

Chapter 8

VESICANTS

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INTRODUCTION

MUSTARD

LEWISITE

PHOSGENE OXIME

SUMMARY

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INTRODUCTION

Vesicants are agents that produce chemical burns. Sulfur mustard, the first vesicant used as a chemical weapon, caused many injuries on the battlefields of World War I and is still considered a major chemical agent.¹⁻⁴ In the years since World War I, a number of recorded and suspected incidents of mustard use have occurred, culminating in the Iran-Iraq War in the 1980s. During this conflict, Iraq used mustard extensively against Iran. Graphic images of badly burned Iranian casualties in the media brought public attention to the horrors of chemical warfare. The possibility that Iraq would again use mustard caused major concern as the United States joined United Nations forces preparing to liberate Kuwait in fall 1990 (fortunately mustard was not used). Although mustard is the most important vesicant militarily, the vesicant category includes other agents such as lewisite and phosgene oxime (Table 8-1). The clinical differences among the vesicants discussed in this chapter are shown in Table 8-2.

There are two types of mustard: sulfur mustard and nitrogen mustard. Despretz probably synthesized poor quality sulfur mustard in 1822, but it was not identified. Riche, in 1854, and Guthrie, several years later, repeated Despretz's reaction to obtain the same product. Guthrie described the product as smelling like mustard, tasting like garlic, and causing blisters after contact with the skin. Niemann, in 1860, also synthesized the compound. In 1886 Meyer prepared higher quality mustard but discontinued his research because of the hazards involved. During World War I, Germany used Meyer's method of synthesis to manufacture mustard.³

Nitrogen mustard was first synthesized in the late 1930s. Although the properties of nitrogen mustard are similar to sulfur mustard, it was not found suitable for use as a weapon. One form of nitrogen mustard, HN2 (Mustargen, manufactured by Merck and Co, West Point, Pa) was found useful for chemotherapy of

TABLE 8-1

CHEMICAL, PHYSICAL, ENVIRONMENTAL, AND BIOLOGICAL PROPERTIES OF VESICATING AGENTS

Properties	Impure Sulfur Mustard (H)	Distilled Sulfur Mustard (HD)	Phosgene Oxime (CX)	Lewisite (L)
Chemical and Physical				
Boiling Point	Varies	227°C	128°C	190°C
Vapor Pressure	Depends on purity	0.072 mm Hg at 20°C	11.2 mm Hg at 25°C (solid) 13 mm Hg at 40°C (liquid)	0.39 mm Hg at 20°C
Density:				
Vapor	approx 5.5	5.4	<3.9	7.1
Liquid	approx 1.24 g/mL at 25°C	1.27 g/mL at 20°C	ND	1.89 g/mL at 20°C
Solid	NA	Crystal: 1.37 g/mL at 20°C	NA	NA
Volatility	approx 920 mg/m ³ at 25°C	610 mg/m ³ at 20°C	1,800 mg/m ³ at 20°C	4,480 mg/m ³ at 20°C
Appearance	Pale yellow to dark-brown liquid	Pale yellow to dark-brown liquid	Colorless, crystalline solid or a liquid	Pure: colorless, oily liquid As agent: amber to dark-brown liquid
Odor	Garlic or mustard	Garlic or mustard	Intense, irritating	Geranium
Solubility:				
In Water	0.092 g/100 g at 22°C	0.092 g/100 g at 22°C	70%	Slight
In Other Solvents	Complete in CCl ₄ , acetone, other organic solvents	Complete in CCl ₄ , acetone, other organic solvents	Very soluble in most organic solvents	Soluble in all common organic solvents

(Table 8-1 continues)

certain neoplasms.⁵⁻⁸ In the early years of chemotherapeutics, HN2 was a mainstay in cancer therapy.

A second group of vesicants is arsenicals. The major compound in this group is lewisite, which was synthesized, developed, and manufactured in the United States during the late stages of World War I.¹ A shipment of lewisite on its way to Europe when the war ended was destroyed at sea. There are no data on lewisite from battlefield use. As a weapon, lewisite has some advantages and disadvantages over mustard that will be discussed later in this chapter.

The third compound considered a vesicant by the US military is phosgene oxime. Phosgene oxime is not a true vesicant—unlike mustard and lewisite, it does not produce blisters; rather, it produces solid lesions resembling urticaria (hives). There are no verified battlefield uses of this compound, and it remains incompletely studied in the Western world. Both lewisite and phosgene oxime remain chemical weapons of concern because they were stockpiled by the former Soviet Union. Mixtures of agents such as mustard and lewisite also exist in these stockpiles.

MUSTARD

Although mustard ([bis-(2-chloroethyl)sulfide, also called 2,2'-dichlorodiethyl sulfide) was introduced late in World War I (July 1917), it caused more chemical casualties than chlorine, phosgene, and cyanide combined. Although lethality from mustard exposure was

low, casualties filled the medical facilities. Considering the ease of its manufacture and extent of existing stockpiles, this fact is especially crucial.

Mustard allegedly received its name from its smell or taste (onion, garlic, mustard) or its color (which

Table 8-1 continued

Environmental and Biological

Detection	Liquid: M8 paper Vapor: CAM	Liquid: M8 paper Vapor: CAM, M256A1 kit, ICAD	M256A1 ticket or card	Vapor, M256A1 ticket or card, ICAD
Persistence:				
In Soil	Persistent	2 wk–3 y	2 h	Days
On Materiel	Temperature-dependent; hours to days	Temperature-dependent; hours to days	Nonpersistent	Temperature-dependent; hours to days
Skin Decontamination	M2581 kit Dilute hypochlorite Water M291 kit	M258A1 kit Dilute hypochlorite Soap and water M291 kit	Water	Dilute hypochlorite M258A1 kit Water M291 kit
Biologically Effective Amount:				
Vapor (mg•min/m ³)	LC _{t50} : 1,500	LC _{t50} : 1,500 (inhaled) 10,000 (masked)	Minimum effective Ct: approx 300; LC _{t50} : 3,200 (estimate)	Eye: <30 Skin: approx 200 LC _{t50} : 1,200–1,500 (inhaled) 100,000 (masked) 40–50 mg/kg
Liquid LD ₅₀ : approx 100 mg/kg		LD ₅₀ : 100 mg/kg	No estimate	

CAM: chemical agent monitor

CCl₄: carbon tetrachloride

ICAD: individual chemical agent detector

LD₅₀: dose that is lethal to 50% of the exposed population (liquid, solid)

LC_{t50}: (concentration • time of exposure) that is lethal to 50% of the exposed population (vapor, aerosol)

NA: not applicable

ND: not determined

TABLE 8-2
CLINICAL DIFFERENCES AMONG VESICANTS

Chemical Agent	Blister	Pain	Onset
			Tissue Damage
Mustard	Fluid filled	Hours later	Immediate; onset of clinical effects is hours later
Lewisite	Fluid filled	Immediate	Seconds to minutes
Phosgene oxime	Solid wheal	Immediate	Seconds

varies from yellow, to light tan, to dark brown).^{3,9} When Germany first used mustard, the Allies called it Hun Stoffe (German stuff), abbreviated as HS; later, it became known as H. Mustard manufactured by the Levinstein process is also known as H; it contains about 20% to 30% impurities (mostly sulfur). Distilled, or nearly pure, mustard is known as HD. Both forms of mustard, H and HD, can still be found today in munitions manufactured over 90 years ago. Sulfur mustard has also been called Lost or S-Lost (for the two German chemists who suggested its use as a chemical weapon, Lommel and Steinkopf); yellow cross (for its identifying mark on World War I shells); and yperite (for the site of its first use, Ypres, Belgium).

Nitrogen mustard has three forms: HN-1, HN-2, and HN-3. These agents are similar to sulfur mustard in many ways and seem to cause equally severe effects, particularly in the central nervous system (CNS). They regularly caused convulsions when administered intravenously to animals. However, the nitrogen mustards were not suitable as military agents for several reasons.¹⁰ They will not be discussed further in this chapter because they have not been used militarily; unless stated otherwise the term “mustard” refers here to sulfur mustard.

Military Use

Mustard has been stockpiled in the arsenals of various countries since it was first used on July 12, 1917, when the Germans fired shells containing mustard at British troops entrenched near Ypres, Belgium.¹² Only a few months later, both sides were using mustard. Mustard caused at least 70% of the chemical casualties in World War I (when a single agent could be identified as the source of injury). The remaining 30% were caused by other agents, such as chlorine and phosgene (see Chapter 10, Toxic Inhalational Injury and Toxic Industrial Chemicals). The proportion of mustard injuries is remarkable considering there were 1.3 million

chemical casualties in World War I (out of a total of 5 million chemical and conventional casualties) and that mustard was introduced only in the last year of the war. Of 180,983 chemical casualties among British soldiers; the injuries of 160,970 (88%) were caused solely by mustard, and 4,167 (2.6%) of these casualties died. Of 36,765 single-agent chemical casualties in the US military; the injuries of 27,711 (75%) were caused solely by mustard. Of all chemical casualties who reached a medical treatment facility (MTF), 599 (2.2%) died.¹¹ The conventional injury mortality rate for World War I was 7%. Although few mustard casualties died, the survivors required lengthy hospitalization averaging 42 days. The combination of long convalescent times and large numbers of casualties demonstrated the effectiveness of mustard.

Since World War I, mustard was reportedly used in a number of isolated incidents. In 1935, Italy probably used mustard against Abyssinia (now Ethiopia); Japan allegedly used mustard against the Chinese from 1937 to 1944; and Egypt was accused of using the agent against Yemen in the mid 1960s.¹²

Chemical agents were not used on the battlefield during World War II; one of several conjectures about why Germany did not use mustard was that Hitler had been a mustard victim during World War I and disdained its use. However, in December 1943, a German air raid destroyed the SS *John Harvey*, a US ship secretly carrying a large stockpile of mustard bombs, while it was docked with other Allied ships in Bari, Italy. There were 617 US mustard casualties (83 fatal) from exploded shells, burning mustard smoke, and oily mustard floating on the water surface. In addition, an unknown number of Italian civilians were casualties as a result of smoke.¹³⁻¹⁵ The incident at Bari is discussed in greater detail in Chapter 2, History of Chemical Warfare.

During the Iran-Iraq War, one source estimated there were 45,000 mustard casualties.¹⁶ In 1989 the journal *Annales Medicinæ Militaris Belgicae* published a

monograph by Jan L Willems that reported the western European experience treating a selected population of Iranian mustard casualties.¹⁷ Willems reported that in March 1984, February 1985, and March 1986, Iranian casualties were sent to hospitals in Ghent, Belgium, and other western European cities for treatment. More casualties arrived in 1987. In an attempt to establish whether chemical warfare agents had been used, three United Nations missions (in 1984, 1986, and 1987) conducted field inspections, clinical examination of casualties, and laboratory analyses of chemical ammunition. The missions concluded that

- aerial bombs containing chemical weapons were used in some areas of Iran,
- sulfur mustard was the primary chemical agent, and
- there was some use of the nerve agent tabun.¹⁷

Since mustard's introduction, multiple accidental exposures have occurred. Several occurred in the North Sea, where fishermen were exposed after dredging up munitions that had been dumped after World War II.¹⁸⁻²¹ Others occurred when children found and played with mustard shells. The children were injured when the shells exploded, and several died.^{22,23} There have also been reported incidents of laboratory workers and, in one instance, of soldiers in their sleeping quarters who were accidentally exposed to mustard. In yet another incident, a souvenir collector unearthed a mustard shell.²⁴⁻²⁶ Recently a US Air Force explosive ordinance disposal team was accidentally exposed to World War II munitions dredged from the Atlantic coast.

Properties

Mustard is an oily liquid generally regarded as a "persistent" chemical agent because of its low volatility, which usually allows the liquid to remain on surfaces longer than 24 hours. At higher temperatures, such as those in the Middle East during the hot season, 38° to 49°C (100° to 120°F), mustard vapor is a major hazard. The persistency of mustard in sand decreases from 100 hours to 7 hours as the temperature rises from 10° to 38°C (50° to 100°F).²⁷

World War I data suggest that the warming of the air after sunrise caused significant evaporation of mustard from the ground.²⁸ Mustard attacks were frequently conducted at night, when the liquid agent did not readily evaporate in the cool night air; however, several hours after daybreak, the sun-warmed air caused the mustard to vaporize. At first, thinking the

danger was over, soldiers removed their masks in the morning and fell victim to the evaporating mustard, but it soon became standard policy not to unmask for many hours after daybreak.

Mustard vapor has a 5.4-fold greater density than that of air, causing it to hug the ground and sink into trenches and gullies. Despite low volatility, more than 80% of the mustard casualties during World War I were caused by vapor, not the liquid form of mustard.²⁹

The freezing/melting temperature for mustard is 57°F. This high freezing point makes mustard unsuitable for delivery by high-altitude aircraft or in the winter. To lower the freezing point, mustard must be mixed with another substance; during World War I it was mixed with chloropicrin, chlorobenzene, or carbon tetrachloride.¹ Mustard has also been mixed with lewisite to increase its volatility in colder weather. The mustard/lewisite combination has a freezing point close to 10°F.

Biochemical Mechanisms of Injury

Over the past few decades, scientists have made major advances in understanding the cellular and biochemical consequences of exposure to mustard and have put forth several hypotheses, two of which are discussed below, to explain mustard injury (Figure 8-1).³⁰⁻³³ The mustards, both sulfur and nitrogen, are alkylating agents that act through cyclization of an ethylene group to form a highly reactive sulfonium or immonium electrophilic center. This reactive electrophile is capable of combining with any of the numerous nucleophilic sites present in the macromolecules of cells. The products of these reactions are stable adducts that can modify the normal function of the target macromolecule. Because nucleophilic areas exist in peptides, proteins, ribonucleic acid (RNA), deoxyribonucleic acid (DNA), and membrane components, researchers have tried to identify the most critical biomolecular reactions leading to mustard injury.

Because of the highly reactive nature of mustard, it is conceivable that the injury following tissue exposure may result from a combination of effects described in both hypotheses below, or injury may result from additional changes not yet described in a formal hypothesis. Whether the initiating event is alkylation of DNA or modification of other cellular macromolecules, these steps would disrupt the epidermal-dermal junction. Once the site of tissue injury is established, the pathogenic process leading to formation of fully developed blisters must involve an active inflammatory response and altered fluid dynamics in the affected tissue. Mustard also has cholinergic action, stimulating both muscarinic and nicotinic receptors.³⁴

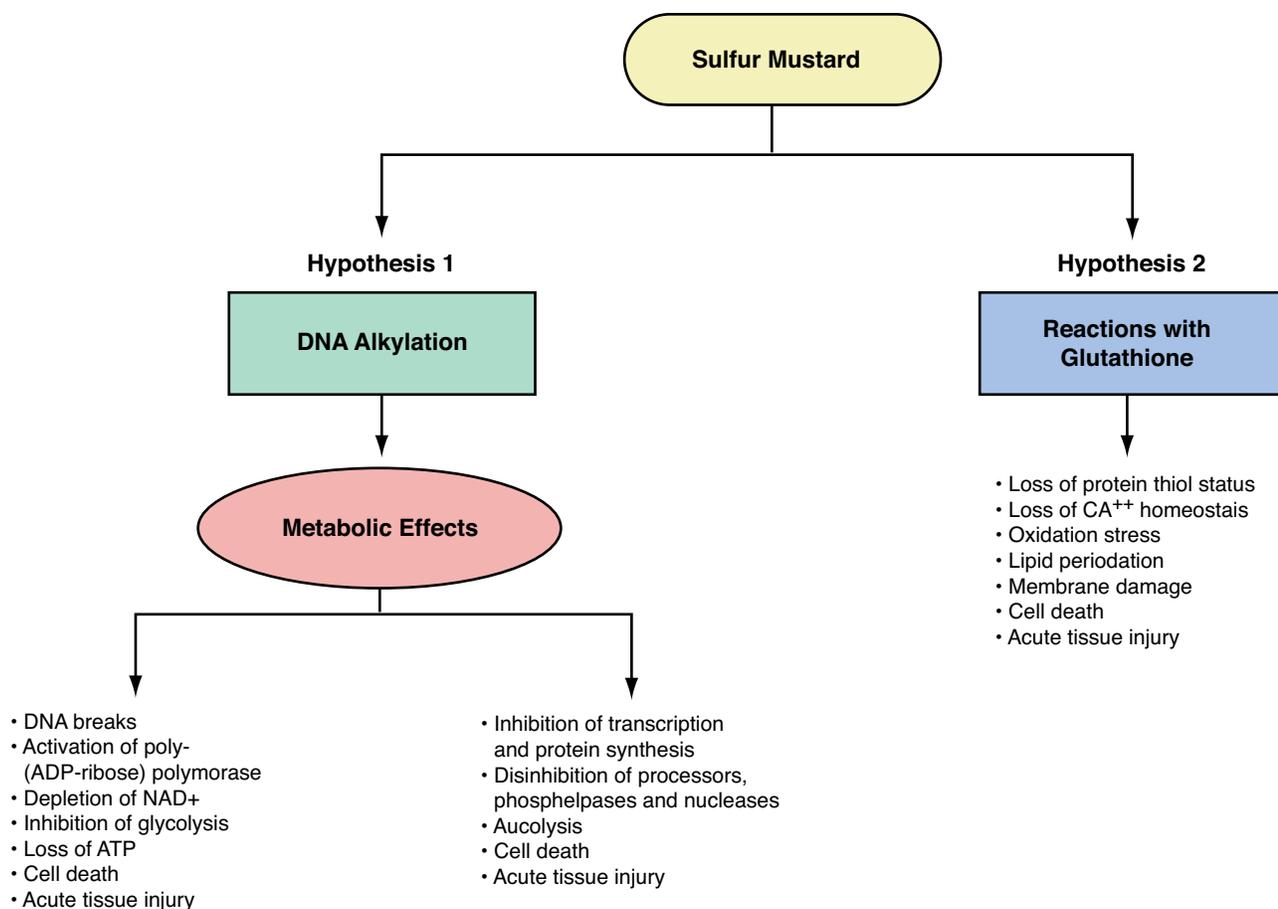


Fig. 8-1. The putative mechanisms by which sulfur mustard causes tissue damage.

ADP: adenosine 5'-diphosphate

ATP: adenosine triphosphate

Ca⁺⁺: calcium ions

DNA: deoxyribonucleic acid

NAD⁺: nicotinamide adenine dinucleotide

Adapted from: US Army Medical Research Institute of Chemical Defense. A global picture of battlefield vesicants, I: a comparison of properties and effects. *Med Chem Def.* 1992;5(1):6.

