

## CHAPTER 3

## VESICANTS (BLISTER AGENTS)

## SECTION I - MUSTARD AND NITROGEN MUSTARDS

**301. Introduction.**

- a. Blister or vesicant agents are likely to be used both to produce casualties and to force opposing troops to wear full protective equipment thus degrading fighting efficiency, rather than to kill, although exposure to such agents can be fatal. Blister agents can be thickened in order to contaminate terrain, ships, aircraft, vehicles or equipment with a persistent hazard. The vesicant agents include sulphur mustard (HD), nitrogen mustard (HN), the arsenical vesicants such as lewisite (L) (this may well be used in a mixture with HD), and the halogenated oximes whose properties and effects are very different from those of the other vesicants.
- b. Vesicants burn and blister the skin or any other part of the body they contact. They act on the eyes, mucous membranes, lungs, skin and blood-forming organs. They damage the respiratory tract when inhaled and cause vomiting and diarrhoea when ingested.

**302. Mustard Agents.**

- a. Sulphur mustard was used extensively in World War I and has been used in more recent military campaigns. Protection against these agents can only be achieved by a full protective ensemble. The respirator alone protects against eye and lung damage and gives some protection against systemic effects. Extensive, slow healing skin lesions will place a heavy burden on the medical services.
- b. Sulphur mustard is the best known of these agents. Synthesised in 1822, its vesicant properties were discovered in the middle of the nineteenth century. As a chemical agent it was used for the first time in 1917 near Ypres from which it derives its French name (Yperite). Mustard is 2,2' -di(chloro-ethyl)-sulphide. It is also known by the name "Lost" in German.
- c. In the US the symbol HD has been given to the distilled product. In this chapter it will be indicated thus. In 1935 it was discovered that the vesicant properties remained when the sulphur atom was substituted by a nitrogen atom. Thus it became possible to synthesise the nitrogen mustards with similar properties, of which there are three, viz:
  - (1) N-ethyl-2,2' di(chloroethyl)amine, or HN1.
  - (2) N methyl-2,2' di(chloroethyl)amine, or HN2.
  - (3) 2,2',2'' tri(chloroethyl)amine, or HN3.
- d. From a military standpoint, HN3 is the principal representative of the group of nitrogen mustards and is the only nitrogen mustard likely to be used in war.

**303. Physical and Chemical Properties.**

- a. The mustards are able to penetrate cell membranes in tissues and a great number of materials: woods, leather, rubber, plants, etc. Due to their physical properties, mustards are very persistent in cold and temperate climates. It is possible to increase the persistency by dissolving them in non-volatile solvents, e.g., chlorinated rubber. In this way thickened mustards are obtained that are very difficult to remove by decontaminating processes.
- b. In warmer climates persistence of mustards is less but higher concentrations of vapour occur.
- c. When dissolved in water, mustards are hydrolysed at an appreciable rate, yielding poly-alcohols and hydrochloric acid (HCl), so that the solution may still be damaging to the skin. In more concentrated solutions, interaction of products becomes more pronounced and several dimers are formed. In 2 hours 22% of the initial concentration is hydrolysed, in 6 hours 35% and in 24 hours 60%. However, as their volatility in water is very poor, two phases are generally formed and hydrolysis of the undissolved bulk is very slow. In running water the contact surfaces are frequently changed and persistency is only a few days, but in stagnant water, persistency can be several months. Mustard is denser than water, but small droplets remain on the water surface and present a special hazard in contaminated areas. Alkalinity and higher temperatures increase the rate of hydrolysis.
- d. Owing to its bivalent sulphur atom, sulphur mustard has very good reducing properties. Depending on their strengths, oxidants oxidise mustard to a greater or lesser extent, e.g., to sulphoxide, sulfone or sulphate. Of these only the sulfone has appreciable vesicant properties.
- e. Nitrogen mustards are much less easily oxidised than sulphur mustard.

**304. Detection.**

- a. Mustards have the interesting property of forming, under certain conditions, coloured complexes with para-nitrobenzpyridine thus making it possible to detect minute amounts.
- b. Mustard agents can be detected by a variety of means. Single and three colour detector papers will detect liquid agent and are available for individual issue. Monitoring devices for local contamination and water testing kits are also available.

**305. Protection.**

- a. Ordinary clothing gives little or no protection against mustard agents. Special equipment including a respirator, NBC suit, gloves and overboots are required. Due to slow absorption of mustard by many materials, protective equipment must be changed regularly according to the appropriate national drills.
- b. No drug is available for the prevention of the effects of mustard on the skin and the mucous membranes caused by mustards. It is possible to protect the skin against very low doses of mustard by covering it with a paste containing a chlorinating

agent, e.g., chloramine. The only practical prophylactic method is physical protection such as is given by the protective respirator and special clothing.

### 306. Decontamination.

- a. *General.* The decontamination of clothing, equipment, arms, vehicles, materials, buildings and terrain does not come within the framework of this manual. Decontamination of food and drinking water is discussed in Chapter 12. Only the decontamination of the skin, mucous membranes, eyes and wounds is dealt with here. Exposure to mustard is not always noticed immediately because of the latent and sign-free period that may occur after skin exposure. This may result in delayed decontamination or failure to decontaminate at all.
- b. *Decontamination of Mucous Membranes and Eyes.* The substances used for skin decontamination are generally too strongly irritant to be used on mucous membranes and the eyes. In this case the affected tissues should be flushed immediately with water from the water bottle (canteen). The eyes can be flushed with copious amounts of water, or, if available, isotonic sodium bicarbonate (1.26%) or saline (0.9%).
- c. *Decontamination of the Skin.* Each soldier is given the means for a preliminary decontamination of the skin, the means being based on physical adsorption or on the combination of physical adsorption and chemical inactivation. Physical adsorption can be achieved by adsorbing powders. Chemical inactivation is often effected by chlorinating compounds incorporated into adsorbing powders, ointments, solutions or organic solvents. Mustards should not be decontaminated with water, except for the eyes, as this may spread the agent.
- d. *Additional Procedures.* Whatever means is used has to be efficient and quick acting. Within 2 minutes contact time, a drop of mustard on the skin can cause serious damage. Chemical inactivation using chlorination is effective against mustard and Lewisite, less so against HN3, and is ineffective against phosgene oxime. In the case of thickened mustard, where the usual procedure is inadequate, the agent may be scraped off with a knife or similar hard object. This maybe followed by wetting the surface with a cloth drenched in an organic solvent, e.g., petrol (unleaded gasoline) and subsequent application of the usual decontaminating procedure. If water is available in abundant amounts these procedures should be followed by copious washing.
- e. *Decontamination of Wounds.*
  - (1) Mustard may be carried into wounds on fragments of cloth. These wounds should be carefully explored using a no-touch technique. Fragments of cloth should be removed and placed in a bleach solution. This removes the hazard from mustard vapour off-gassing.
  - (2) Wounds should be irrigated using a solution containing 3000-5000 ppm (parts per million) free chlorine (dilute "milton" solution) with a dwell time of approximately 2 minutes. The wound should then be irrigated with saline. Irrigation of the contaminated wound should not be used in the abdominal, or thoracic cavities, nor with intracranial head injuries.

