CRITICAL
CARE
CLINICS

Vesicants

John McManus, MD, MCR, FACEP[a],*, Kermit Huebner, MD[b]

[a]US Army Institute of Surgical Research, 3400 Rawley E. Chambers Avenue,
Fort Sam Houston, TX 78234-6315, USA
[b]US Army Medical Research Institute of Infectious Diseases, 1425 Porter Street,
Fort Detrick, MD 21702, USA

Gas! GAS! Quick, boys!
An ecstasy of fumbling
Fitting the clumsy helmets just in time,
But someone still was
yelling out and stumbling
And flound'ring like a man in fire or lime–
Dim through the misty panes
and thick green light,
As under a green sea, I saw him drowning.
In all my dreams before my helpless sight
He plunges at me, guttering, choking, drowning.

(British poet Wilfried Owen, 1918)

From the use of smoke by the Mohist sect in China in fourth century BC through the use of incendiary shells filled with sulfa and belladonna in the fifteenth century, the use of chemicals and irritants during battle has been well documented throughout the centuries. However, most sources credit the origin of modern chemical warfare to the German's release of thousands of cylinders of chlorine gas on French and Algerian troops near Ypres, Belgium, in April of 1915 during World War I (WWI) [1]. Use of chemicals had already escalated

---

during the previous year by the French who used chloroacetone, and by the Germans who used odianisidine chlorosulfonate. These chemical weapons reduced combat effectiveness of enemy forces through logistical disruption and by inflicting injury rather than by causing direct mortality. Approximately 125,000 tons of chemical agents were used during WWI and produced an estimated 1.3 million casualties [2]. The use of vesicants, particularly sulfur mustard, was responsible for nearly 80% of the casualties and sulfur mustard became known as ''king of the battle gases'' [1].

Vesicants (blister agents) are cytotoxic alkylating compounds that are chemical agents sometimes collectively known as ''mustard gas'' or simply ''mustard'' (military designator: H). Other blister agents are nitrogen mustard (HN); sulfur mustard (HD); lewisite (L), a vesicant that contains arsenic; and phosgene oxime (CX), a halogenated oxime that has different properties and toxicity from the other agents. Blister agents are an exception to the limited utility of classic chemical agents. These agents have been used effectively and extensively throughout modern warfare. Vesicants are rarely lethal but they inflict painful burns and blisters, which require medical attention even at low doses. Because vesicants can inflict many casualties and create confusion and panic, they were used in battle throughout the twentieth century.

The 1925 Geneva Protocol [3], which was endorsed by many world nations, included a pledge to never use gas or bacteriologic methods of warfare; however, chemical agents, specifically mustard, have been used continually since WWI. Italy allegedly used mustard in the 1930s against Abyssinia during the invasion of Ethiopia. The Japanese used both mustard and lewisite agents against Chinese troops from 1937 to 1944. Although Egypt denies allegations, they were accused of using mustard and nerve agents in the 1960s against Yemen [3]. Most recently, Iraq used mustard against Iran and against the Kurds during the 1980s. As many as 34,000 Iranians were known to have been exposed to sulfur mustard, which resulted in many chronic medical problems [4].

Mechanism of toxicity

Proposed use as a weapon

Exposure to vesicants may occur in a variety of settings. Environmental exposures are possible in areas where chemical weapons are produced, tested, or stored. Additionally, the Environmental Protection Agency has located sites where sulfur mustard can be found in contaminated soil or containers [5]. Sulfur mustard may also be found at sea. Dumping sulfur mustard at sea was a standard method of disposal from WWI until the 1970s, and accounts of sulfur mustard surfacing during fishing expeditions have been reported. Stockpiles of chemical munitions still exist in the United States; however, according to the international Chemical Weapons treaty, these stockpiles of mustard agents must be destroyed by April 2007. The most likely exposure scenario is occupational

exposure, caused by aged storage containers, of personnel working with these agents in storage facilities or depots. A 100-gallon spill from a 1-ton container occurred in 1993 at Tooele Army Depot, Utah, and other leaking munitions have been discovered as recently as 2002 [5].

The greatest concern today is the use of a vesicant agent in a terrorist attack. Unlike environmental or occupational exposures, the use of a vesicant agent by a terrorist has the potential to create a significant number of casualties. Additionally, the use of these agents has the potential to (1) create fear and panic because of the grotesque nature of the injuries inflicted, (2) overwhelm the medical infrastructure, and (3) substantially impact the nation's economy. The factor that limits terrorist use is acquisition of the vesicant agent. Fortunately, security at United States military storage sites is significant; however, there are several other countries that are known to have chemical munitions, including vesicants, or possess the knowledge to produce these weapons [3].

