

Vesicants (Blister Agents)

MUSTARD AND NITROGEN MUSTARDS

Introduction

Blister or vesicant agents are likely to be used both to produce casualties and to force opposing troops to wear full protective equipment. These will degrade fighting rather than kill (although very severe exposure to vesicants can be fatal). Blister agents can be thickened in order to enhance persistency and contaminate terrain, ships, aircraft, vehicles or equipment. The vesicant agents include sulphur mustard (H - HD refers to distilled mustard), nitrogen mustard (HN), the arsenical vesicants such as Lewisite (L) (this may well be used in a mixture with H), and the halogenated oximes, eg. phosgene oxime, (CX) whose properties and effects are very different from those of the other vesicants.

Vesicants burn and blister the skin or any other part of the body surface they contact. They act on the eyes, mucous membranes, lungs, skin and blood-forming organs: bone marrow and spleen. They damage the respiratory tract when inhaled and cause vomiting and diarrhoea when ingested. Blister agents may also cause bone marrow suppression and have effects on other germ cells.

MUSTARD AGENTS

Sulphur mustard was used extensively in World War I and has been used more recently in Iran/Iraq. Protection against these agents can only be achieved by a full protective ensemble. The respirator alone protects against eye and lung damage, but does not give sufficient protection against systemic effects. Extensive, slow healing skin lesions and other effects will place a heavy burden on the medical services.

Sulphur mustard is the best known of these agents. It was first synthesised in 1822, and its vesicant properties were discovered in the middle of the nineteenth century. It was used for the first time as a CW agent in 1917 near Ypres, Belgium, 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.

In the US, the symbol HD has been given to the distilled product; this abbreviation will be used in this section. 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:

- (1) N-ethyl-2,2'-di(chloroethyl)amine, (HN1).
- (2) N-methyl-2,2'-di(chloroethyl)amine, (HN2).
- (3) 2,2',2''-tri(chloroethyl)amine, (HN3).

All of the above nitrogen mustards are alkylating agents and HN2 was introduced in 1935 as the first chemotherapeutic agent. 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.

Physical and Chemical Properties

The mustards are able to penetrate most tissues they come into contact with and a great number of materials: woods, leather, rubber, plants, etc. Mustards are very persistent in cold and temperate climates. In warmer climates the persistence of mustards is reduced but the hazard from vapour increases. It is possible to increase the persistency by thickening mustard with finely powdered material such as chlorinated rubber. These thickened mustards are very difficult to remove by decontaminating processes.

Mustards may be hydrolysed in water but thorough mixing is required for this to be achieved. Alkalinity and higher temperatures increase the rate of hydrolysis. In running water, the contact surfaces are frequently changed and persistency is only a few days, but in stagnant water, they can persist for several months. Mustard is more dense than water, but small droplets remain on the water surface and present a special hazard in contaminated areas. Spreading can also occur when decontaminating the skin with aqueous solutions; this effect can be minimised by flushing with copious amounts of water and emulsifying agents.

The bivalent sulphur atom of sulphur mustard confers very good reducing properties. Oxidants will oxidise mustard to a greater or lesser extent (depending on their strength) to sulfoxide, sulfone or sulphate. Of these, only the sulfone has appreciable vesicant properties. Nitrogen mustards are

much less easily oxidised than sulphur mustard.

Detection

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 vapour hazard and water testing kits are also available.

Protection

Ordinary clothing gives little or no protection against mustard agents - a respirator, NBC suit, gloves and foot protection are required. Due to slow absorption of mustard by many materials, protective equipment must be changed regularly. There is no drug available to prevent the effects of mustard on the skin and the mucous membranes; the only practical preventative method is physical protection. Anti-Gas barrier creams were developed in WW2 and subsequently (Figure 17); work to develop and deploy more effective protective topical barrier creams is progressing in some NATO countries.



Fig 17. Anti Gas ointments and cake from post-WW2.