### 307. Mechanism of Action.

- a. Sulphur and nitrogen mustards are bifunctional alkylating agents, containing two reactive chloroethyl functions. Interaction products with cellular components can occur via formation of ethylenesulfonium (sulphur mustards) or ethylenimanium ions (nitrogen mustards) through cyclisation and subsequent binding. (See Figure 3-1.) In deoxyribonucleic acid (DNA), monofunctional adducts are formed predominantly (the second chloroethyl function is converted into hydroxyethyl), but bifunctional binding, leading to formation of cross-links, does occur. (See Figure 3-1.) Also alkylation of ribonucleic acid (RNA), proteins, cellular membrane components and cross-links between DNA and proteins can be the cause of cellular damage. Among the DNA- and RNA-bases guanine is affected most.
- b. The formation of reactive species of sulphur mustard and the interaction with guanine residues in DNA are shown in Figure 3-I.
- c. The binding of reactive sulphur or nitrogen mustard species to DNA produces a range of effects.
  - (1) Due to their relative instability, N7-alkylated guanine residues may be released from the DNA. Upon DNA replication, the remaining apurinic sites do not provide a proper template of information, which results in erroneous incorporation of nucleotides. This may lead to mutations and synthesis of non-functional proteins.
  - (2) In general, the presence of damage to DNA can include cellular repair mechanisms, which are not error-free. These processes thus may also give rise to erroneous DNA replication.
  - (3) Crosslinks, in particular interstrand crosslinks, for example between two guanines (as shown in Figure 3-I), may play an important role in the cytotoxicity of the sulphur and nitrogen mustards. They inhibit the DNA replication process when they are not properly repaired.

### 308. Toxicity.

- a. HD and HN3 are the most feared vesicants historically, because of their chemical stability, their persistency in the field, the insidious character of their effects by attacking skin as well as eyes and respiratory tract, and because no effective therapy is yet available for countering their effects. Since 1917, mustard has continued to worry military personnel with the many problems it poses in the fields of protection, decontamination and treatment. It should be noted that the ease with which mustard can be manufactured and its great possibilities for acting as a vapour would suggest that in a possible future chemical war HD will be preferred to HN3.
- b. Three distinct levels of biological action can be discerned following exposure to mustards: cytostatic, mutagenic and cytotoxic effects. In the present state of knowledge one cannot rule out the possibility that some effects might be due to reactions with cellular membranes or critical enzymes. The actions of mustards resembling those produced by ionising radiations and mustards have been called radiomimetic compounds.

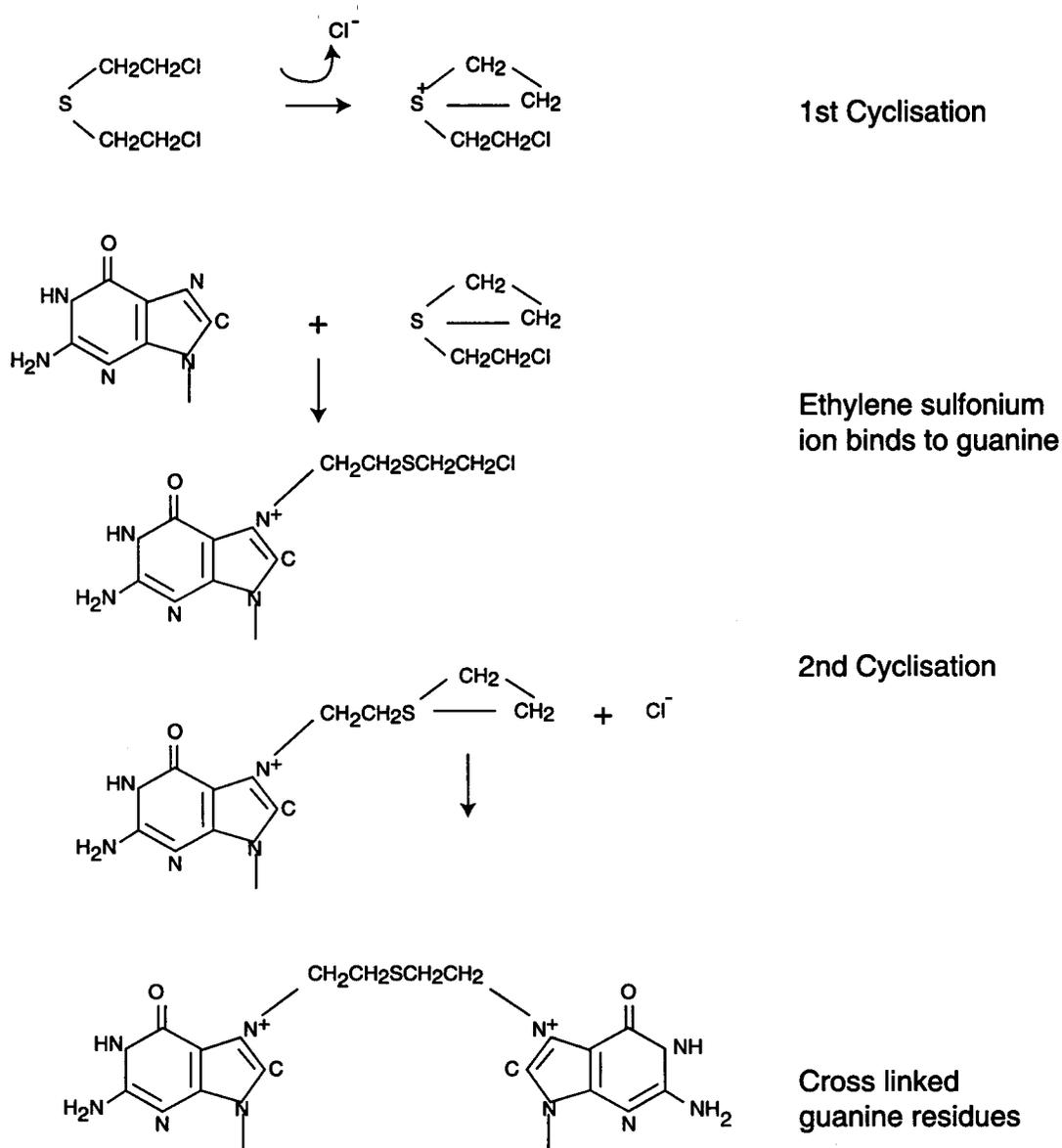


Figure 3-1. Formation of Reactive Sulphur Mustard and Interaction with Guanine in DNA

- c. Actively proliferating cells are affected most; thus basal epidermal cells, the haemopoietic system and the mucosal lining of the intestine are particularly vulnerable.

## SECTION II - CLINICAL-PATHOLOGICAL EFFECTS

### 309. Eyes.

- a. In a single exposure the eyes are more susceptible to mustard than either the respiratory tract or the skin. Conjunctivitis follows exposure of about 1 hour to

concentrations barely perceptible by odour. This exposure does not effect the respiratory tract significantly. A latent period of 4 to 12 hours follows mild exposure, after which there is lachrymation and a sensation of grit in the eyes. The conjunctival and the lids become red and oedematous. Heavy exposure irritates the eyes after 1 to 3 hours and produces severe lesions. Mustard burns of the eyes may be divided as follows:

- (1) Mild conjunctivitis (75% of cases in World War 1). Recovery takes 1 to 2 weeks.
  - (2) Severe conjunctivitis with minimal corneal involvement (15% of cases in World War 1). Blepharospasm, oedema of the lids and conjunctival occur, as may orange-peel roughening of the cornea. Recovery takes 2 to 5 weeks.
  - (3) Mild corneal involvement (10% of cases in World War 1). Areas of corneal erosion stain green with fluorescein dyes. Superficial corneal scarring and vascularisation occurs as does iritis. Temporary relapses occur and convalescence may take 2 to 3 months. Hospital care is indicated for casualties of this type.
  - (4) Severe corneal involvement (about 0.1% of World War 1 mustard casualties). Ischaemic necrosis of the conjunctival may be seen. Dense corneal opacification with deep ulceration and vascularisation occurs. Convalescence may take several months and patients are predisposed to late relapses.
- b. Although temporary blindness may occur, permanent blindness is very rare. Casualties should therefore be reassured and a positive attitude taken.
- c. Care must be exercised to avoid transferring liquid agent from the hands to the eyes.

