Chapter 7

VESICANTS

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INTRODUCTION

A *vesicant* (ie, an agent that produces vesicles or blisters) was first used as a chemical weapon on the battlefields of World War I[1–3]; that same vesicant—sulfur mustard—is still considered a major chemical agent. In the intervening years between World War I and today, there have been a number of recorded and suspected incidents of mustard use, culminating with the Iran–Iraq War in the 1980s. During this conflict, Iraq made extensive use of mustard against Iran. Popular magazines and television brought the horrors of chemical warfare to the public's attention with graphic images of badly burned Iranian casualties. When, in the fall of 1990, the U.S. military joined the United Nations forces in preparation to liberate Kuwait, one of the major concerns was the threat that Iraq would again use mustard. Fortunately, chemical agents were not used in the short ground phase of the Persian Gulf War; however, the threat of an enemy's using chemical weapons against U.S. forces is ever present. Although mustard is the most important vesicant militarily, the vesicant category includes other agents, such as Lewisite and phosgene oxime (Table 7-1). The clinical differences among the vesicants discussed in this chapter are shown in Table 7-2.

There are two types of mustard: sulfur mustard and nitrogen mustard. An impure sulfur mustard was probably synthesized by Despretz 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 a much purer mustard but discontinued his research because of the hazards involved. During World War I, the Germans used Meyer's method of synthesis to manufacture mustard.[3]

Nitrogen mustard (or more correctly, the nitrogen mustards) was first synthesized in the late 1930s; and although the properties of nitrogen mustard were only slightly different from those of sulfur mustard, none was found to be suitable for use as a weapon. However, a nitrogen mustard (HN_2, Mustargen, manufactured by Merck & Co., West Point, Pa.) was found useful for chemotherapy of certain neoplasms[4–7]; for years, it was a mainstay in cancer therapy until it was replaced by other compounds.

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

The third compound considered to be a vesicant by the U.S. military is phosgene oxime. This is not a true vesicant because, unlike mustard and Lewisite, it does not produce fluid-filled blisters; rather, it produces solid lesions resembling urticaria. There has been no verified battlefield use of this compound, and there has been little study of it in the western world.

MUSTARD

$$S \underset{CH_2CH_2 - Cl}{\overset{CH_2CH_2 - Cl}{\big\langle}}$$

HD
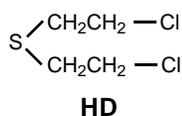
Mustard [bis-(2-chloroethyl) sulfide; also called 2,2'-dichlorethyl sulfide] is one of the two most important known chemical agents (the group of nerve agents is the other). Although mustard was introduced late in World War I (July 1917), it caused more chemical casualties than all the other agents combined: chlorine, phosgene, and cyanogen chloride. While lethality from mustard exposure was low, casualties filled the medical facilities. Despite 75

years of research, there is still no antidote for mustard. This fact is especially crucial when we consider that probably at least a dozen countries have mustard in their arsenals today.

Allegedly, mustard received its name from its smell or taste (onion, garlic, mustard)[3,8] or its color (which varies from yellow, to light tan, to dark brown). When mustard was first used by the Germans, the Allies called it Hun Stoffe (German stuff), abbreviated 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, mus-

TABLE 7-1

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)	0.39 mm Hg at 20°C
			13 mm Hg at 40°C (liquid)	
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
Environmental and Biological				
Detection	Liquid: M8 paper	Liquid: M8 paper	M256A1 ticket or card	Vapor, M256A1 ticket or card, ICAD
	Vapor: CAM	Vapor: CAM, M256A1 kit, 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)	LCt_{50}: 1,500	LCt_{50}: 1,500 (inhaled) 10,000 (masked)	Minimum effective Ct: approx 300; LCt_{50}: 3,200 (estimate)	Eye: < 30 Skin: approx 200 LCt_{50}: 1,200–1,500 (inhaled) 100,000 (masked)
Liquid	LD$_{50}$: approx 100 mg/kg	LD$_{50}$: 100 mg/kg	No estimate	40–50 mg/kg

CAM: chemical agent monitor
ICAD: individual chemical agent detector
LD$_{50}$: dose that is lethal to 50% of the exposed population (liquid, solid)
LCt_{50}: (concentration • time of exposure) that is lethal to 50% of the exposed population (vapor, aerosol)
NA: not applicable
ND: not determined

TABLE 7-2

CLINICAL DIFFERENCES AMONG VESICANTS

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

tard is known as HD. Both forms of mustard, H and HD, can still be found today in munitions manufactured over 50 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: *Lo*mmell and *St*einkopf); "yellow cross" (for the identifying mark on the World War I shells); and yperite (for the site of its first use).

Nitrogen mustard has not been used on the battlefield and is not thought to be an important military agent. There are three forms of this compound (HN_1, HN_2, HN_3); for several reasons, the nitrogen mustards were not suitable as military agents. These agents are similar to sulfur mustard in many ways, but they seem to cause more severe systemic effects, particularly in the central nervous system (CNS): they regularly caused convulsions when administered intravenously to animals.[9] Because nitrogen mustards have not been used militarily, they will not be discussed further. Unless stated otherwise, in this chapter the term "mustard" refers to sulfur mustard.

Military Use

Mustard has been contained 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.[1,2] Soon both sides were using mustard.

When a single agent was identified as the source of injury, it was estimated that mustard caused about 80% of the chemical casualties in World War I; the remaining 20% were caused by other agents such as chlorine and phosgene (see Chapter 9, Toxic Inhalational Injury). The British had 180,983 chemical casualties; the injuries of 160,970 (88%) were caused solely by mustard. Of these casualties, 4,167 (2.6%) died. Of the 36,765 single-agent U.S. chemical casualties, the injuries of 27,711 (75%) were caused solely

by mustard. Of the casualties who reached a medical treatment facility (MTF), 599 (2.2%) died.[10]

Although mustard caused large numbers of casualties during World War I, very few of these casualties died. Most of those who did eventually die had been hospitalized for several days. Mustard survivors, likewise, required lengthy hospitalization: the average length of stay was 42 days. Combine this length of hospitalization with the vast number of casualties caused by mustard and we can easily see how the use of mustard can greatly reduce an enemy's effectiveness.

Since the first use of mustard as a military weapon, there have been a number of isolated incidents in which it was reportedly used. 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.[11]

Chemical agents were not used during World War II: it is thought that Germany did not use mustard because Hitler had been a mustard victim during World War I and was loath to use it. However, in December 1943, the USS *John Harvey*, which was carrying a large number of mustard bombs, was attacked while docked in Bari, Italy. There were 617 U.S. mustard casualties (83 fatal) from exploded shells in the water and from the smoke of the burning mustard. In addition, an unknown number of Italian civilians were casualties from the smoke.[12,13] (The incident at Bari is discussed in greater detail in this volume in Chapter 3, Historical Aspects of Medical Defense Against Chemical Warfare, and in *Occupational Health: The Soldier and the Industrial Base*,[14] another volume in the *Textbook of Military Medicine* series.)

Iraq employed mustard against Iran during the Iran–Iraq War (1982–1988). One source[15] estimates that there were 45,000 mustard casualties. In 1989, the journal *Annales Medicinae Militaris Belgicae* pub-

lished a monograph by Jan L. Willems[16] that reported the western European experience treating a selected population of Iranian casualties of mustard. Willems reports 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. Because the hospital physicians lacked clinical experience in treating chemical warfare casualties, treatment policies varied.

In an attempt to establish whether chemical warfare agents had been used during the war, 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[16]

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

Since mustard was introduced, a number of nonbattlefield exposures have occurred. Several occurred in the North Sea, where fishermen were exposed to mustard after dredging up munitions dumped there after World War II.[17–20] Others occurred when children found and played with mustard shells; the children were injured when the shells exploded, and several of the children died.[21,22] There have also been reported incidents of laboratory workers[23] and, in one instance, of soldiers in their sleeping quarters[24] who were accidentally exposed to mustard. In yet another incident, a souvenir collector unearthed a mustard shell.[25]

Properties

Mustard is an oily liquid and is generally regarded as a "persistent" chemical agent because of its low volatility. In cool weather there is little vapor; however, mustard's evaporation increases as the temperature increases. At higher temperatures, such as those in the Middle East during the hot season, 38°C to 49°C (100°F–120°F), mustard vapor becomes a major hazard. For example, the persistency of mustard (in sand) decreased from 100 hours to 7 hours as the temperature rose from 10°C to 38°C (50°F–100°F).[26] Although heat increases the vapor hazard, the rapid evaporation decreases the task of decontamination.

