Mustard Gas

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Chemical blistering agents, predominantly sulfur mustard, have been used in warfare since World War I. The Iran-Iraq War saw widespread, documented injury to thousands of Iranian soldiers and Kurdish civilians. Although the use of sulfur mustard agents is rare in the Western hemisphere, the potential toxic effects of these chemical agents to military and civilian populations in times of war or civil conflict cannot be overstated. Many of the world's arsenals, including those of the United States and those of the republics of the former Soviet Union, stockpile this deadly class of weapons. Mustard gas affects the skin, eyes, and respiratory systems of its victims. We know that mustard gas triggers profound cytotoxic effects, but few studies have determined optimal, and therefore uniform, treatment regimens. [PSRQ 1992;2:92–97]

HISTORICAL BACKGROUND

Mustard gas is a class of chemical agents capable of causing mass death in warfare. These vesicants, or blistering agents, were first synthesized in the 1800s yet were not used effectively as weapons until World War I. Known chemically as alkylating agents, the prototype "mustard gas" (so nicknamed by British soldiers because of its noxious smell), 2:2 dichloroethyl sulfide, was first reported by Guthrie in 1859. The first documented use to harm humans did not occur until 1917 against the Allies at Ypres, Belgium—hence its common name, yperite [1] Other mustard gases, such as bis-b-chloroethylsulfide, were synthesized as early as 1822 and were characterized as "blister" fluids nearly a century before their widespread use. Lewisite (2-chlorovinyldichloroarsine), another vesicating agent, has seen limited use, although it has been stockpiled since World War I in what was the Soviet Union and in the United States [2,3]

Sulfur mustard was the major cause of chemically induced morbidity in World War I. Of those exposed, 2.0% to 3.0% were killed, primarily from respiratory exposure [1,4]. Of 28,000 United States victims in World War I, approximately 600 (or 2.0%) died [4]. The major nations of the world except for Japan and the United States, appalled by the horrors caused by chemical agents, joined the Geneva Protocol of 1925 to forbid the first use of asphyxiating, poisonous, or other gases and all analogous liquids,

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materials, or devices [6]. Japan and the U.S. joined the treaty some 50 years later, and now nearly all the countries of the world are parties to the Protocol.

The Germans did not use chemical agents against the Allies in World War II, although large stockpiles of these, and the newer nerve gases, were found in Germany after the war. A British merchant ship, secretly storing American mustard bombs in Bari, Italy, was shelled by German forces on December 2, 1943. Although the Allies denied it for many years, a mustard-in-oil solution on the water's surface was blamed for at least 616 casualties, including 83 deaths [4,7]. The dumping of similar material into the Baltic Sea by the Allies after the war, and the eventual corrosion of container shells, led to significant exposure to at least 23 trawl fishermen during the 1980s [1,8].

Mustard gases have been used infrequently in regional conflicts during the last 50 years. Mustard gas, phosgene, lewisite, and other agents were used on a limited scale by Japan against China in the Sino-Japanese Conflict (1937–45) [3,9]. The recent Iran-Iraq War constituted the first major instance of prolonged use of these agents for wartime purposes since World War I and caused approximately 45,000 military and civilian casualties [1,2,10–13,15–17].

Iranian military casualties from the Iran-Iraq conflict were sent to hospitals in Ghent, Belgium and to other European hospitals for treatment from 1984 through 1987. This tremendous and unusual medical challenge is extensively documented by Willems, at the Heymans Institute of Pharmacology in Belgium, and his work represents the most thorough experience with mustard gas since World War I [13].

On March 17, 1988, Iraqi bombers carried out an air raid utilizing sulfur mustard on the Kurdish residential areas of Halabja in Iraq, followed by similar attacks on several nearby townships [14,18–20]. Security Council investigations were eventually launched to document these events [19,20].

