Chapter 27

CHEMICAL WARFARE AGENTS

FREDERICK R. SIDELL, MD

INTRODUCTION

CHEMICAL WARFARE AGENTS AND THEIR CLINICAL EFFECTS
- **Nerve Agents**
- **Vesicants**
- **Cyanide**
- **Pulmonary Agents**
- **Incapacitating Agents**
- **Riot-Control Agents**

MANAGEMENT OF CHEMICAL AGENT CASUALTIES
- **Nerve Agents**
- **Vesicants**
- **Cyanide**
- **Pulmonary Agents**
- **Incapacitating Agents**
- **Riot-Control Agents**

PERSONAL PROTECTION

DECONTAMINATION

FIELD MANAGEMENT
- **The Service Member's Role**
- **Echelons of Care**
- **At the Medical Facility**

SUMMARY

F. R. Sidell; Chemical Casualty Consultant, Bel Air, MD 21014; formerly, Chief, Chemical Casualty Care Office, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Md

INTRODUCTION

Chemical agents have been used in warfare since ancient times. The first use of a chemical weapon, which in a broad sense includes smoke and flame, is generally considered to have been in 423 BC during the Peloponnesian War. Boeotians and their allies attacked Delium and succeeded in taking this village by burning a mixture of coals, sulfur, and pitch and sending the smoke and flame into the village through a hollowed out log. The walls were burned by the flame, the inhabitants were overcome by the smoke, and the village was captured.[1] A thousand years later, the Greeks used a similar mixture, known today as "Greek fire," against their enemies. Throughout the medieval period poisons of various types were used, particularly on crops and in water supplies.

The first modern day, or industrial era, use of chemical agents—and the only time in which US military personnel have been involved—was during World War I. Riot-control agents were used initially in small battles, but the first large-scale use was of chlorine by the Germans in April 1915. Chlorine, phosgene, and other lung-damaging agents were widely used for the next several years. In July 1917, mustard, a compound that damages the skin and the eyes as well as the lungs, was introduced and was the major chemical agent used throughout the remainder of the war. Overall, about a third of US casualties were from chemical agents and about a third of these were from mustard.

Between World War I and World War II, there were several instances in which chemicals were allegedly used, but although both sides had these weapons during World War II, they were not used. In more recent years, alleged uses of these materials against the Hmong in Laos, the Cambodian refugees, and the Afghans have not been proven.

Chemical agents—mostly nerve agents and mustard—were widely used in the Iraq-Iran war (1980–1988). Iraq had a production facility that remained active until the Persian Gulf War (1990–1991). US forces and the military forces of other members of the Coalition were prepared to face these agents at the beginning of the liberation of Kuwait. Fortunately, the agents were not used.

Despite the destruction of Iraq's known chemical agent production facilities and despite the efforts of United Nations inspection teams, it is possible that Iraq still has chemical weapons. Libya has been involved with producing chemical agents.[2] Some people feel that at least 20 other countries possess chemical weapons.[3]

Today, chemical agent use is not confined to the battlefield and to warfare. Chemical agents are not difficult to produce, and it is very possible that future use of chemical agents against US citizens could be on US soil by terrorists rather than against US military personnel on foreign soil.

CHEMICAL WARFARE AGENTS AND THEIR CLINICAL EFFECTS

Nerve Agents

The Agents

Nerve agents are the most toxic chemical agents. They produce biological effects by inhibiting the enzyme acetylcholinesterase and thus preventing the destruction of the neurotransmitter acetylcholine; this excess acetylcholine then causes hyperactivity in muscles, glands, and neurons.

The nerve agents are GA (tabun), GB (sarin), GD (soman), GF, and VX. (The letters are the North Atlantic Treaty Organization designations for these agents.) The United States has large stockpiles of GB and VX and a very small amount of GA. These are in bulk storage containers and obsolete weapons at six depots throughout the continental United States and at an island in the Pacific Ocean, Johnston Atoll, where the agents and weapons are being destroyed.[4] The Soviet Union had large stockpiles of several of these agents, and these stocks are somewhere in the independent states that emerged from that country. Iraq used nerve agents in its war with Iran, and it has been alleged that Iran also retaliated with nerve agents.

In addition to their military potential, these agents have been used as terrorist weapons. In June 1994, sarin was released in the city of Matsumoto, Japan, injuring about 300 civilians and killing seven. A larger attack took place the following year when on March 20, 1995, sarin was released in the subways in central Tokyo. Although 5,510 people sought medical attention after this incident, only about a quarter of these had effects from the agent. Most of the victims had mild effects, although several dozen required intensive care and 12 died. Both attacks were blamed on members of the Aum Shinrikyo Cult.

The first of what we know today as nerve agents was synthesized before World War II by a German

scientist. Germany had these agents in munitions during that war but did not use them. The remainder of the weaponized nerve agents were synthesized between World War II and the early 1950s. From the early 1950s until the mid-1960s, the United States manufactured GB and VX; these stockpiles are now being destroyed.[5,6] The only known battlefield use of these agents was in the war between Iran and Iraq. Iraq's widespread use has been well publicized, and Iran may have also used nerve agents but in smaller amounts.

The nerve agents are clear, colorless liquids. Several (eg, GA, GD) have slight, not-well-described odors, but these odors are not characteristic and should not be used for detection or warning. Their freezing points range from –30°C (GF) to –56°C (GB) and their boiling points from 158°C (GB) to 298°C (VX). The most volatile is GB, followed by GD, GA, GF, and VX.[7] The volatility of GB is similar to that of water, whereas that of VX is similar to that of light motor oil.

GA is the least toxic by vapor exposure, followed by, in order of increasing potency, GB, GD, and VX. (Data are not available for GF.) Toxicity on the skin is in the same order, with VX being the most potent. Several of the G agents, (eg, GB, GA) require very large amounts on the skin to produce toxicity because much of these volatile agents evaporates.

