Clinical Aspects of Large-Scale Chemical Events

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Overview

Since the dawn of civilization, chemical materials have been a part of human life. Nearly 100,000 different commercial chemicals are known, and several thousand new chemicals are developed yearly. Of these new chemicals, nearly a thousand reach the commercial market. Annual worldwide chemical production is estimated at 363 million metric tons (400 million short tons). Of this production, most is bulk stored and bulk transported. Thus, there is a risk of large-scale release with resulting environmental and health effects. In the past century, specific chemicals have also been developed to use as weapons with the intention to harm or kill humans.

Human toxicity from chemical exposure has been well recorded since the beginning of the industrial age. Recognition and investigation of those effects have allowed the development of therapeutic interventions. Toxic effects of chemicals may result from exposures to small amounts such as present in foods or medications, or larger amounts resulting from accidental or intentional releases from storage or transportation facilities. But the actual toxicities of each compound are not always well understood because of the huge number of possible interactions with thousands of chemicals and individual patient variability.

The human toxic effects of smaller chemical exposure events have generally been well managed because there are rarely more than one or two patients requiring care at a time. Large-scale exposures vastly complicate the medical response to a toxic chemical event, principally because of overwhelming logistical difficulties.

Interactions between chemicals and people depend on pharmacokinetics (absorption, distribution, metabolism, and elimination) and specific toxicities or modes of action. Much of the clinical information about toxic (warfare) chemical effects has been collected from studies of young, healthy military men. Extrapolation of those data to other subsets of the population (children, the elderly, females, persons with complicating medical illnesses, immunocompromised patients, patients on medications, and the mentally ill) can be difficult. Additionally, research findings in nonhuman systems may correlate poorly with human systems.

Immediate and near-term lethal sequelae of chemical events, even those intentionally orchestrated, rarely occur in more than 3–5% of exposed individuals. But longer-term sequelae are often poorly understood and may not develop for many years. This has, in many cases, given rise to claims of causation which result in years of litigation.

Large-scale chemical events trigger public anxiety and fear to a degree that is strikingly disproportionate to the number of deaths. The media appears to be a primary contributor to this public anxiety, largely as a result of its presentation format. The medical community must assist the media with both its presentation of content and methods.

The mode of death in most chemical exposures results from respiratory failure, so attention to pulmonary function is always a major part of chemical preparedness. But many chemicals cause protean, multi-organ effects, some of which can be delayed. A good example is the delayed keratopathy seen years after sulfur mustard exposure. Programs to address the chemical threat must be multifaceted and span multiple medical disciplines.

During the time period termed “recovery,” the medical community has unique responsibilities. Critical assessment of the long-term clinical aspects of the event should include both medical and psychological sequelae. Careful long-term evaluations of all the victims from an exposure should be undertaken in a fashion similar to the follow-up programs after the September 11, 2001, U.S. terrorist attacks in New York City. Carefully documented clinical and laboratory victim data should be collected in a medically accessible database for future review and use. This long-term clinical/medical review should be undertaken independent of legal, political, or commercial interests in the event. Critical assessment must also be made of the medical aspects of mitigation, preparedness, and response in the event. This assessment must be compiled and produced as a reference document, available for immediate and later review. This is a disaster preparedness review with a medical focus and should also be produced independent of legal, political, or commercial interest in the event. These two types of review should begin as soon as possible after a chemical release.
CURRENT STATE OF THE ART

Chemical History

Since at least 1000 BC, chemicals in some form have been used as weapons. Initially those chemicals were found as natural materials that could be used to produce a particular desired effect when extracted from geological deposits. Recent archaeological discoveries in Dura-Europos, in present-day Syria, the site of a battle between the Persians and Romans in 276 AD, seem to indicate that the defending Persians used bitumen and sulfur to asphyxiate their enemies attempting to take the fortress by tunneling into it.¹

In approximately 670 AD, the Byzantine Greeks developed a combination of materials that, when ignited, became an effective weapon. So-called Greek fire was a combination of uncertain composition that probably contained naphtha, sulfur, salt peter, and pitch. When used against enemy ships, this “wet, dark, sticky fire” would float on water, stick to ships, and even continue to burn underwater. It was almost impossible to extinguish and hence was particularly effective against enemy wooden ships. Greek fire not only produced substantial physical damage, but also, perhaps much more importantly, spread extraordinary fear among the enemy. That fear was the result of failures to anticipate the use of the material as a weapon, develop adequate weapon protection, control the immediate effects of the weapon, and learn the method of manufacture of Greek fire and develop plans for its future use.

Substantial effort was expended in attempting to educate sailors about the methods of use and effects of Greek fire. Fear that this was a weapon “of the devil” was mollified. Training in methods of flame control helped ease anxiety as well. These early forms of “disaster preparedness” helped overcome the advantage of fear that Greek fire carried.

By the eighteenth century, the discovery of unique chemicals such as cyanide and chlorine was quickly followed by recognition of their harmful effects. Shortly thereafter, various military forces around the world proposed use of these materials, specifically for their toxic properties. Although no army had yet weaponized chemicals, this concern was sufficient to merit specific mention in the Geneva Protocols, ratified in 1899. During World War I, large-scale production and use of chemical agents as toxic weapons became common.

French riot control agents were perhaps the first chemical weapons of WWI. They had previously been deployed by the Paris police. Riot control agents were relatively ineffective, however, because highly motivated soldiers could easily tolerate their irritant effects.

On April 22, 1915, after extensive preliminary preparation and some false starts, the Germans released approximately 136 metric tons (150 short tons) of chlorine from approximately 6,000 cylinders over a 7-km front line near Ypres, Belgium. Large clouds of a yellow-green, intensely irritating gas spread in the direction of the opposing French. Chlorine gas is heavier than air. As a result, the clouds settled into the very trenches that the soldiers thought would protect them. Choking and gasping, those soldiers ran from an unknown substance, perhaps inhaling greater quantities simply as a result of their physical activity. The effects of that first attack, by some accounts, included 2,000 deaths and up to 20,000 wounded.²

The Allies quickly identified the chemical agent used and shortly retaliated in kind. Within months, chlorine, and later phosgene, diphosgene, and chloropicrin, were produced, weaponized, and used in large quantities by both the Germans and the Allies. These agents are primarily toxic by inhalation. Accordingly, the development of increasingly effective gas masks diminished the “value” of these agents. Of course, gas masks were useful only if the soldiers had adequate education and training and were highly motivated. Use of the gas mask for any period of time was exceptionally uncomfortable. As a result, the soldiers often used them only when their noses provided an alarm. Chlorine, with its intensely irritating aroma, prompted immediate mask use and thus could be avoided. Phosgene, a later weapon development, had a more pleasant smell, likened to newly mown hay. As a result, inhalation of toxic amounts of phosgene easily occurred prior to donning of the mask. A delayed physiological effect, with frequently lethal pulmonary edema, occurred in 4–12 hours. Victims, appearing and feeling normal during the first few hours after exposure, would often continue full military activities. Later, it was learned that exercise during the “latent period” prior to development of pulmonary edema resulted in a more rapid onset of more intense disease. This delayed onset of a sometimes-lethal respiratory failure was commonly seen in an individual who initially appeared and felt well. Extreme fear and anxiety resulted among the troops who never knew where or when they would become affected. Intensive efforts to provide the soldiers with a better understanding of chemical weapons and the circumstances/likelihood of their use were combined with improved mask protection. There was a resulting decrease in medical aid station visits for both real and imagined gas exposures.

Because improved Allied education, training, and equipment, especially gas masks, led to a decrease of effectiveness of the German chemical attacks, the Germans introduced a novel chemical material. On December 17, 1917, sulfur mustard, active either as a liquid (below 14°C) or as a vapor, was first released. Sulfur mustard damaged any topical/epithelial surface of contact. Unprotected eyes, skin, and respiratory tracts suffered inflammatory damage to a degree related to the “dose” to which the individual was exposed. Sulfur mustard had a unique aroma, often characterized as similar to garlic or horseradish; however, severe exposure, particularly to the liquid, could occur with a minimal warning aroma. The primary molecular effect of the chemical agent, alkylation of nucleic acids, occurred within the first few minutes of contact. An intense, irritating, inflammatory biological response to that contact would typically occur after a latent period of some hours to days depending on the exposure dose. As a direct result, soldiers would often develop clinical symptoms distant in time and place from their original exposure. There was no available technology to permit identification of sulfur mustard–contaminated areas. As a result, soldiers were unable to identify contaminated places or even people. Fear of cross-contamination seriously compromised their daily activities. Blindness, painful skin blisters, and respiratory symptoms including cough, wheezing, and substantial shortness of breath occurred in soldiers without obvious sulfur mustard contact. An overwhelming sense of fear of chemicals resulted. Soldiers would avoid any areas that had unusual smells, suspecting that mustard might be present. Certainly this fear was one of the most important effects of the use of chemical weapons.

By the end of the war more than half of all shells fired were filled with a chemical agent, often sulfur mustard. Estimates suggest that approximately 25% of all WWI casualties were chemically related, of which 70% or more were caused by sulfur mustard. The ease of chemical weapon manufacture attracted the
attention of many countries after WWI. This resulted in substantial research, manufacture, weaponization, and stockpiling of chemical agents, particularly including mustard, in anticipation of possible future needs.

Since the discovery of mustard in 1850 by Guthrie, the intense inflammatory effects of mustard have been recognized. There has been substantial research regarding its cellular and systemic toxicity; however, no specific antidote has been identified to date. Each instance of its use subsequent to WWI has been associated with production of large numbers of debilitated and disabled individuals. Medical statistical assessment of these injuries during WWI has documented the frequency, distribution, and duration of illness of each of the bodily systems involved. Of perhaps greatest interest is the documentation of a 3–5% death rate, largely respiratory. An important comparison is the WWI Allies’ 25% death rate from conventional weapons. This statistically and perhaps surprisingly low death rate appears consistently throughout records of subsequent large-scale chemical events, whether accidental or terrorist-related.

The organophosphate nerve agents were originally developed by the IG Farben chemical company in Germany in 1938–1940 as possible insecticides. They are now considered the most toxic and significant chemical weapons with respect to military and civilian planning. Although the first two nerve agents, tabun and sarin, were weaponized and stockpiled by Nazi Germany during World War II, they were never used on the battlefield. American and Soviet forces discovered German rounds filled with these agents, as well as soman, which was developed too late in the war to be weaponized, and immediately began production of munitions containing nerve agents. The first attested battlefield use of these weapons was by Iraq during the Iran–Iraq War from 1984–1987. Sarin was also used by the Japanese cult Aum Shinrikyo in the famous Tokyo subway attack of 1995.

Despite the (relatively) low death rate that has historically occurred from chemical events, both military and public perception is that chemical events, whether accidental or intentional, are to be greatly feared. The degree of fear surrounding chemical events appears to be disproportionate to the degree of actual illness and death. Similar degrees of seemingly excessive public fear are evident in nearly every report of a chemical event. Fear of a chemical event, in fact, seems to create much more public distress than the actual morbidity and mortality created by the release itself. For this reason, disaster preparedness professionals have expressed concern about possible terrorist use of easily available toxic industrial chemicals (TICs). In theory, the difficulty of acquiring or manufacturing a military-style agent could be bypassed and an equally large-scale public effect could be achieved by making use of commercially available chemicals. In the public mind, chemicals are “all cut from the same cloth” and hence reports of any release are likely to provoke substantial public reaction: fear and terror. It appears that even the threat of TIC use may be enough to trigger intense public anxiety and terror.

**Chemical Warfare and Terrorism Agents: Clinical Considerations and Treatment Recommendations**

Healthcare personnel should suspect an exogenous chemical attack whenever there are multiple patients with similar acute symptoms, especially after exposure to air with an odd smell or color. Chemical agents likely to be used in a large-scale terrorist attack overwhelmingly fall into four categories of compounds: pulmonary intoxicants, cyanides (mislabeled “blood agents”), vesicants, and nerve agents. Two categories, cyanides and nerve agents, have specific antidotes that must be administered in a time-sensitive manner. For the other two categories of agents, only supportive care is available.

Of the four categories, pulmonary intoxicants and vesicants tend to produce delayed effects. Unlike biological agents with incubation periods typically lasting days, the latent period for these chemical agents tends to be on the order of hours to a day. For cyanides and nerve agents, symptoms are more likely to be immediate or to appear with a latent period of only seconds to minutes.

Certain general principles apply for any suspected mass casualty event involving chemical agents. Decontamination is the most important. Although decontamination of patients exposed to chemical agents may be useful for the patients, it is even more important in order to avoid contamination of other patients, healthcare providers, and treatment facilities. During the Tokyo sarin attack in 1995, an estimated 10% of the emergency department staff developed miosis, the first sign of sarin vapor poisoning. This was because they failed to remove patients’ clothes before the exposed victims entered the emergency department. Sarin vapor, trapped in air cells of clothing, caused symptoms in the healthcare workers. A useful concept for chemical agent exposures is to consider patients as contagious without being infectious. This concept will remind properly trained emergency staffs to remove clothing and do at least a brief decontamination of patients suspected of chemical exposure before they enter the facility.

The specific physical state of the agent is an important consideration in determining efficacious decontamination procedures. True vapors or gases require much less attention to full-body decontamination, since clothing removal will eliminate 90% or more of the risk to healthcare workers. Cyanides and pulmonary intoxicants are likely to be only vapor or gas hazards because they are all vapors at standard temperature and pressure. Mustards and nerve agents, on the other hand, are liquids at standard temperature and pressure. Liquid chemical agents require full-body decontamination. Thus, it is critical to obtain the exposure history. Even though mustards and nerve agents are liquids at standard temperature and pressure, in many likely scenarios, exposure to patients will only be in the vapor phase. Agents such as the nerve agent sarin, which evaporates rapidly from the liquid phase at standard temperatures, can overwhelmingly cause vapor hazards rather than liquid hazards. In the Tokyo subway attack, 30% sarin solution was spilled out onto the floor and seats of subway cars. Although the agent causing intoxication was liquid, essentially none of the roughly 5,500 people who presented for care were directly touched by the liquid. Instead, they inhaled sarin vapor, which evaporated from the floor of the subway car and was carried throughout the subway system by the movement of the train.