World War I data[27] suggest that the warming of the air after sunrise caused significant evaporation of mustard from the ground. Mustard attacks were frequently conducted at night, and the liquid agent did not readily evaporate in the cool night air. Several hours after daybreak, however, the sun-warmed air would cause the mustard to vaporize. By this time, thinking the danger from the attack was over, the soldiers had removed their masks; thus they fell victim to the evaporating mustard. This combination of events produced a significant number of casualties among the soldiers. Because of these nighttime shellings, it soon became standard policy not to unmask for many hours after daybreak.

Mustard vapor has a density 5.4-fold greater than that of air, causing it to hug the ground and sink into trenches and gullies. When mustard slowly evaporates, a detector held 3 to 6 feet above the ground may indicate no agent in the air; but closer to the ground, at 6 to 12 inches, the concentration might range from 1 to 25 mg/m^3. Despite this low volatility, more than 80% of the mustard casualties during World War I were caused by vapor, not the liquid form of mustard.[27]

The freezing temperature for mustard is 57°F. This high freezing point makes mustard unsuitable for delivery by aircraft spraying or for winter dispersal. Therefore, to lower the freezing point, mustard must be mixed with another substance. During World War I, mustard was mixed with chloropicrin, chlorobenzene, or carbon tetrachloride to lower its freezing point.[1] Today, mustard can be mixed with Lewisite to increase its volatility in colder weather.

Mustard's high freezing point made it useful during those times of the year when the nighttime temperature was about 10°C (50°F) and the daytime temperature was in the 15°C to 21°C (60°F–70°F) range. In warm weather, mustard is 7- to 8-fold more persistent than Lewisite; therefore, it is highly desirable for use in such geographical areas as the Middle East.

Toxicity

For liquid mustard on the skin, the dose that is lethal to 50% of the exposed population (LD_{50}) is about 100 mg/kg, or about 7.0 g for a person weighing 70 kg. This is about 1.0 to 1.5 teaspoons of liquid; this amount will cover about 25% of the body surface area. An area of erythema with or without blisters caused by liquid mustard that covers this or a larger area of skin suggests that the recipient has received a lethal amount of mustard. A 10-µg droplet will produce vesication.

On the other hand, exposure to a vapor or aerosol in air is usually described as the product of the concentration (C, expressed as milligrams per cubic meter) and the time the exposure lasted (*t*, expressed as minutes):

$$Ct = mg \bullet min / m^3$$

Thus, the effect produced by an aerosol or vapor exposure to 0.05 mg/m³ • 100 minutes is equal to the effect produced by an exposure to 5 mg/m³ • 1 minute; in either case, Ct = 5 mg•min/m³. (Ct, and particularly its relation to LD, are discussed in greater detail in Chapter 5, Nerve Agents; see Exhibit 5-1.)

Eye damage was produced by a Ct of 10 mg•min/m³ or less under laboratory conditions[28]; other estimates[29] for the eye damage threshold under field conditions range from 12 to 70 mg•min/m³. The estimated Ct for airway injury ranges from 100 to 500 mg•min/m³. The threshold for skin damage is highly dependent on skin site, heat, sweating, and other factors (localized sweating will lower the threshold on the portion of the skin that is sweating[30]); the threshold is generally in the range of 200 to 2,000 mg•min/m³.

Biochemical Mechanisms of Injury

Although mustard has been considered a major chemical weapon for 75 years, there is still no clear understanding of its biochemical mechanism of action; therefore, no specific therapy for its effects exists. While the chemistry of mustard interaction with cellular components is well defined, the correlation of this interaction with injury has not been made. 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 account for mustard injury (Figure 7-1).[29,31,32]

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
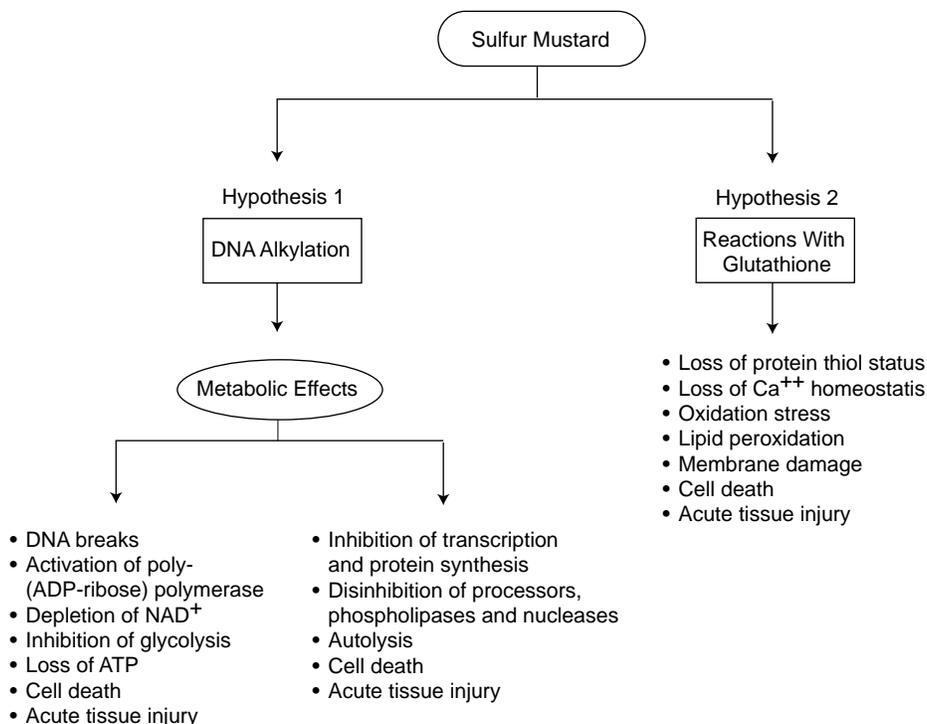

Fig. 7-1. The putative mechanisms by which sulfur mustard causes tissue damage. Adapted from US Army Medical Research Institute of Chemical Defense. A global picture of battlefield vesicants, I: A comparison of properties and effects. *Med Chem Def.* 1992;5(1):6.

acid (RNA), deoxyribonucleic acid (DNA), and membrane components, researchers have tried to identify the most critical biomolecular reactions leading to mustard injury.

Due to the highly reactive nature of mustard, it is conceivable that the injury following tissue exposure may result from a combination of effects described below in both hypotheses; 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, however, 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.[33]

Alkylation of Deoxyribonucleic Acid

The first proposed hypothesis for the possible mechanism of injury for mustard links alkylation of DNA with the cellular events of blister formation.[34] 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(ADP-ribose) polymerase (PADPRP). Excessive activity of this enzyme depletes cellular stores of nicotinamide adenine dinucleotide (NAD+), a critical cofactor and substrate needed for glycolysis.[35–37] Inhibition of glycolysis would cause a buildup of glucose-6-phosphate, a substrate in the hexose monophosphate shunt.[38] Stimulation of the hexose monophosphate shunt results in activation of cellular proteases.[39] Since a principal target of mustard in the skin is the basal epidermal cell,[40] protease from these cells could account for the cleavage of the adherent fibrils connecting the basal epidermal cell layer to the basement membrane.

Thus far, data in animal and cellular systems are consistent with many aspects of this hypothesis, which has DNA damage as the initiating step and PADPRP activation as a critical event. Studies in human skin grafts,[35] epidermal keratinocytes,[41] and leukocytes in culture[36]; and in the euthymic hairless guinea pig[42] have shown decreases in cellular NAD+ as a consequence of PADPRP activation following sulfur mustard–induced DNA damage. Niacinamide and other inhibitors of the PADPRP can ameliorate the pathology developing in both living animal and cellular models.[35,36,42,43] Unfortu-

nately, while niacinamide has some beneficial actions, the protection it affords is never complete and is limited in duration.[41,42] 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.[44] Protease activity is increased in human cells exposed in vitro to mustard.[45–47]

While many aspects of the PADPRP hypothesis have been verified, and there is good linkage between 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*[29]; only those undergoing active investigation are discussed here.

Reactions With Glutathione

The second major hypothesis to explain the effects of mustard is that it 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.[48] In 1987, Orrenius and Nicotera[49] established that menadione-induced depletion of GSH resulted in loss of protein thiols and inactivation of sulfhydryl-containing enzymes. 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.

A report[50] suggested that this mechanism could be activated by mustards and might be the mechanism of mustard injury. 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,[51] no definitive studies have

drawn an association between calcium disruptions and mustard-induced pathology.

Another proposed consequence of the mechanism—based on the depletion of GSH following mustard exposure—is lipid peroxidation.[52,53] According to this hypothesis, depletion of GSH allows the formation of oxygen-derived free radicals. The oxidizing compounds thus formed will 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[51] have shown changes in membrane fluidity following sulfur mustard exposure. In addition, in 1989, Elsayed and colleagues[54] demonstrated the presence of lipid peroxidation indicators in the tissue of mice exposed to subcutaneous butyl mustard. However, as with the thiol–calcium hypothesis, no studies have directly linked lipid peroxidation with the mustard-induced injury.