Alkylation of Deoxyribonucleic Acid

The first proposed hypothesis about the mechanism of injury for mustard links alkylation of DNA with the cellular events of blister formation.³⁵ According to this proposal, alkylation of DNA by sulfur mustard results in strand breaks. The strand breaks trigger activation of a nuclear DNA repair enzyme, poly(adenosine diphosphate-ribose) polymerase (PADPRP). Excessive activity of this enzyme depletes cellular stores of nicotinamide adenine dinucleotide (NAD⁺), a critical cofactor and substrate needed for glycolysis.³⁶⁻³⁸ Inhibition of glycolysis would cause a buildup of glucose-6-phosphate, a substrate in the hexose monophosphate shunt.³⁹ Stimulation of the

hexose monophosphate shunt results in activation of cellular proteases.⁴⁰ Since a principal target of mustard in the skin is the basal epidermal cell, protease from these cells could account for the cleavage of the adherent fibrils connecting the basal epidermal cell layer to the basement membrane.⁴¹

Thus far, data from animal and cellular systems are consistent with many aspects of this hypothesis, which considers DNA damage the initiating step and PADPRP activation a critical event. Studies with human skin grafts, epidermal keratinocytes, and leukocytes in culture, and with the euthymic hairless guinea pig, have shown decreases in cellular NAD⁺ as a consequence of PADPRP activation following sulfur-mustard-induced DNA damage.^{36,37,42,43} Niacinamide

and other inhibitors of PADPRP can ameliorate the pathology developing in both living animal and cellular models.^{36,37,43,44} Unfortunately, while niacinamide has some beneficial actions, the protection it affords is never complete and is limited in duration.^{42,43} No evidence currently shows activation of the hexose monophosphate shunt following mustard exposure, but significant metabolic disruptions in human keratinocytes have been reported after mustard exposure.⁴⁵ Protease activity is increased in human cells exposed in vitro to mustard.⁴⁶⁻⁴⁸

Although many aspects of the PADPRP hypothesis have been verified, and there is good linkage between the proposed steps of this pathway and mustard-induced cytotoxicity, no direct correlation with the full range of tissue pathologies seen following mustard exposure has yet been established. Even though DNA is an important macromolecular target of mustard alkylation in the cell, several other hypotheses of mustard toxicity have been developed that are based on mustard's reaction with other cellular components. For a review of all such hypotheses, see *Medical Defense Against Mustard Gas: Toxic Mechanisms and Pharmacological Implications*; only those undergoing active investigation are discussed here.³¹

Reactions with Glutathione

The second major hypothesis to explain the effects of mustard proposes that the agent reacts with the intracellular free radical scavenger glutathione (GSH), thereby depleting it, resulting in a rapid inactivation of sulfhydryl groups and the consequent loss of protection against oxygen-derived free radicals, specifically those causing lipid peroxidation.⁴⁹ In 1987 Orrenius and Nicotera established that menadione-induced depletion of GSH resulted in loss of protein thiols and inactivation of sulfhydryl-containing enzymes.⁵⁰ Included in this class of thiol proteins are the calcium and magnesium adenosine triphosphatases, which regulate calcium homeostasis. With the inactivation of the enzymes that control thiol proteins, intracellular calcium levels would increase. High calcium levels within the cell trigger activation of protease, phospholipases, and endonucleases, which could give rise to the breakdown of membranes, cytoskeleton, and DNA that would result in cell death.

One report suggested that this mechanism could be activated by mustards and might be the mechanism of mustard injury.⁵¹ While several aspects of the thiol-calcium hypothesis (eg, release of arachidonic acid and decrease in membrane fluidity) have been observed in cell cultures following sulfur mustard exposure, no definitive studies have drawn an as-

sociation between calcium disruptions and mustard-induced pathology.⁵²

Another proposed consequence of the assumed depletion of GSH following mustard exposure is lipid peroxidation.^{53,54} According to this hypothesis, depletion of GSH allows the formation of oxygen-derived free radicals. The oxidizing compounds thus formed would react with membrane phospholipids to form lipid peroxides that could, in turn, lead to membrane alterations, changes in membrane fluidity, and eventual breakdown of cellular membranes.

As previously mentioned, studies have shown changes in membrane fluidity following sulfur mustard exposure.⁵² In addition, in 1989 Elsayed and colleagues demonstrated the presence of lipid peroxidation indicators in the tissue of mice exposed to subcutaneous butyl mustard.⁵⁵ However, as with the thiol-calcium hypothesis, no studies have directly linked lipid peroxidation with mustard-induced injury.

Metabolism

As the first step in any of the mustard injury theories, mustard cyclizes to a sulfonium electrophilic center. This highly reactive moiety, in turn, combines with peptides, proteins, DNA, or other substances. After a few minutes in a biological milieu, intact mustard is no longer present; the reactive electrophile has attached to another molecule and is no longer reactive. The rapidity of this reaction also means that, within a few minutes, mustard has started to cause tissue damage. The clinical relevance is that intact mustard or its reactive metabolic product is not present in tissue or biological fluids, including blister fluid, a few minutes after the exposure; however, clothing, hair, and skin surfaces may still be contaminated hours later.

Several studies support the observation that intact or active mustard is not present in tissue or biological fluids after a few minutes.^{31-33,56} Occluding the blood supply to areas of the intestinal tract or to selected bone marrow for a few minutes protected these organs from the effects of a lethal amount of intravenously administered mustard. Approximately 85% of S-labeled mustard disappeared from the blood of humans after several minutes, and the half-life for intravenously administered mustard to disappear from the blood of piglets was about 2 minutes.^{37,57,58} Mustard blister fluid did not produce a reaction when instilled into the eyes of animals or humans or onto the skin of humans.^{59,60} A continuing outbreak of smaller vesicles near a source of blister fluid is probably the result of these areas having received an additional exposure and not from contamination by the blister fluid.^{59,61}

Clinical Effects

The organs most commonly affected by mustard are the skin, eyes, and airways (Table 8-3): the organs with which mustard comes into direct contact. After a significant amount of mustard has been absorbed through the skin or inhaled, the hemopoietic system, gastrointestinal tract, and CNS are also damaged. Mustard may also affect other organs, but rarely do these produce clinical effects.

During World War I, 80% to 90% of US mustard casualties had skin lesions, 86% had eye involvement, and 75% had airway damage; these percentages are not significantly different from those seen in Iranian casualties.⁶² Of a group of 233 severely injured Iranian soldiers sent to western European hospitals by the Iranian government for treatment during the Iran-Iraq War, 95% had airway involvement, 92% had eye signs and symptoms, and 83% had skin lesions.⁶³ In a series of 535 Iranian casualties, including civilians, admitted to a dermatology ward, 92% had skin lesions and 85% had conjunctivitis; of the total number of patients, 79%

had erythema and 55% had blisters. Casualties with more serious problems, including injury to the pulmonary tract, were admitted to other wards.⁶⁴

The slightly higher percentage of airway and eye involvement in Iranian soldiers versus US World War I casualties is perhaps attributable to the higher ambient temperature in the area (compared with Europe), which caused more vaporization. The difference might also have resulted from the limited availability of Iranian protective equipment or poor mask seals with facial hair. In 1984, the year the first Iranian casualties were treated in Europe, protective clothing and gas masks were not commonly worn by Iranian soldiers.¹⁷

Mustard-related death occurs in about 3% of the casualties who reach an MTF; of those who die, most die 4 or more days after exposure. Table 8-4 illustrates the breakdown, in percentages, of British troops who died after exposure to mustard during World War I.⁶² Of the casualties who died, 84% spent at least 4 days hospitalized. The causes of death from mustard exposure are pulmonary insufficiency from airway damage, superimposed infection, and sepsis. Rarely, the mustard exposure is overwhelming and causes death within 1 to 2 days; in these circumstances, death results from neurological factors or massive airway damage.^{10,23} The Willems report on Iranian casualties treated in western European hospitals describes more recent treatment of mustard casualties. Clinical files of 65 of these casualties were studied in detail.¹⁷ Eight patients died between 6 and 15 days after exposure. One patient died 185 days after exposure: he had received ventilatory support for an extended period because of severe bronchiolitis complicated by a series of loculate pneumothoraces. Most patients returned to Iran in fairly good condition after 2 to 10 weeks of treatment. The duration of hospitalization was determined

TABLE 8-3
INITIAL CLINICAL EFFECTS FROM MUSTARD EXPOSURE

Organ	Severity	Effects	Onset of First Effect
Eyes	Mild	Tearing Itching Burning Gritty feeling	4–12 h
	Moderate	Above effects, plus: Reddening Lid edema Moderate pain	3–6 h
	Severe	Marked lid edema Possible corneal damage Severe pain	1–2 h
Airways	Mild	Rhinorrhoea Sneezing Epistaxis Hoarseness Hacking cough	6–24 h
	Severe	Above effects, plus: Productive cough Mild-to-severe dyspnea	2–6 h
Skin	Mild	Erythema	2–24 h
	Severe	Vesication	4–12 h

TABLE 8-4
DAY OF DEATH AFTER EXPOSURE IN WORLD WAR I FATAL MUSTARD CASUALTIES*

Day of Death (After Exposure)	Percentage of Deaths
≤1	1
2	2
3	5
4	8
5	22
≥6	62

*In 4,167 British troops who died from mustard exposure. Data source: Gilchrist HL. *A Comparative Study of World War Casualties From Gas and Other Weapons*. Edgewood Arsenal, Md: US Chemical Warfare School; 1928: 14.

mainly by the time needed for healing of the deeper skin lesions. Despite medical advances since World War I, there was a 14% mortality rate among this group; this higher rate is because some of the most severely injured Iranian patients were sent to Europe.

Skin

The threshold amount of mustard vapor required to produce a skin lesion (erythema) is a Ct of about $200 \text{ mg} \cdot \text{min} / \text{m}^3$. This amount varies greatly depending on a number of factors, including temperature, humidity, skin hydration, and body site. Warm, moist areas with thin skin, such as the perineum, external genitalia, axillae, antecubital fossae, and neck are much more sensitive than other areas of the body. A liquid droplet of about $10 \text{ } \mu\text{g}$ will produce vesication. About 80% evaporates, and 10% enters the circulation, leaving about 10% on the skin surface to cause local topical injury. As little as $1 \text{ } \mu\text{g}$ can cause simple vesicle formation. Evaporation of small droplets is rapid and nearly complete in 2 to 3 minutes; amounts larger than several hundred milligrams may take hours to evaporate.⁶⁵

Mustard vapor rapidly penetrates the skin at the rates of $1.4 \text{ } \mu\text{g} / \text{cm}^2 / \text{min}$ at 70°F , and $2.7 \text{ } \mu\text{g} / \text{cm}^2 / \text{min}$ at 88°F .²⁷ Liquid mustard penetrates the skin at $2.2 \text{ } \mu\text{g} / \text{cm}^2 / \text{min}$ at 60°F and at $5.5 \text{ } \mu\text{g} / \text{cm}^2 / \text{min}$ at 102°F .⁶⁵

The mildest and earliest form of visible skin injury is erythema, which resembles sunburn (Figure 8-2). Erythema begins to appear 1 to 24 hours after the



Fig. 8-2. Erythema of the chest of an Iranian casualty as it appeared 5 days after his exposure to mustard. He also had a pulmonary injury with an associated bronchopneumonia from infection with *Haemophilus influenzae*.

Reproduced with permission from: Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;35:13.



Fig. 8-3. The back of an Iranian casualty seen 16 hours after exposure to mustard. Note the large bullae that have resulted from coalescence of small vesicles.

Reproduced with permission from: Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;35:8.

skin is exposed to mustard, although onset can be later. Erythema is usually accompanied by pruritus (itching), burning, or stinging. After a small exposure, this might be the extent of the lesion. More commonly, small vesicles will develop within or on the periphery of the erythematous areas (like a string of pearls); these vesicles will later coalesce to form larger blisters (Figure 8-3). The effects from liquid mustard appear more rapidly than the effects from mustard vapor. Characteristically, the onset of erythema is about 4 to 8 hours after mustard exposure. Vesication begins about 2 to 18 hours later and may not be complete for several days.

The typical bulla (large blister) is dome-shaped, thin-walled, superficial, translucent, yellowish, and surrounded by erythema; it can be 5 cm in diameter or larger (Figure 8-4). The blister fluid is initially thin and clear or slightly straw-colored; later it turns yellowish and tends to coagulate.^{17,65,66} The blister fluid does not contain mustard and is not itself a vesicant. Thiodiglycol, a breakdown product of mustard, has been found in blister fluid and can be used to aid in diagnosis. Vapor injury is generally a first- or second-degree burn; liquid mustard may produce deeper damage comparable to a third-degree burn.

After exposure to extremely high doses, such as those resulting from contact with liquid mustard, lesions may be characterized by a central zone of coagulation necrosis, with blister formation at the periphery. These lesions are more severe, take longer to heal, and are more prone to secondary infection than lesions resulting from smaller doses.²⁹

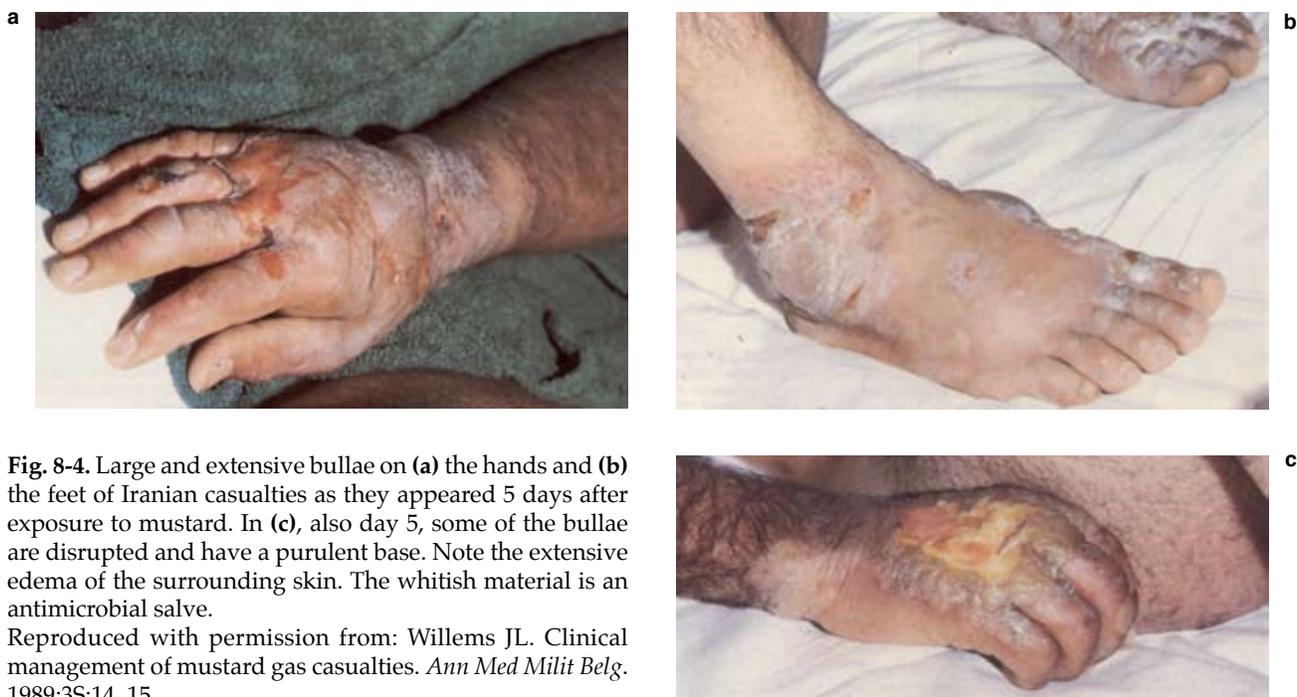


Fig. 8-4. Large and extensive bullae on (a) the hands and (b) the feet of Iranian casualties as they appeared 5 days after exposure to mustard. In (c), also day 5, some of the bullae are disrupted and have a purulent base. Note the extensive edema of the surrounding skin. The whitish material is an antimicrobial salve. Reproduced with permission from: Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;3S:14, 15.

The healing time for mustard skin lesions depends on the severity of the lesion. Erythema heals within several days, whereas severe lesions may require several weeks to several months to heal, depending on the anatomical site, the total area of skin surface affected, and the depth of the lesion (Figure 8-5).¹⁷

A characteristic of the cutaneous mustard injury that Willems reported in the Iranian casualties was transient blackening, or hyperpigmentation, of the affected skin (Figure 8-6).¹⁷ When the hyperpigmented skin exfoliated, epithelium of normal color was

exposed. Vesication was not necessary for hyperpigmentation to occur. The syndrome of hyperpigmentation and exfoliation was commonly recognized in World War I casualties, but less commonly in laboratory experiments using liquid mustard.¹⁷ When the initial skin damage, inflammation, only stimulates the melanocyte (pigment cell), increased pigmentation (hyperpigmentation) can be seen. When the melanocyte is destroyed, hypopigmentation occurs, which lasts several months and occasionally becomes permanent. This blotchy hyperpigmentation and

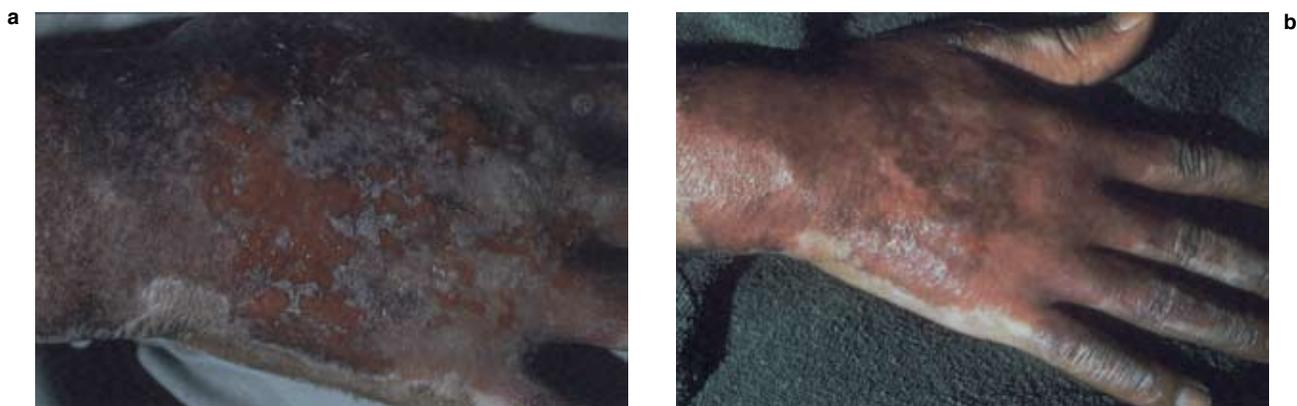


Fig. 8-5. Healing of a deep erosive mustard burn of the hand. (a) The appearance on day 49. Epithelialization occurred by ingrowth of cells from patches of less injured skin. (b) The appearance on day 66, when complete epithelialization had occurred. The thin and fragile nature of the new skin is clearly apparent. Reproduced with permission from: Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;3S:36.



Fig. 8-6. Transient hyperpigmentation of the injured skin is frequently observed following mustard exposure. It is caused by the collection of melanin from dead melanocytes at the base of the soon-to-desquamate epidermis and resolves when the involved skin desquamates. Hyperpigmentation is not dependent on the formation of bullae. (a) An Iranian casualty is shown 5 days following exposure to mustard. Note the extensive desquamation of hyperpigmented skin on his back and the normal appearance of the underlying skin. This patient developed a profound leukopenia (400 cells per μL) and a bronchopneumonia of 10 days' duration. Resolution of these problems required a 5-week hospitalization. (b) A different Iranian casualty, seen 12 days after exposure to mustard, has darkening of the skin, desquamation, pink areas showing regeneration of the epidermis, and yellow-white areas of deeper necrosis. (c) Another casualty's blackening of the skin and beginning desquamation of the superficial layer of the epidermis is shown 15 days after mustard exposure. Note the prominence of these changes in the skin of the axilla. (d) The appearance on light microscopy of a hyperpigmented area. Note the melanin in the necrotic epidermal layer, under which is a layer of regenerating epidermis.

