

unit, and the specialty must be appropriately prepared. Long-term ventilation may be required for neuromuscular problems, toxic pulmonary edema, and associated adult respiratory distress syndrome. Mass toxic casualties will place a heavy burden on emergency and intensive care services as a result of short-term and longer term actions of toxic agents.

In conclusion, close integration of anesthetists into toxic emergency response teams is essential, but finding time for training in protection and detection and the primary management of CB casualties may be difficult. Nevertheless, it is vital that anesthetists, and particularly emergency and trauma specialists, understand the real risks from CB and HAZMAT procedures to provide a clear lead and to avoid becoming the next casualty. The contents of this issue will hopefully help to raise awareness in this important area of practice.

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Preparedness for Bioterrorism

Introduction

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There is nothing that captures the imagination and generates fear like the threat of a massive biologic or chemical weapon attack. This issue of *TraumaCare* explores the concerns surrounding these weapons of mass destruction. Articles detail the signs and symptoms to look for in patients being assessed. Treatment options are also discussed, as well as a primer for preparedness. Finally, the history of biologic and chemical weapons is covered going back to ancient times.

The key to treatment of biologic and chemical weapons victims is to realize that the patient has suffered such an attack. Since these agents are not routinely treated in the United States, recognition is the key to successful outcome. While mortality for patients is high, health care workers must take adequate protection to avoid becoming victims themselves. Agents to treat these diseases need to be readily at hand – yet there is expense involved as many pharmaceuticals may never be used in the massive doses needed to treat a biologic or chemical weapons attack.

Read carefully the articles in this issue, for knowledge and preparedness are the best defenses against an attack. Take comfort in the history of the use of these weapons, for although deadly viruses and bacteria have been produced, they are rarely used. Chemical weapons, outside of the massive campaigns of the First World War have not been used – another reassuring historical sign.

Be prepared, be suspicious of these agents especially when several patients with similar symptoms present, and be careful to protect yourself and other health care workers. Only

then will we be able to lessen the fear chemical and biologic weapons evoke in the general population and ourselves.

A History of Biological Warfare

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Learning Objective:

To help the reader to begin to understand important aspects of the history of biological weapons.

Abstract

The use of biological weapons can be traced to the ancient Greeks. Through time, most biological weapons have been used as a contaminant, rather than as a primary weapon. It is only in the 18th century that an agent, smallpox, was first used, as a biological weapon. Much of the history of biological weapons is a potential history, dealing with the development of weapons of mass destruction, rather than their use. However, when used, there is often a cultural overtone, whereby a group that feels culturally superior to another, will test or use biological weapons to eliminate the “inferior.”

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Introduction

The need to effectively eliminate an opposing army in war is the duty of every nation's armed forces. Conventional weapons such as bow, arrows, swords, spears, rifles, and hand grenades and all the trappings of an army both ancient and modern are geared for this objective. Kill ratios express the bloody duty of men at arms all too well – kill more of the enemy than the enemy destroys of your army. Biological weapons are the logical extension of force of arms. The hope that these weapons will incapacitate or kill more effectively and with less effort, cost, and destruction than conventional weapons at a reduced cost makes them an attractive alternative. Biological weapons are also ideal for terrorists, as they strike fear into the target population. A small vial of agent, easily concealed, may be enough to endanger an entire city. Indeed, the contamination of the water supply of a major metropolitan area has been the plot of many an action novel.

Yet the use of biological material to add to or become weapons is not new. Experience with these weapons, tracing back to the ancients of the Middle East to modern-day Iraq, is long and extensive. Commanders have learned to fear the use of “biologicals” because, if conditions are right, the biological weapon may infect their troops, unleashing the weapon upon themselves instead of the enemy. Cultural issues also play a role in the use of biological weapons. A culture that feels superior, in several historical incidents, has used these weapons of mass destruction on a society it feels is inferior. Finally, biological weapons and their nuclear and chemical counterparts may contaminate the battlefield for countless future years.

The use of biological weapons can be studied by time. Some uses, such as the contamination of potable water through the use of carrion and corpses, continues today. Indeed, a contaminated wound incapacitates a soldier longer than a “clean” wound. Agents like the plague, smallpox, anthrax, and cholera have been used for centuries. Fortunately, much of the history of biological warfare is “potential history.” Having the power to develop a biological weapon of mass destruction is not synonymous with using it!

The Ancient World

Perhaps the earliest recorded use of biological weapons occurred in ancient Greece. The story of Hercules and the sacking of Troy, written by Homer in the eighth century BC, may in fact be the earliest documentation of biological warfare. In slaying the many-headed hydra, Hercules dipped his arrows in the blood of the dead animal, giving him an endless supply of deadly arrows. Interestingly, the word for arrow, *toxon*, is the root for the ancient Greek word for poison, *toxicon*. In an ironic twist of fate, Hercules himself died of the hydra's poison, which in description is similar to the poison unleashed in a viper's bite.¹

Contemporaries of the Greeks and Romans, Scythian archers dipped their arrows in manure and decomposing bodies as a source of poison for their arrow tips.² It is not known if this was any more effective than untainted arrows, but the psychological effect must have been enormous. In the first century BC, at the Battle of Eurymedon during the Second Macedonian War, Hannibal used a novel biological weapon. An advisor to King Prusias I of Bithynia, Hannibal beat King Eumenes II of Pergamon in a naval battle by using earthen vessels filled with venomous snakes. The pots were hurled into the opposing ships.² Imagine the effect as an incoming pot broke upon the deck and released angry

snakes among the crew. Add the pandemonium of battle, and a recipe for disaster is created.

Another example of the use of biological agents in ancient times is the well-known story of the Israelites leaving Egypt. Nine plagues were inflicted upon the Egyptians, of which several biologicals were used: frogs, lice, flies, locusts, and “ashes” from the sky, which caused boils. The latter episode reads like a modern aerosolized anthrax attack.³ Furthermore, the Nile was turned red, which resembles the red tides of the Gulf of Mexico, caused by a bacterial infestation.⁴ Indeed, the ultimate biological weapon in this biblical story caused the death of the first born of every Egyptian, both animal and human. Another biological agent, lamb's blood, painted over the door frame, prevented collateral damage, sparing the “friendly” army of the Israelites.³ The event is recalled in the Judeo-Christian tradition as Passover and is still celebrated by practicing Jews.