Method of exposure

Vesicants burn and blister any part of the body they contact. They act on the eyes, mucous membranes, lungs, skin, and blood-forming organs. They damage the respiratory tract when inhaled, and cause vomiting and diarrhea when ingested. The vesicant agents may be released in several ways, depending on the agent and its physical characteristics. Sulfur mustard is an oily liquid with low volatility and a freezing point of 58°F (14°C) [6]. Lewisite is also an oily liquid that is more volatile than sulfur mustard and has a freezing point of 0.4°F (−18°C) [7]. Phosgene oxime is a solid in the pure form, but munitions grade phosgene oxime is a yellowish brown liquid with a melting point of 95°F to 104°F (35°C to 40°C) [8]. Exposures may include skin contact (even through clothing), inhalation of vapors, and ingestion of the chemical.

The most damaging method of exposure is inhalation of the chemical agent. The physical properties of sulfur mustard make it a better weapon for use in warm environments, where there is greater risk of vapor inhalation; lewisite is a better weapon in colder environments because of its increased volatility. Lewisite may be mixed with sulfur mustard to lower the freezing point of sulfur mustard and increase its effectiveness at lower temperatures [3]. Once it is released into the environment, these compounds may persist for up to a week in temperate climates. Furthermore, vesicant agents can be thickened to contaminate terrain, ships, aircraft, vehicles, or equipment with a persistent hazard.

Biochemical, cellular, and systemic effects

Although chemical agents have been studied, produced, and developed as weapons by several countries, the exact mechanism of action of vesicant agents remains unknown. Sulfur mustard exerts it effects on the cellular level by acting as an electrophile that combines with macromolecules in the cell, including proteins, RNA, DNA, and components of the cell membrane. The end result of these in-

teractions is cell death— either by necrosis, apoptosis, or a combination of both. Theories about the cause of cell death have focused on the alkylation of DNA and reactions with glutathione. The initial step in the cytotoxic pathway may be irreversible alkylation of purines in DNA, which leads to random nuclear DNA fragmentation. The DNA damage activates a polymerase enzyme that depletes NAD and inhibits synthesis of ATP, which leads to cell death [9]. Pretreating cells with N-acetylcysteine has shown benefits in some studies; therefore, it is theorized that cell apoptosis after exposure to sulfur mustard may be related to depletion of reduced glutathione, which results in an increase in free radicals and leads to lipid peroxidation. Cellular death and interactions with cytoskeletal organization leads to decreased cellular adherence and morphologic changes in tissues. Evaluation of endothelial cells revealed that rounding of adherent cells and changes in polymerized actin were visible as early as 2 hours after exposure to sulfur mustard [10].

Histopathological changes in an animal model have demonstrated individual cell death within 2 hours of vapor exposure, and generalized necrosis beginning within 12 hours after exposure. Basement membrane degeneration follows and leads to microblisters, which coalesce to form larger blisters in human exposure. Damage to the upper dermis appears to be an inflammatory response with vascular endothelial swelling and vacuolization, dermal edema, and inflammatory cell infiltrates [11].

Lewisite is arsenic, not an alkylating agent. Arsenics are reported to inhibit the activity of enzymes that contain adjacent sulfhydryl groups, which leads to NADPH and glutathione oxidation. Therefore, membrane damage and disruption of cell metabolism leads to cell death, necrosis, and skin blistering [12].

The mechanism of action of phosgene oxime is unknown, but may be related to the necrotizing effects of the chlorine, the direct effect of the oxime, or the effect of its carbonyl group. The skin lesions of phosgene oxime are not blisters and, therefore, it is not a true vesicant agent. Instead of the blisters seen with sulfur mustard and lewisite, phosgene oxime lesions are wheals that may be followed by dark eschars [3].

Clinical presentation

The clinical signs and symptoms of exposure to a vesicant agent will depend on the route of administration and the vesicant agent used. The predominant organs affected are the skin, eyes, and lungs. Sulfur mustard casualties from WWI and the Iran-Iraq war manifested effects from multiple routes of exposure (cutaneous and ocular lesions from liquid mustard or mustard vapor exposure and respiratory symptoms from inhalation of mustard vapor) [5]. Systemic effects may occur and are radiomimetic in nature.