Clinical Effects

The nerve agents listed above are not the only compounds that inhibit acetylcholinesterase to produce these biological effects. Drugs used in medicine, such as the carbamates, physostigmine, pyridostigmine, and neostigmine, as well as many carbamate insecticides, such as carbamyl, can also be considered "nerve agents" because of their biological activity. Malathion is the best known organophosphate insecticide with this activity.[8]

The nerve agents cause biological effects by inhibiting, or blocking the activity of, the enzyme acetylcholinesterase. The normal function of this enzyme, which exists at the receptor sites of cholinergic nerves, is to hydrolyze, or break down, the neurotransmitter acetylcholine. When the enzyme is inhibited, the intact acetylcholine accumulates and causes continuing stimulation of the receptor site, which in turn causes hyperactivity in the innervated structure. Cholinergic nerves (nerves with acetylcholine as their neurotransmitter) innervate skeletal muscles, smooth muscles, and exocrine glands; preganglionic fibers to autonomic nerves and some cranial nerves are also cholinergic. After inhibition of acetylcholinesterase, there is hyperactivity in all of these structures.[8]

Two other forms of cholinesterase are present in blood—the erythrocyte cholinesterase (also known as acetyl-, "true," or red cell cholinesterase) and plasma cholinesterase (also known as serum, pseudo, or butyryl cholinesterase). They are used as markers for tissue cholinesterase when a person has been exposed or is suspected of having been exposed to a cholinesterase inhibitor. Neither is an exact marker for the tissue enzyme, and the erythrocyte enzyme is a better indicator of the tissue enzyme and of resulting clinical effects.[9]

Vapor Exposure

The most common means of exposure to these agents, based on the Japanese experiences in the mid-1990s and on experiences in research and manufacturing accidents in the United States, is by vapor. After vapor exposure, the effects begin almost immediately, reach maximal intensity within minutes, and do not worsen later. The latent period between exposure and onset is seconds to several minutes at most.

Small amounts of vapor produce effects in the exposed sensitive organs of the face: the eyes, the nose, and the mouth/airways. Miosis is almost always present after exposure of unprotected eyes to nerve agent vapor and is often accompanied by conjunctival injection and pain or discomfort in the eye or head. The patient may complain of dimness of vision (because of miosis and of disruption of cholinergic pathways in the visual system) and after a large exposure, blurred vision. Severe miosis may reflexly cause nausea and vomiting; these effects, including the nausea and vomiting, can be relieved by topical atropine.

Rhinorrhea is common after vapor exposure. Because of increased bronchosecretions and bronchoconstriction, the patient may complain of shortness of breath or tightness in the chest; this is usually accompanied by audible pulmonary abnormalities. The dyspnea may be mild and reverse within 15 to 30 minutes or may cause prolonged severe distress, depending on the amount of vapor inhaled.

Inhalation of a large amount of vapor will cause sudden loss of consciousness followed by a short period of seizure activity and finally cessation of respiration and flaccid paralysis. These are accompanied by copious secretions from the nose and mouth and in the airways and by muscular fascicu-

lations throughout the body. The initial effect is within seconds of inhalation of the agent, and cessation of respiration follows within 10 minutes. Under these circumstances, the exposed person may die before there can be medical intervention, as happened with several casualties in Tokyo.

Liquid Exposure

In contrast to vapor exposure, liquid exposure has an asymptomatic latent period between time of exposure and the onset of effects (unless the amount is much greater than the lethal amount), and effects may continue to worsen after their onset as more agent is absorbed through the skin layers.

A droplet of liquid agent on the skin may initially cause fasciculations and sweating in the area of the droplet, and if the amount is small these may be the only effects. A larger amount will produce systemic effects; if it is a sublethal amount, the first effects will be gastrointestinal: nausea, vomiting, and diarrhea. Later, a feeling of muscular weakness may be followed by generalized fasciculations and twitching. These initial effects may occur anytime from 30 minutes to 18 hours after contact with the agent and may appear even though the area has been decontaminated.

A droplet containing a lethal amount of agent will cause, without noticeable preceding effects, the sudden loss of consciousness and seizure activity, followed by cessation of respiration and flaccid paralysis. These may start within seconds to 30 minutes after agent contact, depending on the amount of the liquid on the skin.

Vesicants

Vesicants are substances that cause vesicles, or blisters. There are many of these in the animal and plant kingdoms (eg, poison ivy). The chemical vesicants of concern are sulfur mustard, Lewisite, and phosgene oxime. In addition to causing blisters, these compounds also damage the eyes, airways, and other organs.

Mustard. Sulfur mustard is probably the best known and has been the most widely used chemical warfare agent. Depretz probably first synthesized sulfur mustard in 1822, although he did not recognize its properties. Other historians give credit to Riche or Guthrie in the mid-1800s for its discovery.[10] Later in the 1800s, Mayer developed a production process. Mustard's potential as a chemical warfare agent was recognized by the Germans, who first attacked with it on July 12, 1917. The Allies soon began using this agent, and it caused more casualties during the last 17 months of World War I than any other chemical agent had during the entire war.[11] It has been used since and gained much notoriety because of Iraq's large-scale use of it during the Iran-Iraq war and the widely publicized photographs of Iranian mustard casualties. Not as well documented are the alleged uses of sulfur mustard by Japan against China in the late 1930s and by Italy against Abyssinia in the 1930s and its use in the Yemenese civil war in the 1960s.[10]

A slightly different form of mustard was synthesized in the pre–World War II period: nitrogen mustard. This contains a nitrogen instead of a sulfur in the molecule, plus some side chains. Nitrogen mustard was found to be unsuitable for warfare use for a variety of reasons. In the early 1940s, however, it was found to be useful as a cancer chemotherapeutic agent,[12] and it remained an important drug for this purpose for several decades. It is no longer considered a chemical warfare agent, and throughout the remainder of this chapter the word mustard will refer to sulfur mustard.

Mustard, also known as H, HD, or HS, is a light yellow to brown oily liquid. It freezes at 14°C (57°F), which makes it unsuitable for cold weather use unless mixed with another compound to lower the freezing point. Its volatility is low, but in warm weather or when there are large amounts of mustard on the terrain, its vapor is a hazard. Most mustard casualties in World War I were injured by the vapor. Mustard has an odor of onions, garlic, or mustard (hence its name).

The biological mechanism by which mustard causes tissue damage is unknown. One hypothesis is that mustard produces DNA alkylation and crosslinking. This produces an inflammatory reaction and death in cells, such as the basal keratinocytes and rapidly dividing cells of the mucosal epithelium and bone marrow. In the skin, protease digestion of anchoring filaments at the epidermal-dermal junction leads to blister formation.[13]

Several known biological activities of mustard are important clinically. Once mustard penetrates skin or mucous membranes, it cyclizes to form a reactive compound. This in turn rapidly attaches to intracellular and extracellular proteins, enzymes, DNA, and other substances. Intact mustard is no longer present and is not present in blood, urine, or blister fluid. A more important consequence is that the biochemical damage takes place within the first minutes after contact with mustard, and de-

contamination done after this may reduce but not prevent damage. Despite this early biochemical damage, the clinical effects from mustard do not appear until hours later. Contact with mustard liquid or vapor causes no immediate pain or other clinical effect.