The Middle Ages and Renaissance

Delivery systems for biological weapons have evolved over time. The medieval catapult was used to hurl all matter of infectivity over city walls during a siege. The French catapulted dead horses and other carrion into the castle of Finn on the Shell River in 1339 during their siege. In 1422, Commander Corbet threw bodies of killed besiegers and 200 cartloads of manure over the walls at the siege of Carolstein. In 1650, the Polish general Simowitz loaded a colosphere on his catapults “filled with the slobber of rabid dogs and other substances that can poison the atmosphere and cause epidemics.”² This strategy was to infect the population of the besieged, causing enough defenders to die so the city could easily be taken. Barring that outcome, the carcasses and cadavers were a tremendous psychological weapon, last used during the Russian Revolution in the early 20th century.⁵

Did the catapult unleash the Black Death on Europe? In 1347, the Mongols, besieging the city of Kaffa (now Feodosia, Ukraine), threw the bodies of plague-infected cadavers over the city walls. The Mongol army, weakened by an epidemic, hoped to spread the disease into the city and win a strategic advantage. The city was soon infected, and the defenders evacuated and returned to Europe. During their retreat, stops were made in Constantinople, Genoa, and Venice, all cities that soon suffered an outbreak of the Black Death. Over the next few years, this plague caused the death of about a quarter of the population of Europe.⁶ Thus, the Mongols unleashed an effective biological weapons campaign.

The Persians, Greeks, and Romans used the strategy of contaminating potable water as far back as 300 BC. Barbarosa used the bodies of dead soldiers to poison wells in 1155. Sixteen years later, the Doge of Venice attacked Regusa. Negotiations were delayed long enough to force the Venetians to drink from wells the Regusians had contaminated. Predictably, the Venetian army became ill and was forced to retreat.⁵

Eighteenth and Nineteenth Centuries

During the 18th century, smallpox was used by a “superior civilized” European culture to eliminate an “inferior” native one. The continental European powers fighting on the North American continent knew the “Indians” were susceptible to smallpox. Sir Jeffrey Amherst, the British commander in North America, wanted to secure the western border of the British colonies from attack. To that end, Amherst reasoned, reducing the native population, which

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was difficult to find and fight in an open European-style battle, would stop their raids against settlers on the frontier.⁷

During the ongoing war, there was an outbreak of smallpox at Fort Pitt. Amherst suggested to his subordinates in the area that they should use this epidemic to spread the disease among the native population, hoping to end the conflict.⁸ Colonel Henry Bouquet, the commander at Fort Pitt, had two blankets and a handkerchief from smallpox patients given to two hostile native chiefs. Just as Lord Amherst suggested, an outbreak of smallpox occurred among the Indians, decimating the population and ending the threat to the English settlers in the area. But, Amherst's motives went beyond ending a difficult military situation. In a postscript to one of his letters to Bouquet, Amherst wrote about his desire to exterminate the entire native population. He applauded the "Spanish Method," in which dogs were used to hunt down and kill native Americans.⁹

During the Civil War, Confederate General Joseph E. Johnson, during the retreat from Vicksburg, tried to deny potable water to the advancing Union Army. He ordered farm animals be driven into ponds and then killed. When Union General William T. Sherman came upon the ponds, he ordered the carcasses be removed before the water was drunk, but no other measures were taken.² The outcome on the Union troops has not been recorded.

"Modern Times"

The First World War, better remembered for the carnage of the trench and the introduction of chemical warfare, had a significant undercurrent of biological weapon development as well. The Germans reasoned that if anthrax killed a large portion of the Entente's horses and mules, their ability to feed their troops, move their artillery, and wage war would be severely limited. The German military attaché in Washington DC, Major Fritz Van Papen, was found with anthrax cultures in his possession. The plan was to contaminate horse fodder in the U.S. bound for the Entente. In 1916, the German litigation in Romania was found to have cultures of anthrax and glanders.¹⁰ The Germans attempted to use anthrax-laced sugar cubes against the reindeer populations in Norway, trying to deny the troops heavy transport animals and meat.¹¹ In 1917 and early 1918, under very suspicious circumstances, 200 mules bound for the Entente died of anthrax and glanders in Argentina – an act thought to be German sabotage.¹⁰

The Germans also hit upon the idea of using cholera to contaminate the potable water supply in Italy. In 1918, at the end of World War I, the German counsel in Zurich had cholera prepared in vials ready for use in Italy. His plan was to smuggle the bacteria across the border and dump it in the water supply of a major Italian city. The Germans hoped to use anarchists as they had used communists to ferment revolution in 1917, which took Russia out of the war. However, the communists were far more effective than the anarchists and the expected cholera outbreak never occurred.²

World War II—The Allies

During World War I, the Germans were the most active in the research and development of biological weapons; World War II was a different story. The Allies, especially the British, were heavily involved in the development of biological

weapons. One British target was the Axis cattle population. Dropping aerosolized anthrax bombs in the German countryside would ensure a food crisis, both civilian and military. The British developed and tested anthrax bombs on Guinard Island off the coast of Scotland. Before the tests began, Guinard Island supported a large population of sheep and a small community of humans. When the prototype anthrax bomb was ready for testing, the human inhabitants were evacuated. The bomb was dropped and all the sheep were killed. For the ensuing 48 years, the island was too contaminated for human or animal habitation.¹² In 1986, the British government took steps to decontaminate the island: the top 4 inches of topsoil were removed, and the entire island was washed in a combination of formaldehyde and hot seawater. Subsequently, a flock of sheep was allowed to graze on the island, apparently without ill effect, proving the success of the decontamination. On 24 April 1990, Michael Neubert, the junior defense minister, declared Guinard Island safe and personally removed the warning signs.¹³

The British biological weapons development center during World War II and the Cold War was Porton Down. Having proven the effectiveness of airborne anthrax released from bombs, the researchers turned to cattle feed as a method of delivery. A hole was drilled in the middle of a feed pellet, filled with anthrax, and sealed with a wax plug. The plan was to drop these pellets in bombs over the German countryside. However, the British never used this weapon. The pellets were stockpiled for the next 40 years, and only recently have they been destroyed.⁷

The British developed a biological assassination weapon. Paul Fildes, director of Porton Down research, theorized that if botulinum spores could deeply contaminate a wound, and some small amount of healing occurred, creating an anaerobic chamber, the organism would grow and multiply. With the infection established, toxin would be introduced into the patient's body and kill the intended target. To create a delivery system for the spores, the research staff at Porton Down took a British anti-tank grenade number 73, which normally weighs 4 pounds, and created one that weighed only 1 pound. They removed the top third of the grenade and replaced it with tetanus toxoid and spores.^{7,14}

Reinhardt Heydrich was the British target. Heydrich, as the *Reichsprotektor* of Bohemia and Moravia and an architect of the holocaust, was responsible for many major Nazi atrocities. Operation Anthropoid was launched in October 1941. By December of that year, seven Porton-Down-trained Czech assassins parachuted into the protectorate of Bohemia and Moravia. After studying their target's movements for several months, they launched their attack on 27 May 1942. Jan Kubis threw the doctored grenade, destroying Heydrich's car and wounding him.¹⁴