Cutaneous exposure

Skin exposure can occur from contact with the solid, liquid, or vapor form of a vesicant agent. A 10 microgram liquid droplet is enough to produce skin

lesions, and vapor exposure at 200 mg/min/m^3 can produce lesions. Lesions progress from erythema, beginning within 4–8 hours after exposure, to the development of vesicles in 2–18 hours, which then coalesce to form large blisters over days. The lesions are superficial, translucent, and approximately 0.5–5.0 cm in diameter, but may vary in size. The fluid inside the blister does not contain mustard and is not an exposure threat to health care workers [3]. Mustard lesions differ from thermal burns in that they usually are partial thickness and tend to have slower spontaneous healing rates [13]. Lesions may not heal for weeks or for several months, depending on the location and depth of the injury [3].

Unlike exposure to sulfur mustard, which is painless until the development of erythema, exposure to lewisite typically produces pain and irritation within minutes of exposure. The lewisite blister develops within minutes and expands, unlike the development of multiple vesicles that merge in sulfur mustard lesions [3]. Additionally, lewisite lesions are comparable to thermal burns and heal faster than mustard lesions [13].

Phosgene oxime is not a true vesicant and does not produce blisters. Exposure to phosgene oxime leads to immediate pain, followed by a grayish skin lesion surrounded by erythema. Edema forms around the edge of the lesion and central necrosis ensues with the development of a wheal that regresses over 24 hours and is replaced with a dark eschar [3].

Ocular exposure

The eye is the most sensitive tissue to mustard vapor and can shows signs of irritation at concentrations 10 times lower than the concentration required to affect the airways [14]. In an evaluation of more than 5000 mustard casualties from the Iran-Iraq war, most had ocular symptoms and 10% developed severe ocular damage [15]. Most of the casualties suffered from conjunctivitis, eyelid edema, and blepharospasm. Conjunctival exposure leads to rapid vasodilation, increased vascular permeability, and edema. The corneal epithelium develops vesicles and begins to slough several hours later [16]. More serious symptoms included visual disturbances, keratitis, and corneal ulceration. Approximately 90% of the patients recovered, although in some patients, symptoms of conjunctivitis and photosensitivity persisted for several months [15]. Ocular exposure to lewisite also results in edema of the eyelids, conjunctiva, and cornea. With lewisite exposures, the patient suffers immediate pain and irritation that produces blepharospasm, which helps prevent further exposure [3]. Phosgene oxime causes ocular symptoms similar to lewisite with immediate pain and irritation, conjunctivitis, and keratitis.

Inhalation

Inhalation of mustard vapor leads to damage of the respiratory tree and symptoms typically develop within 4–6 hours of the exposure. Symptoms begin

in the upper airways and progress to the lower airways as the dose and time of exposure are increased. Initial symptoms may include a sore throat, hoarseness, and cough which can progress to laryngospasm, bronchospasm, and severe dyspnea [17]. Blister formation and necrosis of the upper airways may lead to pseudomembrane formation and airway obstruction up to several days after the exposure. Exposures to high concentrations may produce severe symptoms more rapidly and can lead to hemorrhagic bronchitis [18]. The incidence of pulmonary infections in mustard inhalation casualties is high and was a major cause of mortality in American soldiers during WWI. Lewisite vapor exposure results in a clinical syndrome similar to that of mustard; however, the irritating effects of lewisite are manifested much sooner. Exposure to large concentrations of lewisite may result in pulmonary edema. Exposure to phosgene oxime vapor may lead to pulmonary edema, necrotizing bronchiolitis, and pulmonary venule thrombosis [18]. Initial death, although rare with vesicant exposure, is usually the result of suffocation.

Systemic effects

Sulfur mustard has a profound effect on rapidly dividing cells and is often described as a radiomimetic agent. Reports of casualties from WWI and the Iran-Iraq war reveal hematologic effects that include leukocytosis after the injury, followed by leucopenia, and sometimes pancytopenia 3–4 days after the exposure. Leukopenia may be severe: white blood cell counts ≤200 cells/μL. Mustard is also mutagenic and has been linked to a slight, but statistically significant incidence of lung cancer deaths in mustard casualties from WWI. A study that followed German factory workers with occupational exposures to sulfur mustard for a 20-year period, revealed a statistically significant increase in bronchial carcinoma, bladder carcinoma, and leukemia [19]. Lewisite has not been shown to affect the hematopoeitic system and has not been associated with an increase in malignant tumors. However, lewisite may cause "lewisite shock." Exposure to large amounts of lewisite may result in systemic absorption that leads to capillary damage and results in protein and plasma leakage with hemoconcentration and hypotension [3].