The most commonly seen signs of mustard exposure are in the skin, eyes, and airways. Even small concentrations of vapor will cause eye effects. When absorbed systemically in sufficient amounts, mustard also damages bone marrow, the gastrointestinal (GI) tract, and other organs. The LD_{50} (the dose that is lethal to 50% of those exposed) on the skin is about 7 gm of the liquid; the lethal amount of vapor is less than half of the lethal amount of cyanide vapor.

The characteristic effect of mustard on skin is erythema and blistering. On the skin, a droplet of 10 mcg will cause a blister. Between 2 and 24 hours after exposure to mustard vapor (the time is shorter after liquid exposure), erythema appears and is accompanied by pruritis or burning, stinging pain. This may be the extent of the lesion, but more commonly small vesicles develop within the erythematous area. These later coalesce to form bullae, which characteristically are dome shaped and thin walled and filled with translucent yellowish fluid. If the amount of mustard was large, a central zone of coagulation necrosis may develop within the lesion.

Mild conjunctivitis may be the only evidence of eye exposure to mustard vapor, but usually this develops into a moderate-to-severe conjunctivitis with lid edema and inflammation, blepharospasm, and possibly corneal damage. The eye does not blister; instead edema and clouding of the cornea occurs, which may progress to corneal vascularization. Inflammation of the iris and lens may lead to later scar formation. Lesions caused by liquid mustard are generally more severe and may cause perforation of the cornea. Except in severe cases, recovery is complete.

Mustard damage to the airways consists of destruction of the mucosa, and this damage descends in a dose-dependent manner from the nares to the smallest bronchioles. Mild exposure involves the nose, sinuses, and pharynx and causes irritation and pain in these areas. There may be voice changes or total aphonia, along with an irritating nonproductive cough. As mustard descends to the trachea and larger bronchi, the irritation and cough become worse, and smaller airway involvement causes dyspnea and an increasingly severe cough with sputum production. In severe instances, there may be necrosis of the terminal bronchioles and hemorrhagic edema into surrounding alveoli. Except under these circumstances, pulmonary edema is rarely a feature of mustard poisoning. The necrotic mucosa and inflammatory reaction in the airways often lead to the formation of pseudomembranes; these tend to obstruct the airway where they form or sluff off and obstruct lower airways.

The mucosa of the GI tract is very susceptible to damage from absorbed or ingested mustard. After systemic absorption of a large amount of mustard, the mucosa necroses, which leads to large fluid and electrolyte losses. This terminal event resembles radiation damage, and mustard has been called a radiomimetic agent. A small exposure to mustard may cause nausea and vomiting within the first 24 hours of exposure. This is self-limiting, is not related to GI mucosa damage, and is thought to be due to cholinergic stimulation by mustard or to stress.

Large amounts of absorbed mustard damage or destroy the precursor cells of the bone marrow, which leads to leukopenia followed by decreases in circulating erythrocytes and platelets. After an initial leukocytosis in the first day or two after mustard exposure, there may be a decline in leukocytes beginning about 3 to 5 days after exposure. If the exposure was not too large, these will return over the following days, but after a large exposure the leukocyte count may fall to under $200/mm^3$.

Nonspecific psychological problems have been described in people exposed to mustard. These may begin shortly after exposure and have been described a year or two later.[14] Mustard (particularly nitrogen mustard) also has neurological effects; it regularly caused convulsions when large amounts were given intravenously to animals.[15]

Death from mustard vapor exposure is usually the result of airway damage. This invites infection, and this in turn often leads to sepsis, which in the absence of a functioning bone marrow is usually fatal. Occasionally a pseudomembrane will obstruct airways, leading to death. If exposure was only to liquid on the skin with no inhalation of the vapor, tissue damage and death are similar to those caused by radiation: GI damage and massive fluid and electrolyte loss.

Lewisite. Lewisite was synthesized and produced during World War I, but supplies did not reach Europe before the war terminated, so it was not used. Japan allegedly used Lewisite against China in the late 1930s, but otherwise there is no known battlefield use of this agent.

Lewisite is a trivalent arsenic and combines with many thiol groups, but the mechanism by which it produces toxicity is unknown. It is an oily, colorless liquid with a geranium odor, it is more volatile

than mustard, and it has a much lower freezing point.

The clinical effects caused by Lewisite are similar to but more severe than those produced by mustard, with skin, eyes, and airways as the main targets. The skin lesions produced by Lewisite are usually deeper with more necrotic tissue. An important clinical distinction between mustard and Lewisite is that Lewisite vapor or liquid is extremely irritating and causes pain on contact with skin or mucous membranes. The casualty knows he or she has been exposed to something and masks or leaves the area and takes steps to decontaminate, whereas with the painless mustard exposure the victim usually does not realize he or she has contacted an agent. The Lewisite lesion appears sooner, with grayish dead epithelium appearing 5 to 10 minutes after Lewisite contacts the skin. Erythema and blisters also follow sooner than for a similar mustard exposure. Pulmonary edema is more likely to occur than with mustard. Lewisite does not damage bone marrow, but it does damage systemic capillaries and makes them permeable to fluid loss. This may lead to hypovolemia, hypotension, and organ damage.

Phosgene Oxime. Phosgene oxime is a urticant or nettle agent. Instead of fluid-filled blisters, it produces solid urticaria. It causes severe tissue necrosis and might be thought of as a corrosive agent. There has been no known battlefield use of this agent, and few investigations of its biological activities have been undertaken.

On the skin, phosgene oxime is extremely irritating and causes immediate pain, followed by blanching and erythema within 30 seconds. A wheal appears in about 30 minutes and is followed by necrosis. Lesions in the eyes and airways are similar to those of mustard and Lewisite except that the pain and tissue damage are more severe. Phosgene oxime can produce pulmonary edema after inhalation or after contact of the liquid with skin.