Decontamination

Exposure to mustard is not always noticed immediately because of the latent and sign-free period that may occur after skin exposure.

Decontamination of Mucous Membranes and Eye

The substances used for skin decontamination are generally too irritant to be used on mucous membranes and the eyes. The affected tissues should be flushed immediately with water from a 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%)

Decontamination of the Skin

Each soldier is given the means for a preliminary decontamination of the skin; this is 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. Water should not be used to decontaminate mustard (except for the eyes) - this will disperse the agent over the skin.

Additional Procedures

Time is of the essence - decontamination within 2 minutes of contact may prevent or greatly reduce the clinical effects of mustard exposure. However, a degree of protection is provided by late decontamination. 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 bulk of the agent may have to be scraped off with a knife or similar object. This should be 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. If the combat clothing is contaminated, it should be removed as soon as possible.

Mechanism of Action

The exact mechanism of action is not known, however, work over the last decade has revealed many specific mechanisms which may contribute to the development of the mustard injury. Central to many of these mechanisms is the ability of sulphur and nitrogen mustards to alkylate a very wide range of biologically important molecules. Sulphur and nitrogen mustards are bifunctional alkylating agents, containing two reactive chloroethyl functions. Interaction products with cellular components can occur via formation of ethylene-sulfonium (sulphur mustards) or ethylenimmonium ions (nitrogen mustards) through cyclisation and subsequent binding. In deoxyribonucleic acid (DNA), mono-functional adducts are predominantly formed (the second chloroethyl function is converted into hydroxyethyl), but bi-functional binding, leading to formation of cross-links, does occur. Additionally, alkylation of ribonucleic acid (RNA), proteins, cellular membrane components and cross-links between DNA and proteins can be the cause of cellular damage. Guanine is affected most of the DNA- and RNA-bases.

The binding of reactive sulphur or nitrogen mustard species to DNA produces a range of effects.

- 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, resulting in erroneous

incorporation of nucleotides. This may lead to mutations and synthesis of non-functional proteins.

- After damage to DNA, cellular repair mechanisms may not be error free. These processes thus may also give rise to erroneous DNA replication.
- Crosslinks, in particular interstrand crosslinks, between two guanines for example, may play an important role in the cytotoxicity of the sulphur and nitrogen mustards. They inhibit the DNA replication process.

Toxicity

Three distinct levels of biological action can be discerned following exposure to mustards: cytostatic, mutagenic and cytotoxic effects. In the present state of knowledge, the possibility that some effects might be due to reactions with cellular membranes or critical enzymes cannot be dismissed. The actions of mustards partly resemble those of ionising radiation and as such, mustards have been referred to as radiomimetic compounds. Actively proliferating cells are affected most; thus basal epidermal cells, the haemopoietic system and the mucosal lining of the intestine are particularly vulnerable.

CLINICAL-PATHOLOGICAL EFFECTS

Eyes

The eyes are more susceptible to mustard than either the respiratory tract or the skin (Figure 18). Mild effects may follow exposure to concentrations barely perceptible by odour of about 1 hour. This exposure does not effect the respiratory tract

significantly. A latent period of 4 -12 hours follows mild exposure, after which there is lachrymation and a sensation of grit in the eyes. The conjunctivae and the lids become red and oedematous. Serious exposure irritates the eyes after 1 to 3 hours and produces severe lesions.

Mustard burns of the eyes may be divided thus:

- Mild conjunctivitis (75% of cases in World War 1) - recovery takes 1 to 2 weeks.
- Severe conjunctivitis with minimal corneal involvement (15% of cases in World War 1), blepharospasm, oedema of the lids and conjunctivae occur, as may "orange-peel roughening" of the cornea - recovery takes 2 to 5 weeks.
- 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.
- Severe corneal involvement (about 0.1% of World War 1 mustard casualties). Ischaemic necrosis of the conjunctivae may be seen; dense corneal opacification with deep ulceration and vascularisation occurs. Convalescence may take several months and patients are predisposed to late relapses even after many years. Late relapses have a bad prognosis and are refractory to therapy.