Differential diagnosis

The differential diagnosis for vesicant exposure can be quite large, but can be narrowed down with a comprehensive history and physical examination. The differential diagnosis may include thermal burns, other chemical burns, pemphigus vulgaris, bullous pemphigoid, toxic epidermal necrolysis, staphylococcus scalded skin syndrome, and Stevens-Johnson syndrome. Although exposure to vesicants is not typically listed high on the differential diagnosis for dermatologic conditions, ocular conditions, or respiratory symptoms, history may reveal an occupational exposure or environmental exposure from old munitions. An intentional release

from terrorists will result in large numbers of casualties with similar symptoms and a common source of exposure, such as a large public gathering.

Physical examination of the skin will assist in identifying the vesicant agent used. Sulfur mustard lesions are initially painless. Mustard lesions typically become painful with the onset of erythema 4–6 hours after the exposure, and develop a string of small vesicles that coalesce to form larger blisters. Lewisite causes pain and irritation at the time of exposure and leads to a vesicle that enlarges. Phosgene oxime exposure results in immediate pain, a lesion that is initially gray and develops into a wheal, followed by necrosis and a black eschar. The tricothecene mycotoxins (T-2 mycotoxins) are biologic toxins that are dermally active and cause lesions similar to sulfur mustard. The T-2 mycotoxins are also considered radiomimetic and may result in bone marrow depletion.

Casualty and injury distribution

Multiple variables will affect the number of casualties resulting from a terrorist release of vesicant agents. Considerations include the agent, the dispersal method, the ambient conditions, and the number of people near the exposure site. More than 80% of mustard casualties are from vapor exposure. Warm, moist areas of skin, such as the armpits and groin, appear to have an increased potential for damage. Of 6980 cases of mustard burns during WWI, the location of the lesions were eyes (86%), respiratory tract (75%), scrotum (42%), face (27%), anus (24%), legs (11%), buttocks (10%), hands (4%), and feet (1.5%). The overall mortality rate was 2%–3% and most fatalities were related to pulmonary complications [20].

The presentation of mustard casualties may be delayed for several hours after exposure, especially if exposed to low doses. Casualties from lewisite and phosgene oxime are more likely to present immediately after an incident because of the immediate pain and irritation that occurs. Additionally, consideration needs to be given to those that may present for evaluation that do not have symptoms or have not had a true exposure. The recommended guidance is to plan for a ratio of 5:1 (5 unaffected casualties to one affected casualty). During the sarin release in the Tokyo subway, there were 5510 victims that sought medical care at 278 different health care facilities. Of these, 12 casualties died, 17 casualties were critically ill, 37 were seriously ill, 984 were moderately ill, and 4000 victims were not exposed to any significant amount of the chemical agent [21].

Management and evaluation

Decontamination

Decontamination is mandatory to prevent continued exposure to the agent and to protect health care workers. Vesicant agents do pose a threat to health care

workers if casualties are not decontaminated or are incompletely decontaminated. Full personal protective equipment is recommended until full decontamination is accomplished. Vesicant casualties need decontamination as soon as possible to prevent further injuries. The chemical agent must be physically removed to achieve successful decontamination. Victims should remove clothing, remove any visible agent on the skin, and move to an area free of vapor hazards. Physical removal may be accomplished by several methods: wiping off the agent with dry powders (such as flour, powdered soap, or dirt), showering, washing with soap and water, washing with 0.5% hypochlorite solution, or using resin decontaminants, which are used by the military [22]. Hypochlorite solutions may be used for patients immediately after the exposure; however, if skin erythema has developed, it is preferable to use soap and water rather than hypocholorite to avoid further skin injury. A comparison of decontamination effects of hypochlorite and water in an animal model has shown that similar amounts of sulfur mustard were removed by each method [23]. Hypochlorite solutions should not be used on the eyes or mucus membranes; however, eyes should be irrigated with water or saline as there tends to be a significant number of casualties that develop ocular symptoms.