Cyanide

The Agent

Cyanide is widely used in industry for a variety of purposes (hundreds of thousands of tons are manufactured annually), it occurs in natural products and foods (eg, peach pits and cassava, a food staple in some parts of the world), and it is a product of combusion of many synthetic materials, such as plastics and fibers.[16] But it also has a reputation as a very deadly chemical. This reputation is probably based its rapidity of action; large amounts cause effects within seconds and death within minutes. Cyanide was not a useful agent when it was briefly used in World War I because the amount required to produce effects and lethality is high, because it causes few effects at small amounts, and because hydrogen cyanide—the form used—is lighter than air and tended to leave the area where it was delivered. According to press reports, cyanide was used against the Kurds at Halabja, Iraq, in March 1988, but this was neither proved nor disproved.

Salts of cyanide, specifically the sodium, potassium, and calcium salts, are the forms used for various purposes in industry. When a strong acid is mixed with a cyanide salt, hydrogen cyanide gas is released. This was used by the Nazis in concentration camps and has been used for executions in state "gas chambers." These chemicals were found in restrooms in Tokyo subways in the months following the March 1995 nerve agent release. Cyanide is occasionally used for suicides or homicides. In the 1980s and early 1990s, it was the substance in the grape drink that cult followers of the Reverend Jim Jones used for their mass suicide in Guyana, it was placed in Tylenol bottles, and it was responsible for deaths among people taking Laetrile (cyanide is released when that drug is metabolized).

The military uses two forms of cyanide. Hydrogen cyanide (hydrocyanic acid, AC) has a boiling point of 25.7°C, so in warm weather it is a true gas. It smells like bitter almonds, but half the population cannot smell it because of a genetic deficiency. It is the only agent that in the vapor or gaseous form is lighter than air. Because it rises and blows away quickly, it is not efficient when used outside. Cyanogen chloride (CK) is a nitrile that liberates cyanide during metabolism. This occurs minutes after it enters the bloodstream, so that cyanogen chloride possesses the biological activity of cyanide. It boils at 12.7°C so is a true gas under temperate conditions.

Clinical Effects

Cyanide inhibits one of the enzymes in the intracellular cytochrome system. Cells then cannot use oxygen; they switch to anaerobic metabolism and soon die. Cells of the central nervous system (CNS) are most susceptible to oxygen deprivation, and most signs and symptoms of cyanide toxicity are of CNS origin.[17] Chronic ingestion of cyanide, such as occurs in people who eat large amounts of cassava, can result in tropical ataxic neuropathy.[18] Other diseases (eg, Leber's hereditary optic atrophy) have been associated with chronic ingestion

of cyanide.

When ingested, small amounts of cyanide cause a brief hyperpnea followed by feelings of anxiety or apprehension, vertigo, a feeling of weakness, nausea with or without vomiting, and muscular trembling. Consciousness is then lost, respiration decreases in rate and depth, and convulsions, apnea, and cardiac dysrhythmias with eventual cardiac standstill follow. The time of progression of these is dose-dependent but may range from minutes to an hour or longer.[15]

After inhalation of a large amount of cyanide, events occur rapidly. In about 15 seconds, a brief period of hyperpnea occurs. Fifteen seconds later convulsions occur, and these are followed within minutes by a decreasing respiration that stops in 2 to 3 minutes. After dysrhythmias, the heart stops 6 to 8 minutes postexposure.

There are few physical findings. Characteristically, the skin is "cherry-red" because venous blood is still oxygenated; however, the skin may be normal or cyanotic in the late stages. Laboratory findings include a high blood concentration of cyanide (normal is < 0.5 μg/mL), a metabolic acidosis (because cyanide stops aerobic metabolism), and a high oxygen content of venous blood. The latter two findings are not specific for cyanide.

Pulmonary Agents

The Agents

Pulmonary agents damage the peripheral portions of the lung, terminal bronchioles, and alveoli. These agents are in contrast to those agents, such as mustard, that damage primarily the central parts of the lung (eg, the airways). The prototype of pulmonary agents is phosgene, which is not to be confused with phosgene oxime. Phosgene was a major agent in World War I until mustard use began. Other chemicals fall into this category, such as perfluoroisobutylene (PFIB), a pyrolysis product of Teflon that lines some military vehicles including personnel carriers; the oxides of nitrogen released from burning gunpowder; and HC smoke, in which zinc is probably the primary toxic compound, although a solvent that hydrolyzes to phosgene may also contribute. Phosgene (carbonyl chloride; CG), however, is the most thoroughly studied and the following discussion will concentrate on this agent, although most of the discussion can be applied to these other chemicals.

Phosgene is the most volatile of the military chemical agents. It boils at 7.6°C, so it is a true gas in most weather. The gas is much heavier than air and sinks into valleys, ditches, and trenches. Its odor is that of new-mown hay or freshly cut grass.

Clinical Effects

Phosgene causes damage at only one anatomic site, the alveolar-capillary membrane, and this damage is a local effect of the agent contacting the membrane. Unless the amounts of agent are extremely high, phosgene causes no effects by skin application, ingestion, or intravenous administration. Inhalation of the agent with subsequent contact of the agent with the most peripheral airways is the only manner in which phosgene produces biological activity.

When the carbonyl moiety of the phosgene molecule, which remains after the chlorine atoms are hydrolyzed off of the molecule, reaches the alveoli, it reacts with proteins and enzymes of the alveolar-capillary membrane to cause loss of integrity of this membrane. This results in plasma loss from the capillary to the alveolus and pulmonary edema, the severity of which depends on the amount of agent inhaled.

Phosgene may cause a transient irritation of the eyes, nose, or upper airways at time of agent contact because of hydrochloric acid released from the molecule, but otherwise the first effect is an increasing shortness of breath, which starts hours after the exposure. This asymptomatic latent period may last from 2 to 24 hours. The increasing dyspnea is accompanied by cough with clear frothy sputum. The time of onset and severity of the dyspnea are dose-dependent. As more plasma leaks into the alveoli, hypovolemia and hypotension are accompanied by hemoconcentration. The decreased fluid volume and subsequent hypoxia may damage organs such as the brain, liver, and kidneys. In people with hyperactive airways, the auscultatory sounds of bronchospasm accompany those of pulmonary edema.

A common complication is infection in the damaged lung. Pulmonary edema developing within several hours of exposure is a predictor of a fatal outcome. Death is caused by pulmonary failure, hypoxemia, and hypotension or a combination of these factors.

Incapacitating Agents

Incapacitating agents cause temporary inability to function appropriately. They should be safe to use (a large overdose will not kill) and leave no permanent effects. In addition to their military battlefield use, incapacitating agents could be useful to law

enforcement officials in other scenarios, such as hostage situations, airline hijackings, or prison riots.