Physical removal of contaminants is superior to all known catalytic or chemical methods of decontamination. Water or soap and water, if applied quickly and in sufficient quantities, is an appropriate decontaminant for a liquid chemical agent on the skin. The U.S. military developed doctrine for tactical situations in which water was not available in sufficient quantities, and has relied on 0.5% bleach for decades. This solution is a tenfold dilution from the commercially available product, which is 5% bleach (a concentration that is damaging to normal skin). Reactive Skin Decontamination Lotion (RSDL) has been licensed by the U.S.
Table 31.1. Recognizing Health Effects of Chemical Agents by Category

<table>
<thead>
<tr>
<th>Agent</th>
<th>Agent Name</th>
<th>Unique Characteristics</th>
<th>Initial Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve</td>
<td>Cyclohexyl sarin</td>
<td>Miosis (pinpoint pupils)</td>
<td>Miosis (pinpoint pupils)</td>
</tr>
<tr>
<td></td>
<td>Sarin</td>
<td>Copious secretions</td>
<td>Blurred/dim vision</td>
</tr>
<tr>
<td></td>
<td>Soman</td>
<td>Muscle twitching/fasciculations</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Tabun</td>
<td></td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td></td>
<td>VX</td>
<td></td>
<td>Copious secretions/sweating</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Muscle twitching/fasciculations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Breathing difficulty</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td>Asphyxiant (“blood agents”)</td>
<td>Arsine</td>
<td>Possible cherry red skin</td>
<td>Confusion</td>
</tr>
<tr>
<td></td>
<td>Cyanogen chloride</td>
<td>Possible cyanosis</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Hydrogen cyanide</td>
<td>Possible frostbite*</td>
<td>Patients may gasp for air, similar to asphyxiation but more abrupt onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Seizures prior to death</td>
</tr>
<tr>
<td>Choking/pulmonary-damaging</td>
<td>Chlorine</td>
<td>Chlorine is a greenish-yellow gas with pungent odor</td>
<td>Eye and skin irritation</td>
</tr>
<tr>
<td></td>
<td>Hydrogen chloride</td>
<td>Phosgene gas smells like newly mown hay or grass</td>
<td>Airway irritation</td>
</tr>
<tr>
<td></td>
<td>Nitrogen oxides</td>
<td></td>
<td>Dyspnea, cough</td>
</tr>
<tr>
<td></td>
<td>Phosgene</td>
<td>Possible frostbite*</td>
<td>Sore throat</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chest tightness</td>
</tr>
<tr>
<td>Blistering/vesicant</td>
<td>Mustard/Sulfur mustard (HD, H)</td>
<td>Mustard (HD) has an odor like burning garlic or horseradish</td>
<td>Severe irritation</td>
</tr>
<tr>
<td></td>
<td>Mustard gas (H)</td>
<td>Lewisite (L) has an odor like penetrating geranium</td>
<td>Redness and blisters of the skin</td>
</tr>
<tr>
<td></td>
<td>Nitrogen mustard (HN-1, HN-2, HN-3)</td>
<td>Phosgene oxime (CX) has a peppery or pungent odor</td>
<td>Tearing, conjunctivitis, corneal damage</td>
</tr>
<tr>
<td></td>
<td>Lewisite (L)</td>
<td></td>
<td>Mild respiratory distress to marked airway damage</td>
</tr>
<tr>
<td></td>
<td>Phosgene oxime (CX)</td>
<td></td>
<td>May cause death</td>
</tr>
<tr>
<td>Incapacitating/behavior-altering</td>
<td>3-Quinuclidinyl benzilate (Agent BZ)</td>
<td>May appear as mass drug intoxication with erratic behaviors, shared realistic and distinct hallucinations, disrobing and confusion</td>
<td>Dry mouth and skin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperthermia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mydriasis (dilated pupils)</td>
</tr>
</tbody>
</table>

* Frostbite may occur from skin contact with liquid arsine, cyanogen chloride, or phosgene.

Source: Modified from State of New York, Department of Health.

Food and Drug Administration (FDA) as a skin decontaminant for all chemical agents. It is not approved in wounds. Therefore, if the skin is broken, providers should use sterile saline or sterile water as a rinse. Work done in the 1950s in the Netherlands, however, shows that many household products including corn oil are equally as effective decontaminants as 0.5% bleach. The key concept is to decontaminate as quickly as possible, using some physical agent that will wash the patient’s skin. Verification of decontamination in a large civilian attack involves confirmation that the patient has been washed. In military settings, detector papers (M8 and M9 paper) that turn specific colors if a liquid chemical agent is still present have been applied to patients’ skin.

Another general principle revolves around logistics. For pulmonary intoxicants and mustards, which have no specific antidotes, proper management to improve survival requires that severely exposed patients be transported to intensive care settings. In these cases, evacuation to a higher level of care may be more valuable than actual emergency treatment. By contrast, for the more rapidly acting cyanides and nerve agents, immediate care may be necessary even before the patient is properly decontaminated, possibly even in the “hot zone.”

Pulmonary intoxicants and cyanides have the potential to result in casualties after industrial accidents in many communities. The vesicants and nerve agents do not generally cause casualties outside of military or terrorist scenarios. Table 31.1 summarizes the initial health effects of the various chemical agent categories. Table 31.2 lists initial decontamination and treatment recommendations for these agent categories. A useful
<table>
<thead>
<tr>
<th>Agent</th>
<th>Decontamination</th>
<th>First Aid</th>
<th>Other Patient Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve</td>
<td>Remove clothing immediately Gently wash skin with soap and water Do not abrade skin For eyes, flush with plenty of water or normal saline</td>
<td>Decontaminate skin Atropine before other measures 2-PAM Cl Repeat as needed Diazepam or midazolam if severe exposure and/or if clinically seizing</td>
<td>Onset of symptoms from dermal contact with liquid forms may be delayed Repeated antidote administration may be necessary</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Remove clothing immediately if no frostbite(\ast) Gently wash skin with soap and water Do not abrade skin For eyes, flush with plenty of water or normal saline</td>
<td>Rapid treatment with oxygen Specific IV cyanide antidotes (sodium nitrite and then sodium thiosulfate, or hydroxocobalamin)</td>
<td>Arsine and cyanogen chloride may cause delayed pulmonary edema</td>
</tr>
<tr>
<td>Pulmonary intoxicants</td>
<td>Remove clothing immediately if no frostbite(\ast) Gently wash skin with soap and water Do not abrade skin For eyes, flush with plenty of water or normal saline</td>
<td>Fresh air, forced rest Semi-upright position If signs of respiratory distress are present, oxygen with or without positive airway pressure may be needed Other supportive therapy, as needed; in severe cases may require intubation</td>
<td>May cause delayed pulmonary edema, even following a symptom-free period that varies in duration with the amount inhaled</td>
</tr>
<tr>
<td>Blistering/vesicant</td>
<td>Immediate decontamination is essential to minimize damage Remove clothing immediately Gently wash skin with soap and water Do not abrade skin For eyes, flush with plenty of water or normal saline</td>
<td>Immediately decontaminate skin Flush eyes with water or normal saline for 10–15 minutes If breathing difficulty, give oxygen Supportive care: may require intubation in severe cases</td>
<td>Mustard has an asymptomatic latent period There is no antidote or treatment for mustard Lewisite has immediate burning pain, blisters later Specific antidote British Anti-Lewisite (BAL) may decrease systemic effects of Lewisite; only available IM in small quantities Phosgene oxime causes immediate pain Possible pulmonary edema</td>
</tr>
<tr>
<td>Incapacitating/behavior-altering</td>
<td>Remove clothing immediately Gently wash skin with water or soap and water Do not abrade skin</td>
<td>Remove heavy clothing Evaluate mental status Use restraints as needed Monitor core temperature carefully Supportive care</td>
<td>Hyperthermia and self-injury are largest risks Hard to detect because it is an odorless and non-irritating substance Possible serious arrhythmias Possible pulmonary edema Specific antidote for cholinergic agents such as BZ (physostigmine) may be available</td>
</tr>
</tbody>
</table>

Pulmonary Intoxicants

A large variety of agents cause pulmonary toxicity by the inhalation route. Many of these are toxic industrial chemicals or materials. A few have been used in warfare or in terrorist attacks. Space does not permit detailed discussion of the entire list.

Most pulmonary intoxicants primarily affect only the respiratory tree and do not cause systemic or multi-organ toxicity. With this generalization in mind, further categorization is useful. Highly reactive or water-soluble pulmonary intoxicants cause toxicity in the central compartment of the respiratory tract: the trachea, large bronchi, and larynx. Typical examples of these include hydrochloric acid and ammonia. Among the weaponized agents, sulfur mustard is another good example of intoxicants affecting these structures, although its primary use in terrorism or warfare is as a vesicant. By contrast, pulmonary intoxicants that are less reactive or water-soluble do not react with the structures of the central component, and thus are able to reach the alveoli. They exert primary effects on this peripheral pulmonary compartment. Classic examples of this category include phosgene, oxides of nitrogen (the major...
component of photochemical smog, and perfluorosobutylene, the combustion product of Teflon®. Central agents cause irritation, local edema, and, in severe cases, pseudomembrane formation through sloughing in large airways. Peripheral agents tend to disrupt the alveolar-capillary membrane, causing transudation of fluid and producing non-cardiogenic, toxic pulmonary edema. In phosgene intoxication, this probably occurs due to acylation at the alveolar-capillary membrane. Certain agents, such as chlorine, have mixed effects.5

The distinction between central and peripheral pulmonary toxicants is a matter of degree and is not absolute. Large exposures to peripheral agents can also affect the central structures, and vice versa. But it is a useful distinction in conceptualizing the primary damage caused by the two categories of pulmonary toxicants.

The common industrial and military pulmonary agents are gases at standard temperatures and pressures. While they may be mucous membrane irritants (chlorine is a good example) and thus cause transient tearing and salivation, only their pulmonary effects are life-threatening. Because they are gases, decontamination is a relatively minor issue. Clothing removal and a quick wash-down of the patient should suffice to protect both provider and emergency treatment facilities.

While all pulmonary intoxicants can produce shortness of breath, the peripheral and central syndromes clinically differ. Central pulmonary agent toxicity manifests as stridor, laryngospasm, and dyspnea. These symptoms are often associated with a latent period that varies according to the specific intoxicant and the amount inhaled, but which is typically on the order of several hours. A severe toxic exposure to a centrally acting agent can cause sudden complete airway obstruction either from edema or by the sloughing of pseudomembranes; these patients can deteriorate rapidly.

By contrast, peripheral pulmonary agent toxicity manifests first as dyspnea, with or without chest tightness. These symptoms occur in the absence of coughing or any signs of pulmonary compromise, either on direct auscultation or even on X-ray. This is because the initial phase of pulmonary edema involves leakage of fluid from the capillaries only into the interstitial space. Until fluid has penetrated into the alveoli themselves, there will only be symptoms without signs. After that point, rales and crackles develop with clear signs of edema on X-ray. As the syndrome intensifies, arterial blood gases will show hypoxemia, and sequestration of up to 1 L/h of fluid in the lungs may lead to hypovolemia and hypotension. This clinical picture is very atypical for cardiogenic pulmonary edema. Patients die of respiratory failure due to hypoxia, hypovolemia, or both. WWI data clearly show that exertion during the latent period of peripheral pulmonary toxicity can exacerbate the situation and turn a minor illness into a life-threatening emergency.

At the time this chapter is being written, no biomarker exists that can discriminate between potentially exposed patients who may be at high risk for the development of non-cardiogenic pulmonary edema within hours. Such a biomarker would be of great help to those in charge of the disaster response because it could identify individuals having the highest need for evacuation to an intensive care unit level of pulmonary support.

Although the latent period may be sufficiently long to insure the patient is no longer being exposed at the time of medical evaluation, it is important to confirm that the patient has been removed from the agent’s source. The development of symptoms and signs of pulmonary toxicity within four hours of exposure is a poor prognostic sign regardless of therapy. This is true for both the central and peripheral syndromes. There is no specific therapy for pulmonary agent toxicity. Therapy is entirely supportive.

For central pulmonary toxicity, the key principle is to maintain the integrity of the airway. In severe cases, where pseudomembranes can form and obstruct the airway, endotracheal intubation or even emergency tracheostomy may be required. For primarily peripheral toxicity, intubation with positive end-expiratory pressure may be needed. Fluid management should be judicious. These patients, unlike those experiencing cardiogenic edema, are actually hypovolemic. Thus, diuretics are relatively contraindicated and intravenous fluids may be required in multi-liter quantities. Treat hypoxia directly as warranted by monitoring blood gas results in expectation that supportive care will allow the respiratory system to recover.

There are no specific antidotes for pulmonary damage from any of the pulmonary toxicants.6 More modern forms of respiratory support, including positive end-expiratory pressure (PEEP), are not specific for these syndromes.7 Antibiotics are not generally advocated prophylactically and are given only when cultures prove infection is present. Animal studies have not yet shown value in the use of agents such as N-acetylcysteine. The use of steroids is not supported by animal or clinical experience.8

Most patients with isolated toxicity from inhaled pulmonary intoxicants recover if supportive care is provided in a timely manner. A few peripheral pulmonary intoxicants are associated with interstitial fibrosis post-crisis, including oxides of nitrogen. Phosgene and chlorine, the two most common agents in terrorist scenarios, cause acute syndromes from which patients recover with no apparent lasting structural damage on subsequent pathological examination. This implies that management of patients with these intoxications may become more of a logistical challenge than a medical one.