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hypopigmentation can be extremely distressing to patients, because similar appearing skin changes are often associated with diseases such as leprosy and syphilis. Punctate repigmentation can be seen starting at and around hair follicles where the melanocytes were not destroyed (Figure 8-7).

Cytopathology. The major change at the dermal-epidermal junction, visualized by light microscopy, is liquefaction necrosis of epidermal basal cell keratinocytes (Figure 8-8). Nuclear swelling within basal cells starts as early as 3 to 6 hours after exposure, and progresses to pyknosis of nuclei and disintegration of cytoplasm.^{31,67} The pathological process can be described as follows (Figure 8-9 further illustrates this

process).

By a coalescence of neighboring cells undergoing the process of swelling, vacuolar degeneration, or hydropic degeneration ("liquefaction necrosis") and rupture, spaces of progressively increasing size are formed. This usually involves dissolution of cells of the basal layer, resulting in defects in the basal portion of the epidermis and separation of the upper layers of the epidermis from the corium. At first there are multiple focal areas of such microvesicle formation, with septa of as yet uninvolved epidermal cells.^{68,69} Progressive dissolution of the cells of such septa follows, and although intact or partially degenerated basal cells may initially remain in the floor of the microvesicles, these



Fig. 8-7. By 32 days after exposure, this Iranian casualty has punctate hyperpigmentation in a healing deep mustard burn. This condition may be indicative of postinflammatory changes in the epidermis.

Reproduced with permission from: Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;35:34.

also soon disintegrate as the vesicles enlarge.⁷⁰ An electron microscopy study of mustard lesions in human skin grafted onto nude mice confirmed that damage to the basal cells (nucleus, plasma membrane, anchoring filaments) resulted in the separation of epidermis from dermis and the formation of a subepidermal microblister.⁷¹

Models and histopathology. Morphopathological data at the light microscopy level gathered in controlled laboratory investigations are providing important clues about mechanisms of HD skin toxicity. Typically, mustard histopathology in animal skin is presented as occurring during a prevesication period and a vesication period.^{72,73} In the prevesication period (the first 12 to 24 hours), beginning 4 to 6 hours postexposure, latent, lethal targeting of epidermal basal cells occurs; basal cell attachment mechanisms to the lamina densa of the skin basement membrane are disabled; and inflammatory cells within the dermal vasculature are recruited. Later, a progressive, inflammatory edema of the lamina lucida of the basement membrane zone contributes to the formation of lucidolytic microvesicles, which coalesce and persist as microblisters at the dermal-epidermal junction, leading to eventual subepidermal cleavage of the epidermis from the dermis (the vesication period).^{74,75} Subepidermal vesication evident at 12 to 24 hours post-exposure is the end stage of the pathology presented in laboratory animal models. Processes of healing and reepithelialization become evident during the resolution of microvesicles (see Figure 8-9). Leading contributions to this morphopathological data have been made through the use of *in vivo* models, such as human skin-grafted nude mice, hairless guinea pigs, domestic weanling pigs, and the mouse ear, and *in vitro* systems, such as cultured human skin equivalents

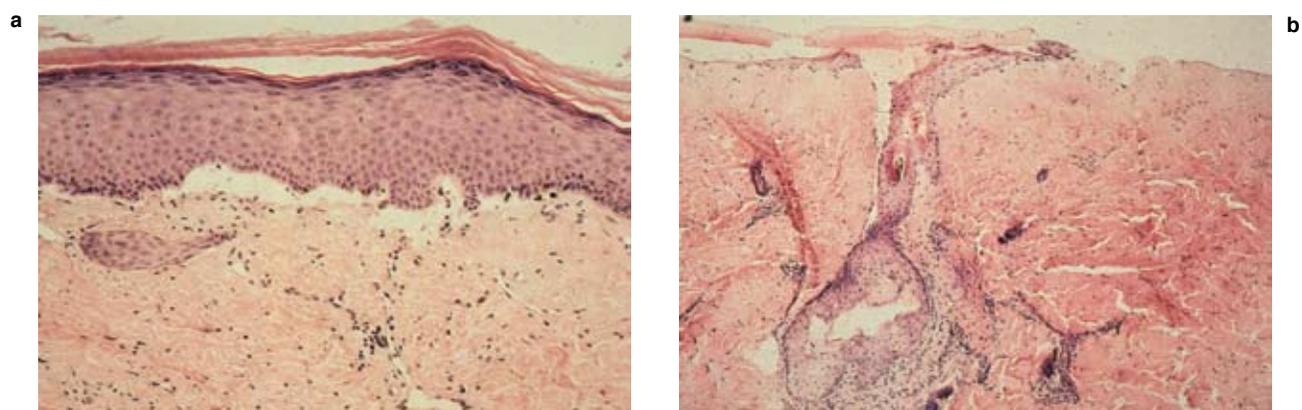


Fig. 8-8. The spectrum of cutaneous mustard injury as seen on light microscopy extends from superficially intact skin to sloughing of the epidermis. **(a)** A skin biopsy taken from an Iranian casualty on the 11th day following exposure to mustard. The gross appearance was of erythema. A cleavage plane is apparent between the dermis and epidermis, with edema extending into the stratum spinosum (note the enlarged spaces between individual cells). Changes in cells of the stratum germinativum are difficult to ascertain at this level of magnification, but nuclei of cells on the extreme right of the figure appear to be pyknotic (shrunken and dark). **(b)** This biopsy was taken at the site of an erosion. The epidermis has sloughed, and the superficial dermis is necrotic. White blood cells have infiltrated the deeper layers of the dermis. Part of an intact hair follicle is seen; the epidermis will ultimately regenerate from such structures.

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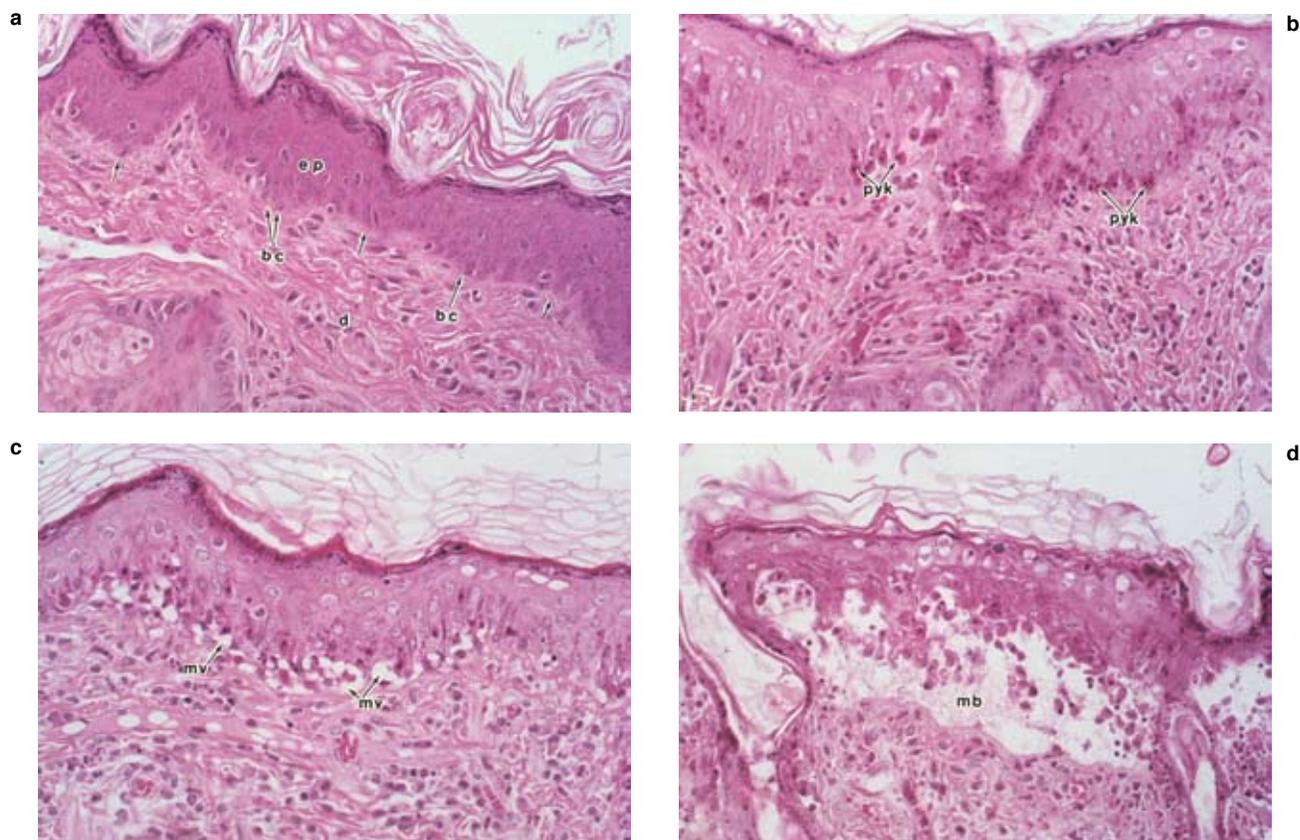


Fig 8-9. Light microscopic (**a, b**) and electron microscopic (**c, d**) presentations of hairless guinea pig skin exposed to sulfur mustard vapor reveal that the epithelial basal cell of the stratum germinativum is selectively affected to the exclusion of other epidermal cells. Following an apparent latency period of 4 to 6 hours, the basal cell pathology progresses to include extensive hydropic vacuolation, swollen endoplasmic reticulum, dilated mitochondria, coagulation of monofilaments, nuclear pyknosis, and cell death. At 12 to 24 hours, microvesicles/microblisters form at the dermal-epidermal junction, which cleave the epidermis from the dermis. The cavity formed within the lamina lucida of the basement membrane as a consequence of basal cell pathology, and perhaps as the result of disabling of basement membrane attachment proteins, is infiltrated with cellular debris, inflammatory cells, fibers, and tissue fluid. (**a**) Unexposed perilesional skin site serves as control, showing epidermis (ep), dermis (d), basement membrane (arrows), basal cells of the stratum germinativum (bc). (**b**) Affected skin 9 hours after exposure to HD vapor, showing degenerating basal cells with karyorrhetic and pyknotic nuclei (pyk). (**c**) Affected skin 12 hours after HD exposure, showing microvesicles (mv) forming at the basement membrane zone in association with the microenvironment of degenerating basal cells. (**d**) Affected skin 24 hours after HD exposure, showing microvesicles that have coalesced to form a characteristic microblister (mb) that separates the epidermis from the dermis. Original magnification $\times 220$.

Photographs: Courtesy of John P Petrali, PhD, US Army Medical Research Institute of Chemical Defense, and Stephanie R Froberg, Graphics Department, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Md.

and isolated perfused porcine skin flaps.⁷⁴⁻⁸⁰

Ultrastructural pathology. Ultrastructural studies of *in vivo* models have expanded mustard investigations to elaborate important effects on subcellular entities of the basal cell and the basement membrane microenvironment.^{73,74,81} During prevesication, models consistently present subcellular nuclear injury to basal cells to the exclusion of cells of other epidermal strata. These injuries, typically presenting at 6 hours postexposure, include nuclear chromatin condensa-

tions with margination, dilatations of the nuclear envelope, mitochondrial swelling, and tonofilament condensations.⁷⁵ These early basal cytopathologic changes were confirmed by immunohistochemistry to be associated with an HD-induced apoptosis. This finding suggests that HD-induced cell death involves early apoptosis and late necrosis, which temporarily overlap to produce a basal cell death pathway along an apoptotic-necrotic continuum (Figure 8-10).⁸²

During vesication, *in vivo* models generate charac-

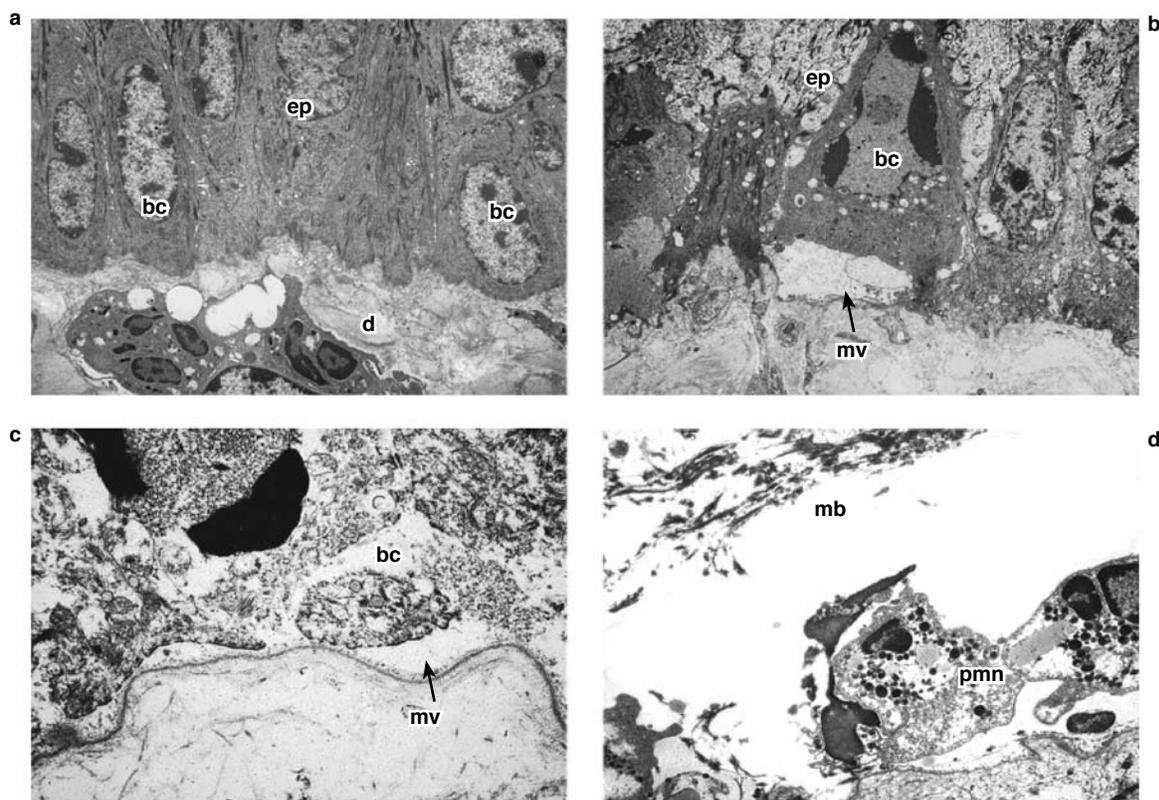


Fig 8-10. Transmission electron microscopy of hairless guinea pig skin. (a) Unexposed skin site at the level of the dermal-epidermal junction; epidermis (ep), basal cells of the stratum germinativum (bc), dermis (d). (b) Skin site exposed to sulfur mustard vapor 4–6 h postexposure; basal cell (bc) undergoing early apoptotic injury with marginal condensation of chromatin and formation of a microvesicle (mv) within the microenvironment of the basement membrane zone. (c) Skin site exposed to sulfur mustard vapor 24 h postexposure; disabling of hemidesmosomes (arrows) contributing to the formation of characteristic microvesicles (mv), basal cells undergoing advanced apoptotic injury and necrosis (bc). (d) The cavity of a large microblister (mb) infiltrated with polymorphonucleocytes (pmn).

Photographs (a, b, and d): Courtesy of John P Petrali, PhD, US Army Medical Research Institute of Chemical Defense, and Stephanie R Froberg, Graphics Department, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Md. Photograph (c) reproduced with permission from: Marlow DD, Mershon MM, Mitcheltree LW, Petrali JP, Jaax GP. Sulfur mustard-induced skin injury in hairless guinea pigs. *J Toxicol Cutan Ocular Toxicol.* 1990;9(3): 179–192.

teristic microvesicles within the lamina lucida of the basement membrane. The cavities of microvesicles formed as a consequence of basal cell pathology and the disabling of anchoring filaments of hemidesmosomes are bound by degenerating epidermal cells at the roof and by the lamina densa of the basement membrane at the floor. Microvesicles rapidly become infiltrated with inflammatory cells, phagocytic cells, degenerating cells, cellular debris, and tissue fluid, all exacerbating the lesion to form pervasive lucidolytic microblisters that later cleave the epidermis from the dermis (Figure 8-11).

Furthermore, investigative evidence shows that percutaneous carriers such as dimethyl sulfoxide can exacerbate mustard-gas-induced skin pathology.⁸³

Ultrastructural studies of monotypic human cells in culture, such as keratinocytes and lymphocytes, have added important subcellular information of HD temporal effects on nuclei, plasma membranes, and cytoplasmic organelles, perhaps reflecting predicted and expected biochemical lesions reported elsewhere in this chapter.

Skin proteins and immunohistopathology. Primary or secondary effects of HD toxicity on extracellular components of the basement membrane microenvironment are presently under investigation. Among these extracellular domains are structural adherent proteins known to be antigenically altered or lost to specific antisera in some clinical bullous diseases.⁸⁴ Although still the subject of study, proteins shown to be altered

directly by the alkylating properties of HD or secondarily by released cellular proteases or by chemical mediators of the accompanying inflammatory response are bullous pemphigoid antigen, α -6 integrins, and laminin-5 (nicein).^{80,85} Bullous pemphigoid antigen and α -6 integrins are recognized integral proteins of the hemidesmosome with complex molecular attachments to heads of anchoring filaments. Laminin-5 or nicein is the resident protein of anchoring filaments. Loss of immunospecificity of these proteins would indicate a pathogenesis associated with the disabling of anchoring filaments within the lamina lucida, a process (*vide supra*) documented by ultrastructural study of HD toxicity.