### 310. Skin.

- a. The hallmark of sulphur mustard exposure is the occurrence of a latent symptom and sign free period of some hours post exposure. The duration of this period and the severity of the lesions is dependent upon the mode of exposure, environmental temperature and probably on the individual himself. High temperature and wet skin are associated with more severe lesions and shorter latent periods. Some people are markedly more sensitive to mustard than others. Burns may be the result of either vapour or liquid exposure.
- b. The sequence of skin changes normally seen is as follows:
- (1) *Erythema (2-48 hour post exposure)*. This may be very striking and reminiscent of scarlet fever. Slight oedema of the skin may occur. Itching is common and may be intense. As the erythema fades areas of increased pigmentation are left. (This sequence is reminiscent of that seen in sun burn.)
  - (2) *Blistering*. Blisters are not, per se, painful, though they may be uncomfortable and feel tense. Blisters at points of flexure, anterior aspects of elbows and posterior aspects of knees, can seriously impede movement. Mustard blisters are delicate and may be easily ruptured by contact with bed linen, bandages or during transport of casualties. Crops of new blisters may appear as late as the second week post exposure. Blister fluid is not dangerous and does not produce secondary blistering if applied to skin.

- (3) *Deep burning leading to full thickness skin loss.* This is particularly likely to occur on the penis and scrotum.
- c. Lesions tend to be painful and some patients complain of very severe pain. Healing of skin lesions is slow. The areas which were markedly erythematous darken and may become very hyperpigmented. Brownish-purple to black discoloration of some areas may occur. These changes tend to disappear over a period of several weeks with desquamation leading to the appearance of areas of hypopigmentation. The appearance of such areas alongside those of hyperpigmentation may be striking.
- d. The sensitivity of the skin depends on its thickness and upon the density of sweat and sebaceous glands. Apart from mucous membranes the most sensitive areas are the face, armpits, genitalia, neck, skin between the fingers and the nail beds. The palm of the hand, sole of the foot and the skin of the scalp are very resistant. If only a small dose is applied to the skin the effect is limited to erythema and after several days the colour changes from red to brown. The itch diminishes progressively and the epidermis desquamates. At higher doses blister formation starts, generally between 4 and 24 hours after contact, and this blistering can go on for several days before reaching its maximum. They are often more than 1 cm<sup>2</sup> and maybe very large and pendulous. Their domes, which are thin and yellowish, contain a relatively clear or slightly yellow liquid. The blisters are fragile and usually rupture spontaneously giving way to a suppurating and necrotic wound. The necrosis of the epidermal cells is extended to the underlying tissues, especially to the dermis. The damaged tissues are covered with slough and are extremely susceptible to infection. The regeneration of these tissues is very slow, taking from several weeks to several months, much longer than the time required for the restoration of skin destroyed by physical means or by caustic compounds. Healing may result in contractures, scarring and fragile skin which may be easily damaged by trauma.

### 311. Respiratory Tract.

Mustard attacks all the mucous membranes of the respiratory tract. After a latent period of 4 to 6 hours, it irritates and congests the mucous membranes of the nasal cavity and the throat, as well as the epitheliums of the trachea and large bronchi. Symptoms start with rhinorrhoea, burning pain in the throat and hoarseness of the voice. This pain may make the patient reluctant to cough. A dry cough gives way to copious expectoration. The vocal cords often become damaged, resulting in aphonia. Airway secretions and fragments of necrotic epitheliums may obstruct the lungs; rales and reduced air entry can be detected by auscultation. There is pronounced dyspnoea. The damaged lower airways become infected easily, predisposing to bronchopneumonia after approximately 48 hours. If the inhaled dose has been sufficiently high the victim dies in a few days, either from pulmonary oedema or mechanical asphyxia due to fragments of necrotic tissue obstructing the trachea or bronchi, or from superimposed bacterial infection, facilitated by an impaired immune response.

**312. Bone Marrow.**

Mustard agents may cause a general depletion of all elements of the bone marrow. The cells of the granulocyte series and megacaryocytes appear more susceptible to damage than those of the erythropoietic system. A reactive leukocytosis may occur during the first three days, followed by a decrease in the peripheral white cell count. The development of a severe leukopenia or an aplastic anaemia indicates a poor prognosis.

**313. Gastrointestinal Tract.**

Ingestion of contaminated food or water may cause destruction of mucous membranes. Symptoms include nausea, vomiting, pain, diarrhoea and prostration. These features may make casualties reluctant to eat. Vomit and faeces may be bloodstained. Shock may occur.

**314. Systemic Action.**

Systemically absorbed mustards by any route, including severe skin exposure, may cause signs similar to those of irradiation, such as headache, nausea, vomiting, leucopenia and anaemia. Gastrointestinal pain commonly occurs. Absorption of high doses may result in CNS excitation leading to convulsions, followed by CNS depression. Cardiac irregularities may occur with atrio-ventricular block and cardiac arrest may follow.

**SECTION III -TREATMENT OF MUSTARD LESIONS****315. Prophylaxis.**

There is no practical drug treatment available for preventing the effects of mustard.

**316. Therapy.**

- a. There is no specific treatment available for the treatment of mustard lesions.
- b. The aim of therapy is to:
  - (1) Relieve symptoms.
  - (2) Prevent infections.
  - (3) Promote healing.

**317. Eye Lesions.**

- a. The effects of mustard on the eyes are very painful. Use of local analgesics may increase corneal damage and are not recommended. Systemic analgesics (narcotics) should therefore be used as required. Secondary infection is a serious complication and increases the amount of corneal scarring. To prevent infection treat with appropriate anti-bacterial preparations. When the lesion proves more serious (blistering of the eyelids, blepharospasm, etc.), continue application of the anti-

bacterial preparation at more frequent intervals. Patients with corneal lesion should receive mydriatics to prevent adhesions between the iris and cornea. In case of troublesome secretions accumulating, the eyes may be carefully irrigated with a 0.9% sterile saline solution and sterile petroleum jelly (Vaseline™) may be applied to the eyelids to prevent sticking. Do not cover the eyes with a bandage, but, if necessary, protect them with dark or opaque goggles. When the eyelids can be separated without too much pain examine the cornea for possible lesions with fluorescein solution followed by lavage: a green spot indicates a lesion, which, when severe should be treated by an ophthalmologist as soon as possible. In some countries ophthalmologists have recommended controversial treatments including the use of citrate and ascorbate eye drops and regular topical steroids.

- b. More severe injuries will cause enough oedema of the lids, photophobia and blepharospasm to obstruct vision. This alarms the patients. To allay their fears, the lids may be gently forced open to assure them that they are not blind.
- c. Although temporary blindness may occur, permanent blindness is very rare. Casualties should therefore be reassured and a positive attitude taken.