Metabolism

The mechanism or mechanisms by which mustard is thought to cause tissue damage are described above. As the first step in any of the 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[29,31,32,55] support the observation that intact or active mustard is not present in tissue or biological fluids after a few minutes. 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[36] disappeared from the blood of humans after several minutes,[56] and the half-life for intravenously administered mustard to disappear from the blood of piglets was about 2 minutes.[57] Mustard blister fluid did not produce a reaction when instilled into the eyes

of animals or humans[58] or onto the skin of humans.[59] A continuing outbreak of smaller vesicles near a source of blister fluid is probably the result of these areas having received an additional amount of exposure and not from contamination by the blister fluid.[58,60]

Clinical Effects

The organs most commonly affected by mustard are the skin, eyes, and airways (Table 7-3): the organs with which mustard comes in 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

TABLE 7-3

INITIAL CLINICAL EFFECTS FROM MUSTARD EXPOSURE

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

damaged. Mustard may also affect other organs but rarely do these produce clinical effects.

During World War I, 80% to 90% of U.S. mustard casualties had skin lesions, 86% had eye involvement, and 75% had airway damage.[61] These percentages are somewhat different from those seen in Iranian casualties, however. 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.[62] 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).[63]

The slightly higher percentage of airway and eye involvement in Iranian soldiers versus U.S. World War I casualties is perhaps attributable to the higher ambient temperature in the area (compared with Europe), which caused more vaporization; it might also have been because Iranian protective equipment was not as good as that used during World War I, or the masks may not have been completely sealed because of 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. Later, when gas masks became available, they probably were not fully effective; it is not known whether masking drills were carefully performed by the soldiers.[16]

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 7-4 illustrates the breakdown, in percentages, of British troops who died after exposure to mustard during World War I.[61] Of the casualties who died, 84% required at least 4 days of hospitalization. The causes of death are usually pulmonary insufficiency from airway damage, superimposed infection, and sepsis. Rarely, the amount of mustard will be overwhelming and cause death within 1 to 2 days; in these circumstances, death might be due to neurological factors[9,22] or massive airway damage.

Willems's report[16] on Iranian casualties treated in western European hospitals gives some idea of the effect of medical advances since World War I on the management of mustard casualties. Clinical files of 65 of these casualties were studied in detail. 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

TABLE 7-4

WORLD WAR I DEATHS AFTER EXPOSURE TO MUSTARD[*]

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

[*]In 4,167 fatal mustard casualties among British troops
Data source: Gilchrist HL. *A Comparative Study of WWI Casualties From Gas and Other Weapons*. Edgewood Arsenal, Md: US Chemical Warfare School; 1928: Chart 3, p 14.

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. Their lesions were nearly completely healed, although some lesions remained. The duration of hospitalization was determined mainly by the time needed for healing of the deeper skin lesions.

Skin

The threshold amount of mustard vapor required to produce a skin lesion (erythema) is a Ct of about 200 mg•min/m^3. This varies greatly depending on a number of factors, including temperature, humidity, moisture on the skin, and exposure site on the body. Warm, moist areas with thin skin such as the perineum, external genitalia, axillae, antecubital fossae, and neck are much more sensitive. As was stated earlier, a liquid droplet of about 10 μg will produce vesication. About 80% of this 10 μg evaporates and 10% enters the circulation, leaving about 1 μg to cause the vesicle. Evaporation of small droplets is rapid and nearly complete in 2 to 3 minutes; amounts larger than several hundred milligrams may remain on the skin for several hours.[64] Mustard vapor rapidly penetrates the skin at the rates of 1.4 μg/cm^2/min at 70°F, and 2.7 μg/cm^2/min at 88°F.[26] Liquid mustard penetrates the skin at 2.2 μg/cm^2/min at 60°F and at 5.5 μg/cm^2/min at 102°F. Once mustard penetrates the skin, it is "fixed" to components of tissue and cannot be extracted.[64]

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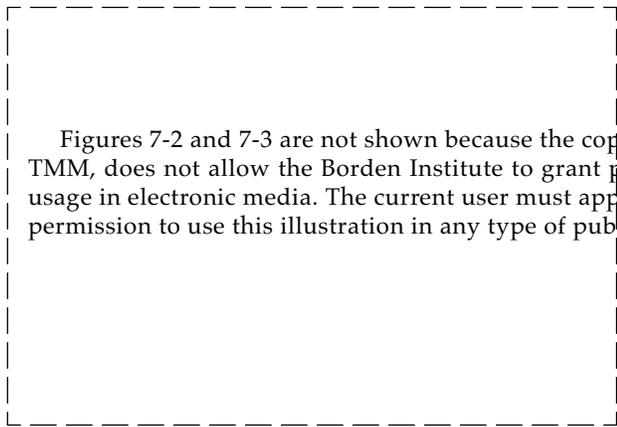
Fig. 7-2. Erythema of the chest of an Iranian casualty as it appeared 5 days after his exposure to mustard. He also had a pulmonary injury with an associated broncho-pneumonia due to infection with *Haemophilus influenzae*. The presence of a nasal oxygen catheter is indicative of the pulmonary insufficiency. Photograph: Reprinted with permission from Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;3S:13.
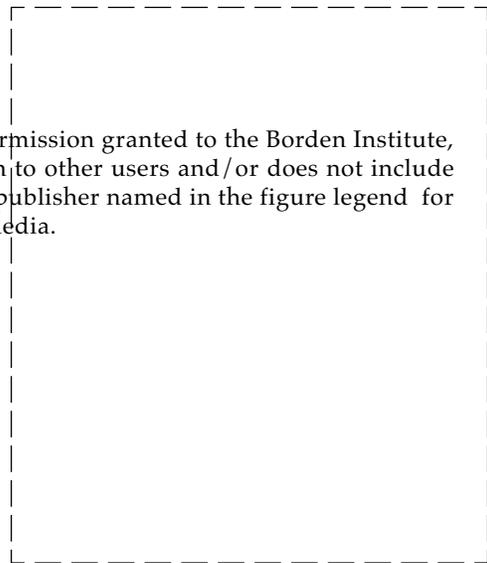
Fig. 7-3. The back of an Iranian casualty seen 16 hours after exposure to mustard. Note the small vesicles in proximity to the large bullae. Photograph: Reprinted with permission from Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;3S:8.

In one group of people, large differences in skin sensitivity to mustard were noted; some individuals were much more sensitive than others, although their skin pigment appeared to be equal. Darkly pigmented individuals were much more resistant than lightly pigmented people. Repeated exposures caused an increase in sensitivity. The horse was the most sensitive among eight nonhuman species tested; the guinea pig and monkey were the least sensitive; the dog most closely matched the sensitivity of humans.[30]

The mildest and earliest form of visible skin injury is erythema, which resembles sunburn (Figure 7-2). It is usually accompanied by pruritus, 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

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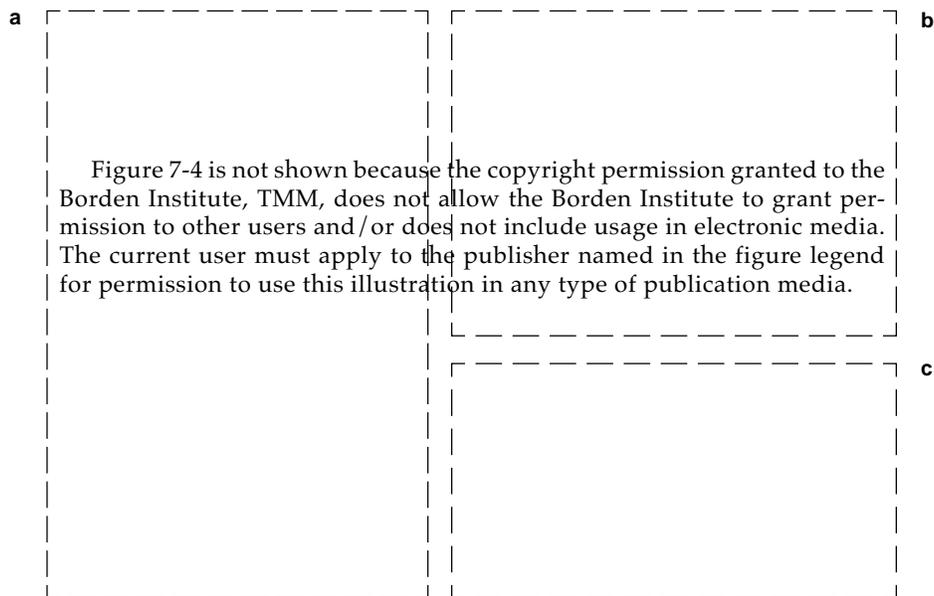
Fig. 7-4. Large and extensive bullae on (**a**) the hands and (**b**) the feet of Iranian casualties as they appeared 5 days after exposure to mustard. (**c**) Some of the bullae are disrupted and have a purulent base. Note the extensive edema that afflicts the surrounding skin. The whitish material is an antimicrobial salve. Photographs: Reprinted with permission from Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;3S:14, 15.

the erythematous areas (like a string of pearls); these vesicles will later coalesce to form larger blisters (Figure 7-3). Erythema begins to appear 1 to 24 hours after the skin is exposed to mustard, although onset can be later. 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 is dome-shaped, thin-walled, superficial, translucent, yellowish, and surrounded by erythema. Generally, it is 0.5 to 5.0 cm in diameter, although it can be larger (Figure 7-4). The blister fluid is initially thin and clear or slightly straw-colored; later it turns yellowish and tends to coagulate.[16,64,65] The blister fluid does not contain mustard and is not itself a vesicant. 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 exposure to 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.[29] Necrosis and secondary inflammation, which were the expected prominent pathophysiological characteristics of a deep burn in the preantibiotic era, are evident.

