Regular review

Chemical weapons

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Chemical warfare has been widely condemned since it was first used on a massive scale during the first world war. Chemical weapons are cheap, can cause mass casualties, and are relatively easy to produce, even by developing nations. They have been used in many conflicts during the 20th century (box), most recently by Iraq during the Iran-Iraq war,[1] as well as in terrorist attacks. The psychological impact of chemical weapons on society makes them ideal for terrorism, as shown by the release of nerve gas in the Tokyo subway system by members of the Aum Shinrikyo sect in 1995.[2] In this review we have focused on the agents that pose the greatest threat, recognising chemical weapons injuries, and the principles of management.

Summary points

- Chemical agents should be considered in major incident planning
- Consider exposure to chemical agents in any casualty with unexplained and unusual symptoms
- Poisoning with many chemical agents, especially nerve agents, can be treated when diagnosed early
- Protective equipment must be worn if there is suspicion that chemical agent remains in the local environment
- Move casualties from contaminated environment to well ventilated area to give first aid
- Decontamination of the casualty involves removal of clothing, shaving contaminated hair, and irrigation with water or dilute sodium hypochlorite to remove residual agent from skin

Methods

We obtained information for this paper from a search of the National Library of Medicine, web based resources, and the collective experience of staff at the Defence Science and Technology Laboratories.

Definition

The North Atlantic Treaty Organisation's definition of a chemical agent is "a chemical substance which is intended for use in military operations to kill, seriously injure or incapacitate people because of its physiological effects."[3] Classic chemical weapons and biological weapons (such as anthrax or plague) are considered to form two ends of a spectrum with "chemicals of biological origin" (such as botulinum toxin or ricin) lying between these two extremes. Chemical weapons can be classified according to their mode of action or by the time they remain active in the environment (persistence) and lethality (fig 1).

Use of chemical weapons in the 20th century

1914-8: Over 1 300 000 people receive gas injuries in first world war, and over 90 000 of them die

1935: Italy begins conquest of Abyssinia (Ethiopia) using mustard gas delivered by aircraft spray

1936: Japan invades China using chemical weapons (including mustard gas, phosgene, and hydrogen cyanide); German chemical laboratories produce first nerve agent—tabun

1963-7: Egypt uses phosgene and mustard aerial bombs in support of South Yemen against the Yemeni royalist forces during the Yemeni civil war

1980-8: Iraq attacks Iran and Iraqi Kurds during Iran-Iraq war using mustard and nerve agents

1994-5: Japanese Aum Shinrikyo cult uses sarin in terrorist attacks at Matsumoto in June 1994 and on the Tokyo underground in March 1995

Methods of dissemination

Chemical agents can be delivered in artillery shells or missiles, by aerial bombing, or by spraying. In the Tokyo subway attack in 1995, terrorists left a plastic bag of the nerve agent sarin on an underground train, allegedly piercing them with umbrella tips before escaping. The resultant vapour injured 3796 people and caused 12 deaths.[4]

Nerve agents

Nerve agents are a particularly toxic group of organophosphate compounds first synthesised in Germany before the second world war. All are liquids at room temperature and produce a vapour capable of

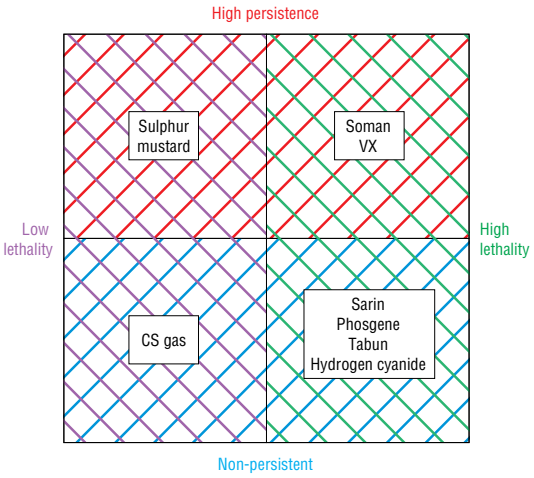


Fig 1 Classification of chemical weapons by persistence and lethality

penetrating the skin, respiratory epithelium, and cornea. The liquid can be absorbed through intact skin and also through the gut after ingestion of contaminated food. VX (O-ethyl-S-[2(di-isopropylamine)ethyl] methylphosphoethioate) has greater potency but lower volatility than other nerve agents. All nerve agents act by inhibiting the enzyme acetylcholinesterase, which breaks down the neurotransmitter acetylcholine. This has clinically important effects, mainly at peripheral nicotinic and muscarinic receptors, but there are also ill defined effects in the central nervous system. The resulting overstimulation of cholinergic receptors produces the clinical effects shown in the table.

