Military Chemical Warfare Agent Human Subjects Testing: Part 1—History of Six-Decades of Military Experiments With Chemical Warfare Agents

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ABSTRACT Military chemical warfare agent testing from World War I to 1975 produced thousands of veterans with concerns of possible long-term health consequences. Clinical and research evaluation of potential long-term health effects has been difficult because the exposures occurred decades ago, the identity of troops exposed and exposure magnitudes are uncertain, and acute effects during experiments poorly documented. In contrast, a companion article describes the large amount of information available about the specific agents tested and their long-term health effects. This short history describes U.S. military chemical-agent experiments with human subjects and identifies tested agents. Finally, the demonstrated need to anticipate future health concerns from military personnel involved in such military testing suggests current and future military researchers should be required, by law and regulation, to fully record the identity of those exposed, relevant exposure magnitude, and complete medical information for all subjects. New study protocols and institutional review board approvals for research involving military personnel should reflect this need.

INTRODUCTION

U.S. veterans have access to cost-free health care and disability compensation through the U.S. Department of Veterans Affairs (VA) for service-connected illnesses and injuries. However, connecting an illness to a specific military environmental or occupational exposure can be difficult, especially when it occurred decades ago, exposure magnitude is uncertain, and health records are not available. Veteran participants in military chemical and biological warfare agent experiments from World War I to the mid-1970s face particular difficulties in this regard. Poor documentation also hampers population-based research studies that might evaluate potential long-term health effects. Consequently, many affected veterans recall these events with a sense of outrage over their apparent unwitting participation in human experiments, and the lack of clear information about any health risks they face today. Finally, reviewers of World War II era experiments note an "atmosphere of secrecy still exists to some extent regarding the World War II testing program," making it occasionally difficult to obtaining relevant health information.[1] Secrecy similarly affects evaluation of more recent 1955–1975 Edgewood/Aberdeen experiments.[2] These issues complicate but nevertheless can still support a clinician's ability to respond to the health concerns of individual-affected veterans. Despite huge gaps in our current knowledge, VA with assistance of Department of Defense (DoD) has assembled significant information on the hundreds of chemical agents tested and their long-term health effects. This review synthesizes available data on these historical events to support providers and policy makers who must continue to respond to this issue. Finally, these events illustrate the need to anticipate health concerns from veterans involved in future testing of military systems. Earlier military researchers failed to anticipate these controversies and made few plans for long-term tracking and evaluation of subjects and for outreach. In response, current and future military researchers should be required, by law and regulation, in study protocols and institutional review board approvals for human subject research to document the identities of those exposed, and relevant exposure data and medical histories for all service members involved in military systems testing.

HISTORY OF U.S. CHEMICAL WARFARE AGENT HUMAN EXPERIMENTS

The U.S. has had an active chemical warfare development and defense program since World War I, involving the large-scale testing, manufacture, and stockpiling of chemical agents and munitions. Today, this stockpile is considered obsolete and federal law and international agreements require it be destroyed. Thousands of human subjects were part of this program through about 1975, but numbers involved and agents tested has changed greatly over time. By one estimate, by the end of World War II, nearly 60,000 U.S. service members were experimentally exposed, mainly to mustard agent and Lewisite.[1] From 1955 to 1975, thousands of U.S. service members participated in military experiments with hundreds of different agents, mostly at U.S. Army Laboratories at Edgewood Arsenal, Maryland. Since then, participants have become increasingly concerned about potential long-term health effects. Even service members involved exclusively in conducting these tests have expressed concerns, e.g., Navy personnel conducting tests in the 1960s to

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evaluate ship (not human) vulnerability to chemical and biological agent attacks.

Although originally conducted in secret, some information is available today in open literature including the identity of tested agents. However, the identity of participants, their exposure magnitudes, and contemporary military medical records are often scant. Many participants were involved in multiple experiments with a variety of agents. Many experiments were intended to enhance defensive capabilities, such as improved protective clothing and respiratory masks. Others evaluated the impact of agent exposure on military personnel operational readiness, or efficacy of agents such as for riot control purposes. Other experiments evaluated the effectiveness of incapacitating and "brainwashing" agents such as cannabinoids and LSD.