Skin

The hallmark of sulphur mustard exposure is latency - a symptom and sign free period for



Fig 18. Mustard vapour burns to the eye.

some hours after exposure. The duration of this period and the severity of the lesions is dependent upon the level and type of exposure, environmental temperature and probably on the individual. High temperature, hydrated, thin or delicate and occluded skin are associated with more severe lesions and shorter latent periods for a given dose. Some people are markedly more sensitive to mustard than others. Burns may be the result of either vapour or liquid exposure.

The sequence of skin changes normally seen is as follows:

- *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 (This sequence is reminiscent of that seen in sun burn.)
- *Blistering*. Erythema is followed by the development of numerous small vesicles which may coalesce to form larger blisters. Blisters are not painful per se, 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 ruptured easily 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 vesicant and does not produce secondary



Fig 20. Mustard vapour burns to the axilla – Iran/Iraq War.

blistering.

- *Deep burning leading to complete epidermal loss*. This is particularly likely to occur on the eyelids, penis and scrotum since the epidermis in these sites is particularly thin, naturally moist and often occluded.

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 discolouration 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.

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 (Figure 19), axilla (Figure 20), 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 cm² and may be very large and pendulous (Figure 21). 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 necrotic debris 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 scarring and fragile

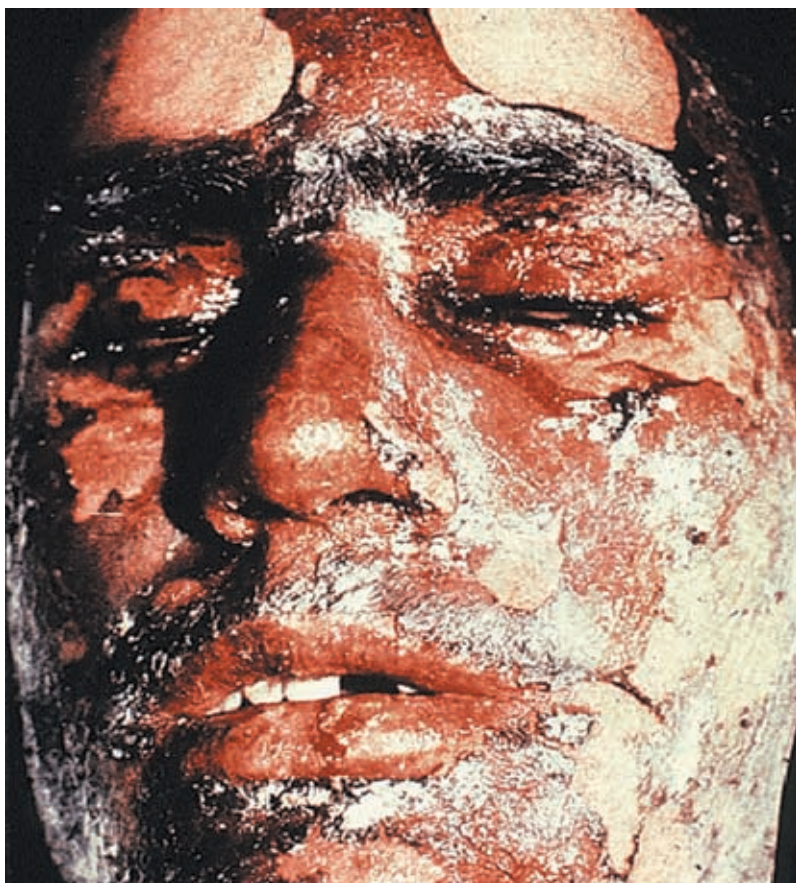


Fig 19. Mustard vapour burns to the face – Iran/Iraq War.