The route of exposure determines which clinical features appear first. After inhalation of vapour, respiratory symptoms, dimming of vision, and miosis are generally the first clinical features to appear. Local sweating and fasciculation of local muscle groups may occur initially after skin absorption of liquid or vapour. If sufficient agent has been absorbed by any route systemic effects will occur.[5]

Blister agents

Sulphur mustard is a yellow oily liquid at room temperature with a faint odour of mustard or garlic. It remains liquid in cold damp conditions but evaporates rapidly in a warm dry environment to produce a vapour that can penetrate ordinary clothing. Sulphur mustard is a bifunctional alkylating agent, reacting readily with most biological molecules including proteins and nucleic acids.[6] In conflict it has been used to incapacitate large numbers of soldiers. Injuries are usually non-fatal (mortality from exposure to sulphur mustard was only 3% during the first world war[7]) but long term.

Sulphur mustard is a powerful blistering agent (fig 2); a 0.1 ml drop of pure sulphur mustard contains 20 000 times the dose required to blister skin. Symptoms may not develop until 12-24 hours after exposure. Erythema precedes the development of large, thin walled, pendulous blisters that rupture easily.[8] The burns tend to be partial thickness but are deeper in the warm, moist areas of the body such as the axillae and groin.[9] In most people with inhalation injuries, initial irritation of nasal mucosa and airways is followed by the development of bronchitis, which resolves in four to six weeks. In severe exposure, necrosis of the respiratory epithelium leads to formation of a pseudomembrane, bronchial plugging, and bronchopneumonia. Systemic absorption produces nausea, vomiting, hypotension, bradycardia, and, after initial leucocytosis, profound leucopenia. Death, although uncommon, is usually due to overwhelming infection.[10]

Phosgene

Phosgene is a gas at ambient temperature. It is 3.5 times denser than air and smells of mouldy hay (although toxic effects can occur before it is smelt). Phosgene is absorbed through contact with the eye or by inhalation. Eye irritation is immediate, probably due to release of hydrochloric acid during hydrolysis of phosgene.[11] When inhaled, phosgene reacts with a variety of tissue macromolecules leading to an increase in capillary permeability. This allows fluid to shift into interstitial and alveolar spaces.[12] Exposed patients may be free of symptoms for several hours before developing severe pulmonary oedema, the onset of which may be precipitated by exercise (table).

Recognition of chemical injuries

Successful management of exposure to chemical agents relies on early recognition. In times of war, awareness is high; suspicious smoke, mist, droplets on vegetation and buildings, or unusual smells are warning signs. Chemical detectors are not widely available to the civilian emergency services and doctors must maintain a high index of suspicion if a chemical injury is to be diagnosed early. Many of the effects of chemical agents overlap with those of common pathological conditions such as respiratory disease and epilepsy. However, the clinical features of exposure (table) may aid diagnosis and clusters of patients with unexplained symptoms of recent onset should be viewed as suspicious. Although the features of severe nerve agent poisoning are dramatic, lower exposure is more challenging to detect.

Clinical features of exposure to sulphur mustard, nerve agents, and phosgene

Chemical agent	Means of exposure	Rate of action	Clinical features of exposure
Sulphur mustard	Skin contact, inhalation	Delayed by 1-24 h	*Skin:* erythema, blistering leading to full thickness burns *Eyes:* lachrymation, conjunctivitis, photophobia, blepharospasm, eyelid oedema *Respiratory tract:* rhinorrhoea, hoarseness and cough, dyspnoea, tracheobronchitis, bronchopneumonia *Haemopoetic system:* leucopenia and anaemia
Nerve agents (tabun, sarin, soman, VX)	Inhalation, skin contact	Very rapid	*Early or mild poisoning:* tightness of chest, rhinorrhoea, increased salivation, dimming of vision/miosis, eye pain/frontal headache *Severe poisoning*: bronchospasm/dyspnoea, vomiting/abdominal pain, urinary and faecal incontinence, muscle fasciculation and convulsions, respiratory failure and death due to anoxia
Phosgene	Inhalation	Delayed by 1-24 h	Dyspnoea, coughing, pulmonary oedema (after latent period), respiratory failure