### **318. Skin Lesions.**

- a. It is important to ensure that no remaining contamination is present before commencing treatment.
- b. The skin turns red and itches intensely. This itching can be diminished by local applications of cooling preparations, e.g., calamine lotion, corticosteroids in solution, or even water. Ointments and creams are not advised for microbiological reasons. Severe erythema around the genitalia may become quite painful and associated weeping and maceration may ensue. Often, treatment with exposure of the area is desirable and care must be taken so that secondary infection of tissue does not occur.
- c. Infection is the most important complicating factor in the healing of mustard burns. There is no consensus on the need to de-roof blisters or on the optimum form of treatment (open or covered, dry or wet). Once blisters have broken, it is best to remove its ragged roof to decrease the possibility of secondary infection. Routine wound inspection aids in the early detection and institution of appropriate therapy for any complicating bacterial infections. Analgesics should be given as required. Skin grafting is rarely required and when it has been attempted, grafts have not taken well. The use of cytokines is undergoing further research.
- d. In a recent review on the casualties from the Iran-Iraq conflict, it appeared that the healing process and the final outcome were more dependent on the severity of the initial lesion than on the treatment applied.

### **319. Respiratory Tract Lesions.**

Mild respiratory tract injury, with hoarseness and sore throat only, usually requires no treatment. Cough may be relieved by codeine. Laryngitis and tracheitis may be treated symptomatically with steam or sterile cool mist inhalations. If more severe respiratory tract

injury is suspected, hospitalisation may be advisable. If a bacterial pneumonia occurs, isolation of the specific organisms with their antibiotic sensitivities should be performed, then antibiotic therapy can be limited to the specific agents.

### **320. Systemic Effects.**

- a. Every effort should be made to maintain adequate metabolic status and to replace loss of fluids and electrolytes. Infection should be treated promptly and vigorously. The use of growth factors is the subject of ongoing research.
- b. It has been suggested by some authorities that sodium thiosulphate will prevent or reduce systemic damage from mustard, provided that it can be given intravenously within 20 minutes of exposure. Its efficacy is very doubtful if given later.

### **321. Burns Caused by High Doses of Vapour.**

After exposure to a high dose of mustard vapour, especially under tropical conditions, nausea, vomiting and symptoms of collapse are usually evident before erythema develops completely. It is important to note that this occurs also among personnel who are masked during exposure. Constitutional symptoms may persist several days, during which burns will increase in severity. Cases of this type should be classed as casualties. Severe vapour burns of the trunk produce a generalised erythema but include pale grey areas that eventually vesicate or become necrotic. It is common to see patches of unaffected skin as a result of protection by overlying equipment.

### **322. Burns Caused by Low Doses of Vapour.**

Mild vapour burns cause erythema, itching, and irritation but do not produce casualties. The medical officer should always consider the interval after exposure in relation to the severity of the burn. Mild lesions may represent early phases of severe exposure to vapour. When the period since exposure is uncertain, rapidity of development and the presence of constitutional symptoms may help to determine the severity.

### **323. Sensitisation Due to Multiple Exposures to Mustard.**

- a. Attention should be paid to the characteristic appearance of "re-exposure" burns. This manifestation may occur in individuals as a result of exposure to mustard 1 to 3 weeks (or more) previously. A small percentage of men and women will become sensitised to the agent and will react differently, both qualitatively and quantitatively, upon re-exposure. Sensitisation will be followed by a more rapid onset of symptoms upon re-exposure. Erythema, with or without oedema, and pronounced itching and burning usually appear within 1 hour. Lower concentrations of mustard may produce effects in a sensitised person than in a non-sensitised person. When erythema and oedema result from exposure to a low dose, they generally develop rapidly and subside within 2 to 3 days. Also, vesication resolves

more rapidly in the sensitised individual.

- b. One of the most frequent manifestations of re-exposure in sensitised individuals is the development of a morbilliform rash. Another characteristic reaction is the appearance of eczematoid dermatitis surrounding old lesions, whether or not they are healed. This may last for several days and resembles dermatitis venenata (from poison ivy). Similar phenomena due to sensitisation have been known to occur with the nitrogen mustards.

### 324. Disposition of Casualties.

- a. Evaluation of lesions that have most generally led to disability of personnel exposed to blister agents during field trials and who subsequently participated in simulated combat exercises, obstacle course tests and marches, resulted in the following observations:
  - (1) Widespread vesication of the trunk produced casualties.
  - (2) Vesication localised in particular areas of the body produced casualties.
  - (3) Burns caused by high doses of the vapour to masked personnel, especially in tropical climates, are of casualty severity partly due to oedema and vesication of the skin and partly to constitutional reactions such as nausea, vomiting and prostration.
  - (4) Burns produced by doses of vapour low enough to cause only such skin reactions as mild erythema, oedema, burning and itching usually do not produce casualties.
  - (5) The stage of development of the lesion must be considered when classifying an individual as a casualty or non-casualty.
- b. The effects of mustard on particular areas of the body are explained below.

### 325. Trunk and Neck.

#### *a. Extensive Vesication of the Trunk.*

- (1) All the patients considered under this heading should be evacuated promptly. Extensive vesication may occur over a large part of the trunk. Intervening areas of skin may be erythematous with pin-point vesication. These burns are more likely to occur on the back than anteriorly.
- (2) Some protection is afforded anteriorly by equipment such as webbing and ammunition pouches. The front of the uniform also gives some anterior protection because it does not cling to the body.
- (3) Extensive vesication may be followed by fever, nausea and vomiting.
- (4) These effects tend to occur more readily in tropical climates.
- (5) Secondary bacterial infection may complicate the clinical course. The medical officer in a forward position is not likely to see infection of vesicated areas because such cases will have been evacuated before secondary infection develops.

#### *b. Localised Vesication of the Trunk.*

- (1) Vesication occurring within the natal cleft (between the buttocks) usually requires evacuation of the casualty. Walking becomes difficult, defecation is

painful and dressings require frequent changing. The lesion is usually most intense at the upper end of the cleft. Vesication of the buttocks usually results from sitting on contaminated ground or in contaminated trousers for prolonged periods. The vesicated area may extend forward across the perineum to involve the scrotum and the penis.

- (2) Trivial burns, such as mild erythema affecting the natal cleft, are not of casualty severity. However, these burns require careful attention because walking or running aggravates the lesions and may break down injured skin.
- (3) Single discrete blisters on the buttocks away from the natal cleft do not produce casualties.
- (4) Blisters on the trunk generally require protective dressings to prevent friction due to clothing. The medical officer must decide whether dressings should remain in position during regular duty.

### **326. Arms.**

- a. Most individuals with blister agent injuries of the arms, when suitably treated, are permitted to continue with their duties. Vesication, when localised produces little or no disability.
- b. Extensive vesication involving the axillae and the elbows, volar or dorsal aspects, partially impairs the movement of the limbs at those joints. Oedema of the surrounding tissue tends further to immobilise the extremities. The dorsal aspects of the elbow and forearm are common sites of severe burns because these parts touch contaminated ground when men and women are firing in the prone position. Casualties of this type should be evacuated.
- c. Widespread vesication of the arms results in partial disability. Casualties of this type should be evacuated.

### **327. Hands.**

- a. Blister agent burns of the hands are often encountered. These burns tend to cause a degree of disability out of proportion to the size of the lesions. Considerable care and judgement are required in correct disposition.
- b. Experience in tropical experimental installations indicates that protective gloves and protective ointment provide adequate protection against high doses of vapour. Yet it is hard to avoid burns of the hands in a heavily contaminated jungle. The palms are more resistant to vesication but blisters affecting the palms are characteristically painful and slow to heal.
- c. A solitary lesion of limited extent may result in little or no disability if treated properly.
- d. Burns from liquid vesicant on the dorsum of the hand result in severe local reactions characterised by intense oedema of the backs of the hands and fingers. Pain is characteristic and is intensified by movement of the fingers or wrist. These patients should be regarded as casualties. An individual exposed within the previous 24 hours and reporting for treatment with apparently trivial blisters may be totally incapacitated the following day. Sharp erythema of the dorsum of the hand, with

vesication beginning 12 to 24 hours after exposure, indicates a lesion that will progress to extensive vesication and oedema. Under such circumstances the individual should be evacuated when first seen.