THE TOXICOLOGY OF MUSTARD GAS

Sulfur mustard, the predominant form of vesicant mustard used in warfare, is a clear, colorless, oily liquid in temperate climates, with a characteristic garlic or onion odor [4]. It is only slightly soluble in water, and it has high lipid solubility and great penetrating capability on human skin and on most

clothing (rubber materials may provide protection for hours) [1,2,4,8]. Its volatility increases with temperature. Its hazardous vapor, although exhibiting excellent "warning properties," is responsible for the majority of disabling skin, eye, and respiratory problems [2,4,17,21].

Sulfur mustard and the chemically related family of nitrogen mustards used predominantly in chemotherapy undergo strong electrophilic chemical reactions through the formation of highly reactive chemical intermediates (e.g., the cyclic sulfonium intermediate in the case of sulfur mustard) in aqueous phase [1,4,22]. After a brief, blood-borne period, these transition complexes covalently link, or alkylate, with various intracellular nucleophilic substances, such as important biological moieties (e.g., amino and sulfhydryl groups) [4]. As such, they irreversibly bind to components of nucleic acids (e.g., DNA and RNA), cellular membranes, and proteins [1,7,21]. Linkage with genetic material yields cytotoxicity after inhibition of cellular glycolysis and translates eventually to human morbidity and mortality [4].

An objective index of morbidity, the *mustard vapor exposure*, is measured as Ct, where $C =$ the concentration of vapor or aerosol in air measured in milligrams per cubic meter (mg/m^3) and $t =$ time measured in minutes (min). Ct is therefore measured as $mg(min)/m^3$. The $LCt50$ is defined as the vapor exposure that yields 50% mortality. Response values for humans have been gleaned from the world literature by Smith [2] (Table).

The toxicity of mustard gas is high, as shown by comparison with other agents. The $LCt50$ of mustard gas exposure by the respiratory route is estimated at 1,500 $mg(min)/m^3$, whereas the $LCt50$ of cyanide gas, by a similar route, is 2,500 to 5,000 $mg(min)/m^3$. The Ct of mustard that causes substantial ocular effects has been estimated at 5 to 200 $mg(min)/m^3$, whereas the Ct of cyanide produces

Table. Sulfur Mustard Exposure: Estimated Response Values*

	Eye†	Respiratory Tract†	Skin†
Threshold	5	50	100–150
Incapacitation	200	300	800
Lethal (LCt50)		1,500	10,000

* Adapted from Smith W, Dunn M [2]. See also Vojvodic [23], Gates and Moore [24], and Renshaw [25].
† Vapor exposure (Ct) = mg(min)/m³

similar effects at 1,000 mg(min)/m^3 and that of phosgene, another deadly gas, at 1,000 to 1,500 mg(min)/m^3 [2,5].

CLINICAL EFFECTS

Systemic Manifestations

Mustard gas causes clinical symptoms after penetration of the liquid form through the skin, by vapor inhalation, by absorption from the conjunctiva of the eye, or after ingestion of contaminated food [8]. Mustard acts at different sites in the body as a radiomimetic, causing headache, nausea, vomiting, anorexia, and epigastric pain [13]. Dizziness, lethargy, and general malaise are also common in significant exposures [2,8,13]. Marrow suppression, in the form of leukopenia, thrombocytopenia, and anemia, has been reported and may partially account for the high incidence of bacterial infections subsequently seen in these patients [13,15].

Respiratory Manifestations

Death from mustard gas is generally from respiratory compromise in the acute phase or first 24 hours. Respiratory compromise is brought on by upper airway edema and lower airway sloughing [2,4]. Typically, injury may extend from the nasopharynx to the bronchioles [2]. Depending on the length of vapor exposure, symptoms may range from severe upper airway signs of hoarseness, lacrimation, sneezing, and rhinorrhea to lower signs including tracheobronchitis, chest pain, cough, and, in some cases, pulmonary edema [1–4,8,15]. Cellular destruction yields pseudomembranes composed of necrotic tissue, cell debris, white blood cells, rare red blood cells, and fibrin products [4,5].