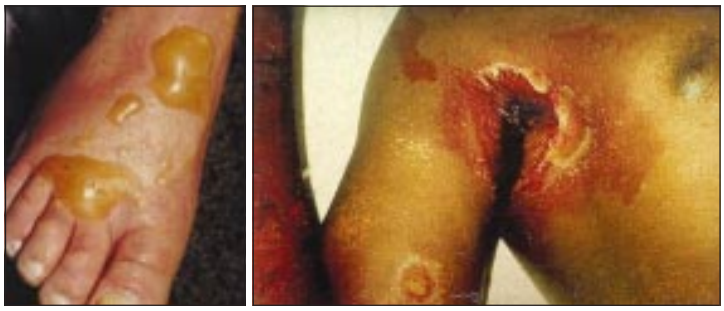


Fig 2 Left: Dorsum of right foot about 48 hours after exposure to sulphur mustard vapour, showing the characteristic blistering of skin. The blister fluid contains no active chemical. Right: A casualty from the Iran-Iraq war illustrating the predilection of sulphur mustard burns for moist areas of the body, in this case the axilla. The lesion is at least 3-4 days old and has ruptured leaving a raw and ulcerated central zone

Immediate first aid and decontamination

When treating patients in an environment where there is a chemical threat, doctors should wear protective equipment. The first priority is decontamination, subject to life saving requirements. The patient should be moved from the contaminated environment into a well ventilated area before removal and safe disposal of clothing and decontamination of the skin. Water can be used in large amounts but dilute sodium hypochlorite solution is more effective. The eyes should be irrigated with copious amounts of water or normal saline.

Treatment of poisoning

Nerve agents

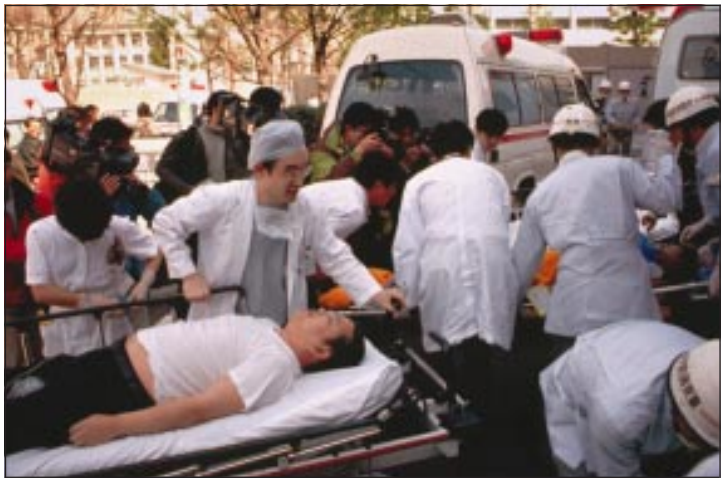
Poisoning with nerve agents is always a serious medical emergency because the agents act rapidly and profoundly. Patients with compromised airways and respiratory failure will require immediate endotracheal intubation and positive pressure ventilation. Aggressive suctioning may be needed to remove increased bronchial secretions. Whole blood cholinesterase concentrations give a broad indication of the degree of poisoning, but the principle should be to treat the patient not the depression of acetylcholinesterase. Treatment includes

- Anticholinergics to antagonise the muscarinic effects
- Oximes to reactivate the inhibited acetylcholinesterase and antagonise the nicotinic effects
- Prophylactic anticonvulsants to prevent seizures.

Immediate treatment with atropine is essential in patients with systemic poisoning. The total dose depends on the degree of poisoning. Intravenous atropine should be given in 2 mg aliquots every 3-5 minutes until the patient is atropinised. Signs of atropinisation include dry mouth, correction of miosis, reduced sweating, and correction of bradycardia. Atropine may need to be continued at 2 mg/hour for at least 24 hours. Complications of atropinisation include euphoria, arrhythmias, delirium, and heat stress.