- e. More commonly, the lesions consist of scattered small vesicles and limited areas of erythema. These lesions can be protected satisfactorily and the individuals returned to duty.
- f. Exposure to vesicant vapour produces diffuse erythema of the dorsum of the hand and wrist. Higher doses cause oedema and vesication as well; patients of this type require evacuation.

### **328. Lower Extremities.**

- a. When the lower extremities are involved, the knees are the most common sites of burns from liquid vesicant. These lesions and those of the ankles often result in incapacitation by interfering with locomotion. Movement of joints tends to aggravate existing lesions by increasing oedema. A further disabling factor is introduced by the wearing of firm dressings applied to mobile joints.
- b. Vesication often spreads over the kneecaps, upward onto the thighs, and down toward the feet. These burns tend to be extensive and are associated with oedema often extending halfway up the thigh and down the leg. Medical officers should evacuate casualties with such lesions.
- c. In general, burns of the leg are more incapacitating than burns of the thigh.
- d. It has been shown that the presence of many superficial blisters on the legs and thighs alone is not enough to make an individual incapable of carrying out routine military duties. Individuals with such lesions, having suitable dressings, were able to take part in daily marches and routine gun drills. In disposing of these cases, the medical officer will consider the mental and physical status of the individual, his or her willingness to carry on, and the tactical situation at the time. Such patients are in the category of partial disability. After suitable dressings have been applied, individuals with high morale and robust physiques may be returned to duty.
- e. A relatively small blister or group of blisters situated in the popliteal area may reduce the efficiency of a man or woman so much that he or she may require evacuation. This is due to aggravation of the lesions by movement of the limbs and interference with ambulation. However, blisters affecting this area are not necessarily casualty-producing. (Inflammation, oedema, infection and lesions on other parts of the body should be considered when deciding upon the disposition of an individual). Available evidence indicates that the mustard blister, size for size, is potentially more incapacitating than a blister from lewisite. This results from the tendency of mustard blisters to be associated with erythema and oedema, while the lewisite blister usually causes little local reaction.
- f. Vesicant lesions also develop near the ankles at the tops of the shoes. Blistered areas occurring at such unprotected points are associated with severe pain due to circulatory impairment and tense oedema of the leg. These patients should be evacuated.
- g. Vapour burns of the legs tend to be most aggravated in the popliteal spaces. Pin-point

vesication is often found here. Higher doses cause intense erythema with scattered areas of vesication over the entire surface of the leg. Such lesions are invariably casualty producing and are generally accompanied by severe burns elsewhere, frequently with severe systemic effects.

- h. Mild vapour burns of the legs produce irritation and itching common to all widespread vapours burns. While these effects are troublesome, they are not casualty producing, and men or women so affected maybe returned to duty.
- i. Extensive vesication of the feet is uncommon. The soles are protected by shoes and are comparatively resistant to vesication. Burns on the dorsal aspect of the foot are often associated with local reactions like those seen on the backs of hands. Individuals with these burns, especially if widespread over the foot, find it difficult or impossible to wear shoes and will require evacuation. Small discrete blisters may be of non-casualty significance. These blisters may be effectively protected so as to allow wearing of shoes and walking with little discomfort.

### **329. Genitalia.**

- a. The genital region, in addition to the eyes and the respiratory tract, is highly sensitive to blister agent burns. In World War I such burns produced many casualties. The majority of these burns were caused by vapour. Despite present methods of protection against blister agents, including impregnated garments designed to protect the genitalia, medical officers (especially in tropical areas) may be confronted with many casualties with such burns.
- b. Vapour is a more common cause of burns affecting the male genitalia than liquid agent. Erythema may not be conspicuous. The most prominent feature of the burn is the oedema involving the penis and scrotum. Fluid accumulates most readily in the prepuce, distending its entire circumference and forming a characteristic semitranslucent ring around the cornea. In more severe cases the entire body of the penis becomes oedematous.
- c. The lesions cause apprehension as well as physical discomfort. Occasionally vesication is superimposed on the oedema. Ulceration is not infrequent at the tip of the prepuce where it may become secondarily infected. In severe cases associated with marked oedema, retention of urine may result from both mechanical and reflex effects.
- d. In mild cases, objective changes of the scrotum often tend to pass undetected due to the normal pigmentation, elasticity, and looseness of the skin. Even considerable oedema may not be enough to reveal its presence. In severe cases the scrotum may become grossly enlarged. The rugae may be partly or completely obliterated. Pin-point vesication may occur, usually after a lapse of a few days. The scrotal skin tends to breakdown resulting in small painful ulcers and fissures.
- e. Burning is the most prominent subjective symptom in involvement of the genitalia. Apprehension and anxiety are distressing during the presence of the objective changes described above. As oedema decreases, itching starts and may persist long after the acute effects have subsided. Sometimes this itching is intolerable. The scrotum may continue to crack and ulcerate for a considerable period, causing pain and irritation.

- f. Mild exposure of the genital region characteristically is followed by a delay in the development of symptoms, often for as long as 4 to 10 days.
- g. Patients with mild burns without oedema or vesication, but who complain of irritation and burning, may be safely returned to duty following treatment. In disposing of mild burns of the genitalia, the medical officer must assure himself that the symptoms are not too early to be judged with finality. Severely affected individuals should be evacuated on the basis of the apprehension that may be suffered as well as the physical discomfort involved.

### **330. Systemic Effects of Cutaneous Burns.**

- a. Systemic effects due to blister agents probably may be encountered with disabling skin lesions and lesions of the respiratory tract. The medical officer should be familiar with the signs and symptoms. These include anorexia, nausea, vomiting, depression and fever and are far more prone to occur in hot than in temperate climates. Malaise and nausea generally are the first reactions and may then progress either to mild, transient vomiting or to severe, persistent vomiting and retching. Anorexia may be the only complaint in mild reactions. The actual time of onset of symptoms is 4 to 12 hours after exposure and symptoms often occur before skin injury is manifest. No rule can be given for the duration of systemic symptoms, although men or women usually have recovered from severe vomiting within 24 to 26 hours. Anorexia and nausea may persist for a longer time.
- b. The temperature may remain elevated for several days. Mental depression may follow mustard burns and persist for several days.
- c. People with systemic reactions will generally be casualties, particularly in view of the probability of associated extensive skin burns. Such casualties should be evacuated quickly.

### **331. Secondary Bacterial Infection in Blister Agent Burns.**

- a. This paragraph considers the problem of secondary bacterial infection after blister agent injuries only as it influences the disposition of affected personnel in forward positions.
- b. Secondary bacterial infection has often been cited as a common complication of mustard burns of the skin. Compared with the incidence of infection in thermal and traumatic wounds, indications are that the incidence of sepsis in mustard lesions is remarkably low according to observations made at experimental installations.
- c. Secondary infection becomes manifest several days after injury. Medical officers are not likely to see secondary infection with extensive blister agent burns in the front lines because severely affected patients should have been evacuated early.
- d. Infection of small lesions does not require evacuation. Infection of multiple lesions is likely to be an indication for evacuation, particularly if constitutional effects are associated. Infection is particularly disabling when it involves the feet, the hands, the genitalia or tissues overlying the joints of the limbs.
- e. Secondary infection is more likely to occur in severe, rather than mild, vapour injury

- to the respiratory tract. Severe respiratory symptoms will almost invariably be associated with severe eye effects. Respiratory lesions may not develop for several days, and by then the individual should have been evacuated as an eye casualty.
- f. Secondary infection is uncommon as a sequel to mild degrees of mustard conjunctivitis and ordinarily would not prevent an individual from continuing duty.
  - g. Mild conjunctival burns maybe associated with pharyngitis, laryngitis, and tracheitis, increasing in severity for several days. Occasionally more extensive respiratory infection may ensue.