Experiments Through World War II

The chemical warfare agent sulfur mustard ("mustard agent") caused nearly 400,000 casualties during World War I—more than any other chemical agent used during that conflict.[1] German use of mustard agent against Polish citizens in 1939 convinced U.S. military planners of the necessity to develop U.S. mustard agent capabilities, and by the close of World War II 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.[1]

Contemporary military planners determined human studies were necessary for evaluating their impact and protective measures, and in 1942, they were given authority to recruit subjects.[1]

Experimentation commonly involved exposure to acutely toxic levels (leading to immediate poisoning signs and symptoms) via small drops applied to the arm or to clothing, or via gas chambers generally to evaluate protective clothing or gas masks.[1] Documented injuries were 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 at Edgewood Arsenal over a 2-year period.[1] Some experiments reportedly involved repeated gas chamber mustard agent or Lewisite exposures for 1 to 4 hours.[1] Subjects were typically evaluated 24 hours later for erythema as evidence of protective clothing failure.[1] Many 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.[1] Some less-protected subjects apparently experienced severe burns to the genital areas, including cases of crusted lesions to the scrotum.[1] Field tests involved troops passing through areas treated with sulfur mustard or Lewisite.[1]

Strikingly, during this period the only combat-related exposure of U.S. troops was a German bombing attack in December 1943 on U.S. ships loaded with mustard agent in the Italian harbor of Bari, Italy, causing thousands of injuries and hundreds of deaths among U.S. service members and others in the area.[1]

Post World War II—Edgewood/Aberdeen Experiments

The end of World War II initially led to less interest in human experiments. However, by the 1950s military planners again saw a need for new testing on a much smaller scale, with potentially more effective agents including the organophosphorus (OP) military nerve agents, nerve agent antidotes, incapacitating agents such as tear gas, and psychoactive agents.[1,3]

From 1955 to 1975, approximately 6,720 soldiers participated in experiments at U.S. Army Laboratories (formerly Army Chemical Center) at Edgewood Arsenal, Maryland, involving more than 250 chemical agents from about half a dozen pharmacological classes.[1–3] These included common approved pharmaceutical agents, anticholinesterase nerve agents such as sarin and common pesticides, glycolate anticholinergic agents such as atropine, nerve agent reactivators, psychoactive compounds including LSD, cannabinoids, and irritants (e.g., tear gases). Experiments commonly began with "range finding" doses among "a few" volunteers, followed by more subjects tested with doses estimated as acute but safe.[2,3] Some involved placebos or common agents such as caffeine and alcohol. Congressional hearings in 1974 and 1975 resulted in significant disclosures, official notification of some subjects, and compensation for a few families of subjects who had died during experiments.[1]

Project SHAD Tests

From 1963 through the early 1970s, DoD conducted tests called "Project SHAD" ("Shipboard Hazard and Defense") designed to evaluate the effectiveness of shipboard protective systems. Tested agents included actual chemical and biological warfare agents, and more commonly, less hazardous "simulants," i.e., relatively nontoxic substitutes with similar physical properties. According to DoD, military personnel were present as staff and not test subjects, were provided appropriate protection, and none were reported to have become ill during testing. Despite these assurances, there has been a perception by some that those involved may have been in some cases unwitting subjects of dangerous experimentation. In 2000, DoD began declassifying available health information for these tests, including Navy ship rosters that thoroughly document who participated. Exposure data, however, is typically poor or nonexistent.

CALLS FOR INDEPENDENT EVALUATION

Public attention about past military human subject experiments increased considerably as affected veterans began to seek compensation from VA for potentially related health problems. However, the absence of supporting documentation complicated filing compensation claims. Service as an experimental subject in World War II era mustard agent and Lewisite experiments was typically not tracked in official military service records.[1] Moreover, at first little scientific or medical information was available on long-term health effects from such exposures.

Responding to mounting concerns, in 1980 DoD requested the independent National Research Council (NRC) to evaluate long-term health effects among the 6,720 Edgewood/Aberdeen subjects. This produced 3 reports[2–4] on the medical and scientific literature of possible long-term health effects from tested agents, and an epidemiological study. Overall, the NRC concluded that long-term health effects among subjects were probably minimal, but that gaps in scientific knowledge made conclusions necessarily tentative.