The wounds were not thought to be fatal. Heydrich removed himself from the car, fired his sidearm at the quickly vanishing partisans, and then collapsed. He was brought to a German military hospital fully conscious and was quickly operated upon. The most serious wound was 3 inches deep. At surgery, splinters of either the grenade or the car were débrided from Heydrich's chest wall and spleen. On 28 May, he declined rapidly and slipped into a coma. On 4 June, Heydrich died. His symptoms included extreme weakness, malaise, dry skin, dilated and unresponsive pupils, dry coated tongue and mouth—all consistent with botulism poisoning. Paul Fildes bragged to a young Alvin Pappenheimer, an American assigned to Porton Down, who later became professor of microbiology at Harvard,

"Heydrich's murder was the first notch in my pistol."^{17,14}

The Soviet Union employed biological warfare on at least one occasion during World War II. Soviet troops used tularemia to help stop the German troops during the Battle of Stalingrad. The resulting outbreak may have halted the Nazi advance, but due to the close quarters, an epidemic of the disease also developed among the Soviet troops after a sudden change in wind direction blew the agent back into the Soviet lines. More than 100,000 cases of tularemia were reported in the Soviet Union in 1942, a 10-fold increase over the incidence in 1941 and 1943. Seventy percent of the 1942 cases were the respiratory form of the disease, making it more likely to have come from a weapon rather than a natural outbreak.¹⁵

World War II—The Axis

Interestingly, the Nazis were not leaders in biological weapons research and development among the Axis powers in World War II. They had done some preliminary work by 1937, and in conquering France in 1940, realized how far behind the French they were. The Germans decided they could not catch up and abandoned the little work already completed. Hitler, it is believed, barred offensive biological weapons research, based on his own experience of being gassed during World War I. Only one known tactical use of biological weapons by the Germans came late in the war, when a large reservoir in northwestern Bohemia was contaminated in May 1945. The Nazis did experiment with several biological agents on concentration camp prisoners in inhumane experiments; no weapons were generated from the research.¹²

On the other side of the Axis world, the Japanese were exceedingly interested in biological warfare. The Imperial Army set up several large research institutes to spread biological weapons research and testing areas throughout occupied China. Shiro Ishii commanded the largest and best known of these research and development establishments, named Unit 731, whose sole purpose was offensive biological weapons research. Ishii commented that defensive research, composed mainly of vaccines, could easily be done in Japan. Offensive weapons research needed to be done in China.¹⁶ Why?

These institutes were set up in China largely because the Japanese felt culturally superior to the Chinese and wanted to have a ready supply of experimental subjects to test the effectiveness of their newly developed agents. In addition to Chinese citizens, the Japanese also used Russian, American, and United Kingdom prisoners of war to test their biological agents. Many were autopsied alive, without an anesthetic. The Japanese thought that anesthesia might change the pathologic findings of infection. They often referred to their Chinese subjects as *marutas*, or logs.¹⁷

Unit 731 and its counterpart Units 100 and EI-1644 were responsible for at least 12 biological field tests. Militarily, the Japanese used biological weapons in a well-documented attack against the much-hated Russians in 1939 on the Manchurian border. Japanese soldiers crossed behind Soviet lines and spread anthrax in an attempt to poison animals and deny the Russians transport capability. They were only partially successful. The infection spread from the animals to the soldiers, and Russians died. The wind shifted, and the anthrax was blown over the Japanese lines, infecting these soldiers as well.⁷

In another incident, Ishii gave chocolates laced with anthrax to the children of Nanking. Other field tests of offensive biological weapons included a cholera outbreak in Chang Chung, and the poisoning of wells in Nanking. The plague was used in Ningpo and Chuhsein in October 1940 and Changteh in November 1941. The results of these field tests were published in the Japanese-language *Chinese Medical Journal* in July 1943.⁷

There is another medical tragedy associated with the spirit of the biological weapons research done by the Japanese during World War II. Thomas Easton, a reporter for the *Baltimore Sun*, detailed the experience of American B29 airmen who bailed out over Japanese-held territory after their planes were hit. Several wound up at Kiushu University on the home island of Japan. The case of one airman, Teddy Ponczka, remains particularly appalling. Documentation of Mr. Ponczka's treatment was provided by Dr. Tushito Todo, an eyewitness to the events. One of Ponczka's lungs was removed because the Japanese physicians wanted to know the effect of surgery on the respiratory system. Later, when he had recovered from surgery, Mr. Ponczka's blood was removed and replaced with seawater, in an experiment designed to see how long circulation could be effectively maintained in the absence of blood. Other American airmen were documented to have partial hepatectomies, epilepsy surgery when they were not epileptic, and stomach resections; all of them later were killed.¹⁸ This treatment is consistent with what the Japanese did in occupied China and other countries. Interestingly, before and during World War II, the Japanese felt culturally superior to the Americans, who they felt were a nation of weak merchants incapable of beating the superior wind warriors.¹⁹

At the end of World War II, the Japanese officers responsible for the biological warfare program were brought to justice. Twenty-three were found guilty: 5 were sentenced to death, 4 were sentenced to life, and 14 to shorter terms. Yet, in September 1950, Douglas McArthur commuted their sentences. He was concerned that Japanese knowledge of biological weapons should stay in American hands. McArthur and the American government were afraid the Japanese knowledge and experience with biological weapons would fall into Russian hands. There were no executions – the Japanese successfully traded their knowledge for their lives.¹⁸

In his book *Biobazard*, Ken Alibek detailed the Soviet Union's biological weapons research program after World War II and confirmed that Japanese knowledge played a large part in the foundation of the Soviet biological weapons program. However, the Soviets took biological weapons research to new heights. For example, they developed antibiotic-resistant microbes and combined various viruses into a super virus capable of killing humans in several different ways. The most disturbing part of the book details what occurred during the collapse of the Soviet Union. Alibek was personally recruited by Iran, Iraq, North Korea, and several other nations to develop a biological weapons program. Alibek notes that several of his colleagues have disappeared, all of whom possessed the knowledge to start a biological weapons program from the ground up.²⁰

Korea, the Cold War, and Vietnam

During the Korean conflict, there were many allegations that the Americans used biological weapons. The North Koreans and Chinese demonstrated that there were many

unexpected outbreaks of cholera and plague on the Korean peninsula during the war. However, public health measures on the peninsula at the time were dismal; unprocessed human and animal waste was used to fertilize crops. Given these conditions, it was not surprising to have periodic outbreaks of these diseases. Today, there is no credible evidence that the Americans used biological weapons against the North Koreans or the Chinese. However, those allegations were used to institute necessary public health measures and change centuries of tradition in fertilization of agricultural fields on the Korean peninsula.²¹