Histopathological and ultrastructural presenta-

tions of sulfur-mustard-induced toxicity—apparently irrespective of the model—demonstrate that epidermal/epithelial basal cells of the stratum germinativum layer are targeted early during the pathology to the exclusion of other epidermal/epithelial cells. Injured basal cells appearing approximately 4 to 6 hours after exposure present progressive signs of apoptosis and irreversible necrotic cell injury and death. Associated with basal cell injury is the apparent disabling of anchoring filaments of hemidesmosomes that leads to detachments within the subadjacent lamina lucida of the epidermal/epithelial basement membrane zone. Superimposed upon this cellular response is the effect on selected basement membrane adherent proteins that lose their immunospecificity to specific antisera

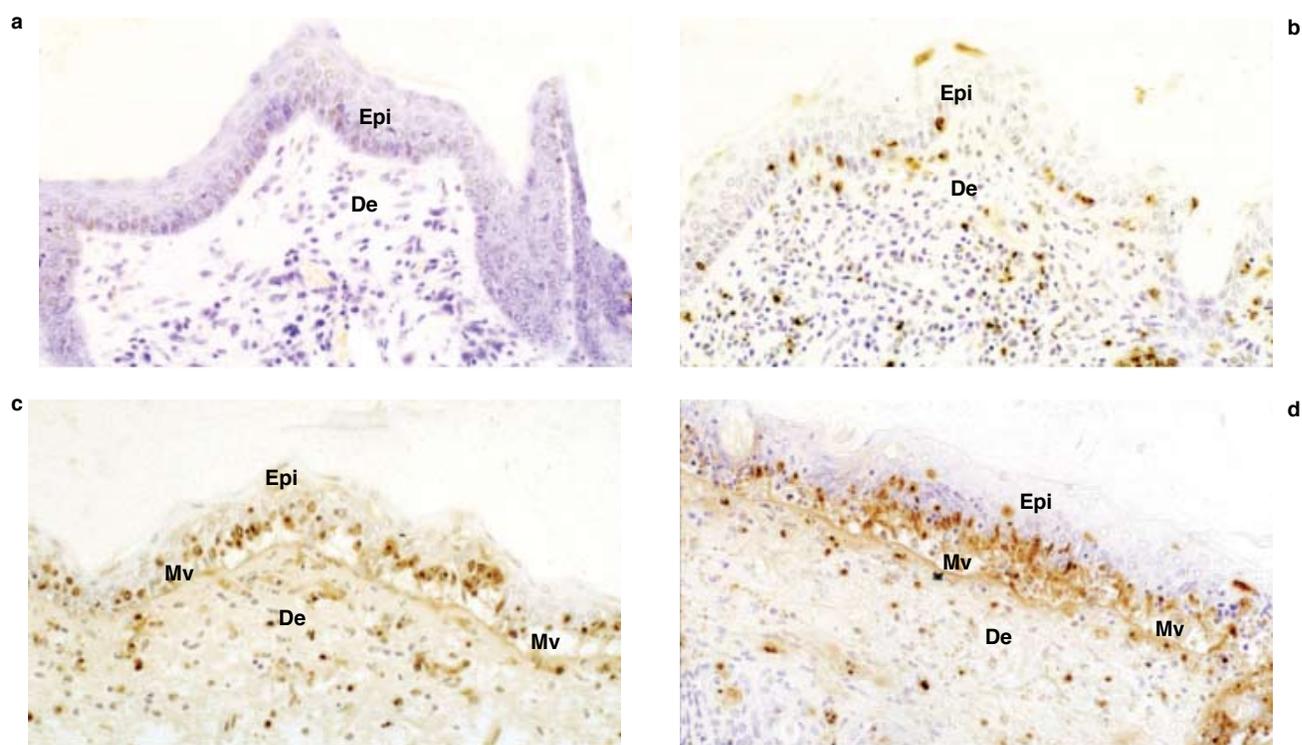


Fig. 8-11. ApopTag (Millipore Corp, Billerica, Mass) staining of paraffin-embedded skin sections demonstrating temporal progression of basal cell apoptotic profiles. **(a)** At 3 hr postexposure, no apoptotic basal cells were observed; only inflammatory cell infiltration was noted in papillary dermis (arrows). **(b)** At 6 hr postexposure, the occurrence of apoptotic basal cells is evident. ApopTag-positive cells exhibit typical characteristics of apoptosis, nuclear condensation, and margination (arrows). **(c)** At 12 hr postexposure, basal cells exhibiting apoptosis significantly increased at areas of microvesication (arrows). **(d)** At 24 hr postexposure, basal cell apoptosis progressed to necrosis, making identification of individual apoptotic cells among cellular debris difficult. Original magnification $\times 66$.

Epi: epidermis

De: dermis

Mv: microvesication

Reproduced with permission from: Kan RK, Pleva CM, Hamilton TA, Anderson DR, Petrali JP. Sulfur mustard-induced apoptosis in hairless guinea pig skin. *Toxicol Pathol.* 2003;31(2): 185–190. Photographs: Courtesy of Stephanie R Froberg, Graphics Department, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Md.

and are predictive of attachment failures. Finally, the inflammatory response appears to exacerbate lesions, contributing to the formation of pervasive microvesicles that eventually cleave the epidermis/epithelium from their supporting, underlying structures, leading to epithelial/epidermal sloughing and denudation of basement membranes.

Eye

The eye is the external organ most sensitive to mustard. The latent period for eye damage is shorter than that for skin damage. Generally, the asymptomatic period varies with the concentration of mustard vapor and individual sensitivity. Eye irritation within minutes after exposure has been reported.^{17,86} After a low *Ct* exposure, a slight irritation with reddening of the eye may be all that occurs (Figure 8-12). As the *Ct* increases, the spectrum of injury is characterized by progressively more severe conjunctivitis, blepharospasm, pain, and corneal damage.^{31,66} Photophobia will appear, and even with mild exposures, may linger for weeks.

Corneal damage consists of edema with clouding, swelling, and infiltration of polymorphonuclear cells. Clinical improvement occurs after approximately 7 days, with subsiding edema. Corneal vascularization (pannus) with secondary edema may last for weeks. Vision will be lost if the pannus covers the visual axis. Severe effects from mustard exposure may be



Fig. 8-12. An eye injury of lesser severity in an Iranian casualty (shown 7 d after exposure) caused by exposure to mustard. The characteristic findings were edema of the lid and conjunctival injection. Corneal ulcerations were found with more severe exposure.

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followed by scarring between the iris and the lens, which restricts pupillary movements and predisposes the individual to glaucoma.^{31,87}

The most severe eye damage is caused by liquid mustard, which may be delivered by an airborne droplet or by self-contamination.⁶¹ Symptoms may become evident within minutes after exposure.⁶⁶ Severe corneal damage with possible perforation of the cornea can occur after extensive eye exposure to liquid mustard. The patient may lose vision, or even the eye, from panophthalmitis, particularly if drainage of the infection is blocked, such as by adherent lids.⁶⁶ Miosis sometimes occurs, probably due to the cholinergic activity of mustard.

During World War I, mild conjunctivitis accounted for 75% of the eye injuries; complete recovery took 1 to 2 weeks. Severe conjunctivitis with minimal corneal involvement, blepharospasm, edema of the lids and conjunctivae, and orange-peel roughening of the cornea accounted for 15% of the cases; recovery from this condition occurred in 2 to 5 weeks. Mild corneal involvement with areas of corneal erosion, superficial corneal scarring, vascularization, and iritis accounted for 10% of the cases; convalescence took 2 to 3 months in these cases. Lastly, severe corneal involvement with ischemic necrosis of the conjunctivae, dense corneal opacification with deep ulceration, and vascularization accounted for about 0.1% of the injuries; convalescence from this condition lasted more than 3 months. Only one person out of 1,016 mustard casualties surveyed after World War I received disability payments for defective vision.¹¹

Studies conducted on rabbit eyes indicate that mustard injury to the cornea is characterized by initial degeneration of the epithelial cells, with changes ranging from nuclear swelling and nuclear vacuolization, to pyknosis and nuclear fragmentation. Epithelial loosening and sloughing occurs either by separation of the basal cells from the basement membrane, or by shearing of the cell just above its attachment to the basement membrane.^{88,89}

Mustard initially causes vasodilation and increased vascular permeability in the conjunctiva, which lead to progressive edema. Secretion of mucus occurs within minutes of exposure. Pyknosis of epithelial cells begins concurrently with or shortly after these changes, leading to desquamation of the epithelium. In the later stages, inflammatory infiltration of connective tissue and exudation are present.^{88,89} Medical personnel have reported seeing delayed keratitis in humans from 8 months to 20 years after mustard exposure.^{29,90} This delayed keratitis, in addition to the chronic inflammation, can lead to erosions and frank ulcerations.

Within approximately 5 minutes, liquid mustard

dropped into the eyes of rabbits was absorbed, had disappeared from the eye's surface, had passed through the cornea and the aqueous, and had produced hyperemia of the iris. Damage to other structures (eg, the Descemet membrane) also occurred within a similar length of time.²⁹ Because absorption and ocular damage occur so rapidly, decontamination must be performed immediately after liquid mustard contaminates the eye; after a few minutes, there will be no liquid remaining on the surface of the eye to decontaminate.

Descriptions of the pathology of ocular toxicity have been largely limited to gross and histological observations. Gross examination of human eye injury has been characterized at its peak as a progressive conjunctivitis with photophobia, blepharospasms, corneal stromal edema, and opacification. Histological examination of controlled animal eye injuries have presented dose- and time-dependent corneal epithelial degeneration and detachment.⁹¹⁻⁹⁴ Ultrastructural studies support progression of basal cell pathology, disabling of hemidesmosomes, and cleaving of the epithelium from the basement membrane, all appearing to be consistent with HD dermal exposure. At variance with dermal exposure is the absence of characteristic microblisters at the epidermal-stromal junction.^{96,97} Lack of microblister formation may be directly attributable to the avascular anatomical organization of the cornea.⁹⁵

Airways

Mustard produces dose-dependent damage to the mucosa of the respiratory tract, beginning with the upper airways, and descending to the lower airways as the amount of mustard increases. The inflammatory reaction, which varies from mild to severe, includes necrosis of the epithelium. When fully developed, the injury is characterized by an acute inflammation of the upper and lower airways, with discharge in the upper airway, inflammatory exudate, and pseudomembrane formation in the tracheobronchial tree. The injury develops slowly, intensifying over a period of days.

After a low-dose, single exposure, casualties might notice a variety of irritating symptoms accompanied by a dry cough; on examination, they might have pharyngeal and laryngeal erythema. Hoarseness is almost always present, and the patient often presents with a barking cough. Typically, this hoarseness may progress to a toneless voice, which appears to be particularly characteristic of mustard exposure. Patients characteristically note a sense of chest discomfort. All of these complaints typically commence approximately 4 to 6 hours after exposure, with sinus tenderness appearing hours later. Vapor concentrations sufficient to cause

these symptoms typically produce reddened eyes, photophobia, lacrimation, and blepharospasm. There may be loss of taste and smell. Patients occasionally experience mild epistaxis and sore throat. Prominent wheezing and dyspnea (shortness of breath) may be present.⁵⁹

Exposures to higher concentrations of vapor result in an earlier onset and greater severity of the above effects. Hoarseness rapidly progresses to aphonia. Severe tachypnea and early radiological infiltrates may appear. More severe respiratory exposures create necrotic changes in the respiratory epithelium that result in epithelial sloughing and pseudomembrane formation. There may be substantial airway occlusion from the inflammatory debris or from pseudomembranes, which can obstruct the upper airways as they form, or they can break off and obstruct lower airways.^{17,59,61}

The initial bronchitis is nonbacterial. White blood cell elevation, fever, pulmonary infiltrates seen on radiograph, and colored secretions may all be present and mimic the changes of a bacterial process. This process is sterile during the first 3 to 4 days; bacterial superinfection occurs in about 4 to 6 days.⁶¹

Mustard has little effect on lung parenchyma. Its damage is usually confined to the airways and the tissue immediately surrounding the airways, except after an overwhelming exposure to mustard and as a terminal event.⁹⁶ The changes are most intense in the upper airways and decrease in the trachea, bronchi, and smaller bronchioles, presumably reflecting a differential disposition of vapor on the mucosal surface.^{70,98} Pulmonary edema is not a usual feature, except in the case of hemorrhagic pulmonary edema with severe exposures, and it may occur in terminal stages.^{61,96}

The lungs of animals exposed to mustard show alternating areas of atelectasis and emphysema. Atelectasis is thought to be caused by mucus clogging the bronchioles, and the emphysema is compensatory; these findings were confirmed when lungs resected at thoracotomy from Iranian casualties from the Iran-Iraq War showed similar effects.^{17,97} As seen in Figure 8-13, the lungs showed bronchiectasis and severe chronic inflammation. The bronchiectasis was caused by full-thickness injury of the airways. In some casualties, this injury healed by scarring of such intensity that severe and unrelenting tracheobronchial stenosis developed.

Gastrointestinal Tract

Nausea and vomiting are common within the first few hours after mustard exposure, beginning at about the time the initial lesions become apparent. The early nausea and vomiting, which are generally transient

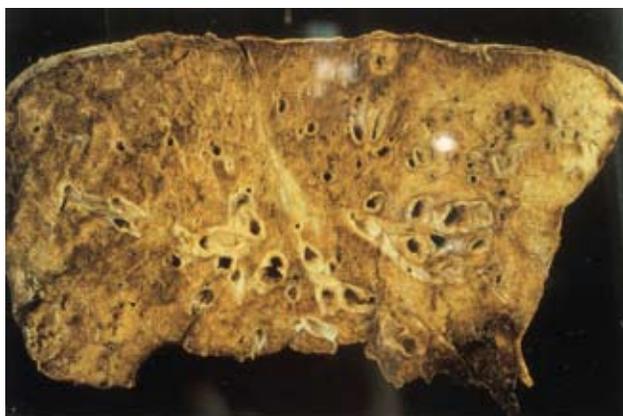


Fig. 8-13. A surgically excised lung from an Iranian mustard casualty showing bronchiectasis and severe chronic infection.

Reproduced with permission from: Freitag L, Firusian N, Stamatis G, Greschuchna D. The role of bronchoscopy in pulmonary complications due to mustard gas inhalation. *Chest*. 1991;100:1438.

and not severe, may be caused by the cholinergic activity of mustard, by a general reaction to injury, or because of the unpleasant odor.^{9,33} Nausea and vomiting occurring 24 to 36 hours later results from the generalized cytotoxic activity of mustard and damage to the mucosa of the gastrointestinal tract.

Diarrhea is not common, and gastrointestinal bleeding seems to be even less common in humans. However, animals that were given potentially lethal doses of mustard administered either intravenously or subcutaneously had profuse diarrhea, which was frequently bloody; however, this was unusual when mustard was administered percutaneously or by inhalation.^{61,98} Diarrhea in animals was more common after nitrogen mustard.¹⁰ None of 107 autopsied human cases involved; and in the 57 cases in which the gastrointestinal tract was thoroughly examined, none had significant lesions.⁹⁹ In several reported series of Iranian casualties, totaling about 700 casualties, few had diarrhea and only a very few who died had bloody diarrhea.^{17,63,100} Constipation was noted in casualties with mild exposure.⁶¹

Central Nervous System

Although the effects are not usually clinically prominent, mustard affects the CNS. Reports of World War I casualties described apathy, depression, intellectual dullness, and languor.⁶¹ Approximately 83% of the 233 Iranian casualties sent to various European hospitals for medical care during the Iran-Iraq War had CNS

complaints; most complaints, however, were mild and nonspecific.⁶³

Large amounts of mustard administered to animals via the inhalational, intravenous, subcutaneous, or intramuscular routes caused hyperexcitability, abnormal muscular movements, convulsions, and other neurological manifestations.^{61,101} Animals died a "neurological death" a few hours after receiving a lethal amount of mustard.¹⁰ Autopsies of these animals disclosed few abnormalities.¹⁰¹

After three children were accidentally exposed to a large amount of mustard, two of them presented with abnormal muscular activity, and the third alternated between coma and agitation. The first two children died 3 to 4 hours after exposure, possibly from neurological mechanisms.²³ It is unknown whether these CNS manifestations are from a cholinergic activity of mustard or from other mechanisms.

Death

Most casualties die of pulmonary damage complicated by infection bronchopneumonia, immunosuppression, and sepsis. When exposure is not by inhalation, the mechanism of death is less clear. In studies with animals in which mustard was administered via routes other than inhalational, the animals died 3 to 7 days after the exposure; they had no signs of pulmonary damage and often had no signs of sepsis. The mechanism of death was not clear, but autopsy findings resembled those seen after radiation.¹⁰² Mustard is considered radiomimetic because of the delayed onset of signs and symptoms and the accompanying immunosuppression with potentially lethal doses.

Diagnosis

The differential diagnosis of mustard casualties on the battlefield after a known chemical attack is not difficult. The history of a chemical attack is useful, particularly if the chemical agent is known. Simply questioning the casualty about when the pain started, whether it started immediately after the exposure or hours later, is very helpful. Pain from lewisite (the other vesicant that causes blistering) begins seconds to minutes after exposure; pain from mustard does not begin until the lesion begins to develop hours later.

Blisters appearing simultaneously in a large number of people, in the absence of a known chemical attack, should alert medical personnel to search the area with a chemical agent detector. The appearance of one or more blisters in an individual does not alone make a

diagnosis. Friction, plants, insects, and other diseases also cause blisters.

Laboratory Tests

No “routine” laboratory test for mustard exposure exists. Investigational studies have demonstrated the presence of significant amounts of thiodiglycol, a major metabolite of mustard, in the urine of mustard casualties (except for being a breakdown product from sulfur mustard, thiodiglycol is harmless). In two studies, Iranian casualties had higher amounts of thiodiglycol in their urine than did control subjects.^{103,104} In a third study, the urinary thiodiglycol secreted by a laboratory worker accidentally exposed to mustard was quantitatively measured for a 2-week period (his postrecovery urine was used as a control); the half-life of thiodiglycol was 1.18 days.²⁴ In a more recent accident, thiodiglycol was also found in the patient’s blister fluid. The procedure for analysis of thiodiglycol is described in the US Army’s Technical Bulletin Medical 296, *Assay Techniques for Detection of Exposure to Sulfur Mustard, Cholinesterase Inhibitors, Sarin, Soman, GF, and Cyanide*.¹⁰⁵ The procedure for handling urine samples of suspected victims is on USAMRICD’s Web site (<http://ccc.apgea.army.mil>). See also Chapter 22, Medical Diagnostics.

Patient Management

Decontamination within 1 or 2 minutes after exposure is the only established, effective means of preventing or decreasing tissue damage from mustard. This decontamination is not done by medical personnel; it must be performed by the soldier immediately after the exposure. Generally, a soldier will not seek medical help until the lesions develop hours later. By that time, skin decontamination will not help. Mustard fixes to the skin within minutes, and tissue damage will already have occurred.⁶⁵

If any mustard remains on the skin, thorough decontamination later will prevent further spreading to other areas. After several hours, spreading will have occurred, because oily substances flow on warm skin. Decontamination at that time, however, will prevent mustard from spreading to personnel who handle the casualty and possible contamination of the MTF. By the time skin lesions develop, most mustard will have been absorbed and fixed to tissue. Unless the site was occluded, the remaining unabsorbed agent will have evaporated.

Mustard droplets disappear from the surface of the eye very quickly. The eye should still be flushed as soon as possible. All mustard casualties must be thoroughly decontaminated before they enter a clean

MTF. This should be done with the realization that by the time a contaminated soldier reaches an MTF, this decontamination will rarely help the casualty; it does, however, prevent exposure to medical personnel.

Mustard casualties generally fall into three categories. Individuals in the first category may be returned to duty. These individuals have a small area of erythema or one or more small blisters on noncritical areas of their skin; eye irritation or mild conjunctivitis; and/or late-onset, mild upper respiratory symptoms, such as hoarseness or throat irritation and a hacking cough. If these casualties are seen 48 to 72 hours after exposure, there is good reason to believe that the lesion will not progress significantly, and they can be given symptomatic therapy and returned to duty.

The second category includes casualties who appear to have non-life-threatening injuries, but who are unable to return to duty. Casualties with the following conditions must be hospitalized for further care:

- a large area of erythema (with or without blisters);
- an extremely painful eye lesion or an eye lesion that hinders vision; or
- a respiratory injury with moderate symptoms that include a productive cough and dyspnea.