The major change at the dermal–epidermal junction, visualized by light microscopy, is liquefaction necrosis of epidermal basal cell keratinocytes (Figure 7-5). Nuclear swelling within basal cells starts as early as 3 to 6 hours after exposure,[66] and progresses to pyknosis of nuclei and disintegration of cytoplasm. The pathological process can be described as follows (Figure 7-6 illustrates this process further):

> By a coalescence of neighboring cells undergoing the process of swelling, vacuolar, 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. Progressive dissolution of the cells of such septa follows, and although intact or partially degenerated basal cells may remain in the floor of the microvesicles at first, these also soon disintegrate as the vesicles enlarge.[67]

An electron microscopy study[68] published in 1990, 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.

a
b

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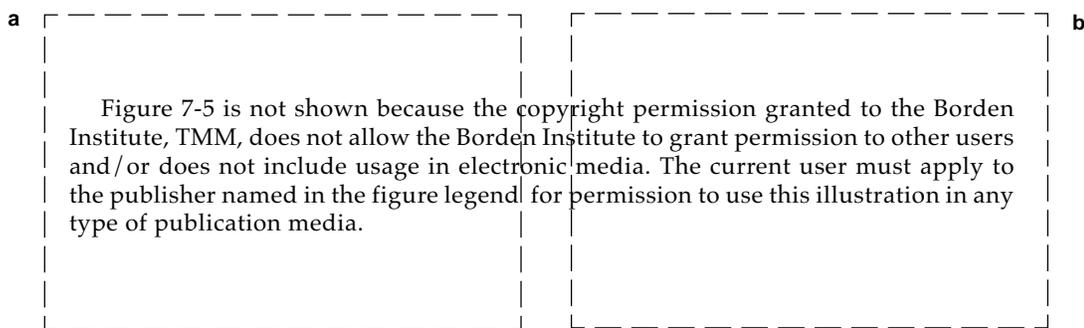
Fig. 7-5. The spectrum of cutaneous mustard injury as seen on light microscopy extends from superficially intact skin to sloughing of the epidermis. (**a**) A skin biopsy taken from an Iranian casualty on the 11th day following exposure to mustard. The gross appearance was of erythema. A cleavage plane 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**) The 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. Reprinted with permission from Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;3S:19.

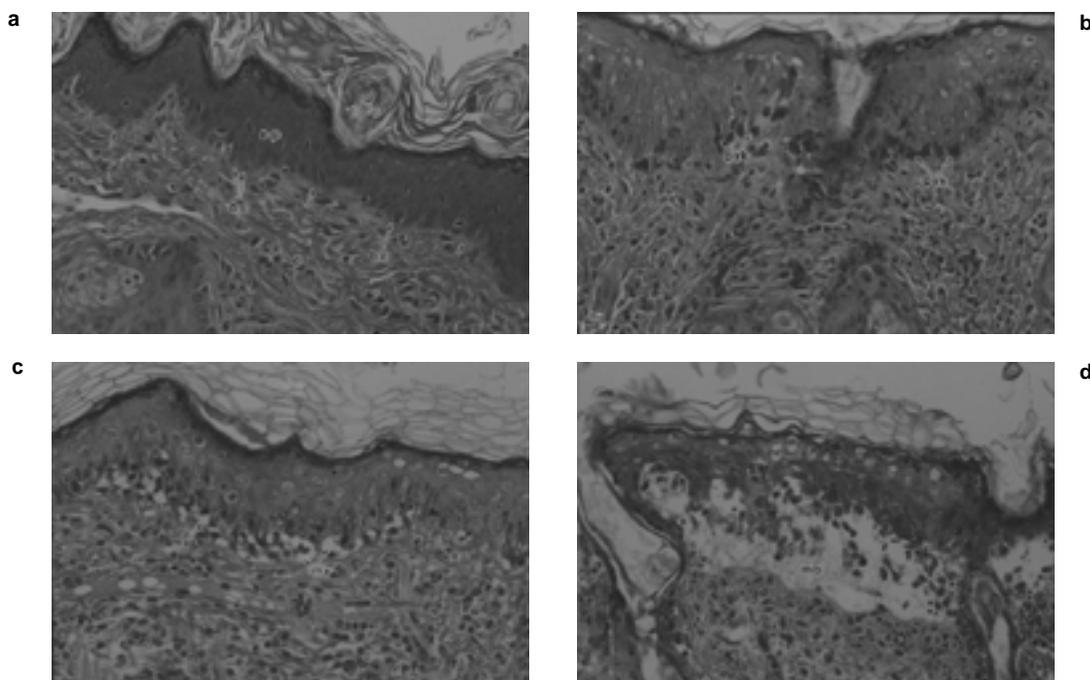**Fig. 7-6**. Light and electron microscopic analysis of hairless guinea pig skin exposed to sulfur mustard vapor reveals that the epithelial basal cell of the stratum germinativum is selectively affected to the exclusion of other epidermal cells. Following an apparent latency period of 4 to 6 hours, the basal cell pathology progresses to include extensive hydropic vacuolation, swollen endoplasmic reticulum, coagulation of monofilaments, nuclear pyknosis, and cell death. At 12 to 24 hours, characteristic 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 adherent basement membrane proteins—is infiltrated with cellular debris, inflammatory cells, fibers, and tissue fluid. (**a**) This hairless guinea pig perilesional skin site not exposed to mustard (HD) vapor serves as the control. Epidermis (ep); dermis (d); basement membrane (arrows); basal cells of stratum germinativum (bc). (**b**) At 9 hours after exposure to HD vapor, degenerating basal cells with karyorrhectic and pyknotic nuclei (pyk) can be seen. (**c**) At 12 hours after HD exposure, microvesicles (mv) are forming at the basement membrane zone in association with degenerating basal cells. (**d**) At 24 hours after HD exposure, microvesicles have coalesced to form a characteristic microblister (mb), which separates the epidermis from the dermis. Original magnification x 220. Photographs: Courtesy of John P. Petrali, Ph.D., U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Md.

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 7-7).[16]

One of the interesting characteristics of the cutaneous mustard injury that Willems[16] reported in the Iranian casualties was the transient blackening, or hyperpigmentation, of the affected skin (Figure 7-8). 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 in which liquid mustard was used.[16] A punctate hyperpigmentation—possibly due to postinflammatory changes—may be apparent in healed, deep mustard burns (Figure 7-9).