Initial decontamination should occur in the pre-hospital setting near the scene of the incident. Pre-hospital personnel need to use appropriate personnel protective equipment while performing on-scene triage and decontamination. Patients should be evaluated for effectiveness of decontamination before they are transported to health care facilities. Emergency departments should expect to receive decontaminated patients from the scene by way of Emergency Medical Services (EMS), but hospital personnel will need to verify that patients have been decontaminated appropriately before allowing patients to enter the facility. If not appropriately decontaminated, health care workers may develop symptoms from exposure to solid or liquid agents, or vapors from solid or liquid agents, on the casualties. Emergency departments must also be prepared to perform decontamination on casualties that arrive by non-EMS means. Decontamination must occur outside of the health care facility by personnel wearing appropriate personal protective equipment.

Patients that are admitted to the intensive care unit should have already undergone decontamination with verification of decontamination before admission. The chance of admitting a contaminated patient to a health care facility is miniscule [22]. The blister fluid does not contain the vesicant agent and poses no threat to health care workers. However, medical personnel should wear protective gear including breathing protection if casualties are not fully decontaminated in the field. Note that chemical (butyl rubber) gloves should be worn during decontamination because latex gloves are not adequate.

Diagnostic studies

Diagnosis of vesicant exposure, without obvious contamination, requires a high index of suspicion when eye, skin, and respiratory signs and symptoms

become evident. Another clue that vesicant exposure has occurred may be the smell of onion, garlic, geraniums, or fish [24]. In general, however, there is no specific medical test to determine if there has been exposure to a vesicant agent. A nonspecific finding of leukopenia may occur 3 to 5 days post-exposure, which may indicate vesicant exposure. A metabolite of mustard, thiodiglycol, has been found in higher concentration than controls in Iranian mustard casualties [25]. With the exception of urinary arsenic excretion, no specific tests exist for lewisite. Phosgene oxime has never been used on the battlefield and no specific tests are currently diagnostic and exposure is made on clinical suspicion. Sulfur mustard, nitrogen mustard, and lewisite may be definitively detected and identified for confirmation and public health and epidemiologic purposes, by sending 25 mL of urine to a regional public health laboratory as described on the website of the Centers for Disease Control and Prevention: www.bt.cdc.gov/labissues/pdf/shipping-samples.pdf and www.bt.cdc.gov/labissues/pdf/chemspecimencollection.pdf.

Antidotes

There are no specific antidotes for mustard exposure. Decontamination within minutes of exposure is the best way to minimize tissue damage and toxic effects from vesicant exposure. The use of N-acetyl-cysteine was shown to decrease the inflammatory response in mustard exposure in an animal model [26]. Also, one animal study suggests that rapid application of providone iodine ointment within 20 minutes of exposure to mustard liquid, may protect the skin from vesication [23,27]. Barrier creams have also been proposed by the United States Army in the past to prevent dermal toxicity from vesicant exposure [28].

A British anti-lewisite agent (dimercaprol) can be used to bind the arsenic group in lewisite and may prevent or decrease both systemic and local toxicity by acting as a chelator. Dimercaprol may be given intramuscularly for systemic toxicity or topically within minutes of exposure for ocular or cutaneous treatment. Indications for dimercaprol administration include severe systemic signs (eg, pulmonary edema or significant burns) and should be given within 15 minutes of exposure. Consultation with the regional poison control center (1-800-222-1222, in the United States), if available, is recommended.

There is no antidote for phosgene oxime exposure and treatment is managed supportively and symptomatically.

Supportive care

Once patients are decontaminated, treatment consists of supportive and palliative measures. Mustard burns should be managed in a manner similar to thermal burns: analgesia, infection control, and fluid replacement. Antibiotic

ointments and silver sulfadiazine creams are recommended for topical burn care [3]. Dermal hypersensitivity may respond to antihistamines or oral or systemic corticosteroids. All patients with ocular exposure should have contact lenses removed, if applicable, and be thoroughly irrigated with saline. Topical mydriatics, antibiotics, and limited steroids (12–24 hours) have been recommended [3,21]. Mild respiratory exposure may respond to antitussives, warm humidified air, and bronchodilators for wheezing or bronchospasm. Persistent symptoms may suggest bronchitis, pneumonia, or pneumonitis, and will require more aggressive therapies.