Some of these conditions may develop into life-threatening injuries. For example, an area of erythema caused by liquid mustard that covers 50% or more of the body surface area suggests that the individual was exposed to a potentially lethal dose. Likewise, dyspnea occurring within 4 to 6 hours after the exposure suggests inhalation of a potentially lethal amount of mustard.

The third category comprises those casualties who appear to have life-threatening injuries when they first present at an MTF. Life-threatening injuries include large skin burns caused by liquid mustard and early onset of moderate to severe pulmonary symptoms. Some of the casualties in this category will die from their injuries. Because conditions listed in category two may become life-threatening (category three), the categories should be used only to assess a casualty’s presenting condition.

Many mustard casualties will fall into the first category, the majority will fall into the second category, and only a very small percentage of casualties will fall into the third category. Data from World War I, in which only 3% of mustard injuries were lethal despite the unsophisticated medical care at that time (eg, no antibiotics, intravenous fluids, or electrolytes), suggest that most mustard casualties are not severely injured and most will survive.

Most casualties of mustard exposure will, however,

require some form of medical care—from a few days to many weeks. Eye care and airway care will promote healing within weeks; skin lesions take the longest to heal and may necessitate hospitalization for months.¹⁷ Casualties with mild to moderate mustard damage need supportive care. Pain control is extremely important. Fluids and electrolytes should be carefully monitored. Although there is not as great a fluid loss from mustard burns (compared with thermal burns), patients will probably be dehydrated when they enter the MTF. Parenteral fluid supplements and vitamins are of benefit. Patients who have lost their eyesight because of mustard exposure should be reassured that they will recover their vision. Casualties who do become critically ill from their exposure to mustard present with large areas of burns, major pulmonary damage, and immunosuppression. Some may die from sepsis or from overwhelming damage to the airways and lungs.

There are no controlled human studies comparing different treatments for mustard exposure; nor have uniform standards of care been developed. However, suggestions for the care required for each organ system is described in the section below. Recommendations for skin care are based on research and experience with thermal burns. Most casualties have more than one system involved, and many of these casualties will be dehydrated and have other injuries as well.

Skin

Current treatments. Significant cutaneous HD injuries can take several months to heal, necessitate lengthy hospitalizations, and result in significant cosmetic and/or functional deficits. There are currently no standardized or optimized methods of casualty management and no specific US Food and Drug Administration (FDA) approved treatment regimens for HD injury. Historically, blister aspiration and/or unroofing (epidermal removal), physical debridement, irrigation, topical antibiotics, and sterile dressings have been the main courses of action in the medical management of cutaneous HD injuries.^{106–110} Current treatment strategy consists of symptomatic management and is designed to relieve symptoms, prevent infection, and promote healing.

Decisions regarding appropriate treatment methods must consider the number of casualties involved and the exposure setting. The management of a small number of workers exposed to liquid HD in a laboratory setting or while handling munitions would be different from the treatment of hundreds of soldiers with vapor exposure in a far-forward environment. Before commencement of any treatment, patient

clothing should be carefully removed and treated as potentially contaminated, and the patient thoroughly decontaminated. For a general overview of decontamination procedures, see Chapter 16, Decontamination of Chemical Casualties.

Skin injury from HD can be considered a chemical burn. Within military medical facilities, chemical burn injuries would meet the criteria established by the American Burn Association for referral to a burn center.¹¹¹ The similarity between HD skin injury and toxic epidermal necrosis (TEN), and between HD lung injury and smoke inhalation injury further support burn center referral, where the requisite expertise to treat these conditions is available. Within the military medical system, the designated center for the treatment of major HD burns and other chemical burn injuries is the US Army Institute of Surgical Research/ Army Burn Center located at Brooke Army Medical Center in San Antonio, Texas.¹¹² In the civilian sector, there are 132 burn centers located in the United States. Locations and contact information for these centers is available through the American Burn Association at 1-800-548-BURN or online at www.ameriburn.org.

The appearance of a superficial to moderate HD skin injury mimics that of a first- or second-degree burn, and the appearance of a deep HD injury resulting from direct liquid contact or secondary infection mimics that of a full thickness or third-degree burn. On this basis, many burn care practitioners erroneously conclude that thermal and HD injuries are the same. However, direct comparisons in the literature between HD and thermal burns are scarce. Papirmeister et al noted that disintegration of the basal cell layer caused by thermal burns has been shown to produce an intraepidermal blister that contains fragments of the basal cell layer attached to the basal lamina, unlike the almost totally denuded basement membrane in HD lesions.³¹ Also, mustard injuries take considerably longer to heal compared to similar-sized thermal or chemical burns. A major argument against the adage “a burn is a burn” is that HD initially targets a specific cell type (epithelial basal cells), unlike a thermal burn, in which damage occurs first at the stratum corneum and then progresses downward.

Since the stratum corneum is the structure largely responsible for barrier function, water loss rates are very high immediately after a thermal burn (140–180 g/m²/h in humans).¹¹³ After a cutaneous HD injury, the stratum corneum remains intact for 2 to 3 days, after which barrier function becomes compromised by loss of sloughing epidermis or unroofing of the blister. Thus, the systemic fluid derangements and nutritional requirements seen in cutaneous HD injury are less than is seen with thermal burns.¹⁷ The recommended

infusion rates and formulas (Parkland, Modified Brooke) used to calculate total volume requirements for thermal burn patients, based on body weight and total body surface area (TBSA) will overestimate fluid needs of HD casualties and should not be routinely applied in HD casualty management.¹¹⁴ Iatrogenic hypervolemia and pulmonary edema documented in HD casualties during the Iran-Iraq War showed that fluid requirements appear to have been relatively independent of TBSA.^{17,108} Fluids and electrolytes should be closely monitored for HD casualties because fluids may be lost to edematous areas, with resultant dehydration. The exact fluid replacement requirements for cutaneous HD injuries should be based on individual patient hemodynamic status and electrolyte balance. Monitoring of heart rate and urine output are simple and reliable field guides to the adequacy of resuscitation. In hospitalized patients, serum sodium levels also accurately reflect water status. The fluids used in replacement fluid therapy for non-HD burns, which would likely be appropriate for use in HD injuries if fluid replacement is required, are described by Settle, Brisebois, and Thomas et al.¹¹⁴⁻¹¹⁶ The requirements of casualties with both HD exposure and multiple traumatic injury will likely follow the resuscitation requirements of the associated traumatic injury.

In some respects, superficial to moderate HD injuries exhibit similarities to exfoliative diseases such as TEN. Although the nomenclature of exfoliative diseases is both controversial and confusing to the nonspecialist, the term TEN type II can be used (on basis of biopsy) to include classic TEN, Lyell disease, erythema multiforme majus or exudativum, acute disseminated epidermal necrosis, and Stevens-Johnson syndrome.¹¹⁷⁻¹¹⁹ Both HD injury and TEN type II patients have skin lesions with a cleavage plane at the dermal-epidermal junction; a decrease in white blood cell count which may become life-threatening; involvement of mucosal surfaces (gastrointestinal and trachea); and intravenous fluid needs greater than maintenance but less than expected for a correspondingly sized thermal burn. There is ample evidence in both the burn and dermatology literature that mortality decreases and outcomes improve when patients with TEN are managed in a burn center.^{117, 119-124} Given the similarities between TEN and HD injury, burn center referral, when available, is advocated.

HD casualties should be kept comfortable and their lesions regularly cleansed to prevent infection. Limbs may need to be immobilized, because movement of joints can aggravate existing lesions. Blisters arising on the trunk require protective dressings to avoid or minimize damage from friction with clothing or bedding.

Current treatment of cutaneous HD injury depends upon the level and extent of skin involvement. The earliest and most superficial manifestation is erythema, which usually has an onset of 4 to 8 hours (range 1-24 h) after exposure. The erythema has the appearance of a sunburn and is usually accompanied by pruritis, burning, or stinging. This level of injury may or may not progress to vesicle formation. If blisters or vesicles do not form and the skin remains intact, management consists of protecting the skin from further damage, and the application of antipruritic creams or lotions (calamine lotion, 0.25% camphor, menthol). Systemic analgesics and antipruritics may be indicated, depending on the discomfort level of the patient. There is some evidence that topical steroid creams may prevent progression or speed healing of superficial injury. Topical steroids should not be applied to open wounds, vesicles, or large body surfaces. Resolution of erythema generally requires several days.

Deeper or more prolonged exposure results in vesicle formation, which typically begins 2 to 18 hours after vapor exposure and continues for several days. The vesicles may start as a "string of pearls" within or at the periphery of sites of erythema. Small vesicles may coalesce to form bulla or blisters, typically 0.5 to 5 cm in diameter. The fluid contained in vesicles or blisters does not contain active agent, does not cause further vesication, and does not pose any hazard to health care providers beyond that of normal body fluids. Blisters less than 1 cm in diameter should be left intact. The area surrounding the blister should be irrigated at least once per day, followed by application of a topical antibiotic. A petrolatum gauze bandage can be put in place over these unbroken blisters, if desired. Any such dressings should be changed every 3 to 4 days.

There is no consensus on whether larger, intact blisters should be unroofed. Blister fluid from intact blisters provides a sterile wound covering, but the blisters are fragile and easily ruptured. For this reason, military medical manuals generally recommend that blisters greater than 1 cm in diameter be unroofed or debrided, irrigating the underlying area two to four times per day with saline, sterile water, clean soapy water, or Dakin solution.¹²⁵⁻¹²⁷ For patients presenting with intact frank blisters, it may be beneficial to aspirate the blister fluid with a sterile needle and syringe, allowing the roof of the blister to act as a sterile dressing until a physician can remove it. Blister roofs have been reattached via epidermal grafting using the tops of suction blisters in the treatment of vitiligo, as well as in experimental suction blisters in humans following aspiration of blister fluid.¹²⁸⁻¹³⁰ (A suction blister is iatrogenically induced by applying suction to the skin to separate the epidermis from the dermis for the purpose of harvest-

ing the epidermis for autotransplantation.) The roofs of HD blisters, however, are not expected to reattach to the blister floor because of HD-induced damage to basal cells and basement membrane zone (BMZ) components. Sloughing will eventually occur. Weak attachment of the neoepidermis to the underlying dermis (fragile skin) has been noted in human HD casualties and experimentally exposed weanling pigs.¹³¹ Once the lesions have fully reepithelialized, protective dressings may initially be needed to avoid or minimize damage from friction with clothing or bedding.

For patients presenting with ruptured HD-induced blisters, careful removal of the blister roof with scissors, application of an antibiotic ointment, and placement of a sterile dressing is warranted. For both of these scenarios, more complete debridement is necessary for large lesions.

In hospital settings, vesicles that have coalesced or become confluent, as well as larger intact blisters can be unroofed and cleansed by gently rubbing the affected areas with a saline soaked course mesh gauze or laparotomy pad under general anesthesia or conscious sedation. Alternately, sharp scissor debridement can be carried out. In field settings, sharp debridement may be more practical. Following debridement or unroofing, the wounds will require protection from infection and desiccation. Options include various topical antimicrobials, or the use of biologic or synthetic dressings.

Intact vesicles or blisters that are debrided in clean hospital settings may benefit from the application of biologic dressings, such as porcine heterograft (pig-skin); collagen-laminated nylon dressings such as Biobrane (Dow Hickam Pharmaceuticals Inc, Sugar Land, Tex); or silver-containing dressings such as Acticoat (Smith and Nephew, Largo, Fla); Silverlon (Argentum, Lakemont, Ga); or Silvasorb (Medline Industries, Mundelein Ill).¹³¹⁻¹³⁷ These dressings create a moist healing environment, decrease pain, and obviate the need for daily dressing changes. Biobrane has the added advantage of flexibility, facilitating movement. If adherent, pigskin and Biobrane may be left in place until reepithelialization occurs. Silver-containing dressings need to be changed every few days, following manufacturers' recommendations. Biologic, synthetic, or silver dressings that are not adhered to the wound bed should be promptly removed, followed by wound cleansing and application of an appropriate topical antibiotic. Fluid could build up underneath dressings that do not remain in complete contact with the wound bed, resulting in maceration. Dressings should also be removed if infection or cellulitis develops. Field application of these dressings is usually impractical because the appropriate level of cleanliness cannot be maintained.

Wounds that are not freshly debrided, are dirty or contaminated, or contain blisters already broken should be unroofed or debrided and cleansed with soap and water or appropriate surgical detergents, such as chlorhexidine gluconate solution. Extrapolating from burn experience, iodine-containing surgical detergents or prep solutions have poor coverage against *Pseudomonas* species and should be avoided. Following cleansing, the area should be liberally covered with a topical antibiotic (eg, 1% silver sulfadiazine cream, aqueous 5% mafenide acetate solution, Dakin solution, 0.5% silver nitrate solution, bacitracin antibiotic ointment, or Neosporin ointment [Pfizer Inc, New York, NY]), and a sterile dressing should then be applied. Biologic or synthetic dressings should not be used in this setting. The choice of antibiotic is largely a matter of personal experience and hospital or battlefield availability, for there is little scientific data in actual HD injuries to strongly advocate one agent over another. The use of bacitracin and Neosporin ointments should be limited to small wounds (less than 1% TBSA) and employed for very brief periods (3–5 days) because of their high capacity to provoke allergic cutaneous reactions.¹³⁸ Bacitracin is only effective against Gram-positive bacteria, but Neosporin has a broader antimicrobial spectrum. The use of 11.1% mafenide acetate cream should be avoided because of the severe pain it causes when applied to partial-thickness wounds and the possibility of metabolic acidosis. Mafenide acetate cream would be appropriate over insensate full thickness injuries caused by liquid HD exposure; over superficial (partial thickness) injuries that become infected and convert to full thickness; or over wounds that are visibly infected (see below). Following application of any topical antibiotic, a sterile dressing should be put in place.

Several antimicrobials are available in liquid form, facilitating wound debridement and inspection. These include 0.5% silver nitrate solution, Dakin solution (0.25%–0.5% sodium hypochlorite), and 5% mafenide acetate solution.¹⁴⁰ Silver nitrate 0.5% solution is inexpensive, readily available, and has bacteriostatic coverage against a broad spectrum of Gram-positive and Gram-negative bacteria and yeast-like organisms. Silver nitrate solution is a primary topical therapy for toxic epidermal necrosis; silver sulfadiazene is a poor choice because sulfa drugs are often the inciting agent. Silver nitrate solution does not penetrate deep wounds and works best on minimally colonized, debrided, or superficial injury.¹³⁹ It has the disadvantages of staining instruments, clothing, and bed linens and causes hypochloremia, hypocalcemia, and hyponatremia with prolonged use. Dakin solution is likewise inexpensive and readily available, with bacteriocidal

activity against a broad spectrum of Gram-positive and Gram-negative organisms.¹³⁹ Dakin solution must be freshly compounded to be effective. Aqueous mafenide 5% solution (acetate or hydrochloride) is bacteriostatic against a broad spectrum of Gram-positive and Gram-negative bacteria and has strong coverage against pathogens commonly encountered in gunshot wounds, blast injuries, open fractures, necrotizing fasciitis, and Fournier gangrene.^{140,141} The drug is particularly active against *Pseudomonas* and *Clostridia* species.¹⁴² The acetate salt is commercially available as Sulfamylon (Bertek Pharmaceuticals, Morgantown, WV). An isoosmolar solution is produced by 50 g of powder mixed in 1 L of sterile water; if mixed in sterile saline, the solution is hyperosmolar and painful on application. Mendelson points out that aqueous mafenide is an excellent battlefield or mass casualty drug, because 5 lb of powder mixed with local water sources can supply sufficient solution to provide a patient with a 50% TBSA burn with 455 dressing changes of 10% solution or 910 dressing changes of a 5% solution.^{140,143} In austere conditions, where gloves and dressing supplies are unavailable, 5% or 10% mafenide solution has been applied with spray bottles to wounds that are then left uncovered.^{140,144,145}

Deep skin injury may be produced by exposure to liquid HD, causing coagulation necrosis. Delayed treatment may allow progression of superficial injury to deeper levels. Concurrent trauma or wound contamination may predispose the wound to infection. Infection complicating superficial HD wounds may convert a partial thickness injury to full thickness. Deep HD skin injuries should be washed twice daily with a surgical detergent (chlorhexidine gluconate solution), rinsed with saline or water, and covered with silver sulfadiazine cream followed by protective gauze dressings. Wounds that are obviously full thickness benefit from “alternating agents,” application of 11% mafenide acetate cream during the day followed by application of silver sulfadiazine cream at night. The combination of these agents provides a broader antimicrobial spectrum, limits emergence of resistant organisms, and has fewer side effects (neutropenia and metabolic acidosis) than when either agent is used alone.¹³⁹ Mafenide acetate cream alone may be applied twice daily on wounds that are very deep, heavily contaminated, or infected. Mafenide acetate cream has the best eschar penetration of any topical agent; it is useful in situations where injuries are deep and battlefield conditions preclude proper wound debridement or excision. Full thickness or infected injuries will also require surgical debridement or excision. Following excision, split-thickness autografting will shorten wound healing time.

Wounds should be inspected periodically for signs of infection. The risk of secondary infection of HD wounds is at least as high as in thermal injury. Infection is a significant factor in causing delayed healing of cutaneous HD injuries, although even uninfected HD burns exhibit delayed wound healing. Infected wounds require surgical debridement or excision. Any biologic or synthetic dressings should be removed when cellulitis is present, the wounds should be debrided of any nonviable tissue, and penicillin should be administered orally. Intravenous antibiotics may be indicated for cellulitis that does not respond to oral antibiotics. There is no indication for the routine administration of systemic antibiotics to patients with HD injury.

The decision to evacuate and hospitalize an HD casualty is based upon the magnitude and type of exposure (vapor versus liquid); systemic, ocular, and pulmonary manifestations; and the extent and severity of skin lesions, in consideration with other injuries that may be present (eg, respiratory, ocular). For patients experiencing only cutaneous HD injuries, erythema covering more than 5% of TBSA in noncritical areas requires hospitalization. Erythema covering less than 5% TBSA may require hospitalization, depending upon the site of the injury (eg, face, inguinal area) and level of impairment (eg, limitation of limb movement due to pain, edema). Multiple or large areas of vesication also require hospitalization. Since blister formation may initially be slight, the patient should be watched for a progression in the size and number of blisters. Topical antibacterial creams such as silver sulfadiazine can be prescribed to patients who do not require close medical monitoring, with instructions to apply a thin layer to the affected area twice, four times a day. Following application of the cream, the area should be covered with a loose gauze dressing such as a petrolatum gauze bandage.

Development of improved therapies. Treatment strategies for improved and rapid healing of cutaneous HD injuries recently formulated by a working group of US and UK researchers and physicians are summarized below.¹³⁸ Research is underway to experimentally support these strategies and determine which medical devices, supplies, and pharmaceuticals are most efficacious. The ultimate goal is to determine the most efficacious treatment regimen to be applied in the clinical management of HD casualties. The ideal regimen should return damaged skin to optimal appearance and normal function in the shortest time. Improved treatment will result in a better cosmetic and functional outcome for patients and enable them to return to normal activities sooner.