Incapacitation can be produced by interfering with mental or physical processes. A compound that will cause loss of vision will incapacitate an individual for most tasks, as will a compound producing hypotension. The latter might prove to be lethal, and there is no compound to cause the former. A sudden "knock-down" effect with temporary loss of consciousness is produced by certain tranquilizers used in dart guns for animals. There are other means of incapacitation, but most compounds considered to be incapacitating agents affect the central nervous system.

Additional considerations in the selection of a compound for incapacitation are the rapidity of onset and duration of the effects. On a battlefield, the onset may be rapid or prolonged but the duration should be hours or days to give the user time to capture the victims. In a hostage situation, the onset should be rapid and the duration rather short so that the incapacitated casualties are not a burden on medical resources.

In the late 1950s and the 1960s, the United States developed incapacitating agents for military use. One, BZ, which is an anticholinergic compound similar to atropine and scopolamine, was put in munitions, but these munitions were destroyed in the late 1980s. There is no information on the military stockpiles of incapacitating agents in other countries, but these agents are not considered threat agents.

The onset time of BZ is about half an hour, and the effects last several days after an effective dose. BZ causes the same effects as atropine: mydriasis, blurred vision, decreased secretions from glands including salivary and sweat glands and glands in the airways and GI tract, decreased motility in the GI tract, and changes in the heart rate consisting of a brief bradycardia followed by a prolonged tachycardia and then normocardia. Similar compounds are used or have been used therapeutically for diseases of the eye and GI tract because of these properties.

BZ causes the same effects on the CNS as large amounts of atropine: confusion, disorientation, misperceptions (eg, delusions, hallucinations), incoherence in speech, inability to concentrate, and ataxia, all of which make up the syndrome known as delirium.

Riot-Control Agents

The riot-control agents are relatively unimportant as battlefield agents but are used in military training. These agents include CS, used mostly for training in the military and also used by law enforcement agencies; pepper spray; and CN (Mace), used in World War I and now commercially available in devices for self-protection. These compounds are solids and are usually delivered in a solution as an aerosol.

These agents produce burning, erythema, stinging, or pain on exposed skin and mucous membranes. In the eye there is burning, tearing, redness, and blepharospasm; in the nose and mouth there is burning on the exposed surfaces; and in the airways there may be discomfort, coughing, and a sensation of shortness of breath.

Capsaicin, or pepper spray, is a new agent that belongs in this category. It is marketed in self-protection devices, is used by some law enforcement agencies, and has been purchased by the military for limited use.

Capsaicin is a pure, crystalline material from the fruit of certain pepper plants, where it is found with the capsaicinoids, or capsicum oleoresin, an impure material containing over 100 chemicals. Both capsaicin and the oleoresins have been found useful topically for certain painful conditions such as arthritis, but toxicological data are scanty.

Capsaicin has about the same effects as CS and CN in the eyes, on the skin, and in the airways. But capsaicin is effective on those under the influence of alcohol or drugs, it causes more rapid effects, its recovery time is longer, its effects are more severe, it does not cause contamination of objects, and there is no danger of dermatitis, eye injuries, or an allergic reaction.

Severe effects after exposure to any of these agents are unusual. Prolonged eye symptoms may follow impaction of a particle in the cornea or conjunctiva. Skin exposure of a large concentration in a hot, humid environment may cause a delayed reaction with erythema and blistering. A person with hyperactive airways may have an asthma-like reaction after inhaling one of these agents. These compounds have a wide margin of safety, and death has occurred only when large amounts of them have been delivered into an enclosed space.

MANAGEMENT OF CHEMICAL AGENT CASUALTIES

The most important aspect of management of a chemically exposed casualty (or a casualty exposed to any type of toxic substance, including biological agents and radiation) is for the medical care pro-

vider to protect himself or herself. Otherwise there will be one more casualty and one fewer medical care provider. This is done by wearing appropriate protective equipment (ie, mask, gloves, suit) or by ensuring that the casualty has been completely decontaminated.

Nerve Agents

The key factor in managing a nerve agent casualty is to block the excess acetylcholine at cholinergic receptor sites and thereby reduce the hyperstimulation of the organs innervated by these nerves. There are many cholinergic-blocking, or anticholinergic, drugs available, but atropine was chosen decades ago because it was effective and produced fewer side effects. Scopolamine is very effective, but its side effects would be devastating in a nonexposed or mildly exposed person who took it unnecessarily.

Atropine is very effective at reducing the clinical effects of nerve agents in those organs with muscarinic receptor sites, such as smooth muscles and exocrine glands. Constriction of the airways and GI musculature is reduced, and secretions from the exocrine glands decrease. Atropine has very little or no effect on those organs with nicotinic receptor sites, namely the skeletal muscles. Thus, after atropine administration the casualty's secretions will dry and he or she will breathe better but will still be fasciculating and twitching.

A second drug that should be used along with atropine is an oxime. Oximes attach to the nerve agent bound to the acetylcholinesterase and remove the agent from the enzyme. The clinical effect of an oxime is seen primarily in those organs with nicotinic receptors, the skeletal muscles. Twitching and fasciculations decrease and strength improves. The oxime used in the United States is pralidoxime chloride (2-PAM Cl; Protopam Chloride).

The two drugs, atropine and oxime, are synergistic when used together. In the military, these are fielded in automatic injectors, one containing 2 mg of atropine and the other containing 600 mg of pralidoxime. These are supplied together in the MARK I kit (Meridian Medical, Columbia, Md).

In the event of mild-to-moderate poisoning by a nerve agent (ie, the casualty is still breathing, is conscious, and has muscular control), one MARK I kit should be self-administered. If the casualty does not improve, additional kits should be given at 5- to 10-minute intervals. Additional atropine should be given after three MARK I kits until there are signs of improvement, but no more than a total of three injectors of oxime should be administered each hour. The casualty who is unable to self-administer the antidotes, who is unconscious, who is breathing with difficulty or not breathing, or who has poor or no muscular control should be given three MARK I kits initially, followed by additional atropine until there is improvement. Improvement is when (*a*) the secretions are dry or are drying and (*b*) the casualty states that his or her breathing is better or there is less resistance to assisted ventilation.

For a severe casualty who is unable to self-administer the antidotes, the anticonvulsant diazepam should also be given. This is supplied in an automatic injector containing 10 mg of the drug. This should be given whether the casualty is convulsing or not.

