE KNOW?

The secrecy under which these experiments took place had an enormous affect our current understanding about the identity of experimental subjects, the agent or agents they were exposed to, and the magnitude of their exposures. For example, during their investigations of World War 2 era mustard and Lewisite experiments, an 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 (NAS 1993)." The more recent Edgewood/Aberdeen studies (from 1955 to 1975) present similar difficulties for evaluating long-term health issues, due to poor contemporary records and the passage of time (NRC 1984).

However, many of these early experimental protocols were probably reasonably consistent with contemporaneous standards, and may have been crude only in comparison with modern pharmacological research. "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 [contemporary] research centers" (NRC 1984). Military Edgewood/Aberdeen experiments commonly began with low "range finding" doses among "a few" volunteers, followed by more subjects being tested with doses subsequently estimated as safe but pharmacologically active (NRC 1984). Additional studies apparently followed up interesting effects, worrisome side effects, or tested potential interventions using experimental antidotes (NRC 1984).

Common Pharmaceutical Agents and Placebos. Available records indicate that many Edgewood/Aberdeen subjects were exposed to a wide range of common placebos and pharmaceutical agents (or their close analogs). However, placebo controls were not always used, possibly consistent with the research goals of military planners (NRC 1984). 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.

Anticholinesterases. Table 2 lists 16 anticholinesterase agents including OP, carbamate and other cholinesterase inhibiting compounds, tested on about 1,400 subjects in the Edgewood/Aberdeen experiments. Subjects were exposed via intravenous, vapor, oral percutaneous, intramuscular routes, and some were treated simultaneously with reactivating and antidote agents (NRC 1982). Contemporary case summaries were "brief and anecdotal," with no reports of neurologic or psychologic examinations (NRC 1982). 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). Many 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 "glycolate" agents related to atropine, tested on about 1,800 subjects in the Edgewood/Aberdeen experiments, via intravenous, vapor, oral percutaneous, intramuscular routes (NRC 1982). Some subjects were treated simultaneously with other agent, and available case summaries were reportedly "brief and anecdotal" (NRC 1982). Although some laboratory results were available, 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. Antidote cholinesterase reactivator such as 2-PAM were tested on about 750 subjects. Irritants (i.e., 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 to CS at Edgewood (NRC 1984) including via aerosol (1,073 subjects), dermal (180 subjects), aerosol and dermal (82 subjects), and ocular (31 subjects). Most experiments evaluated protective equipment and impact on performance of military tasks. In contrast to the earlier World War 2 era experiments that involved about 60,000 subjects, only 147 subjects were exposed to mustard or Lewisite during these more recent experiments (NRC 1982). Some experiments only involved one or two subjects. For example, the period 1962 to 1972 saw 123 irritant chemicals (based upon preliminary animal studies) tested using only two subjects each exposed in a wind tunnel (NRC 1984). 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).

ACUTE EFFECTS AMONG EDGEWOOD/ABERDEEN SUBJECTS.

Some of our best information about the dose experienced by subjects of the Edgewood/Aberdeen experiments comes from contemporary records of acute poisoning signs and symptoms among subjects (Brown and Brix 1999).

Anticholinergics. Anticholinergics, including military OP nerve agents such as sarin and VX, and their closely related OP pesticides act by inhibiting acetylcholinesterases, leading to a well-characterized toxic accumulation of the neurotransmitter acetylcholine. Subjects exposed to anticholinergics reportedly exhibited a wide range of classic 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 evidence of acute toxicity, presumably because of the low dose they received. Others experienced severe clinical acute cholinergic poisoning that required treatment with conventional antidotes such as atropine (NRC 1982). A 1982 NRC review reported no clear

evidence that the anticholinergic agents tested produced any 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 such as 2-PAM are intended to "reactivate" cholinesterases that have been inhibited by an OP nerve agent such as sarin or common OP pesticides. Not surprisingly, reactivators were often given following treatment with anticholinergics. The medical records of subjects treated at Edgewood/Aberdeen apparently included test protocols, physicians' orders, nursing notes, clinical observations, symptom checklist, and laboratory and performance test results, but not reports of physicians' examinations (NRC 1984). Commonly reported effects 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). Clinical responses to conventional reactivators 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).

More severe acute effects were also noted, including one subject (treated with P2S and soman) with significant chronic psychological effects, and a second (treated with 2-PAM alone) experiencing a grand mal seizure (NRC 1984). The NRC 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). Effects reported among Edgewood/Aberdeen subjects were similar to those reported in clinical research from pharmaceutical companies who had evaluated PCP as an anesthetic agent, that is, the military tests "did not involve extraordinary doses" compared to contemporary civilian experiments (although inhalation exposure was unique to the military trials) (NRC 1984).