Adult respiratory distress syndrome (ARDS), with or without secondary bacterial infections, typically occurs at Ct levels above 1,000 mg(min)/m^3. Although lung abscesses have been reported, there is no evidence that sulfur mustard injures the alveoli directly [2,21]. The greatest threat to survival is seen in patients who develop secondary bacterial infections within one to four days of exposure [2,4,5]. Those who die at six to 11 days typically succumb to sepsis brought on by their skin and respiratory compromise [1–3]. The proportion of casualties who fully recover from respiratory injuries varies from 20% to 90% depending on the severity of initial

vapor exposure and the health of the host [2]. Increased incidences of lung and other respiratory cancers in factory workers exposed to low levels of mustard gas for prolonged periods have been reported [26]. An increased incidence of lung cancer has been reported in survivors of World War I exposed to mustard gas [27].

Skin Manifestations

Latency of skin symptoms from vapor exposures less than 200 mg(min)/m^3 may be as long as four to eight hours; these symptoms typically include erythema, itching, and blister formation. Rapid blistering, with concomitant signs of systemic toxicity, occurs at greater exposures and higher temperatures [2,4,17]. Blisters, typically yellow in appearance, may range from a few millimeters to several decimeters [13]. It has been estimated that a 25% body surface area exposure, or exposure resulting from approximately 7 g of liquid sulfur mustard (a little more than a teaspoon), will yield a 50% mortality rate in previously healthy adults. As little as 10 μg may cause vesication [4]. Thinner skin, such as that on the neck, axillae, and groin, is more severely affected [2,4].

The full range of problems associated with thermal and chemical burns is seen with mustard gas exposure. Fluid loss, pain, cosmetic insult, and life-threatening bacterial superinfection have been described [13]. Time for healing may range from one month in mild cases to as long as 10 weeks for extensive areas of denuded skin [2]. Scarring is not uncommon [13].

Eye Manifestations

Low-level vapor exposures typically yield ocular symptoms in four to six hours, although corneal edema has been demonstrated as early as one hour after exposure in animal studies [2,7,28]. Symptoms may include pain, photophobia, blepharospasm, lacrimation, conjunctivitis, corneal lesions, blistering of the eyelids, and suppurative, secondary infections [13]. Blindness may occur secondary to anterior chamber scarring and corneal ulceration [2,13]. The great majority of persons with eye injury are visually disabled for approximately 10 days with conjunctivitis, photophobia, and minimal corneal swelling [2].

PROTECTION

Battlefield protection against sulfur mustard exposure requires wearing of a protective mask and clothing that limits agility and physical endurance, especially at high temperature and humidity [2]. Nonetheless, chemical weapons are the only armaments from which it is possible to protect people without significantly impeding most military operations [3].

Historically, the gas mask alone was credited with preventing scores of casualties during World War I. Most casualties resulted from a failure to wear a mask rather than from penetration through them [9]. NATO protective suits currently consist of a disposable, lightweight, two-piece garment made of a charcoal-containing fabric that protects the wearer from chemical vapor and liquid. Rubber gloves and overboots are also used to prevent entry of vesicants [3,4]. Protective systems and filters have been developed for tanks and armored personnel carriers. Topical skin barrier compounds may afford some protection in limited scenarios, but clinical trials are lacking [2,9].

Modern warfare technology has produced a variety of sensors to detect the presence of chemical agents and potentially to signal troops to don their protective gear. A British hand-held monitor capable of identifying mustard and nerve agent vapors has recently been purchased in bulk by the United States [3].

DECONTAMINATION AND FIRST AID

Skin, clothing, and equipment decontamination is of utmost importance, as liquid sulfur mustard may persist for hours. The decontamination practices of the military include skin irrigation with 0.5% hypochlorite bleach and water, removal of clothing with protective gear, and generous ventilation at exposed sites [1,2,4,8]. Soldiers are issued kits for decontaminating their skin and gear [3]. Antigas powders, such as calcium chloride or magnesium oxide, may be applied to exposed skin and have variable success [8]. Skin is never scrubbed as this may potentially increase absorption. Eyes are copiously irrigated with clean water as soon as possible.