One nerve agent, GD or soman, rapidly binds to the enzyme in such a manner that the oxime cannot remove it; the enzyme-agent complex is refractory to oxime reactivation. This process is known as "aging." After GD poisoning, aging occurs in about 2 minutes. Aging occurs after poisoning with other nerve agents also, but the time of aging is many hours after poisoning, and the process is not significant when treating an acutely poisoned casualty. Aging negates the usefulness of an oxime as an antidote and reduces the effectiveness of the standard atropine and oxime therapy.

Because of the rapid aging of the GD-enzyme complex and because GD was felt to be the major chemical threat agent against the US military, decades of research were devoted to a more effective therapy for GD poisoning. The result was the introduction of a pretreatment compound: pyridostigmine, a carbamate.

Carbamates attach to the active site on acetylcholinesterase the same as nerve agents do, but they remain attached only transiently; carbamylation of the enzyme is spontaneously reversible. Once the carbamate leaves the enzyme, or decarbamylation occurs, the enzyme again functions normally. While the carbamate occupies the active site of the enzyme, the nerve agent cannot attach, so in a sense the carbamate "protects" the active site from the nerve agent.

Pyridostigmine given before the agent exposure increases the efficacy of atropine and oxime therapy after GD poisoning and to a lesser extent after GA poisoning. It does not contribute to the therapy of GB, GF, and VX poisoning and should not be used in anticipation of poisoning by these agents. If pyridostigmine is taken after poisoning by GD and GA, it will contribute to the poisoning, not to the therapy. Pyridostigmine provides no benefit unless atropine and oxime are administered after poisoning. The dosing regimen of pyridostigmine is 30 mg every 8 hours. This regimen is started and stopped on order from the commander.

Additional care of the nerve agent casualty includes ventilation, suction of secretions, and correction of acidosis. The usual ABCs of airway management and ventilation will not be beneficial until the antidotes are given to relax the bronchial constriction. So the mnemonic in this case should be AABC, for antidote, airway, breathing, and circulation.

Vesicants

The most important aspect of the management of a vesicant is to prevent infection on the skin, in the eyes, and in the airways. There are no antidotes for mustard and phosgene oxime poisoning.

Skin care includes application of calamine lotion or other soothing material for erythema. Small blisters should be left intact; larger ones should be unroofed and the denuded area irrigated three or four times a day, followed by liberal application of a topical antibiotic. Systemic antibiotics should be started only when there are signs of infection and the organism has been identified.

Eyes should be irrigated at least daily, although the agent will be gone from the eye by the time the casualty is seen in a medical facility. A topical antibiotic along with topical atropine (or other mydriatic) to prevent later scar formation should be applied several times daily. Petroleum jelly or a similar substance should be applied frequently to the eyelid edges to prevent the lids from sticking together. Pain should be controlled with systemic, not topical, analgesics. Some ophthalmologists feel that topical steroids may reduce the inflammatory process if used within the first 24 hours, but steroids should not be used after this period.

Some form of positive-pressure ventilation (CPAP [continuous positive airway pressure] or PEEP [positive end-expiratory pressure]) might be useful if started at the first sign of airway involvement. Assisted ventilation with oxygen will be needed for someone in airway distress. Bronchodilators should be used for signs of airway constriction; steroids might be considered if bronchodilators are not effective. Antibiotics should be started only after an infecting organism has been identified; daily sputum examinations (Gram stain and culture) should be performed in a casualty with airway involvement.

To date there have been no attempts to replace damaged marrow after mustard exposure. However, marrow transplants or transfusions might be considered if facilities are available.

In animal studies, some forms of sulfur (eg, sodium thiosulfate) have elevated the LD_{50} of mustard when administered preexposure or within 15 minutes after exposure. Sulfur compounds have no effect on the topical lesions of the skin, eyes, or airways.

British anti-Lewisite (BAL) is an antidote for Lewisite and for other substances containing certain heavy metals. When the topical ointments are placed in the eyes or on the skin within minutes after exposure and decontamination, they reduce the severity of damage. However, these topical products are not available. BAL-in-oil (given intramuscularly) will reduce the severity of systemic effects. The lesions of phosgene oxime should be treated as lesions from a corrosive substance.

Cyanide

Cyanide casualties who are conscious when they reach a medical facility usually do not need therapy. Those who are unconscious, apneic, seizing, or any combination of these symptoms should immediately receive the antidotes sodium nitrite and sodium thiosulfate (both given intravenously). These are effective in maintaining life as long as they are administered while the circulation is intact.

Nitrites combine with hemoglobin to produce methemoglobin, which has a high affinity for cyanide. By diffusion processes, cyanide will leave the intracellular cytochrome oxidase and attach to methemoglobin. The intracelluar enzyme then reverts to its normal function. Thiosulfate attaches to free cyanide to form thiocyanate, a relatively nontoxic substance that is quickly excreted in the urine. These compounds come prepackaged in ampules, one containing 300 mg of sodium nitrite and the other containing 12.5 gm of sodium thiosulfate.

A compound used in the first aid treatment of cyanide poisoning is amyl nitrite. This is packaged in a perle, and after the perle is crushed the drug is administered by inhalation. If the casualty is not breathing, the drug can be placed in the ventilation apparatus. If the subject is breathing, he or she generally does not need the drug. Amyl nitrite is not in the military field medical system.

Pulmonary Agents

There is no specific antidote for these agents. Assisted ventilation should be begun as soon as effects appear. The intravascular fluid lost into the alveoli must be replaced to reduce hypovolemia, hypotension, and subsequent organ damage. Fluid replacement should be done in a hospital under the management of those skilled in pulmonary disease. The casualty should be monitored for airway infection by daily sputum examinations; antibiotics

should be begun only after an infecting organism is identified. Bronchospasm should be treated with systemic bronchodilators or, if these fail, with systemic steroids, but the effectiveness of steroids for parenchymal damage is equivocal.[19]

Incapacitating Agents

Physostigmine (eserine, Antilirium) will produce temporary (about an hour) reversal of delirium in a BZ-intoxicated casualty, and its administration should be continued hourly until the casualty recovers. It should not be administered to a severely poisoned casualty with seizures and acidosis. There are no specific antidotes for the other known incapacitants.