The Cold War presented the United States with a challenge. Many people wanted to know the country's degree of susceptibility to a biological attack. *Serratia marcescens*, a bacterium thought to be benign, was released in 1950 in San Francisco Bay. Tracking the bacterium across the Bay area was thought to show how a biological weapon might spread.⁸ The test had unexpected consequences. There were 11 cases of *Serratia* infections at Sanford Hospital and one death. The first report of a case of *Serratia* endocarditis occurred during the test.⁷ Studies with this and other "benign" bacteria continued throughout the 1960s in various parts of the United States.³

In 1966, an experiment was replicated that had first been done in August and September 1933. The study was designed to demonstrate how a biological agent would spread in a subway system. The Paris metro was tried first, and the second part was carried out in the French forts of Magnot Line. In the replicating experiment in the New York Subway in 1966, light bulbs filled with *Bacillus globii* were dropped in ventilator shafts. Within a half hour, this nonpathogenic bacterium was cultured at the most distant points in the system from its release area. The white powder that came from the broken light bulbs was brushed off without concern, and subway passengers continued about their business.²

During the Vietnam War, the Viet Cong used contaminated traps to injure opposing troops. Colin Powell, an Army captain at the time, was a victim. The Viet Cong dug holes in jungle trails and then camouflaged them. The bottom was lined with sharp punje sticks coated in manure. Powell fell into one of these traps. He endured a deep, penetrating leg wound, but fortunately recovered with good medical care and antibiotics.²²

Richard Nixon, in his 1968 Presidential bid, supported a ban on all biological weapons. The Biological Weapons Convention was established in 1972. This treaty prohibited the research, development, and production of offensive biological weapons. With ratification by the United States, the Soviet Union, and others, the United States destroyed its biological weapons arsenal the following year. Seed stocks were kept for research purposes. Theoretically, the United States was out of the offensive biological weapons business.²³

Conclusions

Biological weapons have been with mankind since antiquity. Like most offensive weapons, they have been refined, from the simple dipping of arrows and spear tips into naturally occurring poisons to manmade superviruses and antibiotic-resistant bacteria. Fortunately, much of the history of these weapons of mass destruction is a potential history. They could have been used, but were not. Perhaps the Cold War is the best example of this restraint. While both

sides possessed fearful biological weapons, they were not used in Korea or Vietnam.

The other "lesson" from the history of biological weapons is the darker side of humanity. Feelings of cultural or racial superiority can lead to the testing and occasional use of biological weapons on the "inferior" culture or race. Treatment of fellow human beings is beyond reproach as basic humanity is denied and people are treated simply as experimental organisms. Neither are these weapons easily controlled. Oftentimes, as history has shown, large-scale biological weapons attacks lead to equal numbers of deaths among friend and foe. In 1972, a hopeful step was taken by banning these weapons (the Biological and Toxin Weapons Convention). Yet our scientific knowledge has made creation of these biological weapons fairly easy, and there are nations and organizations willing to use any means necessary to drive home their point. Thus, biological weapons, and our need to be ready to treat mass casualties from them, will remain a part of health care for the foreseeable future.

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Bioterrorism and the Anesthesiologist: An Overview

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Learning Objectives:

1. To present some of the new challenges anesthesiologists face in the age of bioterrorism.
2. To review the categories of biological agents.
3. To consider the role of the anesthesiologist in the event of a bioterrorism attack.
4. To present four basic areas that anesthesia departments can implement as an aid to improving preparedness for a disaster.

Abstract

Most physicians lack formal training in combating the devastating results caused by biological agents. This article discusses the challenges facing today's anesthesiologist in relation to bioterrorism, gives a broad overview of the biological agents, and provides initial steps that anesthesia departments can take to improve preparedness for such an attack.

The vulnerability of the United States of America to terrorist activity was demonstrated on September 11, 2001, with the previously inconceivable attacks in New York City, Washington, DC, and Shanksville, Pennsylvania. Many experts now believe that either a biological or chemical terrorist event will occur within the United States during our lifetime. The unprecedented sales of gas masks, prophylactic antibiotics, and various "antidotes" to Americans who wish to be prepared has taken on the symbolism of building fallout shelters in the 1950s to protect against nuclear attack. One should take some, albeit less than satisfying, consolation in knowing that biological warfare has existed since biblical times and has been used routinely throughout humankind's ignominious history of warfare and revolt.

Like a storm without warning this asymmetric warfare can strike with dreadful consequences. Unfortunately, anesthesiologists, together with most other physicians, have little or no formal training in combating such inhumane attacks. However, our specialty is part of the "first responders" called to treat early victims of bioterrorism. Whether we are consulted by a surgeon to anesthetize a patient, called to the emergency department to intubate someone in respiratory distress, or are the intensivists attending the intensive care unit, one must have a thorough understanding of the pathogenesis, diagnosis, and protective maneuvers for each bioweapons threat. Physicians trained in anesthesiology have expertise in many areas including pharmacology, human physiology, and airway management that make them uniquely

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qualified to deal with the consequences of a modern chemical or biological attack. Indeed, it will be critically important for all health care providers to rapidly diagnose and quarantine when indicated while always using safety precautions. However, as a specialty accustomed to working with one or two patients simultaneously, the prospects of triaging thousands of casualties with limited resources is unimaginable for most anesthesiologists.

Meeting the Challenge

No one ponders the specter of an unplanned disaster in his or her area—regardless of terrorism. Few are even trained to consider such events. However, key steps must be taken to both optimize the chances for full recovery of the victims and limit exposure to caregivers and other unaffected patients. The sheer numbers of victims converging on emergency departments will ensure that many will die because of lack of rapid treatment. Victims of a mass casualty event can suffer from the agents used in the attack alone, or in combination with physical trauma. The exposure of a physically injured victim to a toxic substance in the scenario of mass injury has gained attention among developers of protocols for emergency medical services.¹ Since rapid deterioration and multiorgan involvement are to be expected when a person is exposed to both physical injury and a toxic substance, acute medical and surgical care systems must be able to deliver complex and efficient care to ensure that a maximum number of lives are saved.

The acute care medicine that anesthesiologists deliver on a daily basis necessitates that they become an integral part of this response system. The management of mass casualty events is based on triage principles and acute care measures. Initial rapid assessment of the situation is imperative in order to identify the offending agent. Emergency medical personnel will then undertake swift decontamination and mass evacuation to a medical facility capable of dealing with such emergencies. Since many of these victims will require urgent surgical intervention and prolonged perioperative acute care, it is imperative that anesthesiologists become intimately familiar with agents used in bioterrorism.

Although anesthesiologists will be consulted in the emergency department and the intensive care unit, their expertise will be called upon primarily in the operating room (OR), where life-saving operations will be undertaken. When anesthetizing affected individuals, there are many reasons it may not be possible to meet our usual standard of care.² Depending on the extent of the catastrophe, there may be an inadequate number of trained personnel available to deliver effective care. Individuals unfamiliar with the OR environment would have to be recruited to assist with resuscitative efforts. Most often there is no preoperative assessment available, as is the case with many trauma patients. The sheer size of the event may exhaust local supplies of intravenous fluids, blood, blood products, drugs, and other OR supplies.