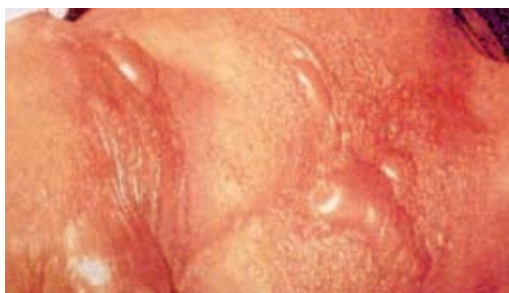


Fig 21. Large blisters from sulphur mustard vapour.

skin which may be easily damaged by trauma, but the overall prognosis of these lesions is better than comparable thermal burns

The systemic fluid derangement seen as a consequence of these injuries is appreciably less than for thermal burns, and therefore the overall outcome is better

Respiratory Tract

Mustard attacks all the mucous membranes of the respiratory tract. After an average latent period of 4 to 8 hours (range 2 to 48 hours depending on dose), mustard irritates and congests the mucous membranes of the nasal cavity and the throat, as well as the epithelium 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 epithelium may obstruct the airways; 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 will die 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).

Gastrointestinal Tract

Ingestion of contaminated food or water may cause destruction of mucous membranes. In the case of ingestion of large amounts, perforation of the gastrointestinal tract with subsequent mediastinitis or peritonitis may occur. Symptoms include nausea, vomiting, pain, diarrhoea and prostration. These features may make casualties reluctant to eat. Vomit and faeces may be bloodstained. Hypovolaemic shock may occur from the loss of fluids and electrolytes from prolonged vomiting and diarrhoea.

Systemic Action

Systemically absorbed mustards by any route, including severe skin exposure, may

cause signs similar to those of irradiation: headache, gastrointestinal pain, nausea, vomiting, leucopenia and anaemia. Mustard agents may cause a general depletion of all elements of the bone marrow. The cells of the granulocyte series and megakaryocytes appear more susceptible to damage than those of the erythropoietic system. A reactive leucocytosis may occur during the first three days, followed 10 days post exposure by a decrease in the peripheral white cell count. The development of a severe leucopenia or an aplastic anaemia makes survival unlikely.

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. Hypotension, refractory to standard resuscitation, has been described on a number of occasions following severe exposure. The prognosis of these rare hypotensive cases is hopeless and no universally accepted mechanism has been advanced.

TREATMENT OF MUSTARD LESIONS

Prophylaxis

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

Therapy

There is no specific therapy available for the treatment of mustard lesions.

The aim of therapy is to:

- Relieve symptoms.
- Prevent infections.
- Promote healing.

Eye Lesions

The ocular effects of mustard 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, appropriate anti-bacterial preparations should be used. When the lesion proves more serious (blistering of the eyelids, blepharospasm, etc.), the anti-bacterial preparation should be applied at more frequent intervals. Patients with corneal lesions 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. The eyes should not be covered with a bandage; if necessary, protect them with dark or opaque goggles. When the eyelids can be separated without too much pain, the cornea should be examined for lesions with fluorescein

solution, followed by lavage. A green spot indicates a lesion, which if severe should be treated by an ophthalmologist as soon as possible. In some countries, ophthalmologists have recommended treatments including the use of citrate and ascorbate eye drops and regular topical steroids.

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. The psychological effects of eye lesions, even of mild degree, are notable. Casualties with blepharospasm may believe they are permanently blinded and become depressed, unless steps are taken to assure them that their sight remains intact.

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 targeted. In cases of overwhelming exposure, severe diffuse lung damage may result and such casualties may need supported ventilation.

Systemic Effects

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 colony stimulating factors can be recommended to shorten the duration of leucopenia.