In 1991, VA announced new guidelines for compensation of veterans involved with mustard and Lewisite experiments that loosened documentation requirements, identified certain illnesses VA would presume associated with these exposures, including asthma, chronic laryngitis, chronic bronchitis, emphysema, corneal opacities, chronic conjunctivitis and keratitis of the eye, and requested the National Academy of Sciences (NAS) Institute of Medicine to review relevant scientific literature on human health effects from these agents (published in 1993).[1]

Past Versus Current Human Research Guidelines

Predictably, some research protocols of experiments conducted decades ago fall short in comparison with current standards regulating human subjects research. Outside reviewers observed "consent information was inadequate by current standards."[3] However, many of these early protocols were probably reasonably consistent with modern standards—crude perhaps mainly 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."[2] Review of 1958–1975 Edgewood/Aberdeen experimental protocols ". . . emphasized that voluntary consent of each human subject was absolutely essential," and "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."[3] Moreover, "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."[3]

AGENTS TESTED AT EDGEWOOD/ABERDEEN

The 1958–1975 Edgewood/Aberdeen experiments involved more than 250 chemical agents, from about half a dozen pharmacological classes, including common approved pharmaceutical agents (Table I), 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 II–IV). Table V shows these pharmacological agent classes and median year tested.

About half (3,200) the subjects were tested with anticholinesterase and anticholinergic agents.[2] About 750 subjects

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

Agent/Simulant Name	Agent Class
Antipyrine	Analgesic (PDR[b], 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
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

[a]Data provided by Department of Defense, Health Affairs, Deployment Health Directorate, 2006. [b]PDR, listed in the Physicians Desk Reference, Medical Economics Company, Inc.

TABLE II. Anticholinesterase Agents Tested on 1,406 Subjects at Edgwood/Aberdeen[b]

Compound Tested	CAS No.[a]	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[b] (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

Common examples of this class include common organophosphorus and carbamate pesticides, and pyridostigmine bromide, commonly prescribed for myasthenia gravis patients.

[a]CAS, Chemical abstract service numbers, which are unique unambiguous numerical designations for a specific compound. Not all compounds tested had CAS numbers. [b]EA numbers are Edgewood Arsenal designations.

TABLE III. Anticholinergic Glycolic Acid Esters Tested on 1,752 Subjects at Edgwood/Aberdeen[b]

Compound Tested	CAS No.[a]	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

Common examples of this class include atropine, a common antidote for poisoning with organophosphorus and other anticholinesterases, and scopolamine, prescribed as a mild sedative and anti motion-sickness drug.

[a]CAS, Chemical abstract service numbers, which are unique unambiguous numerical designations for a specific compound. Not all compounds tested had CAS numbers. [b]EA numbers are Edgewood Arsenal designations. Six-digit numbers are contractor's designations.

were exposed to 1 of 4 cholinesterase reactivators (e.g., anticholinesterase antidotes such as 2-PAM), 260 subjects to phencyclidine (PCP or "angel dust") or to 1 of 10 cannibinoid psychochemicals, and 1,500 subjects to irritants and vesicants including CN, CS, other "tear gas" type irritants, and mustard agent. Anticholinesterases and anticholinergic agents were also commonly tested in combination, because the one functions as treatment for overexposure to the other.[3]

Common Pharmaceutical Agents and Placebos

Many Edgewood/Aberdeen subjects were exposed to various common pharmaceuticals (or close analogs) or placebos, although placebo controls were not always used (Table I).[2]

Anticholinesterases

Table II lists 16 anticholinesterase agents including OP, carbamate, and other cholinesterase inhibiting compounds, tested

TABLE IV. Acetylcholine Reactivators, Cannabinoids, Phencyclidine, and Irritants and Vesicants Tested on 3,500 Subjects at Edgewood/Aberdeen[3]

Compound	CAS No.[a]	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

Common examples of Reactivators include 2-PAM, commonly prescribed for Organo Phosphorus poisoning. The irritants include commonly used "tear gas" and "riot control" agents.

[a]CAS, Chemical abstract service numbers, which are unique unambiguous numerical designations for a specific compound.