Although there is no literature available regarding ventilator management for mustard victims, some recent literature suggests decreased mortality with reduced tidal volumes in patients with acute lung injury and adult respiratory distress syndrome (ARDS) [29,30]. The largest of these studies, The National Institutes of Health ARDS Network [31], conducted a clinical trial of mechanical ventilation in ARDS patients, which compared 6 mL/kg predicted body weight tidal volume to 12 mL/kg predicted body weight in ventilated patients. The 6 mL/kg group had 31% mortality compared with 40% for the 12 mL/kg group. Despite the demonstrated reduction in mortality, low tidal ventilation has not gained universal acceptance. This ventilation approach may, however, protect the lungs from excessive stretch, resulting in improved clinical outcomes for patients with acute lung injury and acute respiratory distress syndrome. On the basis of these results, clinicians may consider using this low tidal ventilation protocol in patients with acute lung injury and the acute respiratory distress syndrome.

Clinical course and prognostic factors

Patients who have ocular or airway symptoms should be admitted to the hospital. Also, moderate to severe skin exposure requires hospitalization. Even patients with mild symptoms need to be observed for 18 to 24 hours for development of delayed symptoms [7]. A total white blood cell count of <500 indicates a poor prognosis. Exposure to mustard agents is also associated with developing chronic health problems including respiratory diseases (eg, asthma, pulmonary fibrosis, and bronchiectasis) [17,24,32], skin lesions (eg, dermal scarring) [28,33], neoplasms [24,34], and ocular problems (eg, keratitis, conjunctivitis and corneal ulcers) [32,35]. Also, blood counts, serum electrolytes, and coagulation times should be monitored for secondary effects of these agents.

Summary

Critical care providers and facilities should be prepared for the treatment and care of large amounts of casualties in the event of vesicant use. The basic

principles for the management of vesicant exposure are containment, prevention of secondary contamination, rapid decontamination, and implementation of symptomatic and supportive care. The ability of care providers to recognize, respond, and appropriately treat chemical casualties will help minimize adverse outcomes.

References

[1] Haber LF. The poisonous cloud: chemical warfare in the first world war. Oxford, England: Charendon Press; 1986.

[2] Prentiss AM. Chemicals in war: a treatise on chemical warfare. New York: McGraw Hill; 1937.

[3] Sidell FR, Urbanetti JS, Smith WJ, et al. Vesicants. In: Zajtchuk R, Bellamy RF, editors. Textbook of military medicine. Part I: Medical aspects of chemical and biological warfare. Falls Church (VA): Office of the Surgeon General, Dept of the Army; 1997. p. 197–228.

[4] Khateri S, Ghanei M, Keshavarz S, et al. Incidence of lung, eye, and skin lesions as late complications in 34,000 Iranians with wartime exposure to mustard agent. J Occup Environ Med 2003;45(11):1136–43.

[5] Agency for Toxic Substances and Disease Registry (ATSDR) toxicologic profile of sulfur mustard (Update). Atlanta (GA): Department of Health and Human Services, Public Health Service; 2003.

[6] Medical management guidelines for blister agents: sulfur mustard agent H or HD & sulfur mustard agent HT. Available at: http://www.atsdr.cdc.gov/MHMI/mmg165.pdf. Accessed March 8, 2005.

[7] Medical management guidelines for blister agents: lewisite and mustard-lewisite mixture. Available at: http://www.atsdr.cdc.gov/MHMI/mmg163.pdf. Accessed March 8, 2005.

[8] Medical management guidelines for phosgene oxime. Available at: http://www.atsdr.cdc.gov/MHMI/mmg167.pdf. Accessed March 8, 2005.

[9] Meier HL, Gross CL, Papirmeister B. 2,2′-Dichlorodiethyl sulfide (sulfur mustard) decreases NAD + levels in human leukocytes. Toxicol Lett 1987;39(1):109–22.

[10] Dabrowska MI, Becks LL, Lelli Jr JL, et al. Sulfur mustard induces poptosis and necrosis in endothelial cells. Toxicol Appl Pharmacol 1996;141(2):568–83.

[11] Brown RF, Rice P. Histopathological changes in Yucatan minipig skin following challenge with sulphur mustard. A sequential study of the first 24 hours following challenge. Int J Exp Pathol 1997;78(1):9–20.

[12] Kehe K, Flohe S, Krebs G, et al. Effects of Lewisite on cell membrane integrity and energy metabolism in human keratinocytes and SCL II cells. Toxicology 2001;163(2–3):137–44.