### 332. Course and Prognosis.

As has already been stated, the great majority of mustard gas casualties survive. Resolution of specific problems can be difficult to predict but the following may provide a guide.

- a. *Eye lesions:* Most are resolved within 14 days of exposure.
- b. *Skin lesions:* Deep skin lesions maybe expected to heal in up to 60 days. Superficial lesions heal in 14-21 days.
- c. *Upper respiratory tract lesions:* It is very difficult to define a time course for complete recovery. Recent experience with patients from the Iran-Iraq conflict during 1984-86 was that they were often discharged whilst still coughing and complaining of expectoration. Lung function tests on patients with purely upper respiratory tract lesions were usually normal on discharge. Patients with parenchymal damage often showed an abnormal pattern on lung function testing.

### 333. Long Term Effects of Mustard Gas Poisoning.

The long term effects of mustard maybe divided into three groups:

- a. Personnel exposed to mustard agents may experience prolonged psychological manifestations including chronic depression, loss of libido and anxiety.
- b. Local effects of mustard exposure may include:
  - (1) Visual impairment (permanent blindness is extremely rare).
  - (2) Scarring of the skin.
  - (3) Chronic bronchitis.
  - (4) Bronchial stenosis.
  - (5) Increased sensitivity to mustard gas.
- c. Sulphur mustard is a known carcinogen. A follow up study of American soldiers exposed to sulphur mustard during World War I revealed an increased incidence of lung cancer (and chronic bronchitis) as compared with soldiers who had sustained other injuries. A study of British workers involved in the production of sulphur mustard during World War II revealed no increase in deaths due to cancer amongst those who had died since 1945, but an increase in the prevalence of laryngeal carcinoma amongst those still alive.

## SECTION IV - ARSENICAL VESICANTS - LEWISITE

**334. Introduction.**

The arsines possessing the  $-AsCl_2$  group are endowed with vesicant properties. Of these lewisite is the best known and the most characteristic. Initially preparations contained considerable impurities, but at the end of World War I it was purified in the US, without having been used on the battlefield. Lewisite is 2-chlorovinyl-dichloroarsine,  $ClCH=CH-AsCl_2$ .

**335. Physical and Chemical Properties.**

- a. *Physical Properties.* In a pure form lewisite is a colorless and odourless liquid, but usually contains small amounts of impurities that give it a brownish colour and an odour resembling geranium oil. It is heavier than mustard, poorly soluble in water but soluble in organic solvents. The physical properties are shown in Table 3-I.
- b. *Chemical Properties.* In contact with water lewisite is hydrolyses at an appreciable rate, forming an oxide that is equally vesicant, according to the reaction:  $ClCH=CH-AsCl_2 + H_2O \rightarrow ClCH=CH-AsO + 2HCl$ . In contact with strong alkalis lewisite is totally decomposed to non-vesicant products. Lewisite is very sensitive to oxidants due to the trivalent arsenic atom.

**336. Detection.**

The detection of lewisite is facilitated by the fact that it forms coloured products with many reagents. Draeger™ tubes are available which react with organic arsenical. However, no automatic detectors are available for use in the field.

**337. Protection.**

Ordinary clothing gives little or no protection against lewisite. Special equipment including a respirator, NBC suit, gloves and overboots are required.

**338. Decontamination.**

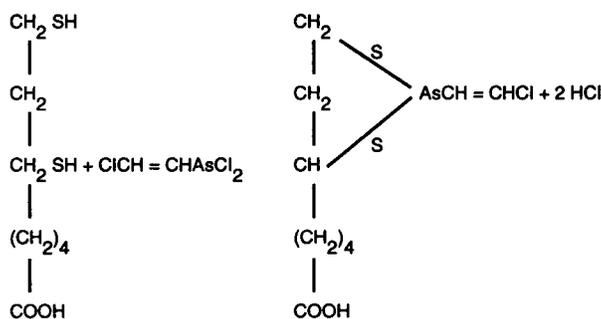
Decontamination is the same as for mustard.

Table 3-1. Physical Properties of Vesicants

Property	Sulphur mustard	Nitrogen mustard	Lewisite	Mustard/lewisite mix	Phosgene oxime
Appearance	Colourless to light yellow liquid, giving off a colourless vapour	Dark coloured liquid giving off a colourless vapour	Dark oily liquid giving off a colourless vapour	Dark oily liquid giving off a colourless vapour	White solid or yellow-brown liquid
Chemical formula	$  \begin{array}{c}  \text{H} & \text{H} & \text{H} & \text{H} & \text{H} \\    &   &   &   &   \\  \text{Cl}-\text{C}-\text{C}-\text{S}-\text{C}-\text{C}-\text{Cl} \\    &   &   &   &   \\  \text{H} & \text{H} & \text{H} & \text{H} & \text{H}  \end{array}  $	$  \begin{array}{c}  \text{CH}_2\text{CH}_2\text{Cl} \\  \diagdown \quad \diagup \\  \text{N} \\  \diagup \quad \diagdown \\  \text{CH}_2\text{CH}_2\text{Cl} \\  \text{CH}_2\text{CH}_2\text{Cl}  \end{array}  $	$  \begin{array}{c}  \text{H} & \text{Cl} \\    &   \\  \text{H}-\text{C}=\text{C}-\text{As}-\text{Cl} \\    &   \\  \text{Cl} & \text{H}  \end{array}  $		$  \begin{array}{c}  \text{Cl} & & \text{H} \\  & \diagdown & / \\  & \text{C}=\text{N}-\text{O}- \\  & / & \diagdown \\  \text{Cl} & & \text{H}  \end{array}  $
Molecular weight	159.1	204.5	207.35	Not applicable	113.9
Density (g.cm <sup>-3</sup> )	1.27 (25°C)	1.24 (25°C)	1.89 (20°C)	1.66 (20°C)	
Melting point	14.5 °C	-3.7°C	-8 to 0.1°C (diff. purity)	-24.4°C	39 to 43°C
Boiling point	217.0 °C	256.0°C	190.0°C	190.0°C	129.0°C
Vapour density	5.4	7.1	7.1	6.5	3.94
Vapour pressure (mmHg)	0.072 (°20C)	0.011	0.087 (0°C) 0.394 (20°C)	0.02 (-10°C) 0.248 (20°C) 1.03 (40°C)	3.6 (20°C)
Volatility (mg.m <sup>-3</sup> )	75 (0°C) 610 (20°C) 2860 (40°C)	13 (0°C) 121 (25°C) 390 (40°C)	1060 (0°C) 4480 (20°C) 8260 (30°C)	240 (-11°C) 2730 (20°C) 10270 (40°C)	20,000 (20°C) 60,000 (35°C)

**339. Mechanism of Action.**

- a. Due to its physical and chemical properties, lewisite can easily penetrate the skin, where it exerts its vesicant action. It can spread through the whole body and act as an arsenical poison. It has been shown that lewisite inhibits a great number of SH (percentage saturation of hemoglobin) group containing enzymes. Inhibition of the pyruvate dehydrogenase system is a property common to all trivalent arsenic compounds.
- b. Lipoic acid is an essential part of the pyruvate dehydrogenase system, acting as a co-enzyme in the formation of acetyl-Co-A from pyruvate. Lewisite is thought to combine with lipoic acid to form a cyclic compound, thereby interfering with energy production within the cell (Figure 3-II).