Cyanides

Cyanides are not considered to be useful battlefield agents, but are high threats for use as a terrorist weapon due to their rapid action. The commonly cited cyanide products, hydrogen cyanide and cyanogen chloride, are close to their boiling points at standard temperatures and pressures. They are occasionally used in criminal scenarios for small-scale attacks, usually against specific individuals, to poison water and food supplies close to the point of consumption.

As a method of large-scale attack against a population, cyanides are not well adapted because the gaseous phase of cyanide ion is lighter than air. Hence, in an outdoor attack, cyanide dissipates rapidly. The reason for the high interest in cyanides as terrorist weapons lies in the possibility of using them in an indoor environment against a large crowd, such as in a sports arena, religious structure, government building, railroad station, or airport terminal.

Cyanide ion, is a normal part of the environment. There is even a normal human cyanide level, based on dietary intake of cyanogenic plants. It is present in all organic media. Smokers of tobacco, for example, average three times the normal human baseline cyanide level in blood. Cyanide ion is also a required cofactor for many human enzymes, including vitamin B12. Because humans evolved in an environment containing cyanide, unlike any of the other chemical agent classes, people also evolved a mechanism to detoxify small quantities of this ion, based on the hepatic enzyme rhodanese. This mechanism underpins antidotal therapy for cyanide poisoning.
Cyanide’s mode of action is to inhibit the electron transport chain in mitochondria, at the level of the last enzyme in the chain, cytochrome oxidase or cytochrome a3. Cyanide ion has a high binding affinity for various metals, including iron, which is the central atom in this enzyme. Once cyanide binds to the iron in this enzyme, aerobic metabolism ceases; cells can only continue metabolism by switching to the inefficient anaerobic metabolic pathway. With nonfunctional electron transport chains, cells cannot utilize oxygen to make glucose and carry out other metabolic functions. As a consequence, venous blood no longer appears blue, and this explains the classic “cherry red” appearance associated with cyanide victims. As a result, cyanide victims are not cyanotic. The term “cyanide” (Greek for blue) originates from Prussian blue (not cyanosis), the compound from which Von Scheele originally isolated the molecule in 1782.

Cyanide causes a primary histotoxic anoxia. It affects cells in direct proportion to their metabolic rate. Cyanide crosses the alveolar-capillary barrier and circulates via the blood, giving rise to the old misnomer “blood agent” for cyanide. This term is still in use despite the fact that the blood is only a passive carrier for cyanide. Blood is essentially unaffected by the passage of cyanide, since most blood cells have very few mitochondria. In humans, the most actively metabolic cells are those in the carotid bodies, which serve as baroreceptors. Thus, inhalation of a sizable cyanide challenge causes initial hyperpnea, hypotension, and syncope. The second most highly metabolic cells are those of the brain. Therefore, the next symptom of cyanide poisoning, which in large exposures occurs almost instantaneously, is loss of consciousness followed shortly by seizures, probably caused by hypoxia. Within seconds to minutes, central apnea affects the medullary breathing centers. Cardiac tissue will become affected next, causing vascular instability leading to cardiopulmonary arrest and death within about 8 minutes if there is no treatment.

Via the inhalation route, cyanide is one of two chemical agent classes that can cause a virtually instantaneous loss of consciousness and seizures. The other is the nerve agents. Key concepts for the differential diagnosis are detailed later.

Removal of the patient from the source of contamination is crucial and may be lifesaving. Because the body has its own detoxification mechanism, humans can metabolize a small amount of cyanide. Clinical experience has shown that simple removal from the source of cyanide can revive mild cases of poisoning.

Although the mechanism is not well understood, nasal or mask oxygen therapy is helpful acutely in cyanide poisoning. While theoretically implausible since mitochondrial electron transport chains are inhibited, rendering cells unable to use oxygen, oxygen therapy should be instituted rapidly as has been proven clinically effective. In addition to oxygen, specific antidotal therapy is valuable for acute cyanide poisoning, but only if it can be instituted in a timely manner. There are two major forms of antidotal therapy, the multi-component cyanide antidote kit and hydroxocobalamin.

The cyanide antidote kit is based on beagle dog experiments performed in the 1930s that showed the components of the kit were capable of saving animals exposed to up to twenty lethal doses of cyanide gas. Conceptually, it consists of two antidotes used sequentially. The first antidote, a nitrite (not nitrate), induces methemoglobin formation. Methemoglobin, with its iron in the Fe3+ (ferric) state rather than the Fe2+ (ferrous) state of normal hemoglobin, binds to cyanide ions with even greater affinity than does cytochrome a3. Hence, creation of a methemoglobin pool, which results from therapy with nitrite, will extract cyanide from cytochrome a3 and rapidly restore normal cell function. Nitrite is given either via inhalation of an amyl nitrite ampoule or via intravenous administration of sodium nitrite. The inhaled ampoules have never been approved by the FDA but are available in the United States in a state of “regulatory discretion.” The dose for sodium nitrite from the vial provided in the cyanide antidote kit is 10 ml. If a repeat dose is required, half of the second vial (5 ml) should be administered. For children, the U.S. military recommends 0.33 ml/kg of the standard 3% nitrite solution given slowly over 5–10 minutes. Nitrite will cause hypotension, and so patients should be lying down when they receive it, whether inhaled amyl nitrite or intravenous sodium nitrite. The use of nitrite alone, however, will create a pool of cyanmethemoglobin in the blood. This is unstable, and unless the second antidote is given, cyanide will eventually dissociate from methemoglobin and cause subsequent toxicity.

The second antidote, sodium thiosulfate, is necessary because the body cannot tolerate a large pool of cyanmethemoglobin indefinitely. In order to permanently eliminate the cyanide ion from the body, sodium thiosulfate, a sulfur donor, is administered as a cofactor to activate the liver stores of rhodanese. The result of this reaction is that rhodanese forms sodium thiocyanate, which is excreted harmlessly in the urine. Sodium thiosulfate is administered via the intravenous route only. The kit contains two 50-ml vials; if the patient requires more than one dose, half of the second vial (25 ml) should be administered. The U.S. military recommends a pediatric dose of 1.65 ml/kg of the standard 25% solution. In fire victims, whose oxygen carrying capacity may have been reduced by exposure to carbon monoxide, it has been standard practice for many years to avoid the methemoglobin former (nitrite) and proceed directly to sodium thiosulfate.

Hydroxocobalamin is commonly used in Europe, and in 2007 was licensed by the FDA as an alternate cyanide antidote (Cyanokit®). It binds stoichiometrically (1:1) to circulating cyanide and forms cyanocobalamin (vitamin B12) which the body tolerates well. One disadvantage is that hydroxocobalamin is a huge molecule and 1:1 binding means that large volumes of hydroxocobalamin must be used via the intravenous route. Additionally, unlike the nitrite and thiosulfate solutions in the antidote kit, hydroxocobalamin must be reconstituted from powder. It also tends to induce an orange color to the skin. Extensive clinical experience from the Paris Fire Brigade has demonstrated that hydroxocobalamin can be used as on-scene treatment by trained first responders. The adult dose is two 2.5-g vials administered intravenously over 15 minutes after reconstitution, with a second dose of two 2.5-g vials given as needed. The most common side effect of hydroxocobalamin is chromaturia (urine tends to turn purple), although this in itself is harmless. In many of the published cases in which hydroxocobalamin has been used, sodium thiosulfate was also given; these treatments are, therefore, not mutually exclusive. Hydroxocobalamin has advantages over nitrite. It does not cause methemoglobinemia (diminishing oxygen carrying capacity) or hypotension, and is safe in pregnancy. However, it takes longer to administer and requires the infusion of large volumes. Cyanide antidotal recommendations are summarized in Table 31.3.

**Vesicants**

Sulfur mustard, the prototypical vesicant agent, has been a military threat since it first appeared on the battlefield in Belgium.
Table 31.3. Antidotal Recommendations for Cyanide Poisoning

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mild (Conscious)</th>
<th>Severe (Unconscious)</th>
<th>Other Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child</td>
<td>If patient is conscious and has no other signs or symptoms, antidotes may not be necessary.</td>
<td>Sodium nitrite: 0.12–0.33 ml/kg, not to exceed 10 ml of 3% solution slow IV over no less than 5 minutes, or slower if hypotension develops and Sodium thiosulfate: 1.65 ml/kg of 25% solution IV over 10–20 minutes</td>
<td>For sodium nitrite–induced orthostatic hypotension, normal saline infusion and supine position are recommended. If still apneic after antidote administration, consider sodium bicarbonate for severe acidosis.</td>
</tr>
<tr>
<td>Adult</td>
<td>If patient is conscious and has no other signs or symptoms, antidotes may not be necessary.</td>
<td>Sodium nitrite: 10–20 ml of 3% solution slow IV over no less than 5 minutes, or slower if hypotension develops and Sodium thiosulfate: 50 ml of 25% solution IV over 10–20 minutes</td>
<td>Hydroxocobalamin (Cyanokit®), one vial reconstituted at scene, administered IV, an effective alternate; given over 15 minutes and repeated as needed</td>
</tr>
</tbody>
</table>

during World War I. In modern times it retains its military potential as well as posing a terrorist threat because of manufacturing simplicity and extreme effectiveness. Sulfur mustard accounted for 70% of the 1.3 million chemical casualties in WWI and an estimated 45,000 Iranian casualties during the Iran–Iraq War. Other vesicants of lesser importance include nitrogen mustard (still used in cancer chemotherapy), Lewisite, and phosgene oxime, which will not be discussed in detail.

Sulfur mustard constitutes both a vapor and a liquid threat to all exposed epithelial surfaces. Like peripheral pulmonary agents, mustard's effects are delayed, appearing hours after exposure. Organs most commonly affected are the skin (erythema and vesicles), eyes (ranging from mild conjunctivitis to severe eye damage), and airways (ranging from mild upper airway irritation to severe bronchiolar damage). Following exposure to large quantities of mustard, precursor cells of the bone marrow are damaged, leading to pancytopenia and secondary infection. The gastrointestinal mucosa may be damaged, and there are sometimes central nervous system (CNS) signs of unknown mechanism. No specific antidotes exist; management is entirely supportive.12

Mustard dissolves slowly in aqueous media, such as sweat. Once dissolved, however, it rapidly forms extremely reactive cyclic ethylene sulfonium ions, which react with cell proteins, cell membranes, and especially DNA in rapidly dividing cells. Mustard's ability to react with and alkylate DNA gives rise to the effects characterized as “radiomimetic” (i.e., similar to radiation injury). Mustard has many biological effects, but the actual mechanism of action is largely unknown. Mustard reacts with tissue within minutes of entering the body. Its circulating half-life in unaltered form is extremely brief.

Topical effects of mustard occur in the eyes, airways, and skin, in that order of sensitivity. Absorbed mustard may produce effects in the bone marrow, gastrointestinal tract, and CNS. Direct injury to the gastrointestinal tract may also occur following ingestion of the compound through contamination of water or food.

Erythema is the mildest and earliest form of mustard skin injury. It resembles sunburn and is associated with pruritus, burning, or stinging pain. Erythema begins to appear within 2 hours to 2 days after vapor exposure. Time of onset depends on the severity of exposure, ambient temperature and humidity, and type of skin. The most sensitive sites are the warm moist locations and thin delicate skin, such as the perineum, external genitalia, axillae, antecubital fossae, and neck.

Within erythematous areas, small vesicles can develop, which may later coalesce to form bullae. The typical bulla is large, dome-shaped, flaccid, thin-walled, translucent, and surrounded by erythema. The blister fluid is a transudate with a clear to straw-color. It becomes yellow over time and tends to coagulate. The fluid does not contain mustard and is not itself a vesicant. Lesions from high-dose liquid exposure may develop a central zone of coagulation necrosis with blister formation at the periphery. These lesions take longer to heal and are more prone to secondary infection than the uncomplicated lesions seen at lower exposure levels. Severe lesions may require skin grafting (Figure 31.1).

Sulfur mustard vapor is a centrally acting pulmonary intoxicant. The primary airway lesion is necrosis of the mucosa with
possible damage to underlying smooth muscle. The damage begins in the upper airways and descends to the lower airways in a dose-dependent manner. Usually, the terminal airways and alveoli are affected when death is imminent.

Necrosis of airway mucosa causes exfoliation of epithelial debris, sloughing, or “pseudomembrane” formation, as with any centrally acting pulmonary agent. These membranes may cause obstruction of the bronchi. During World War I, high-dose mustard exposure caused acute death via this mechanism in a small minority of cases.

The eyes are the organs most sensitive to mustard vapor injury. The latent period is shorter for eye injury than for skin injury and is also exposure concentration–dependent. After low-dose vapor exposure, irritation evidenced by reddening of the eyes may be the only effect. As the dose increases, the injury includes progressively more severe conjunctivitis, photophobia, blepharospasm, pain, and corneal damage, which may lead to severe visual impairment.

Ninety percent of eye casualties heal in 2 weeks to 2 months without sequelae. Scarring between the iris and lens may follow severe exposure; this scarring may restrict pupillary movements and may predispose victims to glaucoma. The most severe damage is caused by liquid mustard. After extensive eye exposure, severe corneal damage with possible perforation of the cornea and loss of the eye can occur. In some individuals, chronic eye irritation, sometimes associated with corneal ulcerations, has been described 10–20 years after exposure.

A few Iranian casualties from the Iran–Iraq War have developed a delayed neovascularization of their corneas that caused late-onset blindness. The relationship of this to an animal model finding known as mustard gas keratopathy is an area of active research.13

The mucosa of the gastrointestinal tract is susceptible to mustard damage, either from systemic absorption or ingestion of the agent. Mustard exposure in small amounts will cause nausea and possible vomiting lasting up to 24 hours. The mechanism for the nausea and vomiting is not understood, but mustard does have a cholinergic-like effect. The CNS effects of mustard remain poorly defined as well. Large exposures can cause seizures in animals. Reports from WWI and Iran described the behavior of persons exposed to small amounts of mustard as sluggish, apathetic, and lethargic. These reports suggest that minor psychological problems could linger for a year or longer.