Skin Lesions

It is important to ensure that no remaining contamination is present before commencing treatment. The skin turns red and itches intensely. This itching can be diminished by local applications of cooling preparations, e.g., calamine lotion, corticosteroid preparations or silver sulphadiazine cream. Severe erythema around the genitalia may become quite painful and weeping and maceration may ensue. Often, treatment with exposure of the area is desirable and care must be taken to ensure that secondary infection of tissue does not occur. 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 their ragged roofs and cover with sterile dressings

as soon as possible. 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.

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.

Trunk and Neck

Extensive Vesication of the Trunk.

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. 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.

Extensive vesication may be followed by fever, nausea and vomiting. These effects tend to occur more readily in tropical climates.

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.

Localised Vesication of the Trunk.

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.

Some burns, such as mild erythema affecting the natal cleft, may not be severe, but require careful attention because walking or running aggravates the lesions and may break down injured skin. Single discrete blisters on the buttocks away from the natal cleft do not cause major disability.

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.

Arms

Most individuals with blister agent injuries of

the arms, when suitably treated, are permitted to continue with their duties. Localised vesication produces little or no disability. 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 to immobilise the extremities further. 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. Widespread vesication of the arms results in partial disability. Casualties of this type should be evacuated.

Hands

Blister agent burns of the hands are frequently encountered following use of sulphur mustard. 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 management.

Experience in tropical experimental installations indicates that protective gloves 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.

A solitary lesion of limited extent may result in little or no disability if treated properly. 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. Severe 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. 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.

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.

Lower Extremities

If the lower extremities are contaminated with liquid vesicant, the knees are the most common sites of burns. These lesions (and

those of the ankles) often result in incapacitation by interfering with locomotion. The movement of joints tends to aggravate existing lesions by increasing oedema. A further disabling factor is introduced by the use of firm dressings on mobile joints.

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 (Figure 22). Medical officers should evacuate casualties with such lesions.



Fig 22. Mustard vapour burns – Iran/Iraq War.

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 had suitable dressings applied, were able to take part in daily marches and routine gun drills. In disposing of these cases, the medical officer should consider the mental and physical status of the individual, his or her willingness to carry on, and the tactical situation at the time. After suitable dressings have been applied, individuals with high morale and robust physique may be returned to duty.

A relatively small blister or group of blisters situated in the popliteal area may reduce the efficiency of a man or woman to the degree that he or she may require evacuation - this arises from aggravation of the lesions by movement of the limbs and interference with ambulation. However, blisters affecting this area are not necessarily incapacitating. Vesicant lesions also develop near the ankles at the tops of the boots/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.

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 invariably produce casualties and are generally accompanied by severe burns elsewhere, frequently with severe systemic effects. Mild vapour burns of the

legs produce irritation and itching common to all widespread vapours burns. These effects are troublesome but they are not casualty producing, and men or women so affected may be returned to duty.

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 effectively protected to allow wearing of shoes; walking may cause little discomfort.

Male Genitalia

Vapour is a more common cause of burns to the male genitalia than is liquid agent. Erythema may not be conspicuous. The most prominent feature of the burn is oedema. Fluid accumulates most readily in the prepuce, distending its entire circumference and forming a characteristic semitranslucent ring around the corona. In more severe cases, the entire body of the penis becomes oedematous.

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.

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. Burning is the commonest symptom. As oedema decreases, itching starts and may persist long after the acute effects have subsided; sometimes the itching is intolerable. The scrotum may continue to crack and ulcerate for a considerable period, causing pain and irritation.

Mild exposure of the genital region is followed by a characteristic delay in the development of symptoms, often for as long as 4 to 10 days. 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 be confident that the symptoms are not too early to be judged with finality.

Apprehension and anxiety are distressing

reactions to burns to this region. Severely affected individuals should be evacuated on the basis of the apprehension that may be suffered as well as the physical discomfort involved.

There is no documented information on specific effects of mustards on female genitalia.