Personal protection is also essential if we are to continue to be effective in caring for the critically ill during the crisis. Patients may need to be decontaminated or isolated and hospital personnel may need to don "spacesuits" (collective protective ensemble [CPE]) while providing care. Challenges inherent to working with limited-vision visors, clumsy suits, and thick-gloved hands will delay most routine tasks until one becomes accustomed to these handicaps.

The Perioperative Physician

The triage, movement, and decontamination of the bioterrorism victim are unfamiliar tasks for most anesthesiologists. However, given the breadth of our specialty and our role as perioperative physicians, anesthesiologists are uniquely qualified to assist this type of patient throughout the continuum of care. The anesthesiologist should be involved from the beginning along with emergency medical services personnel, emergency medicine physicians, surgeons, and infectious disease specialists in preparedness plans for mass casualty situations.

Once victims are brought to the hospital the preoperative assessment should focus on physical injuries, type and severity of exposure, and any antidotal therapy received in the field. Drugs such as pyridoxime and antimuscarinics used as antidotes or therapy for the complications of nerve agents directly affect anesthesia care in the OR and the need for mechanical ventilation. Although the patient could present in no distress, delayed effects of certain agents include pulmonary edema, bronchospasm, and increased shunting, any of which could adversely affect outcome if they are unanticipated. This assessment is crucial because adverse events might not herald themselves for several hours after the initial exposure and because preemptive treatment could save lives.

Delivering anesthesia in the OR or placing patients on mechanical ventilators could present unique challenges. Victims with ventilation/perfusion mismatches causing severe hypoxemia and those with excessive secretions will be difficult to ventilate and will have altered uptake of inhalation anesthetics. Those exposed to nerve agents will have altered responses to both depolarizing and nondepolarizing muscle relaxants. In some cases, excessive doses may be required to intubate a patient, while others may have an extended duration of paralysis requiring prolonged postoperative intubation.

If there is no physically traumatic injury associated with the event, patients will bypass the OR and be admitted to the intensive care unit. In this setting, the challenges are altogether different. Understanding the offending agent's effects and time course is imperative. Potential toxicities including burns, volume depletion, electrolyte disturbances, and muscle weakness will manifest at different times.

One of the most important aspects of being a successful perioperative physician under these circumstances is knowing how to protect yourself from exposure, so that you remain able to adequately treat the victims. Anesthesia and critical care personnel are at increased risk for blood-borne infections, direct contact with pathogens, and inhalation exposures. These practitioners should become familiar with preventive, isolation, and decontamination techniques so they can prevent secondary exposures to patients and themselves.

Anesthesia in Austere Environments

Most anesthesiologists envision themselves providing assistance to victims of mass traumas in the emergency department, the intensive care unit, or the ever-familiar OR. It is increasingly likely that we will find ourselves asked to deliver care at the site of a disaster should a large-scale terror event occur. Moreover, the health care facilities in which we are used to working may themselves be the target of a future terrorist attack. Power outages, flooding, and collapsing

physical structures may make it impossible to deliver care from our well-known and comfortable environment. Anesthesia providers will then be without many of the resources they have come to rely on, which could then make delivering expert care very challenging.

Many anesthesia departments are beginning to use simulation as a tool to teach situational awareness, communication skills, and crisis management in the OR. Anesthesia Crisis Resource Management (ACRM) should be further developed to train personnel how to respond in an austere environment should another terrorist event take place.

Categories of Biological Agents

Sadly, there are a multitude of agents readily available to be used in a terrorist attack against defenseless people. Properties of these ideal infectious biological weapons are outlined in Table 1. Based on recommendations from a group of national experts, the Centers for Disease Control (CDC) simply categorize agents as Category A, B, or C. This rating takes into account the ease of dissemination or transmission. Agents with a high infectivity and high mortality (e.g., smallpox) have the highest priority rating and are grouped in Category A. This grading also accounts for the potential impact on public health resources such as agents with a high morbidity and lower mortality (e.g., *Salmonella*). Finally, the potential for public panic and social disruption are also considered (such as an innocuous gas plume in the subway).

Table 1. Properties of an Ideal Biological Weapon

- Easy to produce in large quantities
- Readily transported and disseminated
- Inexpensive
- Highly infectious and contagious resulting in rapid person-to-person dissemination
- Causes widespread severe morbidity and mortality
- Lacks natural immunity
- Odorless and tasteless
- Survives drying and aerosolization
- Places significant demands on public health and governmental resources
- Results in panic and social disruption

Adapted from Coursin DB, Ketzler JT, Kumar AK, Maki DG. Bioterrorism may overwhelm medical resources new and different patient safety challenges must be anticipated. *Anesthesia Patient Safety Foundation Newsletter* 2002; 17(1):4.

The agents of greatest concern are listed in Table 2. Other articles in this issue address these substances or organisms in detail. Many of the bioagents are designed to incapacitate the respiratory system. Nerve gases and toxins are good examples of lung-affecting weapons. It is important to recognize that the hospital's ventilator and oxygen supplies will become exhausted quickly. Moreover, victims presenting to the OR for coincidental trauma will also experience a protracted hospital course. Re-use of cleaned masks and even endotracheal tubes should be part of one's emergency plan.

Pharmaceuticals are likely to be exhausted quickly if mass casualties present to every hospital in a community. One must consider alternatives to propofol, Pentothal, midazolam, diazepam, all opioids, antimuscarinics, and pressor agents. Consider that nerve gas victims in the Iran-Iraq war needed as much as 200 mg of atropine to treat prolonged bradycardia

and cardiovascular collapse! For the anesthesiologist faced with intubation, one may encounter excessive salivary secretions and sustained hypoxemia due to marked pulmonary bronchial and vasoconstriction. Thus, intubation with the inability to adequately ventilate should be anticipated. Barotrauma is likely to occur due to excessively high peak pressure, which will be needed.