TABLE V. Chemical Class and Median Year of Tests on 6,720 Subjects at Edgwood/Aberdeen[2]

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

on about 1,400 subjects, via intravenous, vapor, oral percutaneous, and intramuscular routes, including some simultaneously treated with a corresponding reactivating or antidote agent.[3]

Anticholinergics

Table III lists 24 anticholinergic "glycolate" agents (related to atropine) tested on about 1,800 subjects, via intravenous, vapor, oral percutaneous, and intramuscular routes, including some simultaneously treated with other agents.[3]

Cholinesterase Reactivators, Cannabinoids, Irritants and Blister Agents, Phencyclidine, and LSD

Table IV lists 4 cholinesterase reactivators, 11 cannabinoids, 9 irritants and vesicants and phencyclidine (PCP or "angel dust"), tested on about 3,500 subjects. Antidote cholinesterase reactivator such as 2-PAM were tested on about 750 subjects. Irritants and vesicants were tested on about 1,500 subjects, including the riot control agents CN, CS, chloropicrin (PS), diphenylaminochlorarsine (DM, Adamsite), other ocular and respiratory irritants, and mustard agent.[2] For example, from 1958 to 1973 at least 1,366 human subjects underwent experimental CS exposure at Edgewood[2] including via aerosol (1,073 subjects), dermal (180 subjects), aerosol and dermal (82 subjects), and ocular exposures (31 subjects), mainly to evaluate protective equipment and impact on performance. Only 147 subjects were exposed to mustard or Lewisite.[3] Some experiments involved only 1 or 2 subjects, e.g., from 1962 to 1972, 123 candidate irritants (identified from preliminary animal studies) were tested on 2 subjects exposed in a wind tunnel.[2]

Psychoactive agents including phencyclidine ("angel dust," PCP) and 11 related synthetic cannabinoids were tested on about 260 subjects.[2] In addition, the U.S. Army Chemical Corps and the U.S. Army Intelligence Corps conducted human experiments with LSD from 1955 through 1967, involving at least 741 individuals.[5] Intended to test LSD as a chemical warfare agent, these 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)."[5] However, "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," and "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."[5]

Agents Tested In Project SHAD

DoD declassification efforts have provided good data on the identity of tested chemical and biological agents in Project SHAD. Biological agents included *Coxiella burnetii*, *Francisella tularensis*, and staphylococcal enterotoxin B. Biological agent simulants included *Bacillus globigii* (BG), *Escherichia coli*, *Serratia marcscens*, and zinc cadmium sulfide. Although considered safe at the time, some simulants known now to be opportunistic pathogens under unusual circumstances that were probably not relevant to most participants. Common surface-sterilizing agents were also used, presumably following experiments with live biological agents, including β-propiolactone, ethyl alcohol, Lysol, peracetic acid, potassium and sodium hydroxide, and sodium hypochlorite (household bleach). Although most tests with chemical warfare agents used simulants such as methylacetoacetate or sulfur dioxide, common OP nerve agents including sarin, VX, tabun, and soman were also tested.

ACUTE EFFECTS AMONG EDGEWOOD/ABERDEEN SUBJECTS

Contemporary medical case summaries for most Edgewood/Aberdeen experiments were "brief and anecdotal" with little or no long-term medical follow-up.[3,6]

Anticholinergics

Anticholinergics, including military OP nerve agents such as sarin and VX, and their closely related OP pesticides, inhibit acetylcholinesterases, causing well-characterized toxic accumulation of the neurotransmitter acetylcholine. Some anticholinergic-exposed Edgewood/Aberdeen subjects exhibited 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.[3] Severe and even life-threatening cholinergic poisoning occasionally required antidote treatment with atropine.[3]

Reactivators

Reactivators such as 2-PAM "reactivate" cholinesterases inhibited by an OP nerve agent such as sarin or common OP pesticides. Contemporary medical records of reactivator-treated subjects include some nursing notes, clinical observations, symptom checklist, and laboratory and performance test results, but not reports of physicians' examinations.[2] Common acute 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—"the manifestations experienced by subjects in these tests . . . were the moderate clinical effects that have been reported in the literature [that] disappeared within 24 hours."[2]

Severe acute effects were noted in 2 subjects including 1 treated with P2S and soman (with significant chronic psychological effects) and another treated with 2-PAM (experiencing a grand mal seizure).[2] However, "with the possible exception of those two cases, the records contained no evidence of delayed or persistent effects after administration of the cholinesterase reactivators,"[2] although potential long-term or delayed effects would not be ruled out.