*Figure 3-II. Formulation of Cyclic Compound From Lewisite*

## SECTION V - CLINICAL-PATHOLOGICAL EFFECTS

**340. Eyes.**

Liquid arsenical vesicants cause severe damage to the eye. On contact, pain and blepharospasm occur instantly. Oedema of the conjunctival and lids follow rapidly and close the eye within an hour. Inflammation of the iris usually is evident by this time. After a few hours, the oedema of the lids begins to subside, while haziness of the cornea develops and iritis increases. The corneal injury, which varies with the severity of the exposure, may heal without residual effects, induce pannus formation, or progress to massive necrosis. The iritis may subside without permanent impairment of vision, if the exposure was mild. After heavy exposure, hypopyon may ensue, terminating in necrosis, depigmentation of the iris and synechia formation. Liquid arsenical vesicants instantly produce a grey scarring of the cornea, like an acid burn, at the point of contact. Necrosis and sloughing of both bulbar and palpebral conjunctival may follow very heavy exposure. All injured eyes are susceptible to secondary infection. Mild conjunctivitis due to arsenical vesicants heals in a few days without specific treatment. Severe exposure may cause permanent injury or blindness.

### 341. Skin.

- a. *Pathology.* Liquid arsenical vesicants produce more severe lesions of the skin than liquid mustard. Contamination of the skin is followed shortly by erythema, then by vesication which tends to cover the entire area of erythema. The surrounding halo of erythema is less noticeable than with mustard blisters, although the two are often indistinguishable. Microscopically, the blister roof is slightly thicker than the mustard blister roof, consisting of almost the complete thickness of the epidermis and showing more complete coagulation necrosis and less disintegrative necrosis than that of the mustard blister. The yellowish blister fluid is slightly more opaque than that of the mustard blister and microscopically, contains more inflammatory cells. It contains a trace of arsenic but is non-toxic and non-vesicant. There is deeper injury to the connective tissue and muscle, greater vascular damage, and more severe inflammatory reaction than is exhibited in mustard burns. In large, deep, arsenical vesicant burns, there may be considerable necrosis of tissue, gangrene and slough.
- b. *Symptoms.* Stinging pain is felt usually in 10 to 20 seconds after contact with liquid arsenical vesicants. The pain increases in severity with penetration and in a few minutes becomes a deep, aching pain. Pain on contact with liquid arsenical vesicants usually gives sufficient warning so that decontamination may be begun promptly and deep burns thus avoided in conscious victims. After about 5 minutes of contact, there appears a grey area of dead epitheliums resembling that seen in corrosive burns. Erythema is like that caused by mustard but is accompanied by more pain. Itching and irritation persist for only about 24 hours whether or not a blister develops. Blisters are often well developed in 12 hours and are painful at first, in contrast to the relatively painless mustard blister. After 48 to 72 hours, the pain lessens.

### 342. Respiratory Tract.

The vapours of arsenical vesicants are so irritating to the respiratory tract that conscious casualties will immediately put on a mask to avoid the vapour. No severe respiratory injuries are likely to occur except among the wounded who cannot put on masks and the careless, who are caught without masks. The respiratory lesions are similar to those produced by mustard except that in the most severe cases, pulmonary oedema may be accompanied by pleural effusion.

### 343. Systemic Effects.

Liquid arsenical vesicants on the skin, as well as inhaled vapour, are absorbed and may cause systemic poisoning. A manifestation of this is a change in capillary permeability, which permits loss of sufficient fluid from the bloodstream to cause haemoconcentration, shock and death. In non-fatal cases, haemolysis of erythrocytes has occurred with a resultant haemolytic anaemia. The excretion of oxidised products into the bile by the liver produces focal necrosis of that organ, necrosis of the mucosa of the biliary passages with peribiliary hemorrhages and some

injury of the intestinal mucosa. Acute systemic poisoning from large skin burns causes pulmonary oedema, diarrhoea, restlessness, weakness, subnormal temperature and low blood pressure.

## SECTION VI - TREATMENT OF LEWISITE LESIONS

### 344. General.

An antidote for lewisite is dimercaprol (2, 3-dimercapto-propanol,  $\text{CH}_2\text{SH} - \text{CHSH} - \text{CH}_2\text{OH}$ , BAL (British Anti Lewisite)). Purified dimercaprol is a colorless liquid, soluble 1 part in 15 parts of water and more soluble in peanut oil or in ethanol. It can combine with arsenic forming a water soluble complex that can be excreted. With arsenical, the complex formed possesses a pentagon with two carbon atoms, two sulphur atoms and one arsenic atom at the comers. This is the same mechanism by which lewisite blocks two adjacent SH groups of pyruvate dehydrogenase system. The therapeutic action of dimercaprol can thus be explained by the law of mass action: dimercaprol provides the organism with a great number of adjacent SH groups that displaces the arsenic bound to enzymes. The enzymes are reactivated and can resume their normal biological activity. However, the toxicity of dimercaprol itself must be considered. It sometimes provokes local irritation.

### 345. Eyes.

- a. Dimercaprol eye ointment may diminish the effects of lewisite if applied within 2 minutes of exposure. Its value is questionable if applied later than this.
- b. In severe cases, the systemic use of morphine may be necessary for control of pain. When the conjunctival oedema subsides enough to permit ophthalmic examination, the cornea should be stained with fluorescein to detect erosions and the iris should be examined for iritis. Atropine sulphate ointment should be instilled to obtain and maintain good mydriasis in all cases with corneal erosions, iritis cyclitis or with marked photophobia or miosis. Antibiotics may be used to combat infection. Sterile petroleum jelly (Vaseline™) applied to the lid margins will help prevent their sticking together. Irrigations of the eye should be sparing, employing isotonic solutions. Occlusive dressings or pressure on the globe must be avoided.

### 346. Skin.

- a. Dimercaprol (British Anti-Lewisite (BAL)) ointment may be applied to skin exposed to lewisite before actual vesication has begun. Any protective ointment already on the skin must be removed before application of BAL ointment because it may destroy the latter. BAL ointment is spread on the skin in a thin film and allowed to remain at least 5 minutes. Occasionally, BAL ointment causes stinging, itching or urticarial weals. This condition lasts only an hour or so and should not cause alarm. Mild dermatitis may occur if BAL ointment is frequently applied on the same area of skin; hence, this property precludes its use as a protective ointment. Dimercaprol is chemically incompatible with silver sulphadiazine and the two should not be used together.
- b. Some blistering is inevitable in most arsenical vesicant cases which come to the

Medical Services. The treatment of the erythema, blisters and denuded areas is identical with that for similar mustard lesions. A severe third degree burn involving a large surface area is similar to a thermal injury and must be managed by intravenous resuscitation to correct potential hypovolaemic shock. Morphine and splinting of the affected parts may be necessary to relieve pain. When the involved area is greater than 20% of the body surface area, hospitalisation is indicated. Hospitalisation may be indicated when the involved area is less than 20% when the depth of the skin involvement appears to be significant.

### **347. Systemic.**

burns severe enough to cause shock and systemic poisoning are life-threatening. Even if the patient survives the acute effects, the prognosis must be guarded for several weeks.