The causes of death in the majority of cases with mustard toxicity are sepsis and respiratory failure. Mechanical obstruction via pseudomembrane formation and agent-induced laryngospasm is important in the first 24 hours, but only in cases of severe exposure. From the third through the fifth day after exposure, a secondary bacterial pneumonia can be expected due to invasion of denuded necrotic mucosa. The third wave of death is caused by agent-induced bone marrow suppression, which peaks 7–21 days after exposure and causes death via sepsis. Early warning of impending marrow suppression is a drop in the lymphocyte count beginning as early as 24 hours. Polymorphonuclear cells may actually rise at first and then begin falling at 3–5 days.

A patient severely ill from mustard toxicity requires the general supportive care provided to any critical patient as well as the specific care given to a burn patient. Liberal use of systemic analgesics, maintenance of fluid and electrolyte balance, nutritional support, use of appropriate antibiotics, and other general measures are necessary. As stated previously, no specific antidote for mustard exposure exists. This may need to await a better understanding of the underlying pathophysiology, which has eluded researchers for over a century.

The management of a patient exposed to mustard may vary from simple treatments, such as the provision of symptomatic care for a sunburn-like erythema, to complex interventions, such as the provision of sophisticated critical care to an individual with burns, immunosuppression, and multisystem involvement. Before raw denuded areas of skin develop, especially with less severe exposures, topical cortisone creams or lotions may be beneficial. Some basic research data suggest benefit from the early use of anti-inflammatory preparations. Small blisters (< 1–2 cm) should be left intact. Because larger bullae will eventually break, they should be carefully unroofed. Denuded areas should be irrigated three to four times daily with saline, other sterile solutions, or soapy water, and then liberally covered with a topical antibiotic, such as silver sulfadiazine or mafenide acetate, to a thickness of 1–2 mm. Some experts advocate sterile needle drainage of large blisters, collapsing the blister roof to form a sterile dressing. Mustard blister fluid does not contain sulfur mustard, only sterile tissue fluid. Healthcare staff should not fear contamination.

Systemic analgesics should be used liberally, particularly before patient manipulation. Monitoring of fluids and electrolytes is important in any sick patient. However, fluid loss after mustard exposure is not of the magnitude seen with deeper 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 will respond to any of a number of available ophthalmic solutions after the eyes are thoroughly irrigated. A topical antibiotic applied several times a day will reduce the incidence and severity of infection. Animal laboratory data have shown remarkable results with commercially available topical antibiotic/glucocorticoid ophthalmologic ointments applied early. Topical glucocorticoids alone are not of proven value, but their use during the first few hours or days may significantly reduce inflammation and subsequent damage. Ophthalmologic consultation is indicated and further use of glucocorticoids should be at the specialist’s discretion. Vaseline or a similar substance should be applied regularly to the edges of the lids to prevent them from adhering together.

 A productive cough and dyspnea accompanied by fever and leukocytosis occurring within 12–24 hours of exposure is indicative of a chemical pneumonitis. The clinician must avoid use of prophylactic antibiotics to manage this process. Infection often occurs on the third to fifth day and is signaled by fever, pulmonary infiltrates, and an increase in sputum production with a change in color. Initial antibiotic therapy should await evidence of infection from sputum Gram stain; regimens can then be tailored according to the results of sputum culture and sensitivity. Studies suggest that Iran–Iraq War veterans may develop a chemical pneumonitis responsive to treatment with erythromycin 400–600 mg/day, but antibiotic therapy must continue for 6 months following mustard exposure.

 Intubation may be necessary for laryngeal spasm or edema, facilitating better ventilation and suctioning of the necrotic inflammatory debris. Early use of PEEP or continuous positive airway pressure (CPAP) may be beneficial. Pseudomembrane formation may require fiber-optic bronchoscopy for removal of the necrotic debris. Bronchodilators are effective for treatment of bronchospasm. If additional relief of bronchospasm
is needed, glucocorticoids should be added. Otherwise, there is little evidence that the routine use of glucocorticoids is beneficial.

Leukopenia begins approximately 3 days after major systemic absorption of mustard. Marrow suppression peaks at 7–14 days. In the Iran–Iraq War, a white blood count of ≤ 200 cells/μL usually resulted in death of the patient. This value is not apparently a property of mustard toxicity per se, but is a marker of general immune system failure as a whole. AIDS patients who reach such low white counts also have a high risk of death. Sterilization of the gut by non-absorbable antibiotics should be considered to reduce the possibility of sepsis from enteric organisms. Cellular replacement (bone marrow transplants or transfusions) may be successful. In one study, granulocyte colony-stimulating factor produced a 50% reduction in the time for the bone marrow to recover in nonhuman primates exposed to sulfur mustard and should be considered in human exposure.14 Antiemetics may be necessary for gastrointestinal side effects. Mustard has the potential for multi-organ chronic sequelae, including delayed corneal neovascularization causing blindness, chronic pneumonitis or "mustard lung," permanent skin dysfunction in affected areas, and a probable increased incidence of cancers, particularly pulmonary. A recent review summarizes experience from Iranian casualties.15

Lewisite, a chemically unrelated compound, causes a remarkably similar syndrome to sulfur mustard. There are two important clinical differences between Lewisite and sulfur mustard, however. Lewisite is a direct skin irritant, so early detection of exposure is more likely. This means that decontamination may be more effective in preventing systemic damage, thus reducing the probability of use for either a military or civilian terrorist attack. The other difference is that Lewisite is an arsenical compound so it can be treated with a chelating agent that binds arsenic. The antidote, British anti-Lewisite or dimercaprol, was developed in the 1930s and remains available as a chelating agent. The only U.S. FDA-approved formulation is an intramuscular (IM) injection dissolved in peanut oil, to which some patients are allergic.

Nerve Agents

The organophosphorus nerve agents are the deadliest of the chemical warfare agents. 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.16

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. The two-letter codes are a NATO international convention and convey no clinical implications. All of the nerve agents are organophosphorus compounds, which are liquids at standard temperatures and pressures. The "G" agents evaporate at about the rate of water, except for cyclosarin, which is oily, usually evaporating within 24 hours after deposition on the ground. Their high volatility makes a spill of any amount a serious vapor hazard. In the Tokyo subway attack, 100% of the symptomatic patients inhaled sarin vapor that spilled out on the floor of the subway cars. VX, an oily liquid, is the exception. Its low vapor pressure makes it much less of a vapor hazard but potentially a greater environmental hazard. 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 to 100,000.

Acetylcholinesterase inhibition accounts for the major life-threatening effects of nerve agent poisoning. Reversal of this inhibition by antidotal therapy is effective, proving that this is the primary toxic action of these poisons. At cholinergic synapses, acetylcholinesterase, bound to the postsynaptic membrane, functions to terminate neuron stimulation and thus regulate cholinergic transmission. Inhibition of acetylcholinesterases causes the released neurotransmitter acetylcholine to accumulate abnormally. End-organ overstimulation, manifesting as cholinergic crisis, ensues. 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 however, will differ.

Contact with nerve agent vapor is overwhelmingly the most likely exposure route in both battlefield and terrorist scenarios. Vapor exposure will cause cholinergic symptoms in the order that 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."23 Rarely, this can also cause eye pain and nausea. Exocrine glands located in the eyes, nose, mouth, and pharynx are exposed to the vapor next, and cholinergic overload here causes increased secretions manifesting as lacrimation, rhinorrhea, and excess salivation. Finally, toxin interacts with exocrine glands in the upper airway and bronchial smooth muscle causing bronchorrhea and bronchospasm, the combination of which can result in hypoxia.

Once the victim has inhaled the vapor, it passively crosses the alveolar-capillary membrane, enters the bloodstream, and inhibits circulating cholinesterases, particularly free butyrylcholinesterase and erythrocyte acetylcholinesterase. Both enzymes can be assayed but measurement may not be easily interpreted without a baseline, since cholinesterase levels vary enormously between persons and over time in an individual healthy patient.

The gastrointestinal tract is usually the first organ system to become symptomatic from blood-borne nerve agent exposure. Cholinergic overload causes abdominal cramping and pain, nausea, vomiting, and diarrhea. After the gastrointestinal tract is involved, nerve agents affect the heart, distant exocrine glands, muscles, and brain. Because there are cholinergic synapses on both the vagal (parasympathetic) and sympathetic sides of the autonomic input to the heart, changes in heart rate and blood pressure are unpredictable. As discussed earlier, remote exocrine activity will include over-secretion in the salivary, nasal, respiratory, and sweat glands – the patient will be “wet all over.” Blood-borne nerve agents overstimulate neuromuscular junctions in skeletal muscles, causing fasciculations followed by frank twitching. If the process continues, adenosine triphosphate in muscle cells will eventually be depleted and flaccid paralysis will ensue. Overstimulation at the post synaptic membrane also causes prolonged depolarization of these structures, resulting in eventual blockade of neurotransmission and enhancement of flaccid paralysis.

Due to the wide distribution of the cholinergic system in the brain, sufficient doses of blood-borne nerve agents cause rapid loss of consciousness, seizures, and central apnea, leading to death within minutes. If respiration is supported, status epilepticus may ensue. If status persists, neuronal death and permanent
brain dysfunction may occur. In a few cases of mild nerve agent intoxication, patients recovered, but reported weeks of irritability, sleep disturbances, and other nonspecific neurobehavioral symptoms. These may reflect posttraumatic stress or direct nerve agent toxicity that is not well understood.

The time from exposure to development of full-blown cholinergic crisis after nerve agent vapor inhalation can be minutes or even seconds; however, there is no depot effect. Therefore, symptoms do not continually progress over hours and the maximal toxic effects are achieved fairly quickly. Since nerve agents have a short circulating half-life, improvement should be rapid with no subsequent deterioration if the patient is treated with antidotes and supportive care.

Exposure to liquid nerve agents differs in speed and order of symptom onset. A nerve agent on intact skin will partially evaporate and partially be absorbed, causing localized sweating and then localized fasciculations when it encounters neuromuscular junctions. Once in muscle, it will cross into the circulation and cause gastrointestinal discomfort, respiratory distress, heart rate changes, generalized fasciculations and twitching, loss of consciousness, seizures, and central apnea. The time course will be much longer than with vapor inhalation; even a large, lethal droplet can take up to 30 minutes to have an effect, and a small, sublethal dose might require up to 18 hours before toxicity is detected. Clinical deterioration that occurs hours after initiating treatment is far more likely with liquid than with vapor exposure. Additionally, miosis, practically unavoidable with vapor exposure, is not always evident with liquid exposure and may be the last symptom to present. This is due to the relative insulation of the pupillary muscle from the systemic circulation.

Unless a nerve agent is removed by specific therapy (oximes), its binding to cholinesterase is essentially irreversible. Erythrocyte acetylcholinesterase activity recovers at about 1% per day. Plasma butyrylcholinesterase recovers more quickly and is a better guide to recovery of tissue enzyme activity.

Acute nerve agent poisoning is treated by decontamination, respiratory support, and three antidotes – an anticholinergic, an oxime, and an anticonvulsant. In acute cases, all of these forms of therapy may be given simultaneously. Death from nerve agent poisoning is almost always due to respiratory failure. Ventilation will be complicated by increased resistance and secretions. Atropine should be given before ventilation or as it begins, as it will facilitate this intervention.

In theory, any anticholinergic could be used to treat nerve agent poisoning, but worldwide the choice is invariably atropine because of its wide temperature stability and rapid effectiveness. Atropine can be administered either intramuscularly or intravenously. It rapidly reverses cholinergic overload at muscarinic synapses but has little effect at nicotinic synapses. Therefore, atropine can quickly treat the life-threatening respiratory effects of nerve agents but will probably not reverse neuromuscular and possibly sympathetic effects. In the field, military personnel in some countries are given MARK I kits, which contain 2 mg atropine in auto-injector form for intramuscular use (Figure 31.2). In addition, some civilian agencies are now stockpiling this product (FDA-approved in the United States). One can only give a full auto-injector dose; dividing the drug between more than one individual is not possible. The initial loading dose is 2, 4, or 6 mg, with retreatment every 5–10 minutes until the patient’s breathing and secretions improve. The Iranians initially used larger doses during the Iran–Iraq War where oximes were in short supply. Pediatric auto-injectors are now available at dosages of 0.5 and 1.0 mg for rapid IM administration; however, the intravenous route is preferred when this is logistically feasible, especially in small children. There is no upper bound to atropine therapy in a patient either intramuscularly or intravenously. A total average adult dose for a severely toxic patient usually ranges from 20–30 mg.

In a mildly symptomatic patient with miosis only and no other systemic toxicity, atropine or homatropine eye drops may suffice for therapy. This will produce roughly 24 hours of mydriasis. Frank miosis or imperfect accommodation may persist for weeks or even months after all other signs and symptoms have resolved.