PCP

"Phencyclidine," is an illicit drug with a somewhat sinister reputation as the recreational hallucinogen "angel dust." Clinical files for Edgewood/Aberdeen PCP treated subjects varied from sketchy and incomplete notes and one-line summaries, to records that could "serve as models for research documents."[2] Subjects reported "feelings of unreality—dreamlike states with perceptual size changes," with variable affect and mood changes.[2] Some became talkative and uninhibited, although others became passive and withdrawn.[2] At higher doses, symptoms intensified and were accompanied by "visual disturbance, blurred vision, ataxia, limb paresthesias, and memory impairment," and becoming noncommunicative.[2] Amnesia was reported among some. At the largest tested doses, subjects experienced analgesia, nausea and vomiting, and 4 experienced collapse and prostration or incapacitation without convulsions, with recovery over the next few hours.[2] In general, signs and symptoms disappeared within 6 to 8 hours, although at the largest doses symptoms persisted for 24 or 48 hours.[2] No clinically abnormal effects, including renal or hepatic toxicity, were noted in available records. Acute effects were similar to those reported in clinical research by pharmaceutical companies that evaluated PCP as an anesthetic.[2] Strikingly, despite PCP's "street reputation" for causing aggression, no subjects were reported to have become overly assertive, hostile, or unmanageable.[2]

Cannabinoids

Edgewood/Aberdeen subjects were exposed to the active ingredient of marijuana and related synthetic "cannabinoids," via oral, intramuscular, and intravenous routes. Reported effects 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.[2] At the largest tested doses, subjects often showed marked psychomotor retardation, sluggishness, difficulty in concentrating, and blurred vision up to 48 hours.[2] Tachycardia and orthostatic hypotension were reported.[2] Importantly, these effects disappeared in most subjects after 24 hours, although occasionally persisted for several days.[2] Finally, there was a "lack of evidence of severe mental or emotional disturbances" even among subjects experiencing intense and persistent cardiovascular effects.[2]

LSD

Little information is available about acute effects among 741 subjects involved with military LSD experiments from 1955 through 1967.[5]

Irritants and Vesicants (Mustard Agents, Lewisite, CS, CN, CR, DM, CA, Chloropicrin, Nonanoyl Morpholide, CHT, and 123 Other Miscellaneous Irritants)

Edgewood/Aberdeen experiments from 1955 to 1965 with these agents involved aerosol chamber and skin droplet exposures, causing intense lacrimation and respiratory distress (irritants) or reddening and blistering of the skin (vesicants).[2] Acute mustard agent effects are typically delayed for hours. Subjects reportedly experienced dermal erythema on trunks, extremities, and backs.[2] Some experienced blistering that required hospitalization with injuries that "might have been severe enough to cause permanent scarring."[2] No subject was reported to have sustained ocular or respiratory tract injuries, perhaps from protective equipment.[2]

These acute effects echo more recent reports of combat-related mustard agent exposure during the 1980s Iran-Iraq war.[1] A report of 1984 Iraqi mustard agent use documents health effects among more than 5,000 Iranian casualties, including first to third degree burns over 20 to 70% of skin similar to that reported for mustard agent casualties in World War I. Effects were typically severe, and casualties suffered

approximately 15% mortality. Eye exposure caused tearing, severe conjunctivitis, and temporary loss of vision. Chemical "burning" of the throat led to pharyngitis and tracheobronchitis. Initial survivors later experienced gastrointestinal complaints, including nausea, vomiting, and diarrhea. After 5 to 7 days, hematologic problems were the greatest health threat.[7]

CS (o-chlorobenzylidene malononitrile)

From 1958 to 1973, at least 1,366 human subjects were experimentally exposed to the "tear gas" and riot control agent CS at Edgewood/Aberdeen, via aerosol, dermal, and eye applications.[2] Subjects typically experienced short-term tearing, nasal secretions, and copious saliva flow requiring "towels rather than handkerchiefs," subsiding 5 to 15 minutes after exposure stopped.[2] CS exposure produced erythma, vesicles, and in some cases burns. "Hepatic dysfunction and urinary abnormalities" were seen in some subjects, and "a high percentage" developed allergic contact dermatitis following repeated exposure.[2] Follow-up evaluations suggested repeat CS exposure may also cause idiosyncratic hepatitis or allergic pneumonitis in some subjects.[2]

CN (chloroacetophenone)

Edgewood/Aberdeen subjects were experimentally exposed to another "tear gas" agent, CN, from 1958 to 1972, as aerosols in chambers or skin application.[2] Aerosol exposure caused transient lacrimation, blepharospasm, conjunctivitis, and rarely, palpebral edema, noropharyngeal irritation, rhinorrhea, and rarely dyspnea, headaches, and dizziness.[2] Skin exposure produced local irritation and occasionally erythema at the exposure site, lasting 7 hours.[2] Laboratory tests for skin exposed subjects were normal.[2]