### **348. Indication for Systemic Treatment.**

The indications for systemic treatment, following exposure to arsenical blister agents by any route are:

- a. Cough with dyspnoea and frothy sputum, which may be blood tinged and other signs of pulmonary oedema.
- b. A skin burn the size of the palm of the hand or larger, caused by a liquid arsenical blister agent which was not decontaminated within the first 15 minutes.
- c. Skin contamination by a liquid arsenical vesicant covering 5% or more of the body surface, in which there is evidence of immediate skin damage (grey or dead-white blanching of the skin), or in which erythema develops over the area within 30 minutes.

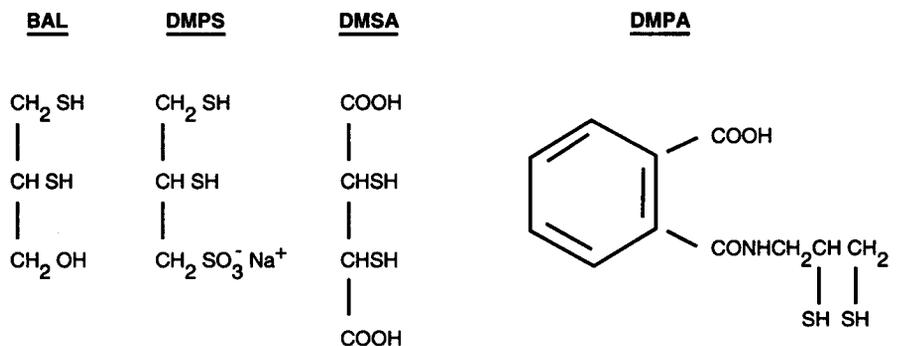
### **349. Types of Treatment.**

- a. The following two types of treatment may be used:
  - (1) Local neutralisation on and within the skin by a liberal application of dimercaprol (BAL) ointment. The affected skin is to be left covered with a layer of ointment. Remove any other protective ointment before treatment with BAL ointment.
  - (2) Intramuscular injection of BAL in oil (10%).
- b. The maximum dosage of BAL is as follows. 3 mg.kg<sup>-1</sup> (200 mg for an average person) intramuscularly repeated every 4 hours for 2 days, every 6 hours on the third day and every 12 hours for up to 10 days. The injection must be by deep intramuscular injection; subcutaneous leakage must be avoided.
- c. Dimercaprol when given by injection often produces alarming reactions including:
  - (1) Increased systolic and diastolic pressure.
  - (2) Tachycardia.
  - (3) Nausea and vomiting.
  - (4) Headache.
  - (5) Burning sensation of lips.
  - (6) Feeling of constriction of the chest.

- (7) Conjunctivitis.
  - (8) Lachrymation.
  - (9) Rhinorrhoea.
  - (10) Sweating.
  - (11) Anxiety and unrest.
- d. Despite these effects “the cure is not worse than the disease” and they pass in a few hours. About 50% of patients will experience such adverse reactions if 5 mg.kg<sup>-1</sup> doses of dimercaprol are given.
- e. Unless unduly severe or prolonged they do not contra-indicate the full course of treatment.

### 350. Therapy.

- a. Dimercaprol is the current therapy for lewisite poisoning. Newer chelating agents, however, have been developed and some look promising for systemic use.
- b. The abbreviations used in this paragraph are as follows:
- (1) DMSA (meso-dimercaptosuccinic acid).
  - (2) DMPS (2,3-dimercapto-1-propanesulfonic acid).
  - (3) Na (salt).
  - (4) DMPA (N-(2,3-dimercaptopropyl)-phthalamidic acid).
- c. Their formulae and that of dimercaprol are shown in Figure 3-III.
- d. The advantages of these compounds include:
- (1) They are water soluble, active when given orally and relatively non-toxic.
  - (2) They are substantially more effective systemically, using the therapeutic index as a measure.
  - (3) BAL produces mobilisation of arsenic from most tissues (for brain see (4)) but is less effective in so doing than DMSA, DMPS and DMPA.
  - (4) BAL given to rabbits poisoned with sodium arsenite produced an increase in brain arsenic levels. DMPA and DMPS on the other hand produced a marked fall in brain arsenic levels.
  - (5) DMSA and DMPS have been identified as having an anti-lewisite action.
  - (6) Of the series DMPS, DMSA and BAL when tested for capacity to reverse or prevent pyruvate dehydrogenase inhibition by sodium arsenite, DMPS proved the most potent and BAL the least potent drug.
- e. The evidence then appears to support the contention that the more recently developed chelating agents should be considered as alternatives to dimercaprol in the treatment of systemic lewisite poisoning. Detailed metabolic studies have not yet been performed on DMSA and DMPS and there is an urgent need for such work.



*Figure 3-III. Formulae for Lewisite Antidotes*

### 351. Course and Prognosis.

The long term effects of exposure to lewisite are unknown.

## SECTION VII - HALOGENATED OXIMES

### 352. Introduction.

The urticant properties of the halogenated oximes were discovered long before World War II. To this group belong diiodofomoxime, dibromofomoxime, monochlorofomoxime and dichlorofomoxime. The last mentioned oxime is the most irritant of the series; it is commonly known as phosgene oxime, symbolised by CX. Its chemical formula is  $\text{CCl}_2 = \text{NOH}$ .

### 353. Physical and Chemical Properties of Phosgene Oxime.

Phosgene oxime is a white crystalline powder. It melts between 39 - 40°C, and boils at 129°C. By the addition of certain compounds it is possible to liquify phosgene oxime at room temperature. It is fairly soluble in water and in organic solvents. In aqueous solution phosgene oxime is hydrolyses fairly rapidly, especially in the presence of alkali. It has a high vapour pressure, its odour is very unpleasant and irritating. Even as a dry solid, phosgene oxime decomposes spontaneously and has to be stored at low temperatures.

### 354. Detection.

The characteristic signs and symptoms of phosgene oxime exposure may suggest its use. There are no automatic detectors available for use in the field.

**355. Protection.**

Ordinary clothing gives little or no protection against phosgene oxime. Special equipment including a respirator, NBC suit, gloves and overboot are required.

**356. Decontamination.**

Chemical inactivation using alkalis is effective, whereas chlorination is ineffective against phosgene oxime. The eyes should be flushed immediately using water or isotonic sodium bicarbonate solution if available. Physical decontamination of the skin using adsorbent powders, e.g., fullers' earth, is advised.

**357. Mechanism of Action.**

In low concentrations, phosgene oxime severely irritates the eyes and respiratory organs. In high concentrations, it also attacks the skin. A few milligrams applied to the skin cause severe irritation, intense pain, and subsequently a necrotising wound. Very few compounds are as painful and destructive to the tissues. Systemic toxicity has been described from parenteral absorption. The exact mode of action is not known. The effects are said to be caused by phosgene oxime reacting with SH and H<sub>2</sub>N groups.

**358. Clinical-Pathological Effects.**

Phosgene oxime also affects the eyes, causing corneal lesions and blindness and may affect the respiratory tract causing pulmonary oedema. The action on the skin is immediate: phosgene oxime provokes irritation resembling that caused by a stinging nettle. A few milligrams cause intense pain which radiates from the point of application, within a minute the affected area turns white and is surrounded by a zone of erythema which resembles a wagon wheel in appearance. In 1 hour the area becomes swollen and within 24 hours the lesion turns yellow and blisters appear. Some days later the area shows desquamation with necrosis of the skin followed by crust formation and a purulent discharge.

**359. Treatment.**

Treat as any other ulcerated necrotic skin lesion (e.g., thermal burn) with due consideration of other supportive measures. Pulmonary oedema should be treated appropriately.

**360. Course and Prognosis.**

Recovery takes 1 to 3 months.