Edgewood/Aberdeen subjects treated with PCP reported "feelings of unreality – dream-like states with perceptual size changes," with variable affect and mood changes (NRC 1984). Some 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 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 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. Reported signs and symptoms were "very similar to those later described over the last 15 years by many research laboratories working with cannabis and THC," and 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 were a 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). They reported that "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). However, 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). Signs and symptoms of acute mustard agent poisoning, which are usually delayed for some hours following exposure, include severe irritation and tissue damage to eyes, skin, and respiratory and gastrointestinal (GI) tracts. Although the vast majority of military human experiments with mustard agents and Lewisite agents occurred before the end of World War 2, experiments with mustard agents were also conducted at Edgewood/Aberdeen from 1955 to 1965. In those experiments, subjects were reportedly removed from exposure typically 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 blistering that 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 echo more recent reports of military exposure to mustard agents. Probably the largest actual military use of mustard agent was during the 1980s Iran-Iraq war (NAS 1993). A report of Iraqi use of mustard agent against Iranian troops in 1984 documented health effects among more than 5,000 Iranian casualties, including first to third degree burns over 20 to 70 percent of the total skin surface, in a pattern similar to that reported for mustard agent casualties in World War 1. 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).

LONG-TERM HEALTH EFFECTS AMONG EXPERIMENTAL SUBJECTS

Although military researchers were primarily interested in short-term acute effects, today, many veterans are concerned more with possible long-term health effects from these experimental exposures. Review of the significant amount of literature on long-term health effects from tested agents can help predict what health affects may be anticipated. Much of this literature is based on studies of the veterans involve. Many studies are also available based on other exposed groups including civilians exposed in accidents or via terrorist incidents. However, the lack of good exposure data significantly limits our ability to predict long-term health effects for individual veterans involved in these experiments.

Mustard Agent and Lewisite. The 1993 NAS committee concluded that some veterans experimentally exposed to mustard and Lewisite had clearly suffered serious and debilitating diseases as a consequence, lasting in some cases for decades (NAS 1993). Many subjects of earlier World War 2 era experiments with these agents also sustained dermal injuries severe enough to cause permanent scarring (NRC 1984). However, the absence of follow-up health assessments such as epidemiological studies of chemical weapons production workers, of chemical warfare munitions handlers and trainers, or of chemical weapon combat casualties, has limited any systematic assessment of long-term health consequences (IOM 1993).

In their broad review of all relevant medical and scientific literature on health effects related to mustard agent exposure the 1993 NAS committee identified a range of related chronic diseases, including (NAS 1993):

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)

Studies of World War 2 Mustard and Lewisite Military Human Subjects. A 2000 study by VA researchers compared mortality among 1,545 World War 2 Navy veterans exposed to mustard agent in World War 2 era experiments to mortality among 2,663 similar Navy veterans not part of these experiments (Bullman & Kang 2000). Long-term health issues had not been evaluated previously for this group. The study found 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). The large sample size produced 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. 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. Ten years after their combat exposure soldiers

exhibited 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 World War 2 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).

Studies of Post World War 2 Edgewood/Aberdeen Subjects. NRC studies in the 1980s reported finding little evidence of any health consequences among participants in the post-World War 2 Edgewood/Aberdeen military experiments. They evaluated long-term morbidity and mortality among the 6,720 subjects exposed from 1955 to 1975 to more than 250 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). Perhaps surprisingly, they reported that these subjects were generally healthier in comparison to era controls, while both subjects and controls were healthier than the general population (NRC 1984). However, the NRC committee pointed out that a range of methodological problems 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 from 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. Researchers focused in particular on evaluation of cancer risks, adverse mental, neurologic, hepatic and reproductive effects that might be associated with participation in the post-World War 2 Edgewood/Aberdeen tests.

Devising an appropriate control group for this study was complicated because the exclusively military subjects were apparently also subjected to further significant physical and psychological screening for inclusion in these studies (NRC 1985). Moreover, experiments involving hazardous chemical warfare agents selectively used more fit subjects, leaving less fit subjects as controls or tests with placebos (NRC 1985). Finally, experimental subjects were commonly used in multiple tests with exposure to a range of different 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.

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. NRC researchers were careful to document the significant study limitations they faced: "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 subsequent to the experiments, 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 detected, and, for subjects exposed to anticholinesterases, neoplasms occurred at a range of sites with no consistent pattern or correlation with exposure 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, 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).

The more recent follow up studies of Edgewood/Aberdeen subjects reported only two statistically significant effects (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. Strikingly, in this study, 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.

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 subsequent to these experiments (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 with at least 741 individuals (US Army 1980). In 1978, the US Army Health Services Command initiated a follow-up health evaluation of subjects, although their evaluation was complicated because the experiments had occurred on average 19 years earlier. 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 experiments took place at Edgewood arsenal, but many 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). Age of subjects when surveyed 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 US Air Force personnel were excluded from 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).

Typically, establishing a useful comparison group was problematic because the LSD subjects were clearly not a random sample of the Army population. 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). Moreover, 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, and 10 were listed as "controls" without any actual exposure data. US Army researchers decided that since all 741 subjects had been assigned to LSD experiments, "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. 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 also 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 and consistent with the 1985 NRC evaluation, 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). Nevertheless, some subjects reportedly 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."

Evaluating Project SHAD Veterans. An unpublished 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 early 2007.