Eye

The eye is the organ most sensitive to mustard. The Ct required to produce an eye lesion under field conditions is 12 to 70 mg•min/m^3.[29] The effective Ct for conjunctivitis, or slightly more severe damage, was just under 10 mg/m^3 in 13 subjects; several subjects had lesions at Cts of 4.8 to 5.8 mg•min/m^3.[69] One subject had no symptoms after several hours; however, by 12 hours after the exposure, marked blepharospasm and irritation were apparent.

a

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b

Fig. 7-7. 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, by which time complete epithelialization had occurred. The thin and fragile nature of the new skin is clearly apparent. Reprinted with permission from Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;3S:36.

a **b**

c **d**

Figure 7-8 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.
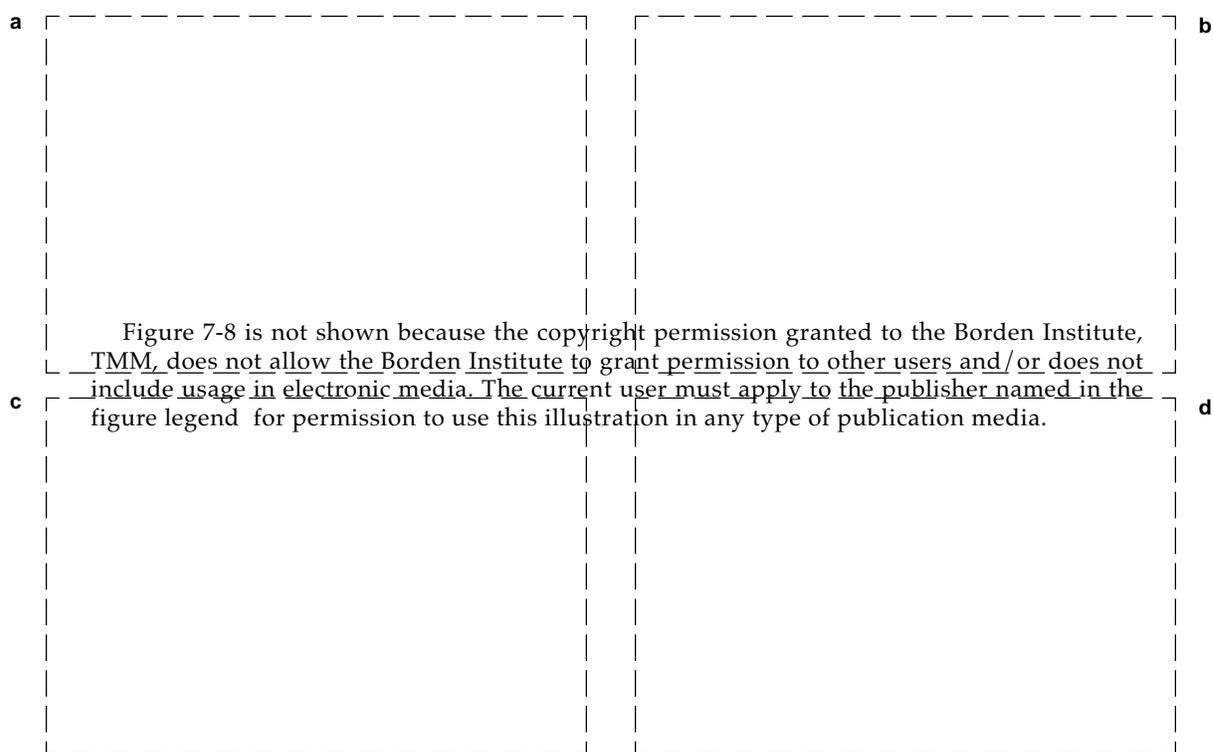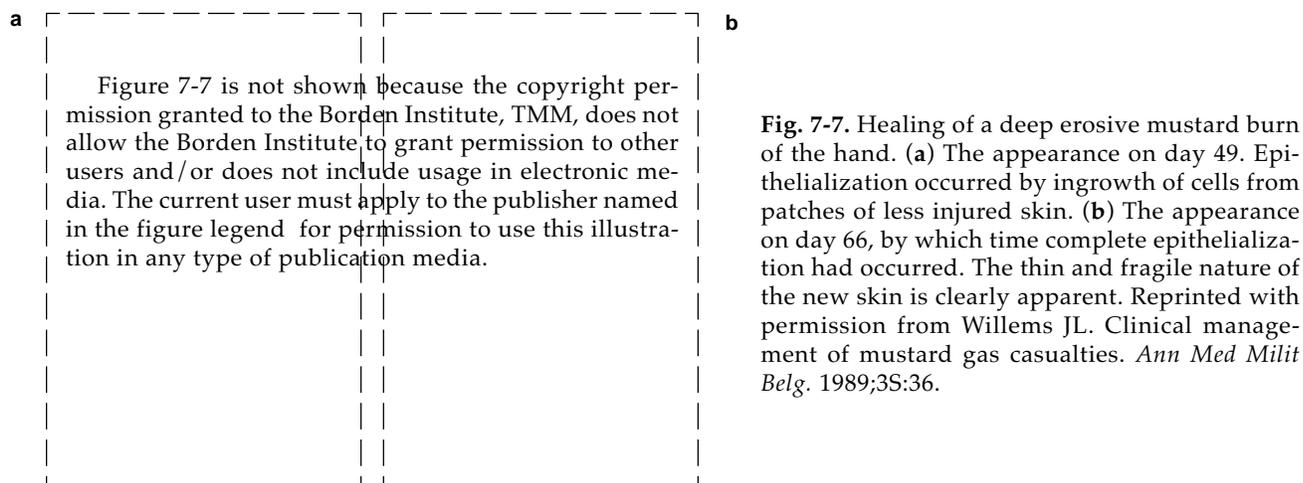
Fig. 7-8. Transient hyperpigmentation of the injured skin is observed frequently following mustard exposure. It is caused by the collection of melanin from dead melanocytes at the base of the soon-to-desquamate epidermis and disappears when the involved skin desquamates. Hyperpigmentation is not dependent on the formation of bullae. (**a**) An Iranian casualty as he appeared 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 casualty 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 seen 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 found a layer of regenerating epidermis. Reprinted with permission from Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;3S:13, 18, 29, 30.

Figure 7-9 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

Fig. 7-9. By 32 days after exposure, this Iranian casualty has punctate hyperpigmentation in a healing deep mustard burn. This condition is perhaps indicative of postinflammatory changes in the epidermis that has regenerated from hair follicles. Reprinted with permission from Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;3S:34.

Generally, the asymptomatic period varies with the concentration of mustard vapor (or the amount of liquid) and individual sensitivity. The latent period for eye damage is shorter than that for skin damage. Eye irritation within minutes after exposure has been reported,[16,69] but the authors of these reports speculate that the irritation might have been due to other causes.

After a low C*t* exposure, a slight irritation with reddening of the eye may be all that occurs (Figure 7-10). As the C*t* increases, the spectrum of injury is characterized by progressively more severe conjunctivitis, blepharospasm, pain, and corneal damage.[29,65] Photophobia will appear and, even with mild exposures, may linger for weeks.

Corneal damage consists of edema with clouding (which affects vision), swelling, and infiltration of polymorphonuclear cells. Clinical improvement occurs after approximately 7 days with subsiding edema. Corneal vascularization (pannus development, which causes corneal opacity) 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 followed by scarring between the iris and the lens, which restricts pupillary movements and predisposes the individual to glaucoma.[29,70]

The most severe eye damage is caused by liquid mustard, which may be delivered by an airborne droplet or by self-contamination.[60] Symptoms may become evident within minutes after exposure.[65] Severe corneal damage with possible perforation of the cornea can occur after extensive eye exposure

to liquid mustard. The patient may lose his vision or even his eye from panophthalmitis, particularly if drainage of the infection is blocked, such as by adherent lids.[65] 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 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. 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 lasted more than 3 months. Of 1,016 mustard casualties surveyed after World War I, only 1 received disability payments for defective vision.[10]

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.[71,72]

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Fig. 7-10. 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. Reprinted with permission from Willems JL. Clinical management of mustard gas casualties. *Ann Med Milit Belg.* 1989;3S:12.

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.[71,72] Medical personnel have reported seeing delayed keratitis in humans months to years after mustard exposure.[28,73]

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. Likewise, damage to other structures (eg, Descemet's membrane) also occurred within a similar length of time.[28] Decontamination must be performed immediately after liquid mustard contaminates the eye because absorption and ocular damage occur very rapidly; after a few minutes, there will be no liquid remaining on the surface of the eye to decontaminate.