Riot-Control Agents

Medical assistance is not commonly needed for people exposed to riot-control agents. Removal of an impacted particle from the eye and other eye care should be done by an ophthalmologist. A casualty with a bronchospastic episode should receive bronchodilators and assisted ventilation. A delayed-onset dermatitis should be treated as a vesicant lesion.

PERSONAL PROTECTION

Personal protection is provided by service-specific protective garments and masks. The US Army and Marine Corps use an ensemble of jacket and trousers lined with activated charcoal, rubber boots and gloves, and the M40 mask. The mask is smaller than the older M17 series of masks, and it has a single external canister or filter instead of the two internal filters of the M17 series. The Navy and Air Force have similar suits but are less bulky and more fire resistant. The masks for all services are designed to fit the needs of the user. For example, the M24 mask for pilots has an adapter to attach to an oxygen supply and a microphone to permit use of the intercom system.

DECONTAMINATION

Decontamination is the process of removing or reducing contamination. There are three types of decontamination: self-decontamination, casualty decontamination, and decontamination of unit personnel who are not casualties. Decontamination of unit personnel (performed at what is sometimes called the Personnel Decontamination Station or MOPP exchange) is not a medical-specific matter and will not be discussed further.

After exposure to a liquid chemical agent, decontamination is an urgent matter. Nerve agents and vesicants start penetrating the skin within seconds. Skin decontamination done within a minute will not prevent damage from mustard exposure, but the damage from the exposure will be less than if decontamination is done 15 minutes later. Decontamination more than 30 minutes after exposure decreases the size of the lesion negligibly, which is why decontamination of a casualty in a medical facility does not help the casualty, but it does prevent spread of contamination to others, including medical personnel.

Many items might be of use in self-decontamination to remove liquid agent from skin. A popsicle stick can be used to remove a globule. Flushing with copious amounts of water will wash off the contamination. Flour and similar substances will adsorb much of the liquid. None of these actually destroys the agent.

The individual service member carries the M291 kit for self-decontamination. This contains packets of activated charcoal and resins; the charcoal adsorbs the agent as the skin is wiped with the packet, and the resins accelerate the breakdown or destruction of the agent. The destruction takes hours, however, so the major action of this packet is to physically remove the agent by wiping and adsorption.

In the decontamination station (see below), a solution of dilute (0.5%) hypochlorite is used to decontaminate skin. This combines with the agent and oxidizes or hydrolyzes it, but again this process is slow. While the decontaminating solution is placed on the skin and then washed off, the agent continues to penetrate the skin. The most immediate effect is the physical removal of the agent by the decontaminant.

FIELD MANAGEMENT

The Service Member's Role

The management of or care for a chemical casualty on a battlefield begins with the casualty himself. What is done within the first few minutes after exposure to a liquid chemical agent is the most important procedure that can be done. Self-decontamination is necessary because medical personnel

will not be present at this time. The service member should immediately decontaminate himself with the M291 kit if he suspects liquid contamination. In addition, self-administration of the nerve agent antidotes immediately after onset of the effects will reduce the illness. Buddy-aid is crucial if the casualty cannot self-administer the antidotes. There are no antidotes for the other agents that can be given by self- or buddy-administration.

What happens to the casualty next depends on the agent. A service member who had a small nerve agent exposure and was able to self-administer the antidotes will be able to continue the mission. A service member exposed to a large amount of nerve agent who did not receive the antidotes will die. A service member exposed to a large amount of nerve agent who received buddy-aid will continue to be symptomatic and will need medical care. A cyanide casualty will either die within minutes or will recover quickly. In neither instance will he or she require medical care. However, in some instances a casualty may present to the medical facility while still alive, and in those cases drug therapy might be useful. The effects from the other agents are delayed in their onset, and the signs and symptoms will begin hours or days later. At that time the casualty will seek medical care.

Echelons of Care

There are echelons of medical care on the battlefield. The first place a service member might turn to for assistance is to echelon I, which is the combat lifesaver, combat medic, or battalion aid station. Resources for care are limited at this echelon. Division level care, or echelon II care, is provided at the clearing station by the treatment platoon of the medical company. Although resources here are greater than at the battalion aid station (they include emergency care, radiology, a laboratory, and limited patient holding), the care needed may be beyond the capability here, and the casualty might need to be evacuated to an echelon III facility.

At echelon III are Mobile Army Surgical Hospitals, Combat Support Hospitals, and Field Hospitals, all of which are staffed and equipped to provide care for all categories of patients. The largest and most completely staffed medical resource within the military theater is the General Hospital at echelon IV.

At the Medical Facility

At the entrance to any medical facility that receives potentially contaminated chemical casualties is a casualty receiving area. The purpose of this area is to sort casualties and to ensure that contamination does not enter the medical facility. This area contains the entry point, a triage station, an emergency treatment station, a decontamination area, and the hot line. Until the casualty crosses the hot line, he or she is considered contaminated, and all personnel in front of the hot line—the contaminated area—must wear protective clothing, including masks.

Staffing at the casualty receiving area depends on the resources of the medical facility. At echelon I, triage and emergency treatment may be performed by a single senior medic or physician's assistant. The physician or physician's assistant will remain in the noncontaminated area. At a hospital in echelon III, a physician in protective gear may triage and may provide emergency care to a casualty also in protective gear. However, even at this echelon, a medic or physician's assistant may be the person in the contaminated area. Augmentees from the supported unit decontaminate the casualties.

The entry point is a clearly demarcated area into which all casualties arrive. Ambulances and other vehicles carrying contaminated casualties unload at this point. Establishing such a point is necessary so that contaminated vehicles will not enter the noncontaminated areas.

At the triage station, the medic, physician's assistant, or physician sorts the casualties according to priority for medical care. The five categories of triage, as listed in the *Handbook of War Surgery*,[20] are (*1*) urgent, for those needing care within minutes to save life (eg, someone with an airway obstruction or severe nerve agent intoxication), (*2*) immediate, for someone needing life-saving care within an hour or two, (*3*) delayed, for someone who has an injury needing further care that can wait without affecting the outcome (this includes almost all casualties with vesicant injuries), (*4*) minimal, for someone with a minor injury that can be quickly treated and the casualties returned to duty, and (*5*) expectant, for someone with wounds that are beyond the capabilities of the facility to treat.