Immediate treatment. For those patients who are

beginning to present with erythema or those who are in the latent period and suspect an exposure may have occurred, systemic administration of an antiinflammatory agent will likely help decrease the amount of damage ultimately induced. HD-induced inflammatory responses themselves likely contribute to the severity of the pathology, and numerous animal studies have shown the benefits of prophylactic or therapeutic use of antiinflammatory agents.^{32,146-148} It remains to be determined which nonsteroidal antiinflammatory drug (NSAID) or combination of drugs, route of administration, length of administration, and dosing regimen is the most efficacious in preventing or ameliorating the effects of HD on skin. It is likely that an NSAID will need to be administered for 2 to 5 days. Topically delivered intracellular scavengers such as 4-methyl-2-mercaptopyridine-1-oxide and dimercaprol have proven effective in animal experiments in reducing the severity of HD-induced cutaneous injuries, and concurrent use of one of these agents with an NSAID may yield the best results.^{49,148} Corticosteroid antiinflammatory agents, such as hydrocortisone (given systemically or topically for cutaneous HD injuries) and dexamethasone (tested *in vitro* on primary alveolar macrophages and given topically for ocular HD injuries), also appear to be promising therapeutic agents.¹⁴⁷⁻¹⁵⁰ Other topical, steroidal, antiinflammatory agents of much greater potency that would likely be very efficacious if used early in the lesion development stage, such as betamethasone dipropionate, clobetasol propionate, and diflorasone diacetate. Superpotent (class 1), potent (class 2) and upper midstrength (class 3) topical corticosteroids should be tested for their efficacy in ameliorating HD-induced cutaneous injury.

Depletion of GSH and accumulation of endogenous oxidants and ultimate formation of potent oxidizing species (eg, toxic lipid peroxides) may be contributory factors in HD-induced cytotoxicity.³¹ Topically applied HD has been shown to negatively affect antioxidant enzymes in blood cells and body tissues of rats.¹⁵¹ Several antioxidants have been shown to protect liver and lung from oxidative damage following inhalation or percutaneous exposure to HD in a mouse model.¹⁵² It has been suggested that administration of antioxidants may be protective and useful.¹⁵³ Thus, initial antioxidant treatment aimed at affecting the progression of lesions that is instituted during the erythema phase may prove to be of benefit. The effectiveness and role of the interruption of the inflammatory cascade by the inclusion of topical and systemic antioxidant agents as well as a determination of the optimal timing for such therapy are important and intriguing avenues for investigation.¹³⁸

Placement of an occlusive or semioclusive dress-

ing will likely prove helpful in promoting autolytic debridement and preventing desiccation. Debridement plays a central role in improving the healing of cutaneous HD lesions, and beginning the process early may be beneficial. How soon following exposure these dressings can be applied remains to be determined. Although maintaining a moist environment has long been known to facilitate wound healing, caution needs to be observed because very early occlusion that increases moisture levels in the skin will exacerbate the lesion.¹⁵⁴⁻¹⁵⁷ Additionally, there is a period following exposure to sulfur mustard during which off-gassing of unbound HD occurs in weanling pigs and African green monkeys.^{131,158} These studies have suggested that off-gassing after a large exposure can continue for 24 to 36 hours. Limiting the escape of this unbound HD by occlusive dressings may worsen the lesion, so delayed placement of occlusive dressings for at least 24 hours following exposure should be considered. Keeping clothing off of the exposed area to prevent vapor build-up may also be of benefit.

Injury assessment. Before HD injuries can be appropriately treated, assessment of the injuries must occur. TBSA of the injuries should be established and depth of injury determined. TBSA can be determined using Wallace's rule of nines and the Lund and Browder chart for estimating burn severity.^{159,160} Determination of injury depth is a more challenging task; however, accurate depth assessment is important because it dictates how aggressive treatment must be to minimize or prevent cosmetic and functional deficits.

In thermal burns, depth of injury is typically assessed by physical examination, with a goal of wound healing by day 14. Surface appearance, assessment of intact sensation, the pinprick test to assess pain, the blanch-capillary return test to evaluate microcirculation, and surface temperature difference between burned and unburned skin are often utilized.¹⁶¹ Using these methods, diagnosing very superficial burns (which will heal nonoperatively) and very deep burns (which will require immediate excision and grafting) is relatively easy for the experienced burn surgeon. Burns of intermediate depth are more often problematic. At present, no technology reliably predicts which intermediate-depth burns will require grafting and which will heal nonoperatively, a decision best left to the experienced burn surgeon. Determining depth of HD injuries is even more challenging. First, the full extent of cutaneous injury can take several days to manifest. Secondly, superficial appearances do not accurately predict depth of injury nor need for grafting. The presence of blisters in thermal burns is generally associated with superficial dermal injuries, but blistering in HD injuries can occur in deep dermal/full-thickness inju-

ries because of the unique nature of the agent and the unique progression of the injury.

Noninvasively examining cutaneous blood flow can greatly assist the physician in making depth of injury determinations. Laser Doppler perfusion imaging (LDPI) and indocyanine green (ICG) fluorescence imaging may prove to be very valuable tools in prognosticating optimal wound healing of cutaneous HD injuries.¹³⁸

Laser Doppler flowmetry and LDPI have been used for prolonged, noninvasive monitoring of tissue viability and wound healing, and for the assessment of peripheral vascular disease, inflammation, ischemia, reperfusion, skin graft acceptance (take), and burn depth. Brown et al found that laser Doppler perfusion images of vesicant vapor burns on the backs of swine correlated well with histopathological findings (thrombosis and necrosis of subepidermal capillaries) between 1 hour and 7 days postexposure and suggested that clinical management decision making on how to treat early vesicant burns could be aided by LDPI.¹⁶² Chilcott et al used several noninvasive bioengineering methods to monitor wound healing in a large white pig model for 7 days following exposure to HD and lewisite vapors.¹⁶³ They found LDPI to be a promising prognostic tool.

ICG fluorescence imaging is a minimally invasive procedure that requires the placement of an intravenous line. The fluorescence of intravenous ICG has been shown to estimate burn depth in small animals.¹⁶⁴ In contrast to fluorescein fluorescence, ICG fluorescence is capable of distinguishing superficial and deep partial-thickness burns from full-thickness burns.¹⁶⁵ The fluorescence intensity of ICG decreases exponentially with burn depth for burns of similar age.¹⁶⁶ ICG fluorescence was successfully used to estimate burn depth in a porcine model.¹⁶⁷ An imaging system with a diagnostic algorithm was developed at the Wellman Laboratories of Photomedicine (Boston, Mass); the system accurately diagnosed burns that healed within 21 days with minimal scarring from those that took longer to heal by secondary means. The algorithm was shown to be dependent on the age of the burn and independent of the location of the burn. This technology showed promise in plastic surgical applications and accurate determination of thermal burn depth in humans.¹⁶⁸⁻¹⁷⁰ ICG fluorescence imaging also shows promise in diagnosing depth of HD injury.¹⁷¹ Unlike LDPI, multiple images over large areas can be captured in a relatively short period of time. Images are typically collected 5 to 10 minutes after ICG injection to allow uptake and distribution. The dye is then excited (eg, 780 nm), and the resultant fluorescence emission (eg, 810 nm) immediately captured and saved by a com-

puter and analyzed for burn/normal skin fluorescence ratio. ICG binds strongly to plasma globulins, limiting both extravasation within burn-injured vascular epithelia and extravascular transport to areas nearby.¹⁶⁶ Large signals are thought to be the result of vasodilation and hyperemia, and smaller signals are thought to be attributable to vascular occlusion and edema.^{164,166}

Treatment of deep injuries. Previous animal studies have shown that surgically aggressive approaches are needed to prevent or minimize significant cosmetic and functional deficits that result from deep HD injury. For the best outcome, deep dermal/full-thickness cutaneous HD injuries require full-thickness debridement followed by autologous split-thickness skin grafting.^{172,173} To be successful, the skin grafts must be placed on a hemostatically secure wound bed, devoid of blood clots, debris, or necrotic tissue. The recipient bed must have an adequate blood supply to nourish the skin grafts, and the grafts must be protected from shearing forces, motion, and mechanical disruption. A variety of modalities are available for achieving initial graft adherence and subsequent acceptance ("take"). These include sutures, surgical staples, fibrin glue, tie-over bolsters, compression dressings, and a variety of antishear dressing techniques. The choice of fixation and dressing technique is determined by the size and location of the wounds, and the experience and preferences of the surgeon.¹³⁸

In thermal burn management, deep burns are grafted to promote timely wound closure and improve outcome with minimal cosmetic and functional deficits. The decision to graft is based upon depth of injury, and deep HD injuries will require surgically aggressive approaches. As with thermal burns, depth of HD injury should be accurately assessed before treatment begins. Reported long-term effects such as fragile skin and scarring likely indicate that injury depth was not accurately diagnosed and treatment was not sufficiently aggressive.

Treatment of partial-thickness injuries. Epidermal and superficial dermal HD injuries may have greater clinical relevance on the battlefield than deep injuries. Partial thickness injuries need debridement, but not grafting. The standard treatment, after assessing the injury and derroofing frank blisters, is to perform adequate debridement of partial-thickness injuries, then treat the lesions like chronic cutaneous ulcers or partial-thickness thermal burns using contemporary medical approaches. Debridement is followed by one or more treatment adjuncts. Examples of adjuncts under consideration are dressings, growth factors, skin substitutes, and Vacuum-Assisted Closure (VAC) Therapy (KCI, San Antonio, Tex).

Debridement. Experimental approaches to vesicant

wound debridement have included powered dermabrasion, sharp surgical excision, laser debridement, and enzymatic debridement.¹⁷²⁻¹⁸⁰ Powered dermabrasion has been shown to speed up the reepithelialization process of cutaneous HD injuries. Kjellstrom et al found sharp surgical excision with primary suturing of the skin defect to be effective in decreasing healing time of HD vapor lesions in guinea pigs.^{174, 175, 177} Powered dermabrasion, pulsed CO₂ laser ablation and erbium: yttrium-aluminium-garnet (Er:YAG) laser ablation have been shown to accelerate the rate of healing of full-thickness cutaneous lewisite vapor burns in swine without the need for split-thickness skin grafting.^{176, 178} Eldad et al found that excimer laser ablation and Debridase (Biotechnology General Ltd, Kiryat Malchi, Israel) enzymatic debridement were efficacious in improving the healing of partial-thickness nitrogen mustard burns in a guinea pig model.¹⁷⁹

Laser debridement of cutaneous vesicant wounds has proven to be an effective method of improving the rate of wound healing in pig models. Graham et al showed that viability, thickness, and organization of the epidermis were all significantly improved by partial-thickness pulsed CO₂ laser debridement of small, mild to moderately severe cutaneous HD vapor injuries.¹⁸⁰ Laser debridement followed by skin grafting was as efficacious in improving the wound healing of deep HD burns as sharp surgical tangential excision followed by grafting (the "gold standard" in human deep dermal/full-thickness thermal burns medicine).^{172, 173} Middermal debridement by sharp excision or laser ablation without grafting produced less desirable results but was better than no treatment.^{172, 173} A 4-fold improvement in reepithelialization of lewisite injuries was achieved at 1 week following laser dermabrasion, with almost 100% reepithelialization by 3 weeks.¹⁷⁸ It is not apparent why these full-thickness lewisite injuries (10 cm²) did not require grafting, as did HD injuries (12.6 cm²) or as would a full-thickness thermal burn.^{172, 173} There are differences in biochemical action and rates of spontaneous reepithelialization between lewisite and HD.¹⁷⁸ Further studies must be conducted to fully examine the comparative healing of deep lewisite, HD, and thermal injuries.

Laser debridement offers additional benefits, including hemostatic control during surgery, minimal risk of exposure to aerosolized pathogens, and time efficiency. Another major advantage to the use of lasers is the ability to control the amount of normal perilesional skin that is removed. Eldad et al noted that controlling the amount of tissue removed by surgical tangential excision is technically difficult, and laser ablation of nitrogen mustard burns in a guinea pig model enabled control of the amount of tissue removed with minimal

blood loss.¹⁷⁹ Minimizing the amount of tissue removed is a cosmetic benefit to the patient.

A number of lasers manufactured in the United States, Canada, and Europe may be considered for routine debridement of vesicant injuries. Acland and Barlow have reviewed the current uses of lasers in dermatological practice and list the types of lasers used for specific procedures.¹⁸¹ They list CO₂ and Er:YAG lasers as the most appropriate for cutaneous resurfacing. Er:YAG lasers have been used for a wide variety of procedures, ranging from facial resurfacing to burn debridement.¹⁸¹⁻¹⁸⁵ They have been shown to be particularly useful in the debridement of partial-thickness burns and the management of deep lewisite injuries.^{179, 186} Unlike the Gaussian beam profiles created by CO₂ lasers, Er:YAG laser beams tend to be uniform and produce uniform depths of ablation.¹⁸⁵ (These techniques require trained and skilled personnel taking all necessary precautions including eye protection.)

Another alternative under consideration for debridement of HD injuries is enzymatic debridement. The enzymes, categorized as proteolytics, fibrinolytics, and collagenases, are designed to dissolve necrotic tissue from wounds, and they are often used to debride chronic wounds (eg, decubitus ulcers, venous stasis ulcers, arterial insufficiency ulcers, diabetic foot ulcers).¹⁸⁶ Many have been found to be safe and effective in removing devitalized tissue and accelerating healing in burns.¹⁸⁷⁻¹⁹⁴ Any burn eschar present is typically surgically cross-hatched to allow the agent to penetrate into the wound. Other agents, such as the bacterial proteolytic enzymes streptokinase and streptodornase, have given disappointing results in deep burns because they do not break down the collagen that separates vital from nonvital tissue.¹⁹⁵ Use of fibrinolytics may impair wound healing of HD lesions, because fibrin is an early matrix protein essential for wound healing. Fibrinolysin is typically combined with deoxyribonuclease, and this combination also digests DNA in the dividing fibroblasts that play a role in healing.¹⁸⁶ Some effective enzymes have produced better results than others, with enzyme concentration, skin moisture level, and the presence of certain antibacterial agents affecting results. Secondary dressings are needed to keep the wound moist and to allow these agents to work.¹⁸⁶ Klasen offers an excellent review of the use of enzymatic debridement agents in burns.¹⁹⁵ The most popular and effective agents on the market today are collagenases and papain/urea combinations. A promising proteolytic enzyme extracted from the stem of the pineapple plant is in US and European clinical trials for the treatment of deep partial- and full-thickness burns. Enzymatic debridement of HD injuries is a promising and cheaper alternative to laser

debridement, albeit more time consuming. However, burn wound sepsis and bacteremias have been noted in burn patients undergoing enzymatic debridement.^{186,195} Concomitant use of a topical antibiotic that does not interfere with the action of the enzyme under study may be warranted as a preventative measure. Research is underway for determining which enzymatic debridement product is most efficacious in debriding partial-thickness HD injuries.

In addition to vesication and death of epidermal keratinocytes, HD exposure results in sublethal damage to keratinocytes along the periphery of the gross lesion. Damage to the BMZ and underlying collagen in the papillary dermis has also been noted. Unroofing frank blisters followed by timely removal of this adjacent and subjacent damage will likely improve the rate of reepithelialization. Nonlethal damage is clearly noted at the periphery of cutaneous HD lesions and has been reported previously.¹⁹⁶⁻¹⁹⁸ Nikolsky sign, characterized by separation and loss of the epidermis from the dermis when the skin is pressed with a sliding or twisting motion, has been demonstrated in weanling pig skin following HD vapor exposure.^{196,198,199} Nikolsky sign is also a clinical hallmark of TEN, reinforcing the similarity between this disease and HD injury.¹¹⁷ These weakened areas of the dermal-epidermal junction occur along the periphery of gross lesions and are indicative of sublethally damaged basal cells and/or altered proteins of extracellular matrices of the BMZ. Sublethally injured cells at the periphery of an HD lesion and in hair follicles and other adnexal structures may be partly responsible for the slow rate of reepithelialization seen in these injuries. Rice et al suggested that the level of damage to cellular DNA at the margins of HD lesions may be sufficient to delay or prevent effective replication of those keratinocytes.¹⁷⁵ Removal of these sublethally damaged keratinocytes at the margins of the lesions by debridement beyond the visible borders of the lesion will likely speed up the reepithelialization process.

HD induces damage to the BMZ at the level of the lamina lucida.^{200,201} The floor of the blister retains portions of the damaged BMZ and needs to be removed to provide an adequate scaffold over which keratinocytes feeding the reepithelialization process can migrate. Thus, at minimum, debridement needs to proceed down into the papillary dermis after removal of the blister roof. Beyond the BMZ, dermal collagen itself is affected by HD exposure and can impede the wound healing process.^{175,202,203} Brown and Rice reported coagulation and hyper eosinophilia of the papillary dermis in Yucatan minipig skin 12 to 24 hours following saturated HD vapor exposure, with the deeper reticular dermis unaffected.²⁰³ Rice et al¹⁷⁵ and Lindsay

and Rice²⁰² suggested that following exposure to HD, papillary dermal collagen is altered and may no longer function normally as a healthy scaffold over which epidermal cells can migrate.

The question of how deep to debride must be addressed. Ablative lasers that create less than 160 ± 60 μm of residual thermal damage permit optimal skin graft take and healing.²⁰⁴ Domankevitz and Nishioka concluded that lasers that induce residual thermal damage zones of less than 200 μm are useful for cutaneous surgery and burn wound debridement prior to skin grafting.²⁰⁵ Lam et al were able to improve wound healing of full-thickness cutaneous lewisite injuries in pigs by partial-thickness laser debridement.¹⁷⁸ Graham et al were also able to improve wound healing of deep cutaneous HD injuries in pigs by partial-thickness debridement without grafting, albeit not to the extent attained by full-thickness debridement followed by grafting.¹⁷² These studies indicate that retaining some amount of damaged dermal tissue does not significantly impede wound healing. Complete debridement of partial-thickness injury, therefore, will likely not be required. Debridement of partial-thickness HD injury into the papillary dermis or upper reticular dermis will likely be adequate.

Dressings. Following wound debridement of HD injuries, an appropriate dressing will be needed to promote moist wound healing. Beneficial effects of such dressings include prevention of tissue dehydration and cell death, accelerating angiogenesis, increased breakdown of dead tissue and fibrin (eg, pericapillary fibrin cuffs), significant reduction in pain, and potentiation of growth factor and target cell interaction.¹⁵⁷ Helfman et al¹⁵⁴ and Singhal et al¹⁸⁶ have provided overviews of various types of occlusive and semioclusive dressings. Hydrocolloids, hydrogels, foam dressings, alginates, and transparent film dressings are commercially available from a large number of manufacturers. Silver impregnated dressing materials may be of great potential benefit in treating these wounds because of their antimicrobial efficacy and demonstrated ability to enhance rates of reepithelialization.^{132,206-209} A number of these dressing materials are currently employed in burn and chronic wound care; other more advanced silver dressings are in various stages of development. Application of silver impregnated dressings following Er:YAG laser debridement has shown great promise in improving HD wound healing in a weanling pig model.¹³¹

Growth factors. During cutaneous wound healing, growth factors play dominant roles in regulating cell proliferation, differentiation, and synthesis of the extracellular matrix.²¹⁰ Epidermal growth factor, transforming growth factor-beta, platelet-derived growth factor, insulin-like growth factor, keratinocyte

growth factor, hepatocyte growth factor, granulocyte-macrophage colony-stimulating factor, and fibroblast growth factors play important and critical roles in the healing of cutaneous wounds.