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 varies from mild to severe, with 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 catarrhal 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 oppression. 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 oc-

casionally experience mild epistaxis and sore throat. In individuals with abnormal sensitivity (smokers and patients with irritable airways or acute viral illness), prominent wheezing and dyspnea may be present.[58]

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-intense 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 can break off and obstruct lower airways.[16,58,60]

The initial bronchitis is nonbacterial. White blood cell elevation, fever, pulmonary infiltrates seen on radiograph, and colored secretions may all be present to 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. Careful assessment of the sputum by Gram's stain and culture should be done daily.[60]

Mustard has little effect on lung parenchyma. Its damage is confined to the airways and the tissue immediately surrounding the airways, except after an overwhelming exposure to mustard and as a terminal event.[74] These changes are most intense in the upper airways and decrease in the trachea, bronchi, and smaller bronchioles—presumably reflecting a differential disposition of

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Fig. 7-11. A surgically excised lung from an Iranian mustard casualty showing bronchiectasis and severe chronic infection. Reprinted 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.

vapor on the mucosal surface.[71,75] Pulmonary edema is not a feature; however, it may occur in the terminal stages.[60,74]

The lungs of animals exposed to mustard show alternating areas of atelectasis and emphysema. Atelectasis is thought to be caused by the clogging of bronchioles with mucus, and the emphysema is compensatory.[76] These findings were confirmed when lungs resected at thoracotomy from Iranian casualties from the Iran–Iraq War showed similar effects.[77] As seen in Figure 7-11, the lungs showed bronchiectasis and severe chronic inflammation. The bronchiectasis was due to 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 and not severe, may be caused by the cholinergic activity of mustard,[9,33] by a general reaction to injury, or because of the unpleasant odor.[33] Nausea and vomiting that occur days later are probably due to 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. Animals that were given approximately 1 LD_{50} of mustard (administered either intravenously or subcutaneously) had profuse diarrhea, which was frequently bloody[60,78]; however, this was unusual when mustard was administered percutaneously or by inhalation. (Diarrhea was more common after nitrogen mustard.[9])

Diarrhea and gastrointestinal bleeding do not seem to be common in humans. Of 107 autopsied cases, none had experienced diarrhea; and in the 57 cases in which the gastrointestinal tract was thoroughly examined, none had significant lesions.[75] In several reported series of Iranian casualties, totaling about 700 casualties, few had diarrhea and only a very few who died had bloody diarrhea.[16,62,79] Constipation was noted in casualties with mild exposure.[60]

Central Nervous System

Although the effects are not usually prominent clinically, mustard affects the CNS. Reports of World War I casualties described apathy, depression, intellectual dullness, and languor.[60] Of 233 Iranian casualties sent to various western European hospitals for medical care during the Iran–Iraq War, about 83% had CNS complaints; most complaints, however, were mild and nonspecific.[62]

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.[60,80] Animals died a "neurological death" a few hours after receiving a lethal amount of mustard.[9] Autopsies of these animals disclosed few abnormalities.[80]

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.[22] Whether these CNS manifestations are from a cholinergic activity of mustard or from other mechanisms is unknown.

Death

Most casualties die of massive pulmonary damage complicated by infection (bronchopneumonia) and sepsis (resulting from loss of the immune mechanism). 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 from 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.[81] (Mustard is considered to be a radiomimetic because it causes tissue damage similar to that seen after radiation.)

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. Whereas pain from Lewisite (the other vesicant that causes blistering) begins seconds to minutes after exposure, pain from mustard does not begin until the lesion develops 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. Because naturally occurring organisms, both plants and insects, cause similar blisters, the appearance of one or more blisters in only a single individual makes exposure to a natural substance the more likely possibility.

Laboratory Tests

There is no specific laboratory test for mustard exposure. As inflammation and infection occur, signs of these (eg, fever and leukocytosis) will develop. Several investigational studies have demonstrated the presence of significant amounts of thiodiglycol, a major metabolite of mustard, in the urine of mustard casualties. In two studies,[82,83] Iranian casualties had higher amounts of thiodiglycol in their urine than did control subjects. 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.[23] The procedure for analysis of thiodiglycol is described in Technical Bulletin Medical 296.[84]

Patient Management

Decontamination within 1 or 2 minutes after exposure is the only 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 himself 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 the soldier because mustard fixes to the skin within minutes, and tissue damage will already have occurred.[64]

If any mustard remains on the skin, late decontamination will prevent its spreading to other areas of the skin; but after several hours, spreading will probably already have occurred. Decontamination will, however, prevent mustard from spreading to personnel who handle the casualty.

By the time a skin lesion has developed, most of the mustard will already have been absorbed (and the chemical agent will have fixed to tissue); and, unless the site was occluded, the remaining unabsorbed agent will have evaporated. Mustard droplets disappear from the surface of the eye very quickly, so late flushing of the eye will be of no benefit, either.

However, all chemical agent 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 of medical personnel.

Mustard casualties generally fall into three categories. The first is the return to duty category. 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 long after exposure, so that there is good reason to believe that the lesion will not progress significantly, 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, and
- a respiratory injury with moderate symptoms that include a productive cough and dyspnea.

Some of these conditions may develop into life-threatening injuries, and these categories, therefore, should be used only to assess a casualty's *presenting* condition. 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 2 LD_{50} of the agent. Likewise, dyspnea occurring within 4 to 6 hours after the exposure suggests inhalation of a 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. Most of the casualties in this category will die from their injuries.

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), suggest that most mustard casualties are not severely injured and that most of them 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.[16] Casualties with mild-to-moderate mustard damage will need supportive care. Pain control is extremely important. Fluids and electrolytes should be carefully monitored. Although there is not a great deal of fluid loss from mustard burns (compared with thermal burns), a casualty will probably be dehydrated when he enters the MTF; and a sick patient usually does not eat or drink enough. Parenteral fluid supplements and vitamins may be of benefit. Casualties 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 will present with large areas of burns, major pulmonary damage, and immuno-suppression. Some of the casualties may die from sepsis or from overwhelming damage to the airways and lungs. Medical officers should remember, however, that even with the limited medical care available in World War I, very few deaths were caused by mustard exposure.

Despite the attention given to mustard since World War I, research has not produced an antidote. Because casualties have been managed in different eras and, more recently, in different medical centers, there have been no standard methods of casualty management, nor have there been any controlled studies of one method compared to another. The following advice describes care by organ system. Most casualties will have more than one system involved, and many of these casualties will be dehydrated and have other injuries as well.

Skin

The general principles for managing a mustard skin lesion are to keep the casualty comfortable, keep the lesion clean, and prevent infection. The burning and itching associated with erythema can be relieved by calamine or another soothing lotion or cream such as 0.25% camphor and menthol. These lesions should heal without complication.

Small blisters (< 1 cm) should be left alone; however, the surrounding area should be cleaned (irri-

gated) at least once daily. An application of a topical antibiotic should immediately be applied to the blisters and the surrounding area. The blisters and the surrounding area do not need to be bandaged unless the casualty will be returning to duty.

Larger blisters (> 1 cm) should be unroofed and the underlying area should be irrigated (2 to 4 times daily) with saline, sterile water, or clean soapy water, and liberally covered (to a depth of 1 mm) with a topical antibiotic cream or ointment (silver sulfadiazine, mafenide acetate, bacitracin, or Neosporin [Burroughs Wellcome Co., Research Triangle Park, N. C.]). Dakin's solution (hypochlorite) was used on patients in World War I[60] and during the Iran–Iraq War[16] as an irrigating solution. It does not detoxify the chemical agent in the skin, as was once thought; however, it is an adequate antiseptic and keeps the area clean. Multiple or large areas of vesication necessitate hospitalization for frequent and careful cleaning; a whirlpool bath is a useful means of irrigation. In general, care of mustard skin lesions is the same as that of second-degree thermal burns, although the pathophysiology is different.

Systemic analgesics should be given liberally, particularly before manipulation of the burned area. Systemic antipruritics (eg, trimeprazine) may be useful. Fluid balance and electrolytes should be monitored. Fluids are lost into the edematous areas, but fluid replacement is of less magnitude than that required for thermal burns. Medical personnel accustomed to treating patients with thermal burns must resist the temptation to overhydrate mustard burn patients, which could lead to untoward consequences such as pulmonary edema.[16]

Skin healing can take weeks to months but usually is complete, although pigment changes may persist. Scarring is proportional to the depth of the burn. Skin grafting is rarely needed, but it was successful in one person who had a deep burn.[25]

Eyes

The basic principles of eye care are to prevent infection and to prevent scarring. Although it is unlikely that mustard will still be in the eye by the time the casualty is seen, the eye should be irrigated to remove any possible chemical agent that might be on the lashes and to remove 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 con-

sist 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 shut, a small infection could not drain, and a panophthalmitis developed that completely destroyed the eyes.[65])

Topical analgesics may be used for the initial examination; however, they should not be used routinely as they might cause corneal damage. Pain should be controlled with systemic analgesics. The benefit of topical steroids is unknown; however, some ophthalmologists feel that topical steroids may be helpful if used within the first 48 hours after the exposure (but not after that). In any case, an ophthalmologist should be consulted as early as possible on this and other questions of care. Keeping the casualty in a dim room or providing sunglasses will reduce the discomfort from photophobia.

The transient loss of vision is usually the result of edema of the lids and other structures and not due to corneal damage. Medical personnel should assure the patient that vision will return. Recovery may be within days for milder injuries, while those with severe damage will take approximately a month or longer to recover.

Airways

The therapeutic goal in a casualty with mild airway effects (eg, irritation of the throat, nonproductive cough) is to keep him comfortable. In a casualty with severe effects, the goal is to maintain adequate oxygenation. Antitussives and demulcents are helpful for persistent, severe, nonproductive cough. Steam inhalation might also be useful.