Table 2. Agents of Greatest Concern

| | |
|---|---|
| Biologic Warfare | |
| Bacteria | <i>Bacillus anthracis</i> (anthrax) <i>Yersinia pestis</i> (plague) <i>Coxiella burnetii</i> (Q fever) <i>Francisella tularensis</i> (tularemia) <i>Brucella melitensis</i> (brucellosis) |
| Viruses | Variola major (smallpox) Viral encephalitis Viral hemorrhagic fevers (Ebola, Lassa, Marburg, Argentinean) |
| Toxins | <i>Clostridium botulinum</i> (botulism) <i>Staphylococcus aureus</i> enterotoxin B |
| Chemical Warfare | |
| Blister agents/mucosal irritants | (nitrogen/sulfur mustards, lewisite, phosgene-oxime) |
| Nerve agents/lethal | (tabun, sarin, soman, VX, Novichok) |
| Choking agents/respiratory irritants | (chlorine, phosgene, diphosgene, chloropierin) |
| Blood agents/block oxygen uptake | (hydrogen cyanide, cyanogen chloride) |
| Radiologic Warfare | |

Biopreparedness

The impact on our health system and our communities in the event of a terrorist-induced disaster may be cataclysmic. Doctors may be faced with massive casualties, limited stockpiles of supplies, few personnel, containment issues, personal protection, panic and irrational behavior, and the prospects of triaging otherwise viable victims. Currently, all municipalities are developing disaster plans to obviate some of these impediments. All physicians should incorporate some limited reading on this topic and have a folder with quick reference material readily available.

Several basic scenarios should alert health care professionals to the possibility of exposure to biological weapons. Single cases of unusual pathogens, the occurrence of a disease outside its natural geographic boundaries, a cluster of patients with suspicious clinical illness, an unusually high attack or mortality rate of a disease cluster, or an unusual age distribution of otherwise common diseases should alert physicians to the possibility of a biological weapons exposure.

In the early stages (hours) of a bioweapons attack, caregivers should be suspicious of acute outbreaks of severe respiratory, neuromuscular, dermatologic, gastrointestinal (diarrhea), and encephalopathic symptoms or signs. Moreover, one must be suspicious of atypical patients (under 50 years old, healthy) being afflicted with severe and unexpected acute

illnesses. Multiple cases presenting with similar symptoms and common syndromes outside the usual infectivity season (flu) are also worrisome.

The reporting mechanisms for the aforementioned events begin locally, but could quickly involve the federal government, depending on the scope of the disaster. The chain of events begins with contacting the local health department, which, in turn, will contact the state health department, which may then contact the necessary federal agencies.

Conclusions

Most anesthesiologists are poorly trained to deal with biological or chemical terrorism. There are four basic areas that departments can begin with to aid in improving preparedness for a disaster. First, good communication in a time of crisis is extremely important. Create a departmental telephone tree and keep it current. Make sure you have alternative ways to get in contact with your colleagues. It is also important to be able to contact other hospital departments after hours and to know how to communicate with local first responders, county, state, and federal agencies.

A frequently overlooked area is OR security. Is the OR area monitored, or can just anyone walk through? Does anyone know how the HVAC system works? It is important to know how to isolate the OR suite in case of an airborne disaster. Where are the intakes to the HVAC system located and how are they guarded? Are they under video surveillance? Most OR personnel do not know the answers to these critical questions.

A third area of importance is the hospital inventory. It is just as important to have enough supplies on hand as it is to stock the correct supplies. Under lock-down conditions there are no deliveries, with the remote possibility of air-dropping supplies. In addition to knowing what you have on hand and how much of it is available, you must know where the supplies are kept. Those supplies must also be accessible after hours.

Finally, it is important to run routine drills so that all necessary actions become second nature to the people involved. These drills should be reviewed and critiqued similar to the ACRM model. Staff should also be trained in ACLS/ATLS and know how to treat the most likely threats that will be presented.

Together, these steps will provide a good foundation in preparing the anesthesiologist to meet the challenge presented to us by bioterrorism.

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Chemical Terrorism Response and the Anesthesiologist: Conventional Agents, Emerging Threats, and Management Principles

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Learning Objectives:

1. To review the history and current threat level posed by traditional chemical weapons and consider new emerging threats (combination threats, industrial agents).
2. To review basic principles of disaster response.
3. To review the pharmacology of the nerve agents with special consideration to the role of anesthesiologists and intensivists in the management of toxic exposure casualties.
4. To review the toxicity and basic management principles pertaining to pulmonary agents and vesicants, cyanide and asphyxiants, riot agents, and domestic industrial compounds.
5. To understand that the basic principles of disaster response to a chemical-related mass casualty event remain the basic elements of life support (airway management, cardiovascular and cardiopulmonary support, resuscitation from shock) and specific antidotes where available and where indicated.

Abstract

The threat of domestic deployment of weapons of mass destruction, or chemical terrorism, has never been so great, nor the stakes so high, as it is today. Education, training, rehearsal, and the development of a coordinated response network are required if an effective response is to be made to war, terrorist threat or attack, industrial catastrophes, or natural disasters. The principles of critical care medical management are grounded in basic biochemistry, anatomy, physiology, and pharmacology. Physicians, especially anesthesiologists, are therefore already familiar with the mechanics of triage, resuscitation, and life support. The appropriate and specialized training in disaster response should enable physicians to provide the highest quality medical care under the most adverse circumstances.

Key Words: anesthesiology, ARDS, chemical warfare, cyanide, disaster preparedness, industrial toxins, nerve agents, terrorism, vesicants

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A Brief History of Chemical Weapons

Chemicals agents have been used as weapons throughout recorded history. The discovery of many of these toxic substances was incidental and predated their actual applications in warfare. Only in more recent history have compounds been specifically designed with the strategic intent of weaponization. For example, the Chinese are thought to have used arsenic smoke against invading enemy armies as early as 1000 BC, and historical records show that Greeks used hellebore root to poison the drinking water of their enemies in approximately 600 BC. A Swedish civilian chemist, Carl Scheele, is credited with the discovery of both chlorine gas in 1774 and hydrogen cyanide in 1782. The Germans, however, were the first to weaponize toxic gases and deploy them successfully and effectively in the modern battlefield, at Ypres in 1915 during World War I (WWI). Sulfur mustard was first used on the battlefield by the Germans in 1917 and is estimated to have been responsible for 80% of the casualties of WWI. Thereafter, it is estimated that more than 90,000 deaths are attributable to the use of chemical warfare during WWI alone, and a great number of survivors who had been exposed to mustard gas were left permanently disabled. Later, Italian armies used mustard gas during the Ethiopian conflict in 1935 and the Egyptians used phosgene and mustard gas in the Yemeni Civil War. The Germans were also the first to synthesize nerve gases, the G agents, specifically tabun (GA), in 1936. Sarin (GB) and soman (GD) were synthesized in 1944. These agents were allegedly first developed as insecticides. However, the V (venomous) class of nerve agents was first developed in the United Kingdom in 1952. More recently, chemical agents have been deployed against civilians in the Iraqi-Kurdish conflicts of the 1980s, against passengers on the Tokyo subway system by the Aum Shinrikyo cult in March 1995,¹ and against Chechnyan rebels in a crowded Moscow theater by Russian authorities in October 2002.