In the emergency treatment area, care is limited with both the care provider and casualty in full protective gear. A bandage can be applied, a pressure dressing can be applied to stop bleeding, intravenous fluids can be started, chemical agent antidotes can be administered, and an endotracheal tube can be inserted and assisted ventilation begun. The RDIC (Resuscitation Device, Individual, Chemical, a bag-valve mask with a filter for incoming air) may be used in this area, or the standard bag-valve mask may be used since the vapor hazard would

be minimal and the casualty would probably die without ventilation. Before each procedure, both the casualty's skin and the care provider's gloves must be decontaminated.

The decontamination area consists of two areas, one for walking casualties and one for litter casualties. In the ambulatory area, the casualty is walked through several stations and at each station is told what to do and assisted in doing it by either an augmentee or a buddy. In steps, the casualty's hood is decontaminated and removed, he removes his jacket, his gloves are removed, he removes his outer boots and trousers, and he is monitored for contamination (usually with the CAM [Chemical Agent Monitor]), after which he crosses the hot line into the clean area, where he removes his mask. In the litter decontamination area, augmentees cut off the casualty's mask hood and outer garments, remove the rest of the garments, decontaminate the skin (with 0.5% hypochlorite), and check for contamination (usually with the CAM) before passing the casualty across the hot line into the clean treatment area. The capabilities within this area depend on the facility.

Casualties may be evacuated to a higher echelon either directly from the triage station if the level of care needed is beyond that of the facility or from the clean treatment area after initial treatment. In the former case, a contaminated vehicle would be used, and in the latter a clean vehicle would be used.

SUMMARY

Chemicals have been used as military weapons for more than 2,000 years. From the flame and smoke of ancient Greece to the nerve agents and vesicants of the Iran-Iraq war, theses weapons have killed or incapacitated hundreds of thousands of combatants and innocent civilians. US fighting forces have not been exposed to chemicals on the battlefield since World War I, more than 80 years ago, but the possibility of their use is always present. Many third world countries possess them and are not reluctant to use them. US military forces preparing for Operation Desert Storm had great concern that these weapons might be used.

Nerve agents cause death shortly after exposure, but casualties from this agent can be treated if antidotes and other assistance are begun in time. Mustard, the primary vesicant agent, causes effects that begin hours after exposure and causes death days after exposure. Cyanide produces death within minutes but has characteristics that make it less than ideal as a warfare agent—there are good antidotes if they can be administered before irreversible changes occur in the casualty. The pulmonary agents, such as phosgene, are less potent and less deadly than nerve agents and generally are excluded from lists of modern-day agents. The incapacitating agents do not produce lethality and might be considered for specific uses. The riot-control agents are used for civil disturbances and are not usually considered for battlefield use. This chapter summarizes the effects of these agents, the management of casualties from them, and the general management of chemical casualties on the battlefield.

REFERENCES

1. Thucydides. *The Peloponnesian War*. Crawley R, trans. New York: The Modern Library; 1951: 262.
2. Waller D. Target Gaddafi, again. *Time*. 1996;April 1:46–47.
3. Orient JM. Chemical and biological warfare: Should defenses be researched and deployed? *JAMA*. 1989;262:644–648.
4. *Chemical Stockpile Disposal Program Final Programmatic Environmental Impact Statement*. Aberdeen Proving Ground, Md: Program Manager for Chemical Demilitarization; 1988. Publication A3.
5. Harris R, Paxman J. *A Higher Form of Killing*. New York: Hill and Wang; 1982: 53.
6. Robinson JP. *The Problem of Chemical and Biological Warfare*. Vol 1. In: *The Rise of CB Weapons*. New York: Humanities Press; 1971: 71.
7. *Potential Military Chemical/Biological Agents and Compounds*. Washington, DC: Department of the Army; 1990. Field Manual 3-9.

8. Koelle GB. Anticholinesterase agents. In: Goodman LS, Gilman A, eds. *The Pharmacological Basis of Therapeutics*. 4th ed. New York: Macmillan; 1970: 448–451.

9. Grob D, Lilienthal JC Jr, Harvey AM, Jones BF. The administration of di-isopropyl fluorodate (DFP) to man, I: Effect on plasma and erythrocyte cholinesterase; general systemic effects; use in study of hepatic function and erythropoieses; and some properties of plasma cholinesterase. *Bull Johns Hopkins Hosp*. 1947;81:217–244.

10. Medema J. Mustard gas: the science of H. *NBC Defense Technol Int*. 1986;1:66–71.

11. Gilchrist HL. Statistical consideration of gas casualties. In: Weed FW, ed. *Medical Aspects of Gas Warfare*. Vol 14. In: *The Medical Department of the United States Army in the World War*. Washington, DC: Government Printing Office; 1926: 273–279.

12. Gilman A. The initial clinical trial of nitrogen mustard. *Am J Surg*. 1963;105:574–578.

13. Papirmeister B, Gross CL, Meier HL, Petrali JP, Johnson JB. Molecular basis for mustard-induced vesication. *Fundam Appl Toxicol*. 1985;5:S134–S149.

14. Balali-Mood M, Navaeian A. Clinical and paraclinical findings in 233 patients with sulfur mustard poisoning. In: *Proceedings of the Second World Congress on New Compounds in Biological and Chemical Warfare*. Ghent, Belgium; 1986: 464–473.

15. Marshall EK Jr. Physiological action of dichlorethyl sulphide (mustard gas). In: Weed FW, ed. *Medical Aspects of Gas Warfare*. Vol 14. In: *The Medical Department of the United States Army in the World War*. Washington, DC: Government Printing Office; 1926: 369–406.

16. Homan ER. Reactions, processes and materials with potential for cyanide exposure. In: Ballantyne B, Marrs TC, eds. *Clinical and Experimental Toxicology of Cyanides*. Bristol, England: Wright; 1987: 1–21.

17. Ballantyne B. Toxicology of cyanides. In: Ballantyne B, Marrs TC, eds. *Clinical and Experimental Toxicology of Cyanides*. Bristol, England: Wright; 1987: 41–126.

18. Hall AH, Rumack BH, Schaffer MI, Linden CH. Clinical toxicology of cyanide: North American clinical experiences. In: Ballantyne B, Marrs TC, eds. *Clinical and Experimental Toxicology of Cyanides*. Bristol, England: Wright; 1987: 312–333.

19. Diller WF, Zante RA. A literature review: Therapy for phosgene poisoning. *Toxicol Ind Health*. 1985;1:117–128.

20. Bowen TE, Bellamy RF, ed. *Emergency War Surgery*. 2nd rev US ed. Washington, DC: Department of Defense, Government Printing Office; 1988.