CR (dibenz[b,f][1,4]oxazepine)

CR is another "tear gas" agent tested from 1963 to 1972 on Edgwood/Aberdeen subjects, via aerosol (chamber) and dermal (patch) exposures. Transitory effects were primarily respiratory and ocular.[2] Aerosol exposure caused upper respiratory tract irritation with choking, and sometimes dyspnea. Dermal exposure produced stinging and erythmea at the exposure site, resolving within 24 hours.[2] Laboratory analyses 7 days after exposure showed no abnormalities.[2]

DM (diphenylaminochlorarsine)

DM (Adamsite) "tear gas" agent was tested on Edgewood/Aberdeen subjects in 1958, and from 1966 to 1968, via aerosol chambers. Major symptoms included respiratory tract burning sensations, choking, dysphonia, dyspnea, coughing, sneezing, and nausea.[2] Less frequent effects included retching, anorexia, headache, dizziness, lacrimation, salivation, and increased urinary frequency. "Although DM has greater acute toxicity to the respiratory tract than CS and CN, Edgewood subjects appeared to recover shortly after exposure."[2] Laboratory results 7 days after the exposure showed no abnormalities.[2]

CA (bromobenzyl cyanide)

In 1966, Edgwood/Aberdeen subjects were experimentally treated with the "tear gas" agent CA in aerosol chambers. Transient effects included ocular irritation, often accompanied by conjunctivitis, and upper respiratory tract irritation with rhinorrhea.[2] Blood and urine laboratory analysis 7 days after exposure for 12 subjects showed minimal leukocytosis (WBC 12,800) not seen before exposure.[2]

PS (chloropicrin)

Chloropicrin "tear gas" agent was tested from 1955 to 1971 at Edgewood/Aberdeen in chambers experiments. Subjects were reportedly testing gas mask function. Although records were incomplete, no acute effects were documented.[2]

Nonanoyl morpholide

Nonanoyl morpholide was another experimental "riot control" agent tested on Edgewood/Aberdeen subjects in 1958 in chamber experiments.[2] Transient effects included respiratory tract irritation, rhinorrea, cough, substernal pain, and dyspnea.[2] Nausea was commonly reported, and vomiting if the subject had eaten before the test. Headaches sometimes occurred 1 hour after exposure, and for 1 subject the headache persisted for a week.[2] 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. Transient physical effects included lacrimation and incapacitation from eye closure, and blurred vision "lasting several minutes after the exposure" with "complete resolution by 15 minutes after leaving the chamber."[2] Dermal irritation and rhinorrhea also were reported. Laboratory analysis 9 days later reported 2 subjects with slight increases in SGOT (31.5 and 44.5)—slightly less than double pre-exposure values.[2] However, SGOT was normal 1 month later.

One Hundred Twenty-Three Other Miscellaneous Irritant Chemicals

From 1962 to 1972, 123 other irritant "tear gas"-like compounds were tested at Edgewood/Aberdeen, typically with 2 subjects per compound.[2] Human experiments typically used a single aerosol chamber exposure lasting a minute or less.[2] Of the 123 tested chemicals, 64 caused slight or no effects, while 42 caused mainly ocular effects (eye irritation, lacrimation, and conjunctivitis), of which 34 caused only very mild effects.[2] Eight produced more severe effects, including prolonged incapacitation from lacrimation and eye closing.[2] However, "the discomfort associated with the exposures was marked, but exposures were short and recovery appeared complete."[2]

CONCLUSIONS

The U.S. military personnel who participated in these Cold War experiments took significant health risks in the service of their country. They deserve our respect and assistance for any health problems that resulted from exposures to toxic substances during these military tests. Some experiments potentially caused significant harm to the veterans' health, other participants may have had only minimal or even no hazardous exposures, although participation alone can increase risk for long-term psychological effects.

Unfortunately, contemporary records are often not sufficient to determine the exact nature or magnitude of the exposure in many of these experiments. Therefore, in evaluating these veterans today, each must be cared for as an individual and given a thorough clinical evaluation to identify all outstanding health problems.[8–10] This summary of acute- and long-term health effects from exposure to experimental agents should be useful in evaluating the health of affected veterans today.

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