Secondary Bacterial Infection in Blister Agent Burns

This section considers the problem of secondary bacterial infection after blister agent injuries only as it influences the disposition of affected personnel in forward positions. Secondary bacterial infection has often been cited as a common complication of mustard burns of the skin. Observations from experimental burns indicate that compared with the incidence of infection in thermal and traumatic wounds, the incidence of sepsis in mustard lesions is remarkably low. However, experience from the clinical situation suggests that the experimental studies underestimate the true incidence of infection.

Secondary infection becomes manifest several days after injury. Medical officers are not likely to see secondary infection with extensive blister agent burns in forward areas because severely affected patients should have been evacuated. Infection of small lesions does not require evacuation. However, infection of multiple lesions is likely to be an indication for evacuation, as infection is particularly disabling when it involves the feet, the hands, the genitalia or tissues overlying the joints of the limbs.

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 ocular effects. Respiratory lesions may not develop for several days, and by then the individual should have been evacuated as a consequence of the ocular effects. Secondary infection is uncommon as a sequel to mild degrees of mustard conjunctivitis and ordinarily would not prevent an individual from continuing duty. Mild conjunctival burns may be associated with pharyngitis, laryngitis, and tracheitis, increasing in severity for several days. Occasionally more extensive respiratory infection may ensue.

Course and Prognosis

The great majority of mustard casualties survive. Resolution of specific problems can be difficult to predict but the following is a guide:

- *Ocular lesions:* Most are resolved within 14 days of exposure.
- *Skin lesions:* Deep skin lesions may be expected to heal in up to 60 days. Superficial lesions heal in 14–21 days.

- *Upper respiratory tract lesions:* It is very difficult to define a time course for complete recovery. Patients from the Iran-Iraq conflict 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.

Long Term Effects of Mustard Poisoning

The long term effects of mustard may be divided into three groups:

1. Personnel exposed to mustard agents may experience prolonged psychological manifestations including chronic depression, loss of libido and anxiety.
2. Local effects of mustard exposure may include:
 - Visual impairment (permanent blindness is extremely rare).
 - Scarring of the skin.
 - Chronic obstructive airways disease, including chronic bronchitis, emphysema and reactive airways disease.
 - Bronchial stenosis;
 - Gastrointestinal stenosis with dyspepsia after ingestion of agent.
 - Increased sensitivity to mustard.
3. Sulphur mustard is a known carcinogen. A study of American soldiers exposed to sulphur mustard during World War I revealed an increased incidence of lung cancer (and chronic bronchitis) compared to 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. Some solid tumours take 20 years or more to develop, and although there has been no increase in rates, the long term effects in mustard casualties from the Iran/Iraq war are awaited.

ARSENICAL VESICANTS - LEWISITE

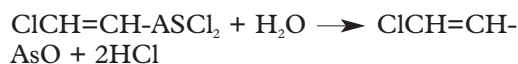
Introduction

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 (but not used operationally). Lewisite is 2-chlorovinyl-dichloroarsine, $ClCH=CH-AsCl_2$.

Physical and Chemical Properties

In a pure form Lewisite is a colourless and odourless liquid, but usually contains small amounts of impurities that give it a brownish colour and an odour resembling geranium oil. Lewisite exists as cis- and trans-isomers. It is heavier than mustard, poorly soluble in water but soluble in organic solvents.

In contact with water, Lewisite is hydrolysed at an appreciable rate, forming an oxide that is equally vesicant:



In contact with strong alkalis, Lewisite is totally decomposed to non-vesicant products. Oxidizing agents (e.g., hypochlorite, peroxide and nitric oxide) oxidize Lewisite to 2-chloroethenylarsonic acid, which is physiologically inactive.

Detection

The detection of Lewisite is facilitated by the fact that it forms coloured products with many reagents. DraegerTM tubes are available which react with organic arsenicals. Detectors are available for use in the field.

Protection

Ordinary clothing gives little or no protection against Lewisite; a respirator, NBC suit, gloves and foot protection are required.

Decontamination

The decontamination procedure is the same as for mustard.