Hypoxia is generally secondary to the abnormalities in the ventilation–perfusion ratio caused by toxic bronchitis. Mucosal sloughing further complicates this abnormality. Underlying irritable airways disease (hyperreactive airways) is easily triggered; consequently, therapy with bronchodilators may be necessary. Casualties with hyperreactive airways may benefit from steroid treatment with careful attention to the added risk of superinfection. Oxygen supplementation may be necessary for prolonged periods; this will depend, primarily, on the intensity of mustard exposure and the presence of any underlying pulmonary disorder.

Hypercarbia may result from a previously unrecognized hyperreactive airways state or from abnormal central sensitivity to carbon dioxide, complicated by increased work of respiration (this state may result from bronchospasm). Bronchodilators are acceptable initial therapy. Ventilatory support may be necessary to assist 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. Steroids should be considered if a prior history of asthma or hyperreactive airways disease is obtained.

Initially, the bronchitis resulting from mustard exposure is nonbacterial. White blood cell elevation, fever, pulmonary infiltrates on a chest radiograph, and colored sputum may all be present; however, careful assessment of sputum by Gram's 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; massive medical support may become necessary for these patients. In these instances, sepsis typically supervenes, and despite combination antibiotic therapy, death commonly occurs.

A casualty with severe pulmonary signs 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. Early use of positive end-expiratory pressure or continuous positive airway pressure may be beneficial. The need for continuous ventilatory support suggests a bad prognosis; of the Iranian casualties treated in western European hospitals who needed assisted ventilation, 87% died.[16]

An especially devastating pulmonary complication, severe and progressive stenosis of the tracheobronchial tree (Figure 7-12), was found in about

a

c

Figure 7-12 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.
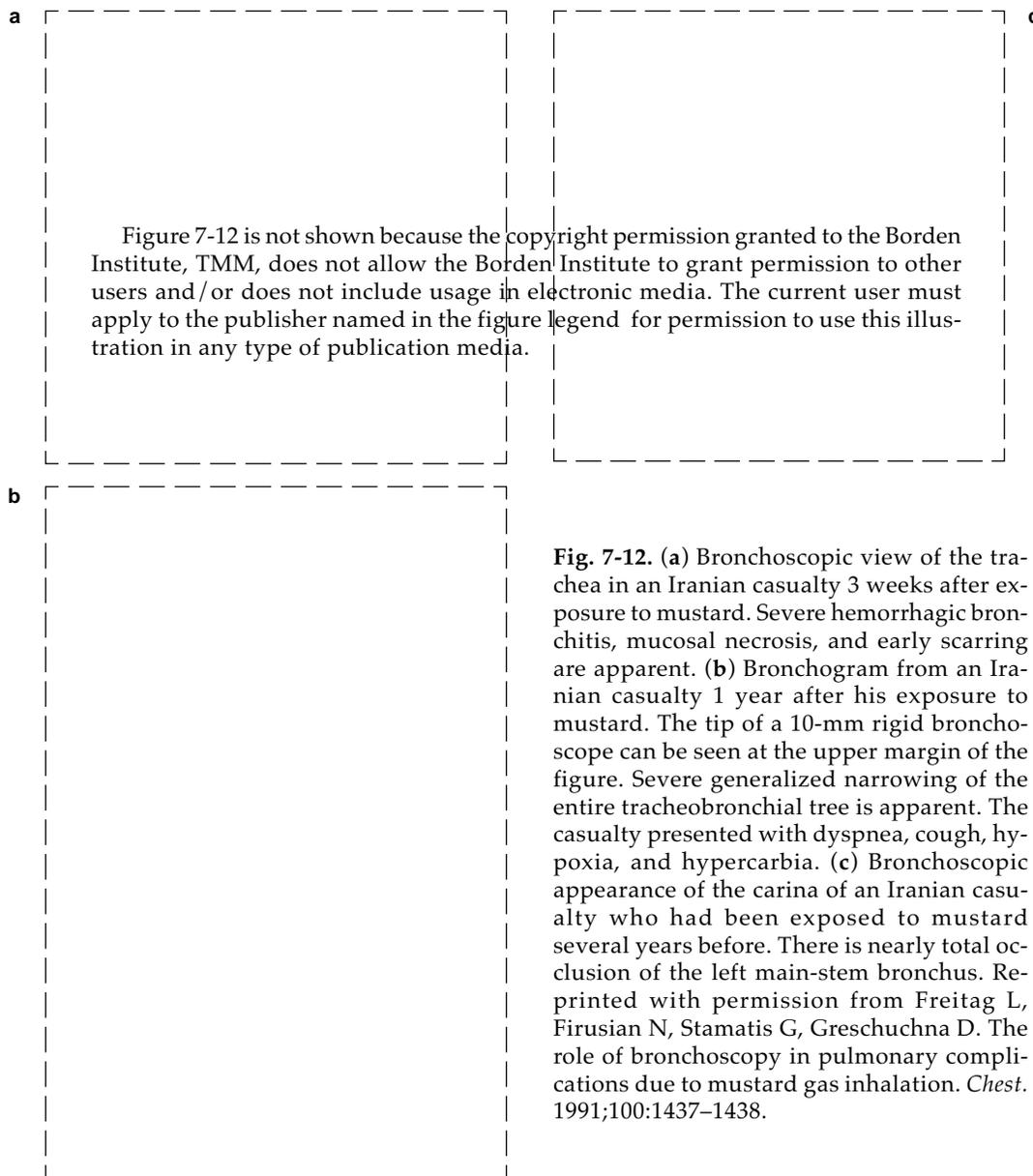
b

Fig. 7-12. (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 his 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. Reprinted 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.

10% of the Iranian casualties treated in western European hospitals during the Iran–Iraq War. This complication was 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: we must remember the primitive nature of early 20th-century medicine and its lack of antibiotics. With the Iranian casualties, bronchoscopy was of value when used both for diagnosis and for therapeutic dilation.[77] However, given the progressive nature of the scarring, unnaturally early death from respiratory failure is to be expected in all such casualties.

Gastrointestinal Tract

The initial nausea and vomiting are rarely severe and can usually be relieved with atropine or common antiemetics. Later vomiting and diarrhea are usually indicative of systemic cytotoxicity and require fluid replacement.

Bone Marrow

Suppression of the hemopoietic elements cannot be predicted from the extent of skin lesions (eg, the lesions might be from vapor and therefore superfi-

cial, but significant amounts of mustard may have been absorbed by inhalation). Frequent counts of the formed blood elements must be done on a casualty who has 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; the red blood cells and the thrombocytes soon follow if the casualty lives long enough or does not start to recover. Typically, leukopenia begins at day 3 through day 5 after the exposure, and reaches a nadir in 3 to 6,[60] or 7 to 9,[16] days. Leukopenia with a cell count lower than 200 cells/mm^3 usually signifies a bad prognosis,[16] as does a rapid drop in the cell count; for example, from 30,000 to 15,000 cells/mm^3 in a day.[60]

Medical personnel should institute therapy that sterilizes the gut with nonabsorbable antibiotics at the onset of leukopenia.[16] Cellular replacement, either peripheral or marrow, may also be successful.

Other Treatment Modalities

A variety of antiinflammatory and sulfhydryl-scavenging agents (such as promethazine, vitamin E, heparin, and sodium thiosulfate) have been suggested as therapeutic drugs. Although animal studies suggest the value of these agents for prophylactic therapy (or therapy immediately after the exposure), there are no data to support their use after the lesions develop.[85–87]

Activated charcoal, administered orally, has been tried with unknown results[16]; however, it may provide some benefit if given immediately after mustard is ingested. Hemodialysis was not only without benefit, it appeared to have deleterious effects.[16] This is not surprising because mustard becomes fixed to tissue within minutes.

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 predisposes the individual to bronchiectasis and recurrent pneumonia.[58]

An important late sequela of mustard inhalation is a tracheal/bronchial stenosis that necessitates bronchoscopy and other procedures.[77] 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.[58,88]

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.[89–91] According to two separate reports,[92,93] the association of one or two exposures on the battlefield with subsequent cancer is not clear; in a third report,[94] the relation between mustard exposure and subsequent cancer is equivocal. Interested readers may consult Watson and associates' 1989 review[95] of the mustard exposure–cancer incidence relation.

In 1991, the National Academy of Science appointed a committee to survey the health effects of mustard and Lewisite.[94] Veterans of World War II, who, as subjects in test programs, had been exposed to mustard and Lewisite, were presenting at Veterans Administration hospitals with complaints of illnesses that they believed were associated with these test programs. 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 8, Long-Term Health Effects of Nerve Agents and Mustard).