The exact quantities and locations of stockpiles of chemical agents in the world remain largely speculative. Aging chemical weapons stockpiles of unknown effectiveness likely exist throughout the former Soviet Union and in areas of the Middle and Far East. At least 40 countries are thought to possess chemical weapons at the present time. However, these weapons, unlike bacteriological agents or nuclear weapons, are relatively easy to manufacture or acquire, and therefore probably exist in large volume. Additional strategic considerations include deployment of new compounds and combination threats (chemical with biological or radioactive agents). For example, the aerosolized fentanyl deployed in Moscow was a new application of a standard opiate narcotic.

Overview of the Modern Chemical Weapons Threat

Technology and intelligence, which make it possible for military personnel to anticipate and rapidly detect chemical attacks and subsequently deploy protective gear and administer effective antidotes, have somewhat diminished the battlefield utility of chemical warfare. However, as global geopolitics is increasingly shaped by undeclared conflicts and organized and unorganized terrorist activity, the use of chemical weapons against unsuspecting and unprotected civilian populations is a clear and credible threat. In a post-9/11 world, the threat of a strategically engineered chemical incident is escalating. The question is not *if* chemical weapons

are likely to be used against the civilian populations of developed nations, the questions are *when* and *where* these weapons will be used. Therefore, public and provider education and preparedness are necessary and essential components of our public health system. Situational awareness and vigilance increase the likelihood of early recognition and detection of a chemical incident. An effective preparedness plan also increases the likelihood that appropriate administrative and medical countermeasures will be deployed; preparation and planning will help to minimize civilian casualties and death.

Chemical agents are highly effective weapons of mass destruction because, like biological agents, they 1) are insidious and difficult to detect, 2) have a lag time between their release and their effect, 3) may have a time lag between exposure and maximal effect, 4) minimize damage to physical infrastructure (buildings, weapons, vehicles), 5) have relatively high dissemination potential, and 6) do not cause permanent contamination of land and structures. Their use incites fear, mass panic, and lasting psychological and social trauma.² Chemical agents are extremely potent, and the casualty rate per volume of agent deployed can be very high. It is estimated that a microdrop of sarin nerve agent released on a commercial jetliner will spread rapidly through the closed space and cause the death of passengers and crew within minutes. The 1995 sarin nerve gas release in the Tokyo subway further demonstrated the lethality of a small volume of agent released in an open but crowded civilian environment; although there were relatively few deaths, more than 5,000 persons were injured.^{3,4}

Chemical agents are especially attractive as terrorist weapons for three reasons: 1) they are easy and inexpensive to manufacture, 2) unlike biological agents they are more easily weaponized and safely deployed, and 3) a great number of dangerous and toxic agents are used domestically and may be indirectly weaponized through diversion or sabotage. Therefore, the concept of a potential chemical attack must be expanded to include not only the traditional chemical warfare agents but a plethora of domestic, commercial, industrial chemical compounds. For example, cyanide, chlorine, hydrofluoric acid, and organophosphate pesticides are often manufactured, stored, or transported through urban areas. A mass chemical civilian casualty incident is probably more likely to occur as a result of an explosion of stored chemicals, a train derailment, or a tanker-truck crash than from conventional chemical warfare agent deployment. The accidental release of methylisocyanate from a Union Carbide chemical plant in Bhopal, India, in December 1984 exemplifies the devastating nature of industrial toxins inadvertently released near populated areas. Furthermore, notions of a chemical weapons attack scenario must be expanded from the traditional "toxic cloud" to include potential attacks on the agricultural and livestock farming system, pharmaceuticals, contamination of industrial compounds, and the integrity of the nation's food and water supply.

Civilian health care providers have not generally been well trained in disaster preparedness or military medicine and they generally lack detailed knowledge about chemical and biological warfare agents and response; additionally, they are inexperienced in the use of protective gear, principles of containment, decontamination, and organizational management. However, a new heightened awareness and accessible educational programs are slowly increasing the readiness of the US civilian health care system for disaster response. The strategy to increase the readiness and

effectiveness of the civilian health care network must be both systematic and system-wide.⁵ A heightened index of suspicion and a foundation of medical theory and knowledge is essential; an effective response requires extensive local, regional, and national coordination of personnel and physical resources.

Rapid and aggressive response is essential to minimize loss of life during chemical attack. However, acute emergency and critical care resources in almost any American urban area are likely to be rapidly overwhelmed by a mass casualty incident. Most emergency departments and intensive care units already operate at or near capacity and are unlikely to be able to handle a sudden influx of critically ill patients. Moreover, some population segments such as the old, the very young, and the infirm are likely to be affected disproportionately in a disaster.^{6,7} Triage principles and rationing decisions must guide the optimal utilization of scarce resources in emergency situations. It is also obvious that the initial hospital response will require the capability to provide critical care services outside the physical confines of the intensive care unit (ICU). Initially this will include all acute care areas and, later, any available bed space with portable monitoring and life support technology.

Among civilian health care providers, anesthesiologists and intensivists are especially well trained to treat victims of chemical warfare because they 1) understand and routinely apply the physiology and pharmacology of cholinergic nicotinic and muscarinic receptors through their daily clinical use of neuromuscular blocking drugs and reversal agents, 2) understand the pharmacodynamics and pharmacokinetics of both toxins and antidotes, 3) are very knowledgeable regarding the pharmacology of benzodiazepines, and 4) are experts in airway management, oxygen-delivery dynamics, cardiopulmonary monitoring, and advanced life-support technology. Moreover, although anesthesiologists are especially and uniquely qualified to provide immediate life support to victims of chemical attacks, they are also very likely to be called on to provide surgical anesthesia to survivors of chemical exposure who have been otherwise injured.

General Principles of Chemical Incident Containment and Disaster Response

The "hot zone," or immediate isolation zone, is the area of immediate contamination in a chemical incident. Access into a hot zone requires special training, protective gear and equipment, and antidote availability. The type of protective gear required depends on the nature of the agent released. Pulmonary agents may require only a "gas mask," vesicants require protective clothing as well as masks, and nerve agents require impermeable gear and masks. Many agents can easily pass through latex gloves. It is imperative that once a hot zone is identified, it is immediately physically isolated and access is absolutely restricted to avoid additional casualties.

The hot zone is rarely a static location. Chemical agents are likely to continue to spread following their release. The area downwind of a release site is an at-risk area or a protective-action zone, which is potentially vulnerable to exposure and contamination, but is also amenable to evacuation. The dispersion dynamics of vaporized chemical agents are such that downwind is rarely a straight line; it is much more likely to be characterized as an expanding plume. Furthermore, since wind direction can change, and there may be unpredictable local vortices, the spread of gases in the

atmosphere is extremely unpredictable. Gases also spread differently in the atmosphere during the day and the night. Humidity will affect the spread and toxicity of many chemical agents; the vesicants notoriously are more effective in humid conditions. Therefore, the prevailing and anticipated meteorological conditions, the surrounding population concentrations, the specific agent and the amount released, and potential evacuation routes are important factors in decisions to either evacuate or shelter in place.⁸ The hot zone is always approached from upwind, and the area upwind is also the closest immediately available, potential evacuation, triage, and treatment area, with the caveat that it is vulnerable to environmental conditions.