Mechanism of Action

Lewisite easily penetrates 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 enzymes rich in SH-groups. Inhibition of the pyruvate dehydrogenase system is a property common to all trivalent arsenic compounds. 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.

CLINICAL-PATHOLOGICAL EFFECTS

Eyes

Liquid arsenical vesicants cause severe damage to the eye. On contact, pain and blepharospasm occur instantly. Oedema of the conjunctivae and lids follows rapidly and close the eye within an hour. Inflammation of the iris is usually evident by this time. After a few hours, the oedema of the lids begins to subside, but haziness of the cornea develops

and iritis increases. The corneal injury, which varies with the severity of the exposure, may either heal without residual effects, induce pannus formation or progress to massive necrosis. The iritis may subside without permanent impairment of vision if the exposure is 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 separation of both bulbar and palpebral conjunctivae 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.

Skin

Pathology

Liquid arsenical vesicants produce more severe lesions of the skin than liquid mustard. Full thickness injury to the skin occurs and burns may penetrate to connective tissue and muscle and cause greater vascular damage and more severe inflammatory reaction than in mustard burns. In large, deep, arsenical vesicant burns, there may be considerable necrosis of tissue and gangrene.

Despite the overall severity of these skin lesions, the spontaneous rate of healing is considerably faster than that of comparable mustard burns. Exposure 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. The yellowish blister fluid is slightly more opaque than that of the mustard blister and microscopically, contains more inflammatory cells. Research has shown that blister fluid contains hydrolysis products which may present a further vesicant risk to the patient if the blister fluid remains in contact with normal skin. Standard clinical protective measures should prevent injury to health care providers when dealing with these patients.

Symptoms

Stinging pain is felt usually within 10 - 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 decontamination may be begun promptly and deep burns thus avoided in conscious victims. After about 5 minutes of contact, a grey area of dead epithelium is evident (resembling that seen in

corrosive burns). Erythema is similar to that caused by mustard but is accompanied by more pain. Itching and irritation persist for only about 24 hours, independent of whether 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.

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 respirators, and the careless, who are caught without respirators. 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.

Systemic Effects

Liquid arsenical vesicants on the skin and inhaled vapour are absorbed systemically and may cause systemic poisoning. A manifestation of this is a change in capillary permeability; there may be loss of sufficient fluid from the bloodstream to cause haemoconcentration, shock and death. In non-fatal cases, haemolysis of erythrocytes may occur 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 haemorrhages and some injury of the intestinal mucosa. Acute systemic poisoning from large skin burns causes pulmonary oedema, diarrhoea, restlessness, weakness, subnormal temperature and hypotension. Some symptoms associated with arsenic poisoning may occur, such as nephritis with proteinuria and neuropathy.

TREATMENT OF LEWISITE LESIONS

An antidote for Lewisite is dimercaprol (2, 3-dimercapto-propanol, $\text{CH}_2\text{SH} - \text{CHSH} - \text{CH}_2\text{OH}$, BAL). It is known as British Anti Lewisite (BAL). Purified dimercaprol is a colourless 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 arsenicals, the complex formed possesses a pentagon with two carbon atoms, two sulphur atoms and one arsenic atom at the corners. 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.

Topical formulations of BAL suffer from problems of chemical stability and this seriously limits their shelf life. BAL would not be used by all NATO nations; other water soluble dimercaprol analogues exist such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-dimercaptosuccinic acid (DMSA).

Eyes

Dimercaprol eye ointment may diminish the effects of Lewisite if applied within 2-5 minutes of exposure. 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 copious, employing isotonic solutions. Occlusive dressings or pressure on the globe must be avoided.

Skin

BAL ointment may be applied to skin exposed to Lewisite before actual vesication has begun, but application after vesication also has benefit. BAL ointment is spread on the skin in a thin film and allowed to remain *in situ* for 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 (this property precludes its use as a protective ointment). Dimercaprol is chemically incompatible with silver sulphadiazine and the two should not be used together.