Oximes are nucleophiles that reactivate a cholinesterase enzyme whose active site has been bound to a nerve agent. Therapy with oximes dissociates the enzyme from the nerve agent, restoring normal enzyme function. These antidotes are indicated primarily for the reversal of muscle paralysis and target nicotinic receptors. They have little impact on secretions or bronchospasm. Oxime therapy is limited by a chemical process referred to as aging. Oximes require the presence of a side chain molecule on nerve agents to be effective. This side chain is removed from the nerve agent by biologic processes at a characteristic time-dependent rate. The nerve agent-enzyme complex has “aged” when the side chain is removed. Aged complexes are negatively charged, and oximes cannot reactivate negatively charged molecules. Therefore, oximes cannot reactivate cholinesterase enzymes once the nerve agent to which they are bound has aged. The practical effect of this differs from one nerve agent to another, since each ages at a characteristically unique rate. VX essentially never ages, sarin ages in 3–5 hours, and tabun ages over a longer period. All of these rates are so much longer than the patient’s expected lifespan after untreated acute nerve agent exposure that they may be ignored from a clinical standpoint. Soman, on the other hand, ages in 2 minutes. Thus, after only a few minutes following exposure, oximes are useless in treating soman poisoning. The oxime used varies by country; the United States has approved and fielded 2-pralidoxime chloride (2-PAM Cl). MARK I kits contain auto-injectors of 600 mg of 2-PAM Cl. Initial loading doses are 600, 1,200, or 1,800 mg. Since blood pressure elevation may occur after administration of 45 mg/kg in adults, field use of 2-PAM Cl is restricted to 1,800 mg/hour intramuscularly. During the time when more oxime cannot be given, atropine alone is recommended. In the hospital setting, 2.5–25 mg/kg of 2-PAM Cl intravenously has
been found to reactivate 50% of inhibited cholinesterase. The usual recommendation is 1,000 mg through slow intravenous drip over 20–30 minutes, with no more than 2,500 mg over a period of 1–1.5 hours.

Dosage recommendations for children are less certain than for adults and are based on extrapolations from adults; further studies are needed in children. In small children weighing less than 10–12 kg (< 25 pounds), auto-injectors, even the pediatric doses, may not be practical. Additionally, the clinical syndromes in children may be harder to recognize; in particular, seizures in children often manifest without tonic-clonic movements and may be missed. The U.S. FDA has approved a single cartridge auto-injector, ATNAA (Antidote Treatment Nerve Agent Auto-injector), which contains both 2.1 mg atropine and 600 mg 2-pralidoxime chloride. This is the military dual-chamber autoinjector; the civilian version is called DuoDote. Photo courtesy US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland.

Nerve agent–induced seizures do not respond to the usual anticonvulsants used for status epilepticus. The only class of anticonvulsants that has been shown to stop this form of status is the benzodiazepines. Diazepam is the only benzodiazepine approved for seizures in the United States in humans, although other benzodiazepines, especially midazolam, work well against nerve agent–induced seizures in animal models. Diazepam is manufactured in 10-mg injectors for intramuscular use and given to U.S. military forces for this purpose. Civilian agencies stockpile this product, convulsive antidote for nerve agent (CANA), which is not generally used in hospital practice. Extrapolation from animal studies indicates that adults will probably require 30–40 mg of diazepam, intramuscularly, to stop nerve agent–induced status epilepticus. In the hospital, or in a child too small to tolerate the auto-injector, intravenous diazepam may be used at similar doses. The clinician may confuse seizures with the neuromuscular signs of nerve agent poisoning. In the hospital, early electroencephalography is recommended in order to distinguish between non-convulsive status epilepticus, actual seizures, and postictal paralysis. Intravenous lorazepam is also effective. Antidotal recommendations for the treatment of acute nerve agent poisoning are found in Table 31.4.

Extensive animal work carried out by the U.S. Army has shown that midazolam is superior to diazepam and all other tested benzodiazepines in stopping nerve agent–induced seizures. Midazolam does not carry FDA approval as an anticonvulsant at the time of writing this chapter, despite being used off-label for this purpose for many years. A New Drug Application for midazolam for this purpose has been accepted by the FDA and it is hoped that approval will be forthcoming. Once this milestone is achieved, both military and civilian authorities plan to recommend IM midazolam as the anticonvulsant of choice. An important milestone in this effort was the completion of a large NIH-funded clinical study in 2012, which demonstrated that IM midazolam was superior to IV lorazepam in stopping status epilepticus of any cause in a community setting. The improved results with midazolam were largely derived from the shorter time to administer IM drugs via auto-injector. This study opened the door to general use of IM auto-injectors in civilian practice for the first time.

The major differential diagnosis for acute nerve agent poisoning is acute cyanide poisoning, particularly in a mass casualty event involving multiple patients presenting similarly. Both can develop acutely and involve loss of consciousness, seizures, and respiratory depression. Cyanide poisoned patients tend to remain non-cyanotic acutely because their venous blood remains red and oxygenated. Cyanide poisoned patients do not show the prominent miosis and increased secretions typical of nerve agent poisoned patients.

**Incapacitating Agents**

During the 1960s there was much interest on the part of U.S. intelligence agencies and military planners in developing an agent which would incapacitate, rather than kill, opposing forces. The only product that ever emerged from this program was 3-Quinuclidinyl benzilate, later termed Agent BZ, a weaponized anticholinergic. The mechanism of action of this compound is the exact opposite of nerve agents; it blocks acetylcholine from interacting with post-synaptic cholinergic receptors. It causes profound, but unpredictable, behavioral and psychiatric syndromes which gradually resolve without treatment. Because of
Table 31.4. Antidote Recommendations Following Exposure to Nerve Agents

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Antidotes Mild/Moderate Effects</th>
<th>Severe Effects</th>
<th>Other Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (0–2 yrs)</td>
<td>Atropine: 0.05 mg/kg IM, or 0.02 mg/kg IV; and 2-PAM Cl: 15 mg/kg IM or IV slowly</td>
<td>Atropine: 0.1 mg/kg IM, or 0.02 mg/kg IV; and 2-PAM Cl: 25 mg/kg IM, or 15 mg/kg IV slowly</td>
<td>Assisted ventilation after antidotes for severe exposure</td>
</tr>
<tr>
<td>Child (2–10 yrs)</td>
<td>Atropine: 1 mg IM, or 0.02 mg/kg IV; and 2-PAM Cl: 15 mg/kg IM or IV slowly</td>
<td>Atropine: 2 mg IM, or 0.02 mg/kg IV; and 2-PAM Cl: 25 mg/kg IM, or 15 mg/kg IV slowly</td>
<td>Repeat atropine (2 mg IM, or 1 mg IM for infants) at 5- to 10-min intervals until secretions have diminished and breathing is comfortable or airway resistance has returned to near normal.</td>
</tr>
<tr>
<td>Adolescent (&gt;10 yrs)</td>
<td>Atropine: 2 mg IM, or 0.02 mg/kg IV; and 2-PAM Cl: 15 mg/kg IM or IV slowly</td>
<td>Atropine: 4 mg IM, or 0.02 mg/kg IV; and 2-PAM Cl: 25 mg/kg IM, or 15 mg/kg IV slowly</td>
<td>Phentolamine for 2-PAM Cl-induced hypertension: (5 mg IV for adults; 1 mg IV for children). Diazepam for convulsions: (0.2–0.5 mg IV for infants &lt; 5 years; 1 mg IV for children &gt; 5 years; 5 mg IV for adults), or bioequivalent doses of midazolam.</td>
</tr>
<tr>
<td>Adult</td>
<td>Atropine: 2–4 mg IM or IV; and 2-PAM Cl: 600 mg IM, or 15 mg/kg IV slowly</td>
<td>Atropine: 6 mg IM; and 2-PAM Cl: 1,800 mg IM, or 15 mg/kg IV slowly</td>
<td></td>
</tr>
<tr>
<td>Elderly, frail</td>
<td>Atropine: 1 mg IM; and 2-PAM Cl: 10 mg/kg IM, or 5–10 mg/kg IV slowly</td>
<td>Atropine: 2–4 mg IM; and 2-PAM Cl: 25 mg/kg IM, or 5–10 mg/kg IV slowly</td>
<td></td>
</tr>
</tbody>
</table>

For chemical and biological agents, the unpredictability of Agent BZ, the U.S. military cancelled its incapacitating agents program in the 1980s and all of the stocks of BZ were destroyed. Since then there have been allegations of use of either BZ or related compounds by Serbian forces in the Yugoslav civil war in 1995 and in alleged chemical attacks in Syria in 2013. In the Moscow theater siege of 2002, Russian security forces attempted to gain control of an establishment that had been taken over by Chechen terrorists who were holding hundreds of occupants hostage. They exposed the captors and hostages to a chemical agent later identified as a derivative of the common anesthetic fentanyl. Unfortunately, the authorities failed to let emergency personnel, especially hospital personnel, know to what category this agent belonged. Additionally, the agent proved to have a low safety factor, and over a hundred of the theater’s occupants succumbed to respiratory failure. Knowledge that the agent was a narcotic would have assisted emergency physicians in choosing naloxone as an antidote. This was the first known application of a fentanyl derivative in a law enforcement scenario. Fentanyl derivatives have never been developed for military use, and have never been used by law enforcement outside of Russia. They, like cyanides, probably are most likely to be used in confined spaces such as the theater.

Chemical versus Biological Emergencies

Because all-hazards preparedness often groups chemical and biological hazards together, it is worthwhile making the differences explicit. Although person-to-person transmission of chemical toxins, such as sulfur mustard, is a real concern, actual person-to-person infection common in plague and smallpox does not occur with chemical agents. This would suggest that preparation for a chemical attack is somewhat easier than for an attack using an infectious agent. But this apparent advantage is largely offset by the speed with which most chemical agents cause illness. In an attack using cyanide or nerve agents, one will have only minutes to administer antidotes to reverse toxicity and prevent death in severely poisoned individuals. The response structure built within the U.S. government for an infectious disease outbreak or biological attack, including distribution of antibiotics and vaccines, is much too slow to be useful in a chemical attack. This is the major reason why those responsible for the SNS in the United States have deployed CHEMPACKs, caches of nerve agent and cyanide antidotes, within 1 hour’s reach of 90% of the U.S. population.

Besides speed of symptom development, the biggest difference between chemical and biological attacks lies in the necessity for decontamination. Decontamination is often unnecessary in biological attacks, since the incubation period of most weaponized agents is on the order of days, and people will have generally bathed and changed clothes before the attack has been identified. In chemical attacks, decontamination plays a more prominent role. Exposed individuals remain potential victims until they have been decontaminated. In addition, those experiencing toxicity are a danger to others, most importantly first responders and medical personnel, until they have been decontaminated. While a detailed discussion of decontamination can be found elsewhere (see Chapter 16), it is worth noting that this has become the rate-limiting step in many civilian exercises; many people are unwilling to disrobe and be decontaminated in a mass casualty setting. At the time of writing this chapter, the U.S. Department of Health and Human Services (HHS) is funding work in several U.S. cities to measure the actual value of decontamination by various methods in a mass casualty...
setting. It is undeniable, however, that in the Tokyo subway attack, 10% of emergency room personnel developed miosis, a sign of poisoning, because their patients had not been decontaminated. Healthcare workers developed mild symptoms from exposure to the vaporized sarin in patients’ clothing. Decontamination will remain a major issue in chemical preparedness for the foreseeable future.

Lastly, for planning purposes, one major difference between chemical and biological hazards is the presence of a robust chemical industry and supply chain in industrialized countries. Boxcars and trucks loaded with toxic chemicals such as chlorine move up and down the railways and highways of countries every day. Chemical facilities are present throughout most regions. This contrasts greatly with the lack of an equivalent risk from biological hazards. A chemical truck or railcar can become a weapon by the simple application of a conventional explosive. Thus, chemicals may be attractive to those seeking to do harm because of their availability.

Examples of Chemical Events: Implications for Disaster Preparedness

Intentional (Non-State-Sponsored) Chemical Events

Cyanide Poisoning of Water Supply in 1985 – The Covenant, the Sword, and the Arm of the Lord

The Covenant, the Sword, and the Arm of the Lord (CSA) was a survivalist group primarily interested in large-scale murder to “hasten the return of the Messiah by carrying out God’s judgments.” The group was conceived in 1971 by a fundamentalist preacher, James Ellison. The group planned and prepared for Armageddon, which would result in the destruction of the American economic system. On April 22, 1985, an FBI raid of the CSA compound revealed a stockpile of machine guns, ammunition, an antitank rocket, and an armored car. The FBI found 114 liters of potassium cyanide. CSA initially explained that the cyanide was to be used for pest poisoning. Further FBI analysis revealed there had been extensive discussions and planning with intent to use the cyanide to poison water supplies in New York, Chicago, and Washington.

General Commentary

The toxicity of a chemical agent is principally dependent on the quantity delivered. Therefore, cyanide, or other toxic materials such as organophosphates, would be sufficiently diluted if placed in a large community water supply, rendering the biological effect negligible.

To poison a population intentionally by contaminating its drinking water requires either extraordinary quantities of agent or delivering the agent within the water pipeline closer to the victims. Small quantities of cyanide have often been used in criminal tampering with drugs and food products. The Chicago Tylenol® contamination event in 1982 was the first documented U.S. incident of food tampering with cyanide. Seven deaths resulted from distribution of the poisoned capsules to six stores in the city. A number of subsequent “copycat” events occurred over the next several years with additional deaths. Despite a $100,000 reward offered by Tylenol® manufacturer Johnson & Johnson, the perpetrator has not been caught. Prior to 1982, tamper-proof capsules and packaging were virtually unknown. Subsequent to the tampering events, public anxiety mushroomed. Manufacturers of packaged foods and medicines promptly responded with development and application of an extraordinary variety of complex and protective packaging. It appears that this extra level of “public protection” consumes many millions of dollars yearly. The cost/benefit of the extra packaging has yet to be measured. On such occasions, public anxiety, often fueled by media speculation, may present a far greater problem than the medical issues.

Mitigation

Communities with public water suppliers routinely participate in a risk assessment and vulnerability analysis concerning possible compromise of their water supplies. Normally, problems of environmental disaster or drought are a primary focus. As a result of such notorious industrial poisonings as the Minamata mercury-poisoning event in Japan (resulting in ~400 deaths and 1,000 permanent injuries), many cities have also become concerned about environmental “pollutant” contamination. Risk assessment and vulnerability studies for possible environmental pollution are, in fact, just the type of action that would be useful for mitigation of possible chemical, biological, or radiation contamination.