Although atropine antagonises the muscarinic mediated effects of nerve agents, oximes are used to reactivate acetylcholinesterase at nicotinic sites. Pralidoxime mesilate is currently licensed for use in the United Kingdom. Oximes must be given early as their efficacy declines with time; spontaneous dealkylation (or ageing) of the inhibited acetylcholinesterase makes it resistant to reactivation. Pralidoxime mesilate 30 mg/kg should be given by slow intravenous injection at 15 minute intervals to a maximum of 2-4 g as soon as possible.[13]

Control of convulsions has been shown to increase survival and reduce subsequent morbidity in animal studies. Patients should be given 5 mg diazepam by any route before the onset of convulsions.[14]



CHIKUMO CHIAKI/AP PHOTO

Subway passengers affected by sarin gas planted in central Tokyo

Sulphur mustard lesions

No specific treatment exists for mustard lesions. Treatment is therefore aimed at relieving symptoms, preventing infection, and promoting healing. Eye lesions are usually mild and heal completely in about two weeks. Treatment consists of topical antibiotics and careful cleaning with saline to prevent the eyelids sticking. Inhalation of vapour may cause severe bronchopneumonia in the worst cases. Physiotherapy, oxygen, antibiotics, and mechanical ventilation are the mainstays of treatment.[10]

Patients with large burns should be resuscitated in line with thermal burn protocols.[15] However, in contrast to thermal burns, the fluid losses do not occur until the blisters form and the fluid lost is a transudate, which means protein losses are less. Tense or broken blisters should be deroofed and dressed with silver sulfadiazine. Partial thickness sulphur mustard burns heal much more slowly than thermal burns of similar depth, taking at least 12 weeks to heal if treated conservatively. This is thought to be due to cellular alkylation affecting normal wound healing processes.[16] Standard excision and grafting of sulphur mustard burns does not reduce healing time in an animal model,[8] but early dermabrasion and laser ablation may be beneficial.[16 17] Pain can be severe, and patients may benefit from chlorpromazine in addition to standard analgesics.[18]

Phosgene

Patients with phosgene poisoning should be rested and kept warm. Codeine 30-60 mg may reduce coughing but can exacerbate respiratory depression at higher doses. Use of steroids has been widely advocated, but evidence of therapeutic benefit remains inconclusive.[19] Phosgene induced pulmonary oedema occurs rapidly, but if patients survive for longer than 48 hours recovery is usually complete. Conventional ventilatory management strategies for high permeability pulmonary

oedema are recommended.[20] Careful maintenance of fluid balance in patients with established pulmonary oedema is essential. However, there is conflicting evidence on the benefit of diuretics in phosgene induced pulmonary oedema.[19 21]

The future

International treaties such as the Chemical Weapons Convention[22] should help control proliferation of chemical weapons and verify disarmament but it would be naive to assume the threat will disappear. Military and emergency services must maintain their ability to manage large scale chemical weapons attacks, and that requires continued education, training, and forethought.

Competing interests: None declared.

1 United Nations Security Council. *Report of the mission despatched by the Secretary General to investigate allegations of the use of chemical weapons in the conflict between the Islamic Republic of Iran and Iraq (S/18852).* New York: UN, 1987.
2 Wessely S, Hyams KG. Psychological implications of chemical and biological weapons. *BMJ* 2001;323:878-9.
3 North Atlantic Treaty Organisation. *Handbook on the medical aspects of NBC defensive operations.* Brussels: NATO, 1996. (AMedP-6 (B).)
4 Tu AT. Overview of sarin terrorist attacks on Japan. *American Chemical Society Symposium Series* 2000;745:304-7.
5 Grob D. The effects and treatment of nerve agent poisoning. *Am J Med* 1953;14:52-63.
6 Somani SM, Babu SR. Toxicodynamics of sulfur mustard. *Int J Clin Pharmacol Ther Toxicol* 1989;27:419-35.
7 Haldane JBS. Callinicus A. *Defence of chemical warfare.* London: Kegan Paul, Trench, Trubner, and Co, 1925.
8 Papirmeister B, Feister AJ, Robinson SD, Ford RD. The sulfur mustard injury: description of lesions and resulting incapacitation. In: *Medical defense against mustard gas: toxic mechanisms and pharmacological implications.* Boston: CRC Press, 1991:13-42.
9 Sinclair DC. The clinical reaction of the skin to mustard gas vapour. *Br J Dermatol* 1949;61:113-9.
10 Willems JL. Clinical management of mustard gas casualties. *Annales Medicinae Militaris (Belgicae)* 1989;3(suppl):1-61.
11 Diller WF. Pathogenesis of phosgene poisoning. *Toxicol Ind Health* 1985;1:7-15.
12 Borak J, Diller WF. Phosgene exposure: mechanisms of injury and treatment strategies. *J Occup Environ Med* 2001;43:110-9.
13 Maynard RL. Toxicology of chemical warfare agents. In: Ballantyne B, Marrs T, Turner P, eds. *General and applied toxicology.* 2nd ed. London: Macmillan, 1999:2079-109.
14 Ecobichon DJ. Toxic effects of pesticides. In: Klassen CD, Amdur MO, Doull J, eds. *Casarett and Doull's toxicology: the basic science of poisons.* 5th ed. New York: McGraw-Hill, 1996:643-89.
15 Mellor SG, Rice P, Cooper GJ. Vesicant burns. *Br J Plast Surg* 1991;44:434-7.
16 Rice P, Brown RF, Lam DG, Chilcott RP, Bennett NJ. Dermabrasion—a novel concept in the surgical management of sulphur mustard injuries. *Burns* 2000;26:34-40.
17 Eldad A, Weinberg A, Breiterman S, Chaouat M, Palanker D, Ben Bassat H. Early nonsurgical removal of chemically injured tissue enhances wound healing in partial thickness burns. *Burns* 1998;24:166-72.
18 Newman-Taylor AJ, Morris AJR. Experience with mustard gas casualties. *Lancet* 1991;337:242.
19 Diller WF. Therapeutic strategy in phosgene poisoning. *Toxicol Ind Health* 1985;1:93-9.
20 Regan RA. Review of clinical experience in handling phosgene exposure cases. *Toxicol Ind Health* 1985;1:69-71.
21 Wells B. Phosgene. A practitioner's viewpoint. *Toxicol Ind Health* 1985;1:81-92.
22 Chemical Weapons Convention. Convention on the prohibition of the development, production, stockpiling and use of chemical weapons and on their destruction 1993. www.opcw.nl/ (accessed 7 Jan 2002).