Platelet-derived growth factor and keratinocyte growth factor have been shown to improve the healing of burns and skin grafted lesions.²¹¹⁻²¹³ A recombinant human platelet-derived growth factor BB has been approved for human use by the FDA and is commercially available. Keratinocyte growth factor is in several ongoing US clinical trials to test its ability to prevent mucositis in patients undergoing chemotherapy with bone marrow transplantation, and for the treatment of venous ulcers and ulcerative colitis. These products may prove useful in improving the healing of cutaneous HD injuries. Concomitant use of protease inhibitors or a dressing designed to bind or inactivate matrix metalloproteases and protect growth factors (eg, Promogran Matrix Wound Dressing, Johnson and Johnson Wound Management Worldwide, Somerville, NJ) will likely be necessary until HD-induced inflammatory responses have subsided.

Skin substitutes. Skin substitutes may provide an excellent temporary wound dressing for debrided HD injuries. Permanent wound closure can only be achieved by spontaneous reepithelialization or by the provision of autologous skin by means of skin grafting. The use of skin substitutes to temporarily restore the multiple functions of normal skin may be of substantial benefit in the management of cutaneous HD injuries.¹³⁸

The selection of the most suitable and effective temporary skin substitute will require a critical assessment of the products attributes when applied to HD wounds, as well as cost, ease of use, availability, and consistency of results.¹³⁸ Skin substitutes are widely used in human thermal burns management and can be (a) temporary or permanent, (b) epidermal, dermal, or composite, and (c) biologic or synthetic.^{133,214-218} They have also been shown to be effective in reducing time to closure of chronic leg and foot ulcers, surgical excision sites, and partial-thickness donor sites. They may be a source of growth factors and are generally semioclusive in nature. Generally flexible and pliable, skin substitutes can provide barrier function; add tensile strength to the wound; markedly reduce pain, inflammation, and drainage; and provide a moist wound healing environment. A number of skin substitutes are available on the market and should be tested for their efficacy in improving wound healing of cutaneous HD injuries. Several marketed products are currently under consideration: (a) living bilayered skin substitutes, (b) bilayered composites consisting of a synthetic epidermal analog and a biologic (collagen-

based) dermal analog, (c) complex weaves of biopolymers that produce a thin protective membrane, and (d) acellular dermal matrices. Permanent skin substitute products that are designed for treating deep injuries and require application of a thin epithelial autograft will likely be inappropriate for use in treating partial-thickness HD injuries.

Cultured epithelial allografts and autografts have been used for about 2 decades as a treatment for chronic ulcers and thermal burns. Keratinocytes can be harvested from skin biopsies and grown to confluence by the method originally described by Rheinwald and Green.^{219,220} Large amounts of stratifying epidermis can thus be grown in the laboratory in short periods of time and used to restore defects in the epidermis.²²¹ Such grafts can be used immediately or cryopreserved for use at a later date. In addition to their usefulness in improving the healing of deep ulcers and burns, these grafts have shown efficacy in improving the rate of reepithelialization of partial-thickness burns and split-thickness skin graft donor sites. Cultured keratinocyte allografts speed healing by providing cover and producing growth factors and extracellular matrix proteins.²²² Because these coverings can be produced in large quantities and would thus be more readily available than cadaver skin, their application in the treatment of debrided partial-thickness HD injuries should be considered. Cultured epidermal autografts (CEAs) would be safer to use from the perspective of disease transmission and would not require donor-screening procedures. They do, however, require lenticular surgical small-punch biopsies collected from the patient and a lag time of about 2 weeks to grow the graft material. Several US laboratories perform this service for their local burn centers. Commercially produced CEAs are also available. Durability has been increased by placing the CEA on a scaffolding of widely meshed autograft.²²³ Alternatively, CEAs placed over deepithelialized allograft (ie, engrafted allodermis) have also proved successful.²²⁴

Finally, application of keratinocytes in suspension has been shown to improve epidermal wound healing in pig and mouse models.²²⁵⁻²²⁸ Keratinocyte suspension technology does not require the length of time necessary to produce cultured epidermal sheets, and it has proven efficacious in treating thermal burns in humans.²²⁹ After a small biopsy is collected, the cells are cultured and expanded in a clinical laboratory, then placed into a syringe-like spraying mechanism and sprayed onto the wound 2 to 5 days following biopsy. Products are commercially available for use in the treatment of partial- to full-thickness burns, donor sites, scars, chronic ulcers, and pigment loss, and for cosmetic skin rejuvenation following laser

resurfacing, dermabrasion, and chemical peels. An innovative medical device currently available (ReCell, Clinical Cell Culture, Coral Springs, Fla) allows rapid harvesting of cells from a thin split-thickness biopsy followed by spray application onto small wounds (up to 2% TBSA) within 30 minutes of collecting the biopsy, without the need of culturing the keratinocytes in a clinical laboratory.

Vacuum-Assisted Closure Therapy. Application of topical negative pressure in the management of chronic wounds and burns has gained popularity in the last 5 years. Also known as VAC, the procedure involves placing an sterile open cell foam into the wound bed (cut to conform to the shape of the wound), sealing it with an adhesive drape, and applying subatmospheric pressure (125 mm Hg below ambient) that is transmitted via an evacuation tube by a vacuum pump.^{230,231} The procedure is becoming widely used for the closure of chronic wounds such as stage III and IV pressure ulcers; venous, arterial, and neuropathic ulcers; and subacute and acute wounds such as dehisced incisions, split-thickness meshed skin grafts, and muscle flaps.^{232,233} This methodology increases local blood perfusion and nutrient delivery to the wound, accelerates the rate of granulation tissue formation, and decreases wound tissue bacterial levels.^{230,231} Before VAC application wounds must be debrided of all necrotic tissue. Contraindications to VAC placement include the presence of fistulas, osteomyelitis, exposed organs, exposed blood vessels or malignancy in or around the wound. The dressings are typically changed every 1 to 4 days until wound closure. VAC has been shown to be effective in preventing progression of partial-thickness burns to a deeper injury in a swine model, likely the result of increased delivery of oxygen and nutrients to the zone of stasis.²³² The method has also been shown to increase the rate of skin graft donor site reepithelialization in pigs and humans, and it is a safe and effective method for securing split-thickness skin grafts, providing improved graft survival.^{233,234} Following debridement of partial-thickness HD injuries, VAC may prove efficacious in significantly speeding the reepithelialization process. Recently the FDA approved the use of VAC in treating partial-thickness burns. Several VAC systems are commercially available, including a lightweight, portable system for ambulatory care.

Eye

The basic principles of eye care are to prevent infection and scarring. Although mustard is unlikely to remain in the eye by the time the casualty is seen, the eye should be irrigated to remove any chemical agent

that might be on the lashes and any inflammatory debris that might be on the surface of the eye. Mild lesions (eg, conjunctivitis) can be treated three to four times daily with a soothing eye solution.

Casualties with more severe eye lesions should be hospitalized. Care for these patients should consist of at least one daily irrigation, preferably more, to remove inflammatory debris; administration of a topical antibiotic three to four times daily; and administration of a topical mydriatic (atropine or homatropine) as needed to keep the pupil dilated to prevent later synechiae formation. Vaseline or a similar material should be applied to the lid edges to prevent them from adhering to each other; this reduces later scarring and also keeps a path open for possible infection to drain. When animals' eyes were kept tightly closed, a small infection could not drain, and a panophthalmitis developed that perforated and structurally destroyed the eyes.⁶⁶

Topical analgesics may be used for the initial examination; however, they should rarely be used routinely because they can cause accidental corneal damage. Pain should be controlled with systemic analgesics. The benefit of topical steroids is not established in humans (see experimental animal data discussed below); however, most ophthalmologists feel that topical steroids may be helpful if used within the first 48 hours after exposure.²³⁵ In any case, an ophthalmologist must be consulted as early as possible. Keeping the casualty in a dim room or providing sunglasses reduces discomfort from photophobia.

The transient loss of vision is usually the result of edema of the lids and other structures rather than corneal damage. Medical personnel should assure the patient that vision will return. Recovery may be within days for milder injuries, although those with severe damage will take approximately a month or longer to recover.

Airways

The therapeutic goal for mild airway symptoms (eg, irritation of the throat, nonproductive cough) is to keep the patient comfortable. In a casualty with severe problems, the goal is to maintain adequate oxygenation.

Hypoxia is secondary to abnormalities in ventilation caused by inflammatory bronchitis. Bronchial mucosal sloughing (pseudomembrane formation) further complicates this abnormality. Bronchospasm is easily triggered, requiring therapy with bronchodilators. Casualties with bronchospasm not responding to bronchodilators may benefit from steroid treatment, with careful attention to increased risk of infection. Oxygen supplementation may be necessary for pro-

longed periods. Ventilatory support may be necessary to assist oxygenation and adequate carbon dioxide clearance. The use of certain antibiotic skin creams (such as mafenide acetate) to treat skin lesions may complicate the acid–base status of the individual by inducing a metabolic acidosis.

Initially, bronchitis resulting from mustard exposure is nonbacterial. White blood cell elevation, fever, pulmonary infiltrates on chest radiograph, and colored sputum may all be present. Careful assessment of sputum by Gram stain and culture demonstrates that bacterial superinfection typically is not present during the first 3 to 4 days. Antibiotic therapy should be withheld until the identity of a specific organism becomes available. Of particular importance is the patient's immune status, which may be compromised by a progressive leukopenia beginning about day 4 or 5. The development of leukopenia signals severe immune system dysfunction; intensive medical support may become necessary for these patients. In these instances, sepsis typically becomes a complicating factor.

Casualties with evidence of deteriorating pulmonary status should be intubated early, before laryngeal spasm makes it difficult or impossible. Intubation assists in ventilation and also allows suction of necrotic and inflammatory debris. Bronchoscopy may be necessary to remove intact pseudomembranes or fragments of pseudomembranes (one of the Iranian casualties treated in western European hospitals during the Iran-Iraq War died of tracheal obstruction by a pseudomembrane, as did World War I casualties). Early use of positive end-expiratory pressure or continuous positive airway pressure may be beneficial. The need for continuous ventilatory support suggests a poor prognosis; of the Iranian casualties treated in European hospitals who required assisted ventilation, 87% died.¹⁷

An especially devastating pulmonary complication, severe and progressive stenosis of the tracheobronchial tree (Figure 8-14), developed in about 10% of the Iranian casualties treated in European hospitals. With the Iranian casualties, bronchoscopy was of value when used both for diagnosis and for therapeutic dilation.²³⁶ (This complication was possibly not recognized in World War I mustard casualties because the degree of exposure required to cause severe tracheobronchial injury resulted in early death from pneumonia.)

Gastrointestinal Tract

Initial nausea and vomiting are rarely severe and can usually be relieved with atropine or common antiemetics. Prolonged vomiting and diarrhea beyond

24 hours are usually indicative of systemic toxicity requiring intensive care.

Bone Marrow

Suppression of hemopoietic elements cannot be predicted from the extent of skin lesions (eg, the lesions might be from vapor and therefore superficial, but significant amounts of mustard may have been absorbed through inhalation). Frequent counts of the formed blood elements must be performed on casualties with significant skin lesions or airway damage. Mustard destroys the precursor cells, and cell elements in the blood are depressed. Because white blood cells have the shortest life span, their numbers decrease first; red blood cells and thrombocytes soon follow. Typically, leukopenia begins at day 3 through day 5 after exposure, and reaches a nadir in 7 to 21 days. Leukopenia with a cell count lower than 200 cells/mm³ usually signifies a poor prognosis, as does a rapid drop in the cell count; for example, from 30,000 to 15,000 cells/mm³ in a day.^{17,61}

Medical personnel should institute therapy with nonabsorbable antibiotics that sterilize the gut at the onset of leukopenia.¹⁷ Cellular replacement may also be successful (see also the comments on granulocyte colony stimulating factor below).

Eye. Research at USAMRICD with rabbits exposed to sulfur mustard showed remarkable results using steroids and antibiotic eye combinations. In the study, the treatments were given both by injection and topically in the form of solutions and ointments. Eyes that would have been nearly destroyed appeared almost normal when these combinations were applied early and frequently. Based on this research, USAMRICD recommended that commercially available ophthalmologic steroid/antibiotic solutions or ointments be added to field medical sets. Recommended use is as soon as possible for even the mildest mustard eye injury. Frequency of use is every 1 to 2 hours until the full extent of the developing mustard injury becomes known. Treatment should then be modified accordingly, with consultation and examination by an ophthalmologist. This initial treatment would be applied only in the absence of a penetrating injury to the eye or in the case of obvious secondary bacterial infection. Eye pain can be severe enough to require narcotic analgesia.²³⁷

Lung. No specific antidotes for the mustard injury to the lung exist. However, a tremendous amount of supportive care is available for all pulmonary injuries. Mustard lung injuries in the trachea and bronchi have a high rate of secondary bacterial infection starting as early as 3 days and developing as late as 2 to 3 weeks



Fig. 8-14. (a) Bronchoscopic view of the trachea in an Iranian casualty 3 weeks after exposure to mustard. Severe hemorrhagic bronchitis, mucosal necrosis, and early scarring are apparent. (b) Bronchogram from an Iranian casualty 1 year after exposure to mustard. The tip of a 10-mm rigid bronchoscope can be seen at the upper margin of the figure. Severe generalized narrowing of the entire tracheobronchial tree is apparent. The casualty presented with dyspnea, cough, hypoxia, and hypercarbia. (c) Bronchoscopic appearance of

the carina of an Iranian casualty who had been exposed to mustard several years before. There is nearly total occlusion of the left main-stem bronchus.

Reproduced with permission from: Freitag L, Firusian N, Stamatis G, Greschuchna D. The role of bronchoscopy in pulmonary complications due to mustard gas inhalation. *Chest*. 1991;100:1437-1438.

after exposure. The late development is especially frequent with exposures leading to significant bone marrow depression. Prophylactic administration of antibiotics is contraindicated and leads to the selection of resistant bacterial infections. Medical personnel should vigilantly watch for early signs and symptoms of infection, using Gram stains, and culture and sensitivity testing to select the most appropriate antibiotic.

Treatment for sloughing of the necrotic bronchial

mucosa is rigorous percussion, postural drainage, and provision of humidified air with supplemental moisturized air or oxygen. Fiberoptic bronchoscopy may be needed to remove blockage. Bronchospasm with asthma-like symptoms can be a frequent complication of mustard lung injury. Medications used for bronchospasm are the same as in asthma: beta adrenergic dilators, steroids, and theophylline-type drugs. Although steroid antiinflammatory agents have yet to be shown

beneficial in preventing human mustard lung injury, steroids may help relieve bronchospasm if beta-adrenergic bronchodilators do not provide complete relief. Caution is warranted in the use of steroids because of the likelihood of secondary bacterial infection.

With significant irritation to the larynx, acute closure caused by laryngospasm is possible and can result in death if a patent airway is not maintained. Pulmonary edema is not a normal feature of mustard lung injury, except in the case of very large exposures, when hemorrhagic pulmonary edema may be seen. Mounting circumstantial evidence suggests the possibility of chronic bronchial disease developing after significant pulmonary exposure.

Mustard is a proven carcinogen, but no cases of cancer have been documented with acute exposures. However, some factory workers chronically exposed to low doses of sulfur mustard in World War I developed cancers of the respiratory tract (nasopharynx, larynx, and lung). A small amount of laboratory data in rats and mice points to reproductive abnormalities. Anecdotal stories now emerging from Iran and Iraq will take years to substantiate with epidemiological studies. The possibility of a causal link between mustard exposure and late onset or chronic health effects should always be investigated in patients with a documented or suspected history of exposure.

Skin. In general, mustard skin burns are more superficial than thermal burns, but the services of an intensive care unit or surgical burn unit are often needed. Mustard can cause tremendous inflammation in skin wounds, and wounds can easily develop secondary bacterial cellulitis. These two conditions can be easily confused. Infection surveillance and specialty consultation may be necessary. Infection requires the use of appropriate systemic antibiotics. Mustard casualties with skin injury may require narcotics for analgesia. Recent studies in the US (USAMRICD) and England (Chemical and Biological Defence Establishment) have shown that appropriate debridement of deeper mustard burns leads to more usual healing times and return to normal skin architecture.

Bone marrow. Sulfur mustard, like nitrogen mustard and certain chemotherapeutic compounds, is an alkylating agent. Systemic absorption of sulfur mustard above 25% of a lethal dosage can lead to significant bone marrow depression. This systemic effect of sulfur mustard has sometimes been described as radiomimetic. The earliest indicator of a significant systemic exposure is nausea and vomiting persisting longer than the first hour or 2 after exposure. Nausea and vomiting 24 hours later is definitely a warning sign. The next most sensitive indicator is a fall in the lymphocyte count; this lymphopenia may occur as

early as the first 24 hours. The polymorphonuclear cell count may actually rise in the first 24 hours. Other cellular components of blood may show a significant decline as early as 3 days after exposure, and patients develop profound marrow suppression by 1 to 3 weeks following exposure. The complication of sepsis or septic pneumonia can be fatal. Treatment may include transfusions, isolation techniques, hormonal stimulation of the marrow, and appropriate antibiotics.

Granulocyte colony stimulating factor is a commercially available product for use in chemotherapy; however, it causes undesirable levels of marrow suppression. Studies in nonhuman primates by the Navy using nitrogen mustard and by the Army with sulfur mustard showed an improved bone marrow recovery time using this product.^{238,239}

Gastrointestinal tract. Severe hemorrhagic diarrhea may be caused either by direct ingestion of sulfur mustard or by systemic absorption following exposure by other routes. High doses of sulfur mustard can induce a necrosis and sloughing of the gastrointestinal mucosa. The most important aspect of treatment is intravenous fluids and electrolytes. Anticholinergics to control bowel spasm and possibly narcotic analgesia are indicated if an acute surgical abdomen is not a complication. Hemorrhage could be severe enough to require transfusion.

Central nervous system. In the first few hours of exposure to sulfur mustard, patients can experience mood swings ranging from depression to euphoria. The mechanism for these mood changes is not understood; supportive care is indicated. A few individuals in World War I who received massive exposures to sulfur mustard experienced seizures and died rapidly. This same phenomenon has been observed in animals.

Guidelines for Return to Duty

Because of the slow healing properties of sulfur mustard injuries, any casualty with significant injury to the eyes, respiratory tract, skin, gastrointestinal tract, or CNS should not return to duty for weeks to months.

Eye. Patients with only the mildest eye irritations to sulfur mustard, those requiring only soothing eye drops, will be able to return to duty. Even the mildest form of conjunctivitis causes a functional blindness from pain, photophobia, and spasm of the eyelid muscles; this conjunctivitis resolves in an average of 2 weeks. As the severity of the injury increases, so does the time for healing. Moderate conjunctivitis may require a 2-month recovery before return to duty is possible. In a few rare instances, blindness may result from severe exposures.

Lung. Only those individuals experiencing irrita-

tion without significant tissue injury will be able to return to duty. Determining the level of injury requires observation for 3 to 7 days. Anyone with documented mustard lung injury producing bronchial pneumonia or pseudomembrane formation will be unable to return to duty for several months. Those with severe cases may never return to duty.