The treatment of the erythema, blisters and denuded areas is identical to that for similar mustard lesions. A severe full thickness burn involving a large surface area is similar to a thermal injury and must be managed by intravenous fluid replacement to avoid hypovolaemic shock. Morphine and splinting of the affected parts may be necessary to relieve pain.

Treatment of Systemic Effects

The following are indications for the use of systemic treatment:

- Cough with dyspnoea and frothy sputum, which may be blood tinged and other signs of pulmonary oedema.
- 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.
- 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.

The following approaches may be employed:

- Local neutralisation on and within the skin by a liberal application of BAL ointment. The affected skin should be left covered with a layer of ointment. Silver sulphadiazine is contraindicated in the presence of BAL.
- Intramuscular injection of BAL in oil (10%).
- Alternative systemic treatment using 2,3-dimercapto-1-propanesulphonic acid (DMPS) and meso-dimercaptosuccinic acid (DMSA).

The maximum dosage of BAL is 3 mg.kg⁻¹ (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. Administration must be by deep intramuscular injection with special attention being given to aseptic technique. These injections are painful and may result in tissue necrosis at the injection site. When given by injection they may produce alarming reactions in some individuals. Symptoms and signs include:

- Increased systolic and diastolic pressure.
- Tachycardia.
- Nausea and vomiting.
- Headache.
- Burning sensation of lips.
- Feeling of constriction of the chest.
- Conjunctivitis.
- Lachrymation.
- Rhinorrhoea.
- Sweating.
- Anxiety and unrest.

The side effects of BAL are so severe that the use of modern alternatives should be considered. The newer chelating agents (DMSA and DMPS) are water soluble and do not produce these alarming side effects when used systemically. The advantages of these compounds are that they are:

- substantially more effective than BAL systemically.
- water soluble, active when given orally and relatively non-toxic.

BAL produces mobilisation of arsenic

from most tissues but is less effective in so doing than DMSA and DMPS. BAL given to rabbits poisoned with sodium arsenite produced an increase in brain arsenic levels. DMPS on the other hand produced a marked fall in brain arsenic levels.

DMSA and DMPS have been identified as having an anti-Lewisite action. 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.

The evidence supports the use of the more recently developed chelating agents (DMSA and DMPS) in preference to BAL for the treatment of systemic Lewisite poisoning.

Maintenance of metabolic status and replacement of fluids and electrolytes is important, particularly in the case of hypovolaemic shock complicating severe exposure. The specific haematological, hepatic and renal effects arising from systemic poisoning by arsenical compounds such as Lewisite may require specialist and possibly intensive medical management.

Course and Prognosis

The long term effects of exposure to Lewisite are unknown. 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.

HALOGENATED OXIMES

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

Physical and Chemical Properties of Phosgene Oxime

Phosgene oxime is a white crystalline powder. It melts at 39 - 40°C, and boils at 129°C. By the use of additives, 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 hydrolysed fairly rapidly, especially in the presence of alkali. It has a high vapour pressure and its odour is very unpleasant and irritating. Even as a dry solid, phosgene oxime decomposes spontaneously and has to be stored at low temperatures.

Detection

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

Protection

Ordinary clothing gives little or no protection against phosgene oxime; a respirator, NBC suit, gloves and foot protection are required.

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 removal of the agent should be carried out as soon as possible.

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_2N groups.

Clinical-Pathological Effects

Phosgene oxime also affects the eyes, causing corneal lesions and blindness and may effect the respiratory tract resulting in 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. Within 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.

Treatment

There is no antidote available. The lesions should be treated as any other ulcerated necrotic skin lesion (e.g., thermal burn) with due consideration of other supportive measures. Systemic analgesia may be required. Pulmonary oedema should be treated appropriately.

Course and Prognosis

There is no clinical experience with casualties arising from this agent and hence accurate prognosis is uncertain.

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