Additional educational resources

US Army. *Medical management of chemical casualties handbook.* 3rd ed. 1999. (www.vnh.org/CHEMCASU/titlepg.html/)

Medical manual of defence against chemical agents. London: HMSO, 1987. (JSP 312.)

Smith KJ, Hurst CG, Moeller RB, Skelton HG, Sidell FR. Sulfur mustard: its continuing threat as a chemical warfare agent, the cutaneous lesions induced, progress in understanding its mechanism of action, its long-term health effects, and new developments for protection and therapy. *J Am Acad Dermatol* 1995;32:765-6.

Canadian Transport Agency–2000 Emergency Response Guidebook. (www.tc.gc.ca/canutec/erg_gmu/erg2000_menu.htm)

Comprehensive guide to identification of specific hazards following chemical incident and to relevant safety precautions.

Organisation for the Prohibition of Chemical Weapons. (www.opcw.nl/)

A wide range of useful links for information regarding chemical agents and the Chemical Warfare Convention.

Stockholm International Peace Research Institute chemical weapons page (http://projects.sipri.se/cbw/)

Federation of American Scientists (www.fas.org/nuke/intro/cw/)

The year was 1941

"Oh," cried my mother illogically, "if only Daddy was here he would know what to do." I say illogically because my father, a prosperous Scottish general practitioner, had been killed by a landmine while he was manning his first aid post.

My mother's problem was selling the practice. All the young doctors were away at the war, and only one offer was made from a doctor already in the town, one that my mother considered inadequate. "I'll just not sell the practice at all. I can't let it go for that."

"But, Mummy," I cried, "you can't let the practice go for nothing."

"No, I can't," she replied bitterly. And so the practice was sold.

As my father was the senior casualty surgeon in the first aid post, he had been paid £45 a year, a sum he split with his general practitioner friend who was not paid and was also killed. Because my father was a paid member of the first aid post, the government granted my mother a private soldier's widow's pension of £2 a week, not a great sum with which to put three children through school and university. And so my mother became an official war widow.

I have always read the names on war memorials with respect. My father's name appears on five war memorials, including that of the BMA. My mother's name does not appear on any, nor do the names of the countless other widows of war, yet it was to them the torches were thrown.

I have seen only one memorial which recognises that the sacrifice of war does not end with the names on a war memorial. This one is at Port Sunlight. The widows are depicted crossing "no man's land" to reach their stricken menfolk. The children are there, too, poignant in their Norfolk jackets, sailor suits, and dropped-waist dresses. As I took in the details of this thoughtful memorial, I found my vision blurred by tears. My tears were not for my father, lost these 60 years, but for my mother and her children.

Stella E G Gibson *retired consultant in public health medicine*

We welcome articles of up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.