Skin. Only patients with small TBSA injuries (less than 5%) in noncritical areas will be able to return to duty following treatment with topical antibiotic, dressings, and oral analgesics. Burns to the hands, feet, face, axillae, and groin are all potentially disabling. (A recent accident victim required hospitalization in a burn center for burns on the arm and leg amounting to 6% to 7% TBSA, sustaining serious disability from a relatively small surface area injury.) For all but the mildest of injuries return to duty will require weeks to months.

Burns by liquid on the skin and in the eye cause the most severe injury. It is possible, however, to receive a nearly total body burn with mustard vapor with effects no more severe than those from a second-degree sunburn. Such a mild vapor burn would take 48 or more hours to develop. However, a vapor burn developing in only a few hours could be as severe as a liquid burn. Severity of a mustard burn is dependent upon the total absorbed dose of vapor and liquid.

Long-Term Effects

Mustard burns may leave areas of hypopigmentation or hyperpigmentation, sometimes with scarring. Individuals who survive an acute, single mustard exposure with few or no systemic or infectious complications appear to recover fully. Previous cardiopulmonary disorders, severe or inadequately treated bronchitis or pneumonitis, a prior history of smoking, and advanced age all appear to contribute to long-term chronic bronchitis; there is no definitive way to determine whether these conditions are the result of aging, smoking, or a previous mustard exposure. Casualties with severe airway lesions may later have postrecovery scarring and stenosis, which predispose the individual to bronchiectasis and recurrent pneumonia.⁵⁹

An important late sequela of mustard inhalation is a tracheal/bronchial stenosis that necessitates bronchos-

copy and possible dilatation, isotonic saline lavages, laser surgery, or silicone stents.²³⁵ Mustard has been reported to create a long-term sensitivity to smoke, dust, and similar airborne particles, probably as a result of clinically inapparent bronchospasm.^{59,240}

The relationship between mustard exposure and subsequent cancer has been the subject of much study. It seems clear that individuals who were exposed to mustard daily for long periods (eg, workers in mustard production plants) have a slightly higher incidence of cancer of the airways, primarily the upper airways.²⁴¹⁻²⁴³ According to two separate reports, the association of one or two exposures on the battlefield with subsequent cancer is not clear; in a third report, the relation between mustard exposure and subsequent cancer is equivocal.²⁴⁴⁻²⁴⁶ Watson and associates reviewed the mustard exposure–cancer incidence relation in 1989, concluding that the maximum estimates of lifetime cancer risks with sulfur mustard are not great, but neither are they entirely negligible.²⁴⁷

In 1991 the National Academy of Sciences appointed a committee to survey the health effects of mustard and lewisite.²⁴⁶ Veterans of World War II who had been exposed to mustard and lewisite as subjects in test programs were presenting at Veterans Administration hospitals with complaints of illnesses they believed to be associated with the exposures. The committee was requested to survey the literature to assess the strength of association between these chemical agents and the development of specific diseases. The committee reported finding a causal relationship between exposure and various cancers and chronic diseases of the respiratory system; cancer and certain other problems of the skin; certain chronic eye conditions; psychological disorders; and sexual dysfunction. They found insufficient evidence for a causal relationship between exposure and gastrointestinal diseases, hematological diseases, neurological diseases, and cardiovascular diseases (except those resulting from infection following exposure). Some of these conclusions were not well supported. For example, there were no cases of skin cancer reported, and the alleged psychological disorders were from the trauma of exposure, not from the agent (see Chapter 9, Long-Term Health Effects of Chemical Threat Agents).

LEWISITE

Lewisite (b-chlorovinyldichloroarsine), an arsenical vesicant, is of secondary importance in the vesicant group of agents. It was synthesized in the early 20th century and has seen little or no battlefield use.²⁴⁸ Lewisite is similar to mustard in that it damages the skin, eyes, and airways; however, it differs from mus-

tard because its clinical effects appear within seconds of exposure. An antidote, British antilewisite (BAL [dimercaprol]), can ameliorate the effects of lewisite if used soon after exposure. For use as a chemical warfare agent, lewisite has some advantages over mustard but also some disadvantages.

Military Use

A research team headed by US Army Captain WL Lewis is generally credited with the synthesis of lewisite in 1918, although German scientists had studied this material earlier.^{1,59,248–250} The United States manufactured a large quantity for battlefield use and sent a shipload to Europe; however, World War I ended while the shipment was at sea, and the vessel was sunk.^{1,250}

No battlefield use of lewisite has been verified, although Japan may have used it against China between 1937 and 1944.²⁴⁶ Lewisite is probably in the chemical warfare stockpile of several countries. Lewisite is sometimes mixed with mustard to lower the freezing point of mustard; Russia has stores of this mixture.²⁵¹

Properties

Pure lewisite is an oily, colorless liquid, and impure lewisite is amber to black. It has a characteristic odor of geraniums. Lewisite is much more volatile and persistent in colder climates than mustard. Lewisite remains fluid at lower temperatures, which makes it perfect for winter dispersal. Lewisite hydrolyzes rapidly, and, on a humid day, maintaining a biologically active concentration of vapor may be difficult.²⁵²

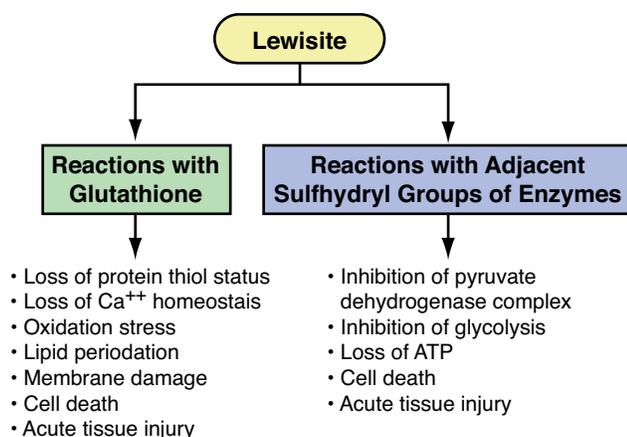


Fig. 8-15. The putative mechanisms by which lewisite causes tissue damage.

ATP: adenosine triphosphate

Ca⁺⁺: calcium ions

Adapted from: US Army Medical Research Institute of Chemical Defense. A global picture of battlefield vesicants, I: a comparison of properties and effects. *Med Chem Def.* 1992;5(1):6.

Toxicity

The toxicity of lewisite vapor is very similar to that of mustard vapor. Vesication is caused by 14 μg of liquid.^{98,250} Blister fluid from a lewisite-caused blister is nonirritating; however, it does contain 0.8 to 1.3 mg/mL of arsenic. In some instances intact lewisite or equally damaging breakdown products have been found in blister fluid.^{59,250}

Biochemical Mechanisms of Injury

Lewisite shares many biochemical mechanisms of injury with the other arsenical compounds. It inhibits many enzymes, in particular, those with thiol groups such as pyruvic oxidase, alcohol dehydrogenase, succinic oxidase, hexokinase, and succinic dehydrogenase (Figure 8-15). As is true with mustard, the exact mechanism by which lewisite damages cells has not been completely defined. Inactivation of carbohydrate metabolism, primarily because of inhibition of the pyruvate dehydrogenase complex, is thought to be a key factor.²⁵⁰

Clinical Effects

Lewisite damages skin, eyes, and airways by direct contact and has systemic effects after absorption. Unlike mustard, it does not cause immunosuppression. Data on human exposure are few. Lewisite was applied to human skin in a few studies; however, most information on its clinical effects is based on animal studies.^{59,253–255}

Skin

Lewisite liquid or vapor produces pain or irritation within seconds to minutes after contact. Pain caused by a lewisite lesion is much less severe than that caused by mustard lesions, and it diminishes after blisters form.⁵⁹ Erythema is evident within 15 to 30 minutes after exposure to liquid lewisite, and blisters start within several hours; these times are somewhat longer after vapor exposure. Lewisite is absorbed by the skin within 3 to 5 minutes (compared with 20 to 30 minutes for an equal amount of mustard) and spreads over a wider area than the same amount of mustard. The lewisite blister begins as a small blister in the center of the erythematous area and expands to include the entire inflamed area, whereas vesication from mustard begins as a “string of pearls” at the periphery of the lesion, and the small blisters eventually merge.⁵⁹ Other differences between the lesions produced by these two chemical agents are as follows:

- the inflammatory reaction from lewisite generally occurs much faster;
- the lesions from lewisite heal much faster;
- secondary infection is less common after lewisite exposure; and
- subsequent hyperpigmentation or hypopigmentation is likewise less common.⁵⁹

Goldman and Dacre provide a further review of lewisite and its toxicology.²⁵⁶

Eye

A person is less likely to receive severe eye injury from lewisite vapor than from mustard vapor because the immediate irritation and pain caused by lewisite will produce blepharospasm, effectively preventing further exposure. A small droplet of lewisite (0.001 mL) can cause perforation and loss of an eye.²⁵⁷

In tests performed on rabbits, lewisite caused almost immediate edema of the lids, conjunctiva, and cornea, as well as early and severe involvement of the iris and ciliary body, followed by gradual depigmentation and shrinkage of the iris stroma.²⁵⁷ Miosis appeared early. In this same study, miosis was not noted after mustard exposure. No long-term effects of lewisite were noted, such as the delayed keratitis seen after mustard exposure.

Airways

Lewisite vapor is extremely irritating to the nose and lower airways, causing exposed individuals to seek immediate protection, thus limiting further exposure. The airway lesion of lewisite is very similar to the lesion caused by mustard exposure except that lewisite vapor is extremely irritating to the mucous membranes. This results in sneezing, coughing, choking, and eventual necrosis of the epithelial surface. In large amounts, lewisite causes pulmonary edema.

After exposure to lewisite, dogs exhibited massive nasal secretions, lacrimation, retching, vomiting, and labored respiration. These symptoms worsened until death occurred. On autopsy, the lungs were edematous, and a pseudomembrane often extended from the nostrils to the bronchi. Tracheal and bronchial mucosa was destroyed, and the submucosa was congested and edematous. Bronchopneumonia was commonly mixed with edema.⁶¹

Other Effects

“Lewisite shock” is seen after exposure to large amounts of lewisite. This condition is the result of protein and plasma leakage from the capillaries and

subsequent hemoconcentration and hypotension. A small amount of lewisite on the skin causes local edema because of its effects on local capillaries. With a large amount of lewisite, the pulmonary capillaries are also affected; there is edema at the site of exposure and pulmonary edema. With even larger amounts of lewisite, all capillaries are affected, and proteins and plasma leak from the circulation into the periphery. Even after small amounts of lewisite, the fluid loss can be sufficient to cause diminution of renal function and hypotension.²⁵⁶ Arsines are known to cause hemolytic anemia, but there is little mention of this in reports on lewisite exposure. A “true or hemolytic anemia” has been noted with lewisite shock.²⁵⁶

Diagnosis

Lewisite exposure can be distinguished from mustard exposure by the history of pain on contact with the agent. Phosgene oxime also causes pain on contact, but phosgene oxime does not produce a liquid-filled blister. If a single individual has an isolated blister, other plant or animal causes of vesication should be sought. See also Chapter 22, Medical Diagnostics.

Laboratory Tests

No specific laboratory test exists for lewisite. Urinary arsenic excretion might be helpful. Hemolytic anemia may be seen in lewisite-exposed patients.

Patient Management

Medical personnel should follow the same principles for managing lewisite skin, eye, and airway lesions that they follow for managing mustard lesions. BAL prevents or greatly decreases the severity of skin and eye lesions if applied topically within minutes after the exposure and decontamination (however, preparations of BAL for use in the eyes and on the skin are no longer available). Given intramuscularly, BAL reduces the severity of systemic effects. BAL binds to the arsenic of lewisite more strongly than do tissue enzymes, thereby displacing lewisite from the cellular receptor sites.^{250,256} BAL reduced mortality in dogs when it was given within 100 minutes after they had inhaled a lethal amount of lewisite.²⁵⁸ Burns of the eyes from lewisite can be prevented if BAL is applied within 2 to 5 minutes of exposure; when it was applied within an hour after exposure, BAL prevented vesication in humans.^{256,259} BAL has some unpleasant side effects, including hypertension and tachycardia; the user should read the package insert.

Long-Term Effects

There are no data on human exposure from which to predict the long-term effects from lewisite. No substantial evidence exists to suggest that lewisite is car-

cinogenic, teratogenic, or mutagenic.²⁵⁶ The National Academy of Sciences committee reported a causal relationship between lewisite exposure and chronic respiratory diseases, and also that acute, severe injuries to the eye from lewisite will persist.²⁴⁶

PHOSGENE OXIME

Phosgene oxime is not a true vesicant because it does not produce vesicles. Instead, phosgene oxime is an urticant or nettle agent: it causes erythema, wheals, and urticaria (hives). Its lesions have been compared with those caused by nettle stings. Because it causes extensive tissue damage, phosgene oxime has been called a corrosive agent. Phosgene oxime is not known to have been used on a battlefield, and there is very little information regarding its effects on humans. This compound must be distinguished from phosgene, which exerts effects on the alveolar-capillary membrane. Phosgene oxime is made from phosgene, hence the name.

Military Use

German scientists first synthesized phosgene oxime in 1929, and Russia and Germany had developed it before World War II. Both countries may have had weapons that contained the agent.^{260,261} The United States also studied phosgene oxime before World War II but rejected it as a possible chemical agent because of its biological effects, or lack thereof, and its instability.¹⁰⁷ The apparent lack of biological effects was later found to result from the low concentrations (1%–2%) used in the pre-World War II studies. Later studies indicated that concentrations below 8% cause no or inconsistent effects.^{261,262}

Phosgene oxime is of military interest because it

- penetrates garments and rubber much more quickly than do other chemical agents and
- produces a rapid onset of severe and prolonged effects.

When mixed with another chemical agent (eg, VX), the rapid skin damage caused by phosgene oxime renders the skin more susceptible to the second agent. Also, if unmasked soldiers were exposed to phosgene oxime before donning a mask, the pain caused by the exposure would prompt them to unmask again.

Properties

Pure phosgene oxime (dichloroformoxime) is a colorless, crystalline solid; the munitions grade com-

pound is a yellowish-brown liquid. Its melting point is 35° to 40°C (95° to 104°F). The solid material produces enough vapor to cause symptoms.²⁵²

Biochemical Mechanisms of Injury

Phosgene oxime is the least well studied of the chemical agents discussed in this volume, and its mechanism of action is unknown. It might produce biological damage because of the necrotizing effects of the chlorine, because of the direct effect of the oxime, or because of the carbonyl group (Figure 8-16). The skin lesions, in particular, are similar to those caused by a strong acid. The agent seems to cause its greatest systemic effects in the first capillary bed it encounters. For example, cutaneous application or intravenous injection of phosgene oxime causes pulmonary edema; injection into the portal vein produces hepatic necrosis but not pulmonary edema.²⁶²

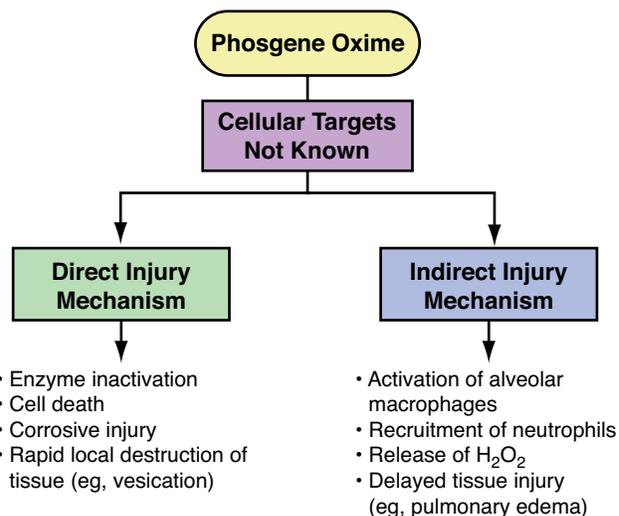


Fig. 8-16. The putative mechanisms by which phosgene oxime causes tissue damage.

H2O2: hydrogen peroxide
Adapted from: US Army Medical Research Institute of Chemical Defense. A global picture of battlefield vesicants, I: a comparison of properties and effects. *Med Chem Def.* 1992;5(1):6.

Clinical Effects

Phosgene oxime affects the skin, eyes, and lungs. The effects are almost instantaneous, and it causes more severe tissue damage than other vesicants. A characteristic of phosgene oxime is the immediate pain or irritation it produces on the skin, in the eyes, and in the airways. No other chemical agent produces such an immediately painful onset followed by rapid tissue necrosis.

Skin

Pain occurs immediately on contact with the liquid or solid form of this agent. Approximately 5 to 20 seconds after solutions containing 8% to 70% phosgene oxime were applied, pain and blanching occurred at the application site. Following the initial exposure, the site became grayish, with a border of erythema. Within 5 to 30 minutes after the exposure, edema formed around the edges of the tissue; the tissue later became necrotic. During the next 30 minutes, a wheal formed but disappeared overnight. The edema regressed over the following 24 hours and the original blanched area became pigmented. A dark eschar formed over the following 7 days; this gradually healed from below by granulation. The lesion extended into the underlying panniculus and muscle and was surrounded by an inflammatory reaction. In some subjects, healing was incomplete 4 to 6 months after exposure.²⁶² In both animal and human subjects, the skin had completely absorbed the phosgene oxime within seconds—by the time pallor appeared.²⁶²

Eye

Eye lesions from phosgene oxime are similar to those caused by lewisite; these lesions result in immediate pain, conjunctivitis, and keratitis.^{261–263} An exact description of these effects, however, is not available.

Airways

The main lesion of phosgene oxime in the lungs is pulmonary edema. This effect occurs after either inhalation or systemic absorption of the agent. The pulmonary edema may be accompanied by necrotizing bronchiolitis and thrombosis of pulmonary venules. A large amount of phosgene oxime on the skin may produce pulmonary edema after a several-hour delay; pulmonary thromboses are prominent.²⁶²

Patient Management

There is no antidote for phosgene oxime, nor is there a recommended therapeutic regimen. Medical personnel should treat necrotic areas of the skin the same way other necrotic lesions are treated, by keeping them clean and preventing infection. The eye lesions require the same care as would be done for damage from a corrosive substance. The pulmonary lesion, noncardiac pulmonary edema, should be managed as suggested in Chapter 10, Toxic Inhalational Injury and Toxic Industrial Chemicals. Decontamination, or self-aid, must be accomplished immediately after contact because the agent is absorbed from the skin within seconds.

SUMMARY

The US military has considered vesicants to be major chemical warfare agents since 1917. Mustard, however, is the only vesicant known to have been used on the battlefield. Mustard and lewisite (in much smaller amounts), are known to be in the stockpiles of other countries.

Mustard was used on a large scale in World War I, causing a great number of casualties; it was also

used during the Iran-Iraq War. Data from World War I indicate that more than 95% of mustard casualties survived but most required lengthy hospitalizations; data from the Iran-Iraq War are not as complete. If mustard is ever used again, military medical personnel must be prepared to accept and care for large numbers of casualties, who will require long-term care.

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