Preparedness

Specific medical preparations for possible water supply contamination have long been an accepted part of military preparedness. Civilian medical systems, however, rarely have adequate detection equipment or response technology to counter intentional contamination of the water supply. By federal regulation, U.S. communities have developed an interactive disaster preparedness committee, the Local Emergency Planning Committee. Primarily through this type of community-wide organizational structure, such issues as water supply risks can be addressed in a cooperative fashion with appropriate assistance requested from organizations such as the Environmental Protection Agency (EPA) at the state and federal levels.

Response

Despite threats by many organizations and individuals, at the time of this writing, no such large-scale intentional water supply contamination has occurred. EPA has undertaken an extensive public information, planning, and preparation effort to assist the general population in understanding the scope of this concern. This is a fine example of national governmental mitigation and preparedness for a perceived risk.

Nerve Agent Use in 1995 – Aum Shinrikyo

On June 27, 1994, a successful chemical attack was undertaken in Matsumoto, a city (population 200,000) situated in the northern Japanese Alps, 201 km northwest of Tokyo. The Aum Shinrikyo, a 40,000 member, well-funded “doomsday” cult perpetrated the attack. The use of sarin, a military organophosphate poison, resulted in seven deaths among nearly 600 victims. Five victims were found dead, two were transported to the hospital in full cardiac arrest, dying within 4 hours, and one victim survived in a vegetative state due to (presumed) hypoxic encephalopathy. This individual ultimately died of respiratory failure in August 2008. There were fifty-six hospitalizations distributed among six hospitals. Several victims required intubation and mechanical ventilation. Generalized seizures were noted in many of the severely affected victims. There were 208 additional outpatient clinical evaluations and 277 symptomatic victims who did not seek medical care. The first report
of the event came as a telephoned request for an ambulance 2 hours after the exposure. Eight of the fifty-two rescuers and one doctor providing care showed symptoms of poisoning as a result of (presumed) cross-contamination. One rescuer required hospitalization. Ten years later, a long-term questionnaire-based survey of local residents showed 73% of exposed and 44% of unexposed residents reporting psychological problems. 21 The intent of the attack, prevention of a legal decision in a local civil suit, was achieved by poisoning the three judges involved. Sarin was specifically identified as the toxic agent in a sample taken from a local pond on July 4, 1994. Those data and other related law enforcement concerns provided sufficient evidence for a police raid of the principal Aum Shinrikyo facilities, planned for March 1995. The Tokyo subway sarin attack, however, occurred first.22

On March 20, 1995, Aum Shinrikyo cult members released approximately 24 liters of a sarin solution estimated to be 30% pure. The perpetrators may have had atropine sulfate injections available for personal use if necessary.23 Sarin was distributed into eleven polyethylene bags, although probably fewer bags were actually opened. Five different subway trains were involved, all of which were scheduled to arrive within 4 minutes of each other between 8:00 and 8:10 AM at the Kasumigaseki Station. The station was selected for its proximity to Tokyo’s National Police Agency and Finance Ministry as part of the cult’s plan to signal the beginning of Armageddon and to specifically attack members of a chemically trained police squad. The first notification of a medical emergency was directed to the city fire department within minutes of the attack. Some fifteen subway stations called within the next several minutes. Area hospitals were notified at 8:16 AM, but the initial report was of a gas explosion. Therefore, the hospitals prepared to receive patients with burns and carbon monoxide poisoning. It was more than an hour before emergency dispatch recognized the disaster as a single event. Ultimately 131 ambulances and 1,364 emergency medical technicians (EMTs) were dispatched to the affected subway stations. Poor communication with the Emergency Operations Center resulted in EMT transport of all nearby victims directly to St. Luke’s International Hospital (SLIH). Even though SLIH had a mutual aid agreement with another nearby hospital to take less ill patients, this agreement could not be implemented because all available transportation was otherwise occupied. SLIH saw 649 victims within the first 24 hours. The EMTs attempted triage at the scene of the release and some medical support; however, there was no on-scene clothing removal, decontamination, antidote administration, or intubation of victims with severe respiratory distress. The EMTs had no personal protective equipment. Of the 1,364 EMTs who worked to transport victims to hospitals, 135 developed clinical evidence of sarin poisoning requiring some medical therapy, including at least twenty-five hospitalizations. SLIH had three entrances, each of which remained open, allowing full access to patients, relatives, television crews, and various bystanders. Not all victims arriving at the hospital were directed to disrobe or shower. As a result, 110 hospital staff members at SLIH (23% of the staff) themselves experienced some symptoms of sarin exposure due to cross-contamination.

There were twelve deaths as a result of the attack. Six deaths occurred within 2 hours of the event and the remaining six deaths occurred from 20–80 days later. Some deaths were among the subway station personnel, who apparently cleared sarin-contaminated waste with bare hands and no respiratory protection. From available medical reports at SLIH, it appears that the two deaths (of 1,000 patient seen) resulted from cardiac arrest. One ultimate survivor arrived in full arrest and was immediately intubated and provided ventilatory support. She recovered and was discharged 5 days later. Of particular interest, this 21-year-old woman apparently received no specific antidote until approximately 90 minutes after her exposure. Notification that sarin was the offending agent did not occur until approximately 10:30 AM, 2.5 hours after the event. Reportedly, a military physician recognized the clinical signs and symptoms as indicative of a nerve agent exposure. Beginning at that time, oxime therapy was provided for those severely affected. SLIH quickly devised a treatment protocol that enabled the victims to be more rapidly treated. An official prosecutor’s report puts the number of injuries at 3,938. Of a total of 4,973 people reportedly seen at Tokyo hospitals within the first 24 hours, approximately 1,100 were hospitalized. Of all patients reporting to Tokyo hospitals complaining of chemical agent exposure, some 74% showed no clinical signs or symptoms. These patients apparently presented largely because of media announcements reporting the event and suggesting that civilians who “felt unwell” should immediately go to the hospital. SLIH conducted a post-event questionnaire-based evaluation of 610 victims. At 1 month after the event, nearly 60% reported symptoms interpreted as indicative of post-traumatic stress disorder (PTSD). Repeated studies at 3 and 6 months showed similar percentages of individuals with such symptoms. People reported flashbacks, insomnia, depression, and nightmares. Some individuals’ very high anxiety prevented their subsequent use of the subway. Long-term (10 years) follow-up has been reported and shows persistence of long-lasting psychological problems and PTSD in some victims.21,24

Despite legal and political action and subsequent intense investigation of the Aum cult, there is evidence of more recent Aum activity in the Ukraine, Belarus, Kazakhstan, and Russia. In March 1998, a reported Aum member telephoned the Russian newspaper Itar-Tass with a threatened plan to spread a toxic gas throughout the Moscow subway system.25

General Commentary

Aum Shinrikyo has produced the greatest number of non-state-sponsored chemical (and biological) attacks on record. Between April 1990 and March 1995, Aum undertook ten biological attacks. There were no recorded casualties. Between November 1993 and July 4, 1995, Aum undertook a total of twelve chemical attacks (one phosgene, two cyanide, five VX, and four sarin) with 20 deaths and approximately 1,300 injured.26 Reports from various medical facilities in Tokyo have expanded knowledge of the time course and clinical response to sarin vapor. Inhalation of sarin vapor produces clinical effects very rapidly, within seconds to minutes. Individuals contaminated by sarin typically demonstrate peak disease symptomatology within the first 30 minutes after contact with the agent, provided further exposure ceases (i.e., removal from the site).27

Individuals who reach a medical care facility alive will likely survive even without specific antidotal therapy unless other complications supervene. At SLIH, one individual arrived in full cardiac arrest. Specific antidotal therapy (atropine and pralidoxime chloride) was not provided until more than 90 minutes after exposure. The victim nevertheless survived without complications. Two other victims suffered respiratory arrest in the setting of seizures after hospital arrival. Immediate provision of diazepam and mechanical ventilation were effective in preventing their deaths.
Of the more than 5,500 individuals reportedly involved in the Tokyo event, some 1,100 were hospitalized, mostly with recognized nerve agent–related signs and symptoms. Assuming that this cohort of 1,100 was “truly” exposed, the death of “only” 12 individuals among this group represents an important detail in terms of disaster preparedness for this and many other chemical events. In a large-scale chemical event, sizeable numbers of patients may be transported or self-present to nearby facilities. As was seen in the Tokyo event, only a very small number of these individuals will likely suffer immediately life-threatening illness. Importantly, the illness in Tokyo primarily presented as respiratory distress. In all cases, immediate identification of severely affected victims with immediate application of respiratory support was sufficient to stabilize the victims even without immediate use of antidote. Certainly, later provision of atropine and oxime appeared to ameliorate the degree and shorten the time of the illness. The rapid application of basic and advanced life support principles appears to have been of critical importance. This observation further suggests that first responders and first receivers should be fully qualified and prepared to provide respiratory support, including ventilation and intubation, possibly even at the scene of the event.

A minority of Tokyo subway sarin attack survivors reported longer-term (months, occasionally years) symptoms of diminished mental acuity, headaches, nightmares, and sleep disorders. One patient was found to have a delayed neuropathy. The relationship of this deficit to his sarin exposure remains unclear.21,23

Mitigation

The medical system in Tokyo supported a complex, well-organized, and well-trained disaster preparedness organization that was in place prior to the nerve agent attacks. The principal threat to the city was considered to be an earthquake. Therefore, much of the planning and training was focused on the medical care for large numbers of trauma victims. As is often the case, the nerve agent event was unexpected in size and scope. There had been no education or training for a large-scale chemical contamination event outside of the military structure. Despite the experiences of World War II, there was no repository of medical knowledge or experience in dealing with large events on which civilian disaster planners could draw. Therefore, a hazard analysis or vulnerability assessment did not exist.

Preparedness

Equipment designed for deployment in a contaminated environment was scarce and first responders were not well trained in its use. Contamination of a very large percentage of the first responders emphasized the importance of such preparation.

Response

The local hospitals managed a very large number of individuals within a short period of time. There was little attention paid to patient decontamination or to health professional self-protection, presumably due to lack of training and complicated by an overwhelming influx of vapor-contaminated patients. Consequently, in some areas of the hospitals, up to 25% of the hospital staff suffered clinical effects of cross-contamination. Nevertheless, the most severely ill victims were identified expeditiously and treated with appropriate focus on critical components of their illness. Respiratory failure and seizures were the principal life-threatening illnesses. These were handled very competently. Of note was the absence of early specific antidotal therapy. Although the victims presented with evidence of cholinergic excess, the possibility of organophosphate toxicity was not considered for about 2 hours. When the etiology was finally identified, individuals with severe illness had either already expired or were significantly improved, having been intubated and ventilated.

Recovery

In the years after the event, the medical authorities in Tokyo have carefully reviewed the medical response, found associated challenges, and enacted realistic improvements in the city’s disaster preparedness plans. Yanagisawa makes a particularly valuable recommendation for organized medical evaluation and follow-up of such a large-scale event by using an integrated team including epidemiological, neurological, and psychiatric disciplines.21 Perhaps the most important result of the event has been the development of a National Disaster Center in Tokyo. This facility is a day-to-day resource and training facility for disaster preparedness. In the event of a large-scale disaster, the facility can be converted to provide medical care for disaster victims.

IMPROVISED EXPLOSIVE DEVICES AS CHEMICAL WEAPONS IN IRAQ FROM 2004–2007

In 2007, improvised explosive devices (IEDs) in various forms became the single greatest cause of death among U.S. troops in Iraq. Nearly 57% of the 327 U.S. deaths during the first 6 months of 2007 were the result of IEDs. The increasing complexity of IEDs has been associated with greater difficulty in detecting and defending against them, resulting in an increasing mortality rate. This has continued to be the case as American involvement in Iraq ended and attention shifted to Afghanistan. Recent escalation of their complexity has resulted from incorporation of chemicals into the device. Both military (sarin and mustard) and industrial (chlorine) chemicals have been added to the devices, resulting in substantially increased anxiety regarding their danger.

In May 2004, an IED constructed from a 155-mm artillery round, possibly left over from a Saddam Hussein-era stockpile, was found to contain the military nerve agent sarin. Two U.S. soldiers who rendered the IED safe received a vapor challenge of sarin, and required treatment for “minor exposure.” Neither individual required antidotes, and both returned to duty after convalescence for 3 weeks and completed their tours of duty in Iraq. But 1 year later, one of the two soldiers developed complaints of memory loss for sequences, crucial to his job as an explosive ordnance soldier, and had abnormal neuropsychological testing results. His status gradually improved over the next 2 years. He remained on active duty and was promoted in a competitive field. It is not possible to say definitively whether his mild and temporary psychological abnormality was due to post-traumatic stress or to some delayed or chronic sarin toxicity.28 During that same month, an IED containing military mustard agent was also found.29

In early February 2007, some vehicle-borne IEDs were found to contain liquefied chlorine canisters. Explosion of these devices resulted in chemical exposure for some victims and associated illness. The addition of chemicals to the IEDs in effect produced a weapon similar to the chemical weapons of World War I. Most of the injuries related to the IEDs were from associated physical trauma, however. The effects of the chemical component achieved in World War I resulted from much larger quantities of chemicals delivered by munitions specially designed for that
purpose. IEDs “accompanied” by chemicals are unlikely to achieve a World War I–equivalent toxic effect. The military/public reaction and associated psychological distress from use of a “chemical warfare agent” may have as much effect as the physical damage itself.\textsuperscript{30} As has been noted before, the best defense against such public (and medical responder) anxiety derives from education and training. Accordingly, concerns regarding a chemical release associated with IEDs have prompted training responses within the United States. Of note is the annual Golden Guardian Exercise undertaken in the State of California. There, focus on the traumatic/explosive effects of an IED has been broadened to incorporate concern about the appropriate response to other materials (e.g., nerve agents), which might possibly be incorporated with the IED.\textsuperscript{31} The military response to incorporation of chemical (and possibly biological and radiological/nuclear) materials with an IED has led to development of various remotely operated robotic devices with detectors capable of identifying chemical, biological, and radiological/nuclear materials (e.g., Talon\textsuperscript{R} Robots).

