solutions, or soapy water and then liberally covered with the topical antibiotic of choice, such as silver sulfadiazine, mafenide acetate, or triple antibiotic ointment to a thickness of 1–2 mm. Some physicians advocate sterile needle drainage of large blisters, with collapsing of the blister roof to form a sterile dressing. Mustard blister fluid does not contain sulfur mustard but rather consists only of sterile tissue fluid. Health care staff should not fear possible contamination. If an antibiotic cream is not available, sterile petrolatum will be useful. Modified Dakin's solution (sodium hypochlorite, 0.5%) was used for field-expedient irrigation and antisepsis both in WWI and for Iranian casualties in the Iran–Iraq war (1984–1987). Large areas of vesication require hospitalization, IV therapy, and whirlpool bath irrigation.

Systemic analgesics should be used liberally, particularly before manipulation of the patient. Monitoring of fluids and electrolytes is important in any sick patient, but it must be recognized that fluid loss is not of the magnitude seen with thermal burns. Overly rigorous hydration seems to have precipitated pulmonary edema in a few Iranian casualties sent to European hospitals.

Conjunctival irritation from a low-vapor exposure responds to any of a number of available ophthalmic solutions after the eyes are irrigated thoroughly. A topical antibiotic applied several times a day reduces the incidence and severity of infection. Animal laboratory data reflect remarkable results with early application of commercially available topical antibiotic/glucocorticoid ophthalmologic ointments. An ophthalmologist should be consulted. Topical glucocorticoids are not of proven value, but their use during the first few hours or days may significantly reduce inflammation and subsequent damage. Further use should be relegated to an ophthalmologist.

Petroleum jelly or a similar substance should be applied regularly to the edges of the eyelids to prevent them from sticking together. Topical analgesics, although of limited value, may be useful initially if blepharospasm is too severe to permit an adequate examination.

A productive cough and dyspnea accompanied by fever and leukocytosis occurring within 12–24 h are indicative of chemical pneumonitis. The clinician must resist the urge to use prophylactic antibiotics for this process. Infection often occurs on the third to fifth day and is signaled by increased fever, a pulmonary infiltrate, and increased sputum production with a change in color. Appropriate antibiotic therapy should await confirmation by Gram's stain and, later, by culture and sensitivity assessment.

Intubation may be necessary if laryngeal spasm or edema makes breathing difficult or becomes life-threatening. Intubation permits better ventilation and facilitates suctioning of necrotic and inflammatory debris. Early use of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) may be beneficial. Pseudomembrane formation may require fiberoptic bronchoscopy for suctioning of necrotic debris.

Bronchodilators are of benefit for bronchospasm. If additional relief of bronchospasm is needed, glucocorticoids should be used. There is little evidence that the routine use of glucocorticoids is beneficial except for additional relief of bronchospasm.

Leukopenia begins around day 3 with major systemic absorption. Marrow suppression peaks at 7–14 days. In the Iran–Iraq war, a white blood cell count of ≤200/μL usually resulted in death of the patient. Sterilization of the gut by nonabsorbable antibiotics should be considered to reduce the possibility of sepsis from enteric organisms. Cellular replacement (bone marrow transplants or transfusions) may be successful. Granulocyte colony-stimulating factor produced a 50% reduction in the time required for bone marrow recovery in nonhuman primates exposed to sulfur mustard. Medication for nausea and vomiting may be necessary for gastrointestinal side effects. Lymphopenia precedes general leukopenia by a day or more and may be a useful clinical tip-off to impending leukopenia.

Excellent experimental assessments of the contributions of DNA alkylation, inflammation, activation of proteolytic enzymes, or lipid peroxidation to the mustard injury have been developed in the past 15–20 years. Some examples include (1) the demonstration of a reduction by up to 75% of inflammation and tissue damage in the mouse ear swelling test by vanilloid compounds and (2) the demonstration of 50–60% protection by *N*-acetylcysteine in the generation of free radicals within guinea pig lung exposed to mustard. In many cases, the demonstration of protection is dependent on the availability of sufficient amounts of drugs with adequate half-lives. Strategies to enhance bioavailability include attachment of polyethylene glycol to the antioxidant drug/enzyme and/or delivery of the drug/enzyme in a liposome.

NERVE AGENTS

The organophosphorus nerve agents are the deadliest of the CWAs. They work by inhibition of tissue synaptic acetylcholinesterase, creating an acute cholinergic crisis. Death ensues because of respiratory depression and can occur within seconds to minutes.

The nerve agents tabun and sarin were first used on the battlefield by Iraq against Iran during the first Persian Gulf War (1984–1987). Estimates of casualties from these agents range from 20,000–100,000. In 1994 and 1995, the Japanese cult Aum Shinrikyo used sarin in two terrorist attacks in Matsumoto and Tokyo. Two U.S. soldiers were exposed to sarin while rendering safe an improvised explosive device in Iraq in 2004.

The "classic" nerve agents include tabun (GA), sarin (GB), soman (GD), cyclosarin (GF), and VX; VR, similar to VX, was manufactured in the former Soviet Union (Table 262e-1). All the nerve agents are organophosphorus compounds, which are liquid at standard temperature and pressure. The "G" agents evaporate at about the rate of water, except for cyclosarin, which is oily and thus probably will have evaporated within 24 h after deposition on the ground. Their high volatility thus makes a spill of any amount a serious vapor hazard. In the Tokyo subway attack in which sarin was used, 100% of the symptomatic patients inhaled sarin vapor that spilled out on the floor of the subway cars. The low vapor pressure of VX, an oily liquid, makes it much less of a vapor hazard but potentially a greater environmental hazard because it persists in the environment far longer.

Mechanism Acetylcholinesterase inhibition accounts for the major life-threatening effects of nerve agent poisoning. The efficacy of antidotal therapy in the reversal of this inhibition proves that this is the primary toxic action of these poisons. At cholinergic synapses, acetylcholinesterase, bound to the postsynaptic membrane, functions as a turn-off switch to regulate cholinergic transmission. Inhibition of acetylcholinesterases causes the released neurotransmitter, acetylcholine, to accumulate abnormally. End-organ overstimulation, which is recognized by clinicians as a cholinergic crisis, ensues (Fig. 262e-4).

Clinical Features Clinical effects of nerve agent exposure are identical for vapor and liquid exposure routes if the dose is sufficiently large. The speed and order of symptom onset will differ (Table 262e-2).

Exposure of a patient to nerve agent vapor, by far the more likely route of exposure in both battlefield and terrorist scenarios, will cause cholinergic symptoms in the order in which the toxin encounters cholinergic synapses. The most exposed synapses on the human integument are in the pupillary muscles. Nerve agent vapor easily crosses the cornea, interacts with these synapses, and produces miosis, described by Tokyo subway victims as "the world going black." Rarely,

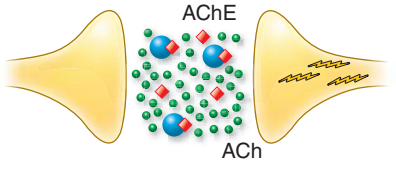

FIGURE 262e-4 Schematic diagram of the pathophysiology of nerve agent exposure. Nerve agent (◆) binds to the active site of acetylcholinesterase (AChE), which is shown as floating free in space but is in reality a postsynaptic membrane-bound enzyme. As a result, acetylcholine (●), which normally is released from presynaptic membrane but then is degraded, accumulates, and this leads (↯) to organ overstimulation and cholinergic crisis.