LEWISITE

$$Cl-\overset{H}{\underset{}{C}}=\overset{H}{\underset{}{C}}-As\overset{Cl}{\underset{Cl}{\diagup}}$$

L

Lewisite (β-chlorovinyldichloroarsine) is an arsenical vesicant but of only secondary importance in the vesicant group of agents. It was synthesized[96] in the early 20th century and has seen little or no battlefield use. Lewisite is similar to mustard in that it damages the skin, eyes, and airways; however, it differs from mustard because its clinical effects appear within seconds of exposure. An antidote, British anti-Lewisite (BAL), can ameliorate the effects of Lewisite if used soon after exposure. Lewisite has some advantages over mustard but also some disadvantages.

Military Use

A research team headed by U.S. Army Captain W. L. Lewis is generally credited with the synthesis of Lewisite in 1918,[96–98] although German scientists had studied this material earlier.[1,58] Large quantities were manufactured by the United States for use in Europe; however, World War I ended while the shipment was at sea and the vessel was sunk.[1,98]

There has been no verified use of Lewisite on a battlefield, although Japan may have used it against China between 1937 and 1944.[93] Currently, this vesicant 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 this mixture.[99]

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.[100]

Toxicity

The toxicity of Lewisite vapor is very similar to that of mustard vapor; the LCt_{50} (the concentration • time that is lethal to 50% of the exposed population) by inhalation is estimated to be about 1,500 mg•min/m^3, and the LCt_{50} for eye and airway damage are about 150 and 500 mg•min/m^3, respectively. Vesication is caused by 14 µg of liquid, and the LD_{50} of liquid on the skin is about 30 mg/kg[100] (or probably higher[98]). Blister fluid from a Lewisite-caused blister is nonirritating,[58,98] but it does contain 0.8 to 1.3 mg/mL of arsenic.

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 7-13). 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.[98]

Clinical Effects

Lewisite damages skin, eyes, and airways by direct contact and has systemic effects after absorption. Unlike mustard, it does not produce immuno-

Lewisite

Reactions with Glutathione

Reactions with Adjacent Sulfhydryl Groups of Enzymes

- Loss of protein thiol status
- Loss of Ca^{++} homeostatis
- Oxidation stress
- Lipid peroxidation
- Membrane damage
- Cell death
- Acute tissue injury

- Inhibition of pyruvate dehydrogenase complex
- Inhibition of glycolysis
- Loss of ATP
- Cell death
- Acute tissue injury

Fig. 7-13. The putative mechanisms by which Lewisite causes tissue damage. 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.

suppression. Data on human exposure are few. Lewisite was applied to human skin in a few studies[58,101–103]; however, most information on its clinical effects is based on animal studies.

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.[58]

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 20–30 min 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, small blisters that eventually merge.[58] Other differences between the lesions produced by these two chemical agents are

- 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 pigmentation is likewise less common.[58]

See Goldman and Dacre[104] for a further review of Lewisite and its toxicology.

Eyes

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.[105]

In tests performed on rabbits,[105] Lewisite caused almost immediate edema of the lids, conjunctiva, and cornea (which was maximal after the lid edema had subsided) and early and severe involvement of the iris and ciliary body, followed by gradual depigmentation and shrinkage of the iris stroma. 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.

Airways

Lewisite vapor is extremely irritating to the nose and lower airways, causing individuals exposed to it 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 the Lewisite vapor is extremely irritating to the mucous membranes. 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 finally 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.[60]

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 will cause local edema because of the effects of this agent on local capillaries. With a large amount of Lewisite, the pulmonary capillaries are also affected (because they are more sensitive to Lewisite than other capillaries or because absorbed Lewisite reaches the lungs before it reaches the systemic circulation); 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.[104]

Arsines are known to cause hemolytic anemia, but there is little mention of this in reports on Lewisite exposure. A "true or hemolytic anemia" was noted with Lewisite shock.[104]

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.

Laboratory Tests

There is no specific laboratory test for Lewisite. Urinary arsenic excretion might be helpful in identifying possible exposure to Lewisite, however.

Patient Management

Medical personnel should follow the same principles for managing Lewisite skin, eye, and airway lesions that they follow for managing mustard lesions. A specific antidote, BAL (dimercaprol), will prevent or greatly decrease 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 will reduce 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.[98,104]

BAL reduced the mortality in dogs when it was given within 100 minutes after they had inhaled a lethal amount of Lewisite.[106] Burns of the eyes from Lewisite can be prevented if BAL is applied within 2 to 5 minutes of exposure[104]; when it was applied within an hour after exposure, BAL prevented vesication in humans.[107] 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. There is no substantial evidence to suggest that Lewisite is carcinogenic, teratogenic, or mutagenic.[104] The committee appointed by the National Academy of Science reported[94] a causal relationship between Lewisite exposure and chronic respiratory diseases, and also that acute, severe injuries to the eye from Lewisite will persist.

PHOSGENE OXIME

$$\begin{array}{c} Cl \\ \diagdown \\ \diagup \\ Cl \end{array} C = N - OH$$

CX
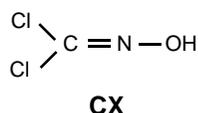
Phosgene oxime (CX) is not a true vesicant because it does not produce vesicles. Instead, phosgene oxime is an urticant or nettle agent: it causes erythema, wheals, and urticaria. Its lesions have been compared with those caused by nettle stings. Because it causes extensive tissue damage, phosgene oxime 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 (CG), which exerts its effects on the alveolar–capillary membrane.

Military Use

German scientists first synthesized phosgene oxime in 1929,[108] and Russia as well as Germany had developed it before World War II. Both countries may have had weapons that contained this agent.[109] The United States also had studied phosgene oxime before World War II but rejected it as a possible chemi-

cal agent because of its biological effects—or lack thereof—and its instability.[109] The apparent lack of biological effects was later found to be due to 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.[109,110]

Phosgene oxime is of military interest because

- it penetrates garments and rubber much more quickly than do other chemical agents, and
- it 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 will render the skin more susceptible to the second agent. Also, if an unmasked soldier were exposed to phosgene oxime before donning his mask, the pain caused by phosgene oxime will prompt him to unmask again.

Properties

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

compound is a yellowish-brown liquid. Its melting point is 35°C to 40°C (95°F–104°F). The solid material will produce enough vapor to cause symptoms.[100]

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 7-14). The skin lesions, in particular, are similar to those caused by a strong acid. This 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, while injection into the portal vein produces hepatic necrosis but not pulmonary edema.[110]

Clinical Effects

Phosgene oxime affects the skin, the eyes, and the 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 that is 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.[109] In both animal and human subjects, the skin had completely absorbed the phosgene oxime within seconds—by the time pallor appeared.[110]

Eyes

The eye lesions from phosgene oxime are similar to those caused by Lewisite; these lesions result in immediate pain, conjunctivitis, and keratitis.[109–111] 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.[110]

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
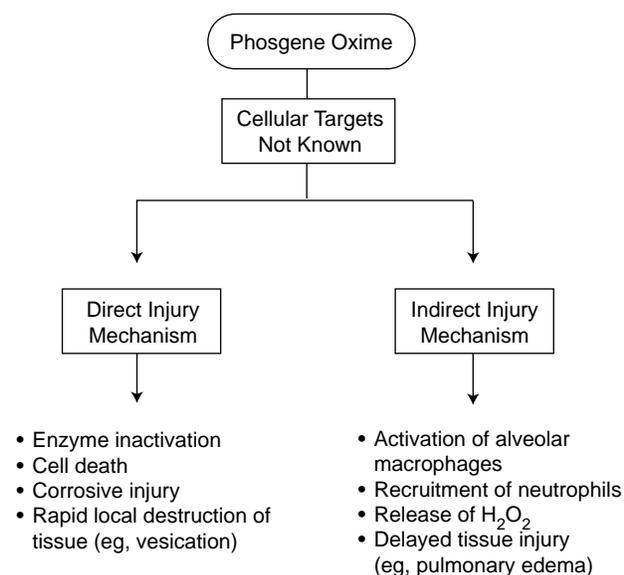

Fig. 7-14. The putative mechanisms by which phosgene oxime causes tissue damage. Adapted from US Army Medical Research Institute of Chemical Defense. A global picture of battlefield vesicants, I: A comparison of properties and effects. *Med Chem Def.* 1992;5(1):6.

the same way other necrotic lesions are treated—by keeping them clean and avoiding infection. The eye lesions require the same care as one would supply for damage from a corrosive substance. The pulmonary lesion, noncardiac pulmonary edema, should be managed as suggested in Chapter 9, Toxic Inhalational Injury.

Decontamination, or self-aid, must be accomplished immediately after contact because the agent is absorbed from the skin within seconds.

SUMMARY

The 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 the Iran–Iraq War are scanty; however, data from World War I indicate that more than 95% of mustard casualties survived but most required lengthy hospitalizations. 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 hospitalization.

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