Examples of Unintentional Chemical Events

Ammonia Release in 2002 in Minot, North Dakota

At 1:37 AM on January 18, 2002, 31 railroad cars (out of 112) derailed in an incident 0.8 km west of Minot (population 36,567), a city in the U.S. state of North Dakota. Five cars carrying anhydrous ammonia suddenly ruptured, releasing an estimated 555,300 liters of the chemical. This vaporized immediately into a large plume. An estimated 11,600 people were residing in the plume-involved area. There were twelve serious injuries, including one traumatic death, and 320 additional individuals sustained minor injuries.

The derailment damaged local power lines at the site. Electricity supplied to 2,820 residences was disrupted. The conductor notified the central emergency dispatch number (911) in Minot by personal cell phone. The violent rupture of the tank cars caused some sections to be propelled as far as 356 meters from the site. Temperature was −21°C and winds were 10–12 km/h from the west. Very low ambient temperature and slow winds kept the plume from rising. Delerious health and medical effects were minimized because most residents were indoors asleep at the time. The plume that formed was an estimated 91 meters high and 4 km wide as it eventually drifted downwind to cover 8 km of the valley containing Minot. The local fire department chief, responding to notification by the 911 emergency dispatch operator, arrived on scene within 10 minutes and established a command post.

In the involved area, one couple attempted to flee their home in a truck. Their vehicle crashed into a house across the street from their residence. The female passenger returned to their house but the 38-year-old male driver collapsed outside. Ammonia vapors were described as so intense as to severely limit visibility in the immediate area. The Incident Commander prohibited first responders from entering the site due to a substantial risk to personal safety. Approximately 3 hours after the event occurred, first responders were allowed entry to begin rescue of victims in the immediate area; 60–65 persons were ultimately evacuated. An attempted rescue of the collapsed truck driver failed due to responders not wearing self-contained breathing apparatus (SCBA). All other residents were instructed to shelter-in-place with notification provided by warning siren, cable television interrupts, and radio notification. Many residents did not hear the siren due to its location, and residents without power did not receive the media notification. The collapsed driver was ultimately rescued approximately 3.5 hours after the event and found to be unresponsive. The 911 system handled over 2,800 calls, and instructed people to remain in their homes, shut down their furnaces and air handling systems, shelter in their bathrooms and turn on their showers, and breathe through wet clothes. Residents with wells, whose power was interrupted, were unable to operate their showers. At 4:15 AM the plume reached the nearest (Trinity) hospital. The hospital was not evacuated. Closing down the heating, ventilation, and air-conditioning system was effective in preventing infiltration of much of the ammonia.

Seven minor injuries requiring hospital evaluation occurred in the 122 firefighters and 11 police personnel who responded, including several dispatchers. These injuries were mostly eye irritation, chest discomfort, respiratory distress, and headaches.

At 2:15 AM, the first casualty reached Trinity Hospital. The hospital disaster plan was activated at 2:30 AM. Ultimately more than 370 persons were evaluated. Eleven individuals required hospitalization, three as the direct result of chemical burns to the eyes and face. Two individuals required mechanical ventilation. The Minnesota National Guard Civil Support Team arrived later that day. The railroad corporation quickly established a claims and assistance center. The rapidity of this action may have reduced much of the public distress after the event.\textsuperscript{32,33}

The National Transportation Safety Board (NTSB) began its activities early that morning, with inspection personnel fully active the same day. Town public meetings were conducted to assure residents that recovery efforts were fully underway. Much of the public commentary, however, focused on the belief that the 911 system as well as other components of the emergency response plan appeared to have failed the community. An informal review of public perception was undertaken in September 2004 during a Department of Justice Disaster Preparedness Program in North Dakota. Many residents spontaneously reported their continued dissatisfaction with the Minot emergency response, reflecting that they felt abandoned by on-scene personnel. The NTSB report noted that Minot had undertaken a disaster preparedness drill the prior September that had enhanced the effectiveness of the emergency response and that a 3-hour restriction of emergency responders from the involved area was appropriate to their personal safety.\textsuperscript{34}

General Commentary

An evaluation of this event, conducted per federal regulation by NTSB, was completed and reported on March 9, 2004.\textsuperscript{35} This was a comprehensive evaluation that also included a brief assessment of disaster preparedness within the first responder and medical community. Although the authors of this particular section of the report were not identified, and so their medical review qualifications are therefore uncertain, there is no other publicly available comprehensive evaluation of the medical (hospital and first responders) response to the event. Public anxiety is typically very difficult to control during a large-scale event. In this case, post-event efforts to explain the sheltering-in-place process and address other public concerns regarding feelings of abandonment were not entirely effective. Two years later, there was persistent public perception of inadequate emergency response. Such perceptions can continue to erode necessary public confidence in the emergency response systems of the community. This is an important public relations issue.
Mitigation
Minot has, for a number of years, performed high-quality hazard analysis and risk assessment in regards to dangers associated with rail transportation of toxic materials.

Preparedness
A citywide exercise involving all emergency responders was conducted 4 months prior to the event. Details of the after-action report for that exercise are not readily accessible; hence specific identified weaknesses are not available for comment. It does appear that first responder equipment and training issues may have contributed to some limitations of movement and work activities for individuals within the ammonia cloud.

Response
Specific response details for the emergency medical system, fire department, and hospital are not readily available. However, the NTSB report provides some insight into the disaster response activities of the prehospital and medical system. Although a more complete first response/medical review would be highly desirable, the NTSB report stands as an example of an available document that allows some degree of retrospective analysis of the event.

Recovery
The city review of the event reportedly identified several problems with communications. These seem to have been addressed; however, important issues of public confidence in Minot’s emergency response system apparently remain.

METHYL ISOCYANATE RELEASE IN 1984 IN BHOPAL, INDIA
On the night of December 2, 1984, an approximately 24 metric ton (27 short tons) leak of methyl isocyanate (MIC) occurred at a Union Carbide of India industrial plant in Bhopal (population 900,000). Atmospheric conditions included a relatively low wind speed and a nocturnal temperature inversion. These conditions resulted in a gas cloud that moved slowly, primarily close to the ground, ultimately covering approximately 40 km² of the surrounding city. The cloud rapidly engulfed the homes of a large number of primarily poor and uneducated residents. The cloud may have contained additional contaminants and decomposition byproducts such as phosgene, mono methylamine, hydrogen cyanide, various oxides of nitrogen, and carbon monoxide, although specific data are unavailable. An estimated 300,000 people were exposed and approximately 3,000–15,000 deaths occurred.Accurate statistics are unavailable for a variety of reasons, but a 2–3% death rate seems consistent with available information.

Most immediate and near-term MIC deaths appear to have occurred due to respiratory effects of the chemical. MIC produces airway inflammatory changes, contributing to airway obstruction. MIC also appears to produce a delayed pulmonary edema, much like phosgene. This effect may have contributed to the impression that phosgene was also released during the event. Additional concern was expressed about the possibility of cyanide or various decomposition products of MIC acting as contributing factors. There was no direct evidence to support that concern.

On the evening of the event, an estimated 400,000 people fled the city in an uncontrolled evacuation. Nearly half of those who lived more than 10 km away from the event site left, reacting out of fear. Approximately 2 weeks later, during attempts to neutralize the remaining MIC at the Union Carbide plant, public fear resulted in a second wave of mass evacuation involving approximately 200,000 people. The local medical system, which consisted of approximately 300 doctors and 1,800 hospital beds, was entirely overwhelmed. An estimated additional 1,500 people are reported to have died in subsequent months due to injuries caused by the release. Insofar as possible, near-term medical care was provided by local facilities that were later assisted by Indian government aid. Additional support was provided by a number of non-governmental organizations. Long-term evaluation of medical and health consequences of exposure have been conducted by a variety of individuals and organizations, both private and public. Their data suggest multiple possible long-term MIC effects that will require further investigation, although such data are somewhat compromised by both ongoing legal/political difficulties and substantial challenges associated with establishing and following a cohort of exposed individuals.

General Commentary
The Bhopal event occurred in a country with limited and poorly developed resources. The sudden release of a large toxic vapor cloud, whether accidental or (as suggested by Union Carbide) intentional, resulted in the world’s single most catastrophic chemical event at the time of this publication. A more careful analysis of the event from a perspective of disaster preparedness is warranted.

Mitigation
The city of Bhopal had a population of 900,000 people at the time of the release. Nearly 200,000 lived within 10 km of the Union Carbide plant. The majority of these individuals were poor, living in housing that often consisted of no more than tin shacks. Recognizing the risks associated with living close to a chemical plant, the provincial government attempted to encourage residents to move away. It appeared, however, that individuals actually preferred to live close to a business that might offer many new, well-paying jobs to the local residents. The local government maintained few records of the identities or even the numbers of these individuals. There was no record maintained of any individuals with special needs. No governmental or local political organization existed that collectively represented these individuals. The few civic organizations responsible for the health or safety of the local population received no effective citizen input. In the absence of a specific citizen action group, there was no organization able to collect information regarding the potential risks of a disaster in the neighborhood of the chemical plant. Thus, no hazard assessment or vulnerability analysis was performed. The nearby first responder community (fire and police) had little awareness or understanding of the possibility of a large toxic leak. Accordingly, there was little education, training, or equipment acquired for that possibility. The local medical facilities and personnel were equally limited in their awareness or understanding of the possibility of a large toxic leak.

Preparedness
The nearby residents were unaware of the risks posed to their community by industrial facilities in the area (specifically the Union Carbide plant). In the absence of an organization like the Local Emergency Planning Committees found in the United States, there was no clear effort directed toward preparing for an industrial chemical event. No evidence exists that local hospitals had become aware of the dangers or risks of the industrial plants
in their immediate area or had made efforts to understand and prepare for those risks. Union Carbide had established a small clinic at the entrance to the facility. A physician was hired 8 months prior to the event to act as an occupational physician for the facility. Evidence is lacking that the physician either initially had or subsequently acquired particular expertise with respect to MIC. Furthermore, there is no evidence that the company physician was active in preparing either the local medical or civilian community for possible chemical exposures.

Response
Immediately after the incident, notification of the surrounding population was ineffective. There had been no community education or training identifying appropriate responses to the alarm sirens. Accordingly, the neighboring residents did not react to the emergency alarm. Arrival of irritating fumes drove many individuals to escape on foot. Running resulted in the need for deeper respirations—likely causing inhalation of greater amounts of MIC with each labored breath. Some individuals, unable or unwilling to run away, effectively sheltered-in-place and survived the toxic event. Emergency communications between the Union Carbide Plant, local government, first responders, and local medical facilities and personnel were poor or nonexistent. Confusion with respect to what particular substance was released appeared to play a major role in complicating both medical and logistical response to the event. There was much criticism regarding the lack of “correct” medical information, training, and appropriate equipment. Although no specific antidote existed, such criticism reflects the deeper problem of failure to educate and train the population. While MIC is now recognized as an irritating substance with pulmonary edema effects similar to phosgene, this information was not available to the local medical community at the time. Accordingly, lifesaving efforts were directed toward immediate symptomatic therapy—principally the control of obvious respiratory failure. Most near-term deaths clearly resulted from respiratory failure. The actual number of deaths can only be estimated. With the data available, it is not possible to determine the relative importance of the following factors in relationship to those deaths:

1. Inadequate/insufficient medical equipment—there is no evidence that specific preparations had been made for large numbers of individuals with respiratory compromise. Even had hundreds of ventilators been available, appropriately trained personnel to manage them were lacking.
2. Inadequate medical knowledge/experience—basic education and training of local medical personnel did not occur. Plant operator could have easily provided details of the risks/toxic effects of MIC and other large-quantity chemicals stored at the Union Carbide facility. This should have been the responsibility of the occupational physician at the facility. As noted, however, the number of victims with respiratory failure would have exceeded even the best preparation with large numbers of ventilators, given the absence of personnel to manage them.
3. Inadequate numbers of medical practitioners—additional numbers of trained medical personnel were needed, but not immediately available. In some countries such as the United States, chemical facilities have trained groups of their on-site industrial workers in basic life support. In case of a chemical event, these on-site workers can act as immediately available first responders.

Medical Response to Large-Scale Chemical Events
In circumstances of large-scale chemical events, early knowledge of the specific materials involved is an ideal medical goal. This is, however, an illusory target. Specific antidotes are available for only two significant types of toxic chemical exposures: organophosphates and cyanide. Commercial/industrial formulations of cyanide and organophosphates typically present as dermal or ingestion exposures. There is a slower onset and progression of the clinical illness, often affording ample time to deliver appropriate antidotal therapy. Military/chemical warfare organophosphates and cyanide, when presenting as inhaled agents, act very rapidly, often within seconds to minutes. Consequently, antidotal therapy of both organophosphate and cyanide inhalational exposures must be delivered immediately on-site. This implies the necessity of establishing stockpiles of antidote as “far forward” or as close to the location of care as possible, in areas of actual or suspected risk.

The U.S. government recognized this requirement for deployment of antidote near the location of patient care when it augmented the SNS. The U.S. Centers for Disease Control and Prevention (CDC) maintains this cache of drugs and equipment, and now has modified it to include a “far forward” CHEMPACK...
component. CHEMPACKs are positioned pre-event at locations all over the United States within 1 hour of 90% of the U.S. population. CHEMPACK stocks contain nerve agent antidotes and cyanide antidotes, and CHEMPACK sites include hospitals, police stations, EMS headquarters, and even a few county jails. CDC pays for the maintenance of these stockpiles and the rotation of expired antidotes. First responders train to break open CHEMPACKs in case of a suspected chemical attack.