[13] Chilcott RP, Jenner J, Hotchkiss SA, et al. In vitro skin absorption and decontamination of sulphur mustard: comparison of human and pig-ear skin. J Appl Toxicol 2001;21(4):279–83.

[14] Smith WJ, Dunn MA. Medical defense against blistering chemical warfare agents. Arch Dermatol 1991;127(8):1207–13.

[15] Safarinejad MR, Moosavi SA, Montazeri B. Ocular injuries caused by mustard gas: diagnosis, treatment, and medical defense. Mil Med 2001;166(1):67–70.

[16] Banin E, Morad Y, Berenshtein E, et al. Injury induced by chemical warfare agents: characterization and treatment of ocular tissues exposed to nitrogen mustard. Invest Ophthalmol Vis Sci 2003;44(7):2966–72.

[17] Parrish JS, Bradshaw DA. Toxic inhalational injury: gas, vapor and vesicant exposure. Respir Care Clin N Am 2004;10(1):43–58.

[18] Bogucki S, Weir S. Pulmonary manifestations of intentionally released chemical and biological agents. Clin Chest Med 2002;23(4):777–94.

[19] Weiss A, Weiss B. Carcinogenesis due to mustard gas exposure in man, important sign for therapy with alkylating agents. Dtsch Med Wochenschr 1975;100(17):919–23.

[20] Dire DJ. CBRNE-vesicants, mustard: HD, HN1–3, H. Available at: http://www.emedicine.com/emerg/topic901.htm. Accessed March 8, 2005.

[21] Guidelines for mass casualty decontamination during a terrorist chemical agent incident. Available at: http://www.au.af.mil/au/awc/awcgate/army/sbccom_decon.pdf. Accessed March 8, 2005.

[22] Hurst CG. Decontamination. In: Zajtchuk R, Bellamy RF, editors. Medical aspects of chemical and biological warfare. Washington (DC): Office of the Surgeon General, Borden Institute; 1997. p. 351–9.

[23] Wormser U, Brodsky B, Sintov A. Skin toxicokinetics of mustard gas in the guinea pig: effect of hypochlorite and safety aspects. Arch Toxicol 2002;76(9):517–22.

[24] Sidell FR, Hurst CG. Long-term health effects of nerve agent and mustard. In: Zajtchuk R, Bellamy RF, editors. Textbook of military medicine. Part I: Medical aspects of chemical and biological warfare. Falls Church (VA): Office of the Surgeon General, Dept of the Army; 1997. p. 229–46.

[25] Wils ER, Hulst AG, van Laar J. Analysis of thiodiglycol in urine of victims of an alleged attack with mustard gas, Part II. J Anal Toxicol 1988;12(1):15–9.

[26] Anderson DR, Byers SL, Vesely KR. Treatment of sulfur mustard (HD)-induced lung injury. J Appl Toxicol 2000;20(Suppl 1):S129–32.

[27] Wormser U. Protective effect of povidone iodine ointment against skin lesions induced by chemical and thermal stimuli. J Appl Toxicol 2000;20(Suppl 1):S183–5.

[28] Smith KJ, Hurst CG, Moeller RB, et al. Sulfur mustard: its continuing threat as a chemical warfare agent, the cutaneous lesions induced, progress in understanding its mechanism of action, its long-term health effects, and new developments for protection and therapy. J Am Acad Dermatol 1995;32:765–76.

[29] Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 1990;16:372–7.

[30] Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338:347–54.

[31] The Acute Respiratory Distress Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301–8.

[32] Emad A, Rezaian GR. The diversity of the effects of sulfur mustard gas inhalation on respiratory system 10 years after a single, heavy exposure: analysis of 197 cases. Chest 1997;112:734–8.

[33] Smith KJ, Hurst CG, Moeller RB, et al. Sulfur mustard: its continuing threat as a chemical warfare agent, the cutaneous lesions induced, progress in understanding its mechanism of action, its long-term health effects, and new developments for protection and therapy. J Am Acad Dermatol 1995;32(5 Pt 1):765–76.

[34] Yamakido M, Ishioka S, Hiyama K, et al. Former poison gas workers and cancer: incidence and inhibition of tumor formation by treatment with biological response modifier N-CWS. Environ Health Perspect 1996;104(Suppl 3):485–8.

[35] Safarinejad MR, Moosavi SA, Montazeri B. Ocular injuries caused by mustard gas: diagnosis, treatment, and medical defense. Mil Med 2001;166:67–70.