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.

PSYCHOLOGICAL IMPACT OF TEST PARTICIPATION.

A significant body of literature suggests that the mere act of participating in military experiments can lead to long-term psychological effects. For example, a study of veteran subjects of U.S. military experiments involving mustard agent exposure reported significant increased risk of Post-traumatic Stress Disorder (PTSD) compared to controls who did not participate (Schnurr et al., 2000). 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 2 mustard agent experiments (Schnurr et al., 2000). Ninety-six percent had participated in gas chamber experiments with mustard agent, and 92 percent reported they had volunteered. Twenty-two percent of the subjects reported that they understood the dangers involved, and 67 percent were ordered to not discuss their participation. Most subjects (83 percent) reported experiencing physical symptoms at the time of mustard agent exposure.

Nearly 5 decades after participating in these experiments, subjects were found to be less psychologically and physically healthy in comparison to men of similar age (Schnurr 1996). Significantly, they exhibited a high PTSD prevalence of 17 percent, with lifetime estimates for full and sub-diagnostic PTSD of 17 and 33 percent, respectively (Schnurr 1996). Only the number of individual exposures to mustard gas during these experiments predicted lifetime full or sub-diagnostic PTSD rates (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 percent of these veterans suffered from full-PTSD, and 10 percent 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).

LONG-TERM HEALTH EFFECTS IN OTHER POPULATIONS

From Military and Insecticide OP Nerve Agents. Four distinct health effects have been described for military and related pesticide organophosphorus (OP) nerve agents, 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). . Because all OP related health effects have threshold exposure levels below which they are clinically not detectable, meaningful predictions of clinical short- and long-term human health effects require information about exposure magnitude (Brown and Brix, 1998, IOM 2000). Moreover, long-term health effects reported among survivors of acutely toxic and even life threatening OP agent poisoning are often subtle, sometimes difficult to differentiate from health effects caused by other diseases or occupational exposures, more readily detectable in exposed populations than in individual cases,

and not reported among individuals experiencing only subclinical exposure (Brown 2006).

In 1998, VA requested the National Academy of Sciences Institute of Medicine (IOM) to review all medical and scientific literature on long-term health effects from exposure to the military OP nerve agent sarin. Two IOM committees (IOM 2000 and IOM 2004) established for this evaluation examined thousands of scientific publications spanning over five decades, including results from human experiments, occupational and accidental exposures, laboratory animals, and from terrorist attacks. They focused on studies of human populations exposed to sarin, including 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 (IOM 2000; IOM 2004).

The two committees confirmed that all long-term health effects from sarin exposure required an initial threshold exposure level sufficient to cause acute, immediate signs and symptoms of cholinergic poisoning. Both IOM committees reached essentially identical conclusions about long-term health effects from sarin at various exposure levels as defined by the magnitude of initial acute poisoning signs and symptoms. 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." They 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).

They 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. No veteran of the 1991 Gulf War has been reported to have experienced an acute exposure to an OP agent, that is, showing immediate cholinergic poisoning signs and symptoms (Brown 2006).

Any terrorist attack upon civilians might be expected to exact some psychological toll. Some of the 1995 Tokyo terrorist victims reported experienced 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 (IOM 2000). One common 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 (IOM 2000).

As an indicator of the extensive scientific literature available on this topic, the 2004 IOM sarin health effects update was able to add about 250 peer-reviewed articles published *after* the earlier 2000 review, including 19 epidemiological studies of sarin health effects among the same

experimentally exposed veterans, industrial workers and terrorist attack survivors that had been previously evaluated, as well as a wide range of new animal studies. The update reiterated the findings of the earlier IOM analysis, and added that 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 (IOM 2004).

From Cannabinoids. A 1999 National Academy of Sciences (NAS) committee review of medical and scientific literature on marijuana health effects addressed potential long-term health effects from exposure to cannabinoids (NAS 1999). They identified a significant body of scientific literature on cannabinoid health effects based on research conducted during the 1980s and 1990s. The committee concluded that cannabinoids have a "natural role in pain modulation, control of movement, and memory" (NAS 1999). 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).

Euphoria is the commonly the sought-for acute reaction to smoking marijuana, however other acute effects include 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).

Evidence is much less clear for any long-term health effects from smoking marijuana. Immunological effects have been reported, but their clinical significance remain uncertain (NAS 1999). Addressing the suggestion that marijuana use 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. Thus, although heavy marijuana use can precipitate schizophrenic episodes, there is less evidence that it can cause the underlying psychotic disorder. Individuals with schizophrenia or with a family history of schizophrenia are likely to be at greater risk for adverse psychiatric effects from cannabinoid use (NAS 1999). There was little evidence that marijuana alone produces a psychosis that persists after the period of intoxication. 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).

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).

Finally, the committee 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" (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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TABLES

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
Amobarbital (Amytal)	Sedative
Chloral Hydrate	Sedative
Meprobamate	Sedative (PDR)
Nembutal	Sedative (PDR)
Secobarbital Sodium	Sedative
Seconal	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*
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.	

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

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