Aside from antidotal therapy, medical management of a large-scale chemical event is generally accomplished by symptomatic assessment. Many have recommended that responders should try to group casualties by syndrome characteristics into exposure from one of the four types of chemical agents discussed previously (syndromic assessment). An extensive medical literature has been produced on the subject of rapid assessment of injured individuals. A large number of medical responders has been educated and trained in a systematic approach to the rapid assessment and categorization of exposed individuals. The Simple Triage and Rapid Treatment (START) system allows very rapid identification of those victims needing immediate, lifesaving care. Assessment of three major bodily systems (airway/respiration, circulation, and neurological) can be quickly and consistently accomplished even by nonmedical personnel with minimal training. Cone and Koenig have proposed a modification of this triage system for use for mass casualties exposed to a chemical agent. A pediatric format (JumpSTART) has been developed as well, however, none of these systems have been adequately validated (see Chapter 14).

As suggested by the examples herein, the majority of immediate and near-term chemical event–related illness results in respiratory compromise. Immediate and near-term toxic respiratory illness caused by a chemical event is very amenable to intervention with relatively simple and inexpensive technology. Thus rapid identification and intervention in these respiratory “immediates” is of the highest value.

The National Library of Medicine’s CHEMM website (see Useful Websites section) was developed to provide just-in-time, government-validated information on possible chemical exposures that could be used in real-time by first responders, regardless of medical background. One feature intended to help with initial assessment is the Chemical Intelligent Syndromes Tool (CHEMM-IST) algorithm, which uses syndromic patterns to categorize the event into one of the four major exposures: pulmonary intoxicants, cyanides, organophosphate/cholinesterase inhibitor, and vesicant/mustard.

The federal response to events in the United States is dictated by the NRF. Many federal agencies play roles in dealing with a chemical event, ranging from the FBI (law enforcement) to the Coast Guard (National Spills Center) to the EPA (cleanup). Information on the NRF, including its founding documents, can be found on FEMA’s website.

RECOMMENDATIONS FOR FURTHER RESEARCH

General Comments
The funding for new research into large-scale chemical events is almost entirely derived from government agencies because there is very little industrial or pharmaceutical market for products that will emerge from such investigations. The two major funding streams in the United States are from the Department of Defense, through its Chemical and Biological Defense Program, and from HHS. These two programs regularly coordinate on multiple levels to ensure that the two departments will synergize and not duplicate efforts. Certain specific areas, such as pulmonary agents and cyanides, which are considered to represent a greater threat to civilians than the military, are of particular interest to HHS. At the time of this writing, the department’s biggest investments are in improved countermeasures against cyanides, which are no longer seen as a major battlefield threat by the military.

Most of the original work on response to chemical agents was carried out by the military, and the treatment protocols that resulted are intended primarily for young, prescreened, healthy adults ages 18–65. Very little work has been done on any of the countermeasures discussed in this chapter in children, the elderly, pregnant women, or immunosuppressed patients. Every suggestion made here should be read as applying to these populations as well, perhaps with greater urgency than the original military population.

The original focus of most research done on chemical agents was only with the acute effects of poisoning. A more general emphasis is needed on the long-term effects. These include a wide spectrum of issues, many of which are still controversial. Examples include: pulmonary fibrosis seen after recovery from poisoning with oxides of nitrogen; delayed neovascularization and blindness seen in Iranian war veterans poisoned with sulfur mustard; possible carcinogenesis seen after sulfur mustard poisoning, particularly in the lung; and questions of chronic neurologic dysfunction alleged in survivors of nerve agent poisoning.

Animal models are a specific research issue. We have imperfect animal models for most of the agents listed. Not only are better animal models urgently needed for research, but they will be crucial in future years for obtaining licensure in the United States from the FDA for any developed countermeasures. None of the standard animal models used for work with sulfur mustard (pig skin, mouse ear) or nerve agents (rats, guinea pigs) exactly replicates the toxidrome seen in humans.

Research Priorities in Specific Categories of Chemical Agents

Pulmonary Agents
After over a century of research, we are still woefully ignorant of the molecular mechanisms of action associated with many pulmonary agents, particularly those that cause delayed peripheral non-cardiogenic pulmonary edema. Phosgene is emblematic of these agents. Presumably, mechanisms of damage are similar across a large number of pulmonary toxicants, including many toxic industrial chemicals. Mixed peripheral-centrally acting pulmonary toxicants, such as chlorine, may pose different problems on the molecular level.

In poisoning by toxicants causing delayed-onset non-cardiogenic pulmonary edema, such as phosgene, we have no reliable way to identify those among the exposed population who are at high risk for the development of pulmonary edema. Since this condition will require intensive care, it should be a priority to develop a diagnostic test, perhaps a biomarker, that can predict which patients are likely to develop edema. Some work has been done with plethysmography; however, this has not proven sufficiently reliable. Development of a predictive marker would have great impact not only on the management of specific patients, but of mass casualty events generally.
Once pulmonary edema develops, management presently consists of intensive care with intubation and pulmonary support. ICU care for pulmonary edema is primarily designed for cardiogenic cases, including diuresis and strict fluid management. Pulmonary edema caused by peripherally acting pulmonary toxicants, by contrast, involves massive fluid displacement from the circulation into the lungs, and these patients are actually fluid-depleted. We need better protocols to manage this unusual form of pulmonary edema.

**Cyanides**

Administration of all currently available cyanide antidotes require intravenous line placement. This is time-consuming, very difficult in children, and ill-suited to rapid treatment of large numbers of casualties. We urgently need a non-intravenous antidote, ideally administrable through an IM auto-injector similar to nerve agent antidotes. HHS is funding work on three promising candidates: cobinamide, sulfanegen, and dimethyl trisulfide. An IM cyanide antidote could make a huge difference in a mass casualty event involving cyanide.

Study of individual cyanide poisoning cases demonstrates that many patients recover without the use of antidotes at all. Available antidotes have significant side effects, notably hypotension from nitrites. In an individual case this may not matter, but in a mass casualty event from cyanide poisoning, a method to identify that minority of cases who absolutely require antidotes would improve scene management and triage.

**Mustard and Other Viscants**

As with pulmonary toxicants, the cellular and molecular mode of action for sulfur mustard remains elusive after 110 years of research. Much experimental work in animals has demonstrated that sulfur mustard works via multiple pathways, including inflammation and bone marrow suppression. We still need better understanding of the critical pathways in the development of mustard injury, both acute and chronic.

It would greatly assist both those caring for individual patients and those responsible for scene management and triage if there was a method to identify individuals exposed to sulfur mustard who will subsequently develop severe injury. Such injuries include pulmonary and upper airway compromise as well as the development of systemic problems such as bone marrow suppression. At present, the only rough guide available is the percentage of body surface area exposed to liquid; this is not helpful in the case of a vapor challenge and is only very approximate for those exposed to liquid. Biomarkers for exposed victims who will require higher levels of care would be extremely helpful in management.

Mustard-induced neutropenia has not been well-studied in the military research program. However, one investigation demonstrated that granulocyte colony stimulating factor (originally developed as a method to protect the bone marrow from cancer chemotherapy) can lessen the impact of sulfur mustard on hematopoietic cells. Data are needed that would support a more robust recommendation for ideal management of patients exposed to unknown levels of sulfur mustard, particularly those who may already be immunosuppressed.

**Nerve Agents**

Midazolam is more rapidly effective against nerve agent–induced seizures than any other benzodiazepine, including diazepam. It also prevents seizures from recurring with greater efficacy than any other drug in this class. At the time of this writing, the military chemical defense program is pursuing FDA approval of midazolam for the indication of nerve agent–induced seizures in adults, while the civilian program is pursuing broader indications. This will probably result in significant near-term improvement in nerve agent poisoning management.

For many years, the military chemical defense program has pursued a bioscavenger. This circulating compound would detoxify a nerve agent before it travels through the bloodstream, interacts with cholinergic synapses, and causes the toxic effects that threaten the patient’s life. In theory, warfighters protected by a circulating bioscavenger could be deployed unencumbered by protective equipment. Human butryrylcholinesterase can function as a circulating bioscavenger in animals and is safe in humans. However, it is only effective stoichiometrically (i.e., one molecule of butryrylcholinesterase detoxifies one molecule of nerve agent). Consequently, the effective dose is quite large, and because butryrylcholinesterase has to be isolated from human plasma, the expense of this product will be in excess of $10,000 per dose. Efforts are underway to identify a catalytic bioscavenger that would detoxify the nerve agent but require only a fraction of the dose of a stoichiometric bioscavenger. Unfortunately, animal experiments to date demonstrate that the only way to achieve this outcome is probably to develop a cocktail of scavengers, some of which may require only the G-series nerve agents and others that may require only the V-series.

A better oxime is needed that effectively targets rapidly aging nerve agents such as soman. The military chemical defense program is working on several possible replacements for 2-PAM Cl that will have greater efficacy against such nerve agents.

The U.S. military program is also investigating scopalamine, a well-known anticholinergic drug, as an addition to the present nerve agent treatment regimen. Unlike atropine, it crosses the blood-brain barrier and treats CNS nerve agent poisoning. Its ultimate role in the management of nerve agent victims is not yet clear and much developmental work remains.

Defining the long-term negative clinical effects from nerve agent exposure is crucial, particularly those impacting neurobehavioral functions. We do not yet have a clear understanding of how many of the alleged chronic effects seen after nerve agent poisoning are due to actual chemical toxicity and how much is potentially due to psychological trauma (PTSD), to hypoxia, or to the postictal state. Improved understanding of this pathophysiology has been hampered by failure to develop good animal models.

Efforts have been underway for several years to develop a neuro-protectant for the central nervous system. This product would insure improved neurologic function after nerve agent exposure. Several compounds are being studied in both the military and civilian programs, including the centrally acting cholinesterase galantamine and several experimental drugs. One hurdle for this program is reliably defining animal behavioral abnormalities to facilitate research.

**Incapacitating Agents**

It remains unclear how much research should be devoted to incapacitating agents. No investigations are presently underway in any western country examining anticholinergics such as Agent BZ, which is no longer stockpiled by any government. Efforts are underway to better understand the toxicity of many different fentanyl derivatives.
Research Priorities in Response to Chemical Attacks

Perhaps the most urgent need in response research is validation and optimization of best practices for mass casualty decontamination. Decontamination doctrine is a mixture of old principles inherited from World War I practice and animal studies. A large workshop held in 2012 by the U.S. Department of Homeland Security demonstrated that we still lack a clear understanding of how effective various methods of decontamination are at reducing hazards, both to patients and to caregivers. At the time of this writing, HHS has funded its first grant in this area. Evidence-based guidelines are needed specifically for the civilian setting that optimize the process of decontamination. These guidelines should take into account such issues as age diversity, current medical conditions, and the challenge of disrobing during an incident. Military doctrine does not deal with these issues.40,41

In a chemical incident, the speed of response is much more crucial than it is for biological incident. However, the response system, particularly on the federal level, is really designed for the slower pace of a biological event. Exercises utilizing both moulaged victims and tabletop instruction at local, state, and federal levels are important in developing a response system robust and flexible enough to address a rapidly evolving chemical incident.

Part of the response to a chemical incident is the development of a tiered system of medical care. For victims exposed to pulmonary and vesicant agents, the highest priority for care will be evacuation to a location where ICU-type interventions are available. Immediate on-scene treatment is less critical. This is fundamentally different from the usual approach to triage in mass casualty events. Practicing triage strategies that incorporate evacuation is an essential part of exercises held at all levels, with modifications for each locality’s specific needs.

Another aspect of the local response is the proper use of media to disseminate important messages. This could include broadcasts requesting that exposed but asymptomatic individuals shower at home and then present for evaluation at an out-of-hospital treatment center. Without advanced planning and execution, local, state, and federal authorities will not have established relationships with media outlets that could be extremely helpful in alerting the public. Media relations should be part of plans and should be exercised and practiced along with other aspects of the response.

Even the possibility that one has been exposed to a toxic chemical can be a severely stressful experience. No consensus exists on the best way to manage acute or subacute/chronic psychological stress among those who either were exposed or who think they were exposed to an agent. The scale of this problem is huge. In the 1995 Tokyo attack, 80% of patients presenting for care had no signs or symptoms of poisoning. Research on the most expeditious way to deal with the fears of large numbers of people would be very helpful to planners and responders.

At present, the disaster medicine community lacks a robust, standardized medical review process. CDC carries out epidemiologic studies, but has never formalized a full-scale process of review. This assessment should include not only traditional epidemiology, but review of first responder and hospital professional actions as well. One model for this in the United States is the Chemical Security Emergency Preparedness Program (CSEPP), which took a comprehensive review of care in the communities where the Army’s eight former chemical stockpile sites were located. CSEPP still operates at the two sites where demilitarization has not yet concluded. This could serve as a national model.

Useful Websites

In the United States, the National Library of Medicine, part of the National Institutes of Health (NIH), has created a Chemical Hazards Emergency Medical Management website, open to anyone without pre-registration. It is specifically intended for the civilian first responder. It includes a quick syndromic differential diagnosis, CHEMM-IST, to aid the civilian first responder in categorizing a chemical mass casualty event by toxidrome. The tool is intended to facilitate rapid field diagnosis. It is updated by NIH and other government experts on an ongoing basis.

For more detailed information on specific agents, the reader is directed to the Medical Aspects of Chemical Warfare portion of the Textbook of Military Medicine, published by the Borden Institute and Walter Reed Army Medical Center.42 This volume, as well as the shorter treatment handbook published by the Chemical Casualty Care Division of the U.S. Army Medical Research Institute of Chemical Defense, is available on the division’s website.43 Non-military organizations must register for the website in advance, a process that usually takes 2–3 business days. Emergency personnel who may need to care for chemical casualties should therefore register their organizations during the planning phase so that they can access current data during an event.

Acknowledgments

This chapter incorporates material written for a previous edition of this textbook by John S. Urbanetti, MD. The opinions herein expressed are solely those of the author and not necessarily those of the Joint Program Executive Office for Chemical/Biological Defense, the Department of the Army, or the Department of Defense.

REFERENCES