TREATMENT

Large-scale battle scenarios will require rapid gear removal and additional facilities for copious water and bleach irrigation as outlined above. Decontamination areas—consisting of hoses for body and eye irrigation, trenches for contaminated gear, and treatment cots where antigas powders may be applied—must be set up early on the chemical warfare battlefield. Plans must be made for wide-scale evacuation of the seriously exposed to safe hospital sites.

In addition to first-aid measures outlined above, sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$) may represent a potential, systemic antidote if administered within 20 minutes of exposure (i.e., before toxic intermediates become intracellular). The thiosulfate anion ($S_2O_3^{2-}$) acts as a mustard "scavenger" by combining with unstable, cyclic compounds shortly after absorption [1,4]. Thiosulfate was shown to be protective in dogs when injected intravenously before mustard gas exposure [29]. Effective dosing regimens remain controversial. One group gave 250 to 500 ml of a 10% solution in an uncontrolled manner. Improvement or prevention of symptoms in this small cohort was not demonstrated [13].

On largely theoretical grounds, 65 mustard gas casualties of the Iran-Iraq War, described by Willems, were offered prophylaxis against stress ulcers with H_2 blockers, prophylaxis against deep venous thrombosis with subcutaneous heparin, general support with high doses of vitamin C, vitamin B_{12}, and folic acid, and protection against tissue damage, usually with a single injection of 2 g of methylprednisolone [13]. Many were admitted to intensive care areas. Although long-term follow-up of this cohort was lacking, no disadvantageous effects of these general support measures were demonstrated.

Prolonged treatment of mustard gas exposure varies according to symptoms [17]. Skin effects are treated as burns. Fluid maintenance must be monitored and adjusted accordingly. Many authors advocate sterile incision of large blisters and the application of moist dressings, with or without silver sulfadiazine cream [8,17,21]. Analgesics and antihistamines were required to control pain and itching in the analysis by Willems [13]. Lidocaine gel, topical steroids, and oral carbamazepine have also been cited as being effective in pain control [13,21]. Septicemia resulting from cutaneous or respiratory insult requires systemic antibiotics.

Respiratory intervention may include the use of bronchodilators, theophylline, systemic steroids, and mechanical cleaning of the airways with bronchoscopy [4,13]. Rapid development of incapacitat-

ing respiratory symptoms may require prophylactic intubation before additional edema progresses [2,4]. Prophylactic antibiotics have not proved to be effective [4].

In addition to copious irrigation with water, topical antibiotic ointments should be applied to those patients with symptomatic ocular lesions [13]. Mydriatics, to ease pain induced by ciliary spasm, have been advocated [17]. In 1942, Hughes advised against closed-eye treatment because of fear of adhesions [30]

CONCLUSION AND DISCUSSION

The threat of injuries from mustard gas, while largely dormant in the years since World War I, has re-emerged with the recent Iran-Iraq War and the sporadic exposure to fishermen in the Baltic Sea Possible injury to civilians and military personnel during war or civil conflict and the possibility of accidental exposure to stockpile workers dictate an understanding of the devastating potential of these chemical agents.

Despite instances of documented mustard gas use spanning more than 70 years, much controversy and ignorance still surround potential methods of treatment. The logistics of treating large numbers of casualties, many of them conceivably dressed in cumbersome protective suits, with intravenous sodium thiosulfate remains problematic and unexplored Indeed, the difficulty of having enough water on hand to quickly decontaminate large numbers of victims would represent a tremendous challenge.

Ongoing political efforts to reinforce the Geneva Protocol's prohibition of chemical weapons, such as the Paris Conference on the Prohibition of Chemical Weapons, attended by 149 states in January 1989, and the negotiations at the Conference on Disarmament in Geneva aimed at achieving a verifiable ban on the production, possession, and use of chemical weapons, reduce the real threats of these armaments. Negotiations regarding destruction of international stockpiles (estimates of the cost of destroying chemical weapons in the United States alone range from $2 billion to $10 billion) must continue [31] Furthermore, verification of chemical stockpiles, both to detect violations of the Geneva Protocol and to deter further transgressions, must remain an important focus of future chemical war-

fare conferences, as 20 or more countries were suspected of either possessing or seeking the capability to produce chemical weapons as of 1989 [31–33].

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