Before persons or material leave the hot zone, they must be decontaminated by dilution or neutralization. Gases may rapidly dissipate and dilute within the atmosphere; therefore, less rigorous decontamination is necessary in those instances where dense liquid or oily agents are used. However, medical staff can still be contaminated by the slow release of gas from clothing, especially where there was dense exposure or in areas where there are many exposed casualties. Where liquid or aerosol agents have been deployed, a secondary decontamination of medical staff and equipment, such as stretchers and monitors, must be accomplished by removal of any residual agent either physically or by chemical neutralization. Copious irrigation with water or 1–2% sodium hypochlorite solution is used to dilute and remove any residual agent. Notably, precautions must be taken for proper disposal of the decontamination effluent, which is often heavily and dangerously contaminated with chemical agent.

The indicators of nerve gas release will resemble the consequences of other weapons of mass destruction; there will be many acute casualties with similar symptoms. Additionally, there may be a suspicious dispersal device, unexplained gaseous clouds, vapors, or odors; incapacitated persons; or an absence of animal, bird, or insect life. Alternatively, there may be definitive intelligence based on threats or reports, or agent detection or identification by remote or point-of-use chemical detectors.

Medical staff will rarely coordinate operations at a hot zone. The efforts of untrained personnel to direct operations will increase the casualty rate and greatly decrease the effectiveness of the response effort. Medical personnel should focus their efforts on medical care. Immediate medical considerations include triage, antidote administration where indicated, airway management and hemodynamic support, management of secondary injuries, and patient identification and evacuation.⁹ Plenary administrative considerations include communications, defining a command center, collecting evidence, and making an inventory of all important resources such as available hospital beds, medications, monitors, and life-support equipment. Local supplies of drugs with relatively rare clinical uses such as amyl nitrite, pralidoxime chloride (2-PAM), and thiosulfate are likely to become rapidly scarce and unavailable; supplies of drugs such as atropine will be rapidly exhausted in a mass casualty event because of the unusually large doses required and the large number of people potentially affected.

In addition to victims with toxic exposure, casualties will include persons who sustain injuries resulting from falls, blunt trauma, motor vehicle crashes, and burns and those who develop acute exacerbations of preexisting co-morbidities such as chronic lung disease and myocardial ischemia. These patients will need to be treated according to established medical principles including the standard ABCDs of acute

care. The basic principles of anesthesia care, such as airway management in “full stomach” trauma patients,¹⁰ do not materially differ from the usual management of other perioperative patients.¹¹ Moreover, the principles of mechanical ventilatory support and management of acute respiratory distress syndrome (ARDS), principles of vascular access and hemodynamic monitoring, and pharmacologic management of shock are the same as those used in the care of other critically ill patients.

Chemical Weapons:

Classification of Chemical Warfare Agents

Chemical agents are most frequently classified on the basis of how they cause incapacitation. Thus, the most common military chemical agents fall into one of the following categories: nerve agents, pulmonary irritants, “blister agents” or vesicants, cyanide, and other asphyxiants. Biochemical toxins such as ricin, which is derived from the castor bean plant (*Ricinus communis*), botulinum toxin (or “Botox”) isolated from the anaerobe *Clostridium botulinum*, and staphylococcal enterotoxin B isolated from *Staphylococcus aureus* are examples of plant and animal byproducts that can be isolated or manufactured in large quantities; these will not be discussed here. In addition, there are a large variety of incapacitating and riot-control agents, such as “tear gases” and other generally unclassified agents. Finally, there are a large number of chemically diverse industrial toxins that must be considered in any discussion of disaster preparedness and terrorist response.

Nerve Agents. The nerve agents are synthetic organophosphate compounds,¹² esters of phosphoric acid, chemically similar to the insecticides malathion, parathion, and mevinphos. Nerve agents are considered to be the most dangerous of all chemical weapons and among the most lethal synthetic compounds known to mankind. For example, hydrogen cyanide is approximately 500 times less potent than VX gas. The important nerve agents are tabun, sarin, soman, GF, and VX.¹³ These organophosphate derivatives (Table 1) inhibit the enzyme acetylcholinesterase (AChE) by irreversible covalent phosphorylation of the enzyme’s esteratic site. The nerve agents thereby cause a buildup of acetylcholine in the synaptic clefts and precipitate parasympathetic, sympathetic, and neuromuscular (somatic) hyperactivity.

Table 1. Nerve Agents

| Agent | Symbol | Odor | LC ₅₀ mg-min/m ³ | LD ₅₀ mg | Vapor Pressure mm Hg at 20°C |
|-------|--------|---------------------|---|------------------------|---------------------------------|
| Sarin | GB | None | 100 | 1700 | 2.1 |
| Soman | GD | Fruity ^a | 50 | 350 | 0.40 |
| Tabun | GA | Fruity ^a | 400 | 1000 | 0.037 |
| VX | VX | None | 10 | 6–10 | 0.0007 |

LC₅₀: the product of concentration and time that will cause death in 50% of the exposed population. LD₅₀: the percutaneous dose that will cause death in 50% of the exposed population

^aThe odors of these gases are not characteristic.

Acetylcholine is the neurotransmitter for the parasympathetic nervous system, the sympathetic ganglia, the adrenal medulla, sweat glands, somatic nerves, innervating muscle, and areas in the central nervous system. Cholinergic receptors are divided into muscarinic receptors, which are found at bronchial smooth muscle, at the sinoatrial node of the heart, and in salivary glands, and nicotinic receptors found in autonomic ganglia and skeletal muscle (Table 2). Thus, in some ways these compounds have actions similar, but not identical, to anesthetic drugs such as succinylcholine (a depolarizing neuromuscular blocking agent) and AChE inhibitors routinely used to reverse nondepolarizing neuromuscular blockade (such as edrophonium or neostigmine).

Nerve agents are classified as either V agents (primarily VX) or G agents, which include tabun (GA), sarin (GB), and soman (GD). The V agents are sulfur-containing organophosphates that are less volatile, more persistent, and more likely to exist in liquid form following deployment. On the other hand, the G agents are fluorinated cyanide-containing organophosphates that are generally colorless and odorless liquids whose vapors are heavier than air so they tend to settle nearer the ground; they exist in mainly gaseous form.

Nerve agents can be inhaled or absorbed percutaneously; they can be ingested, but this type of exposure is rare. Therefore, nerve agents are also classified on the basis of their volatility into nonpersistent (G) agents that vaporize more rapidly and are absorbed primarily through the lungs but also dissipate rapidly, and the less volatile agents (VX) that typically persist as oily droplets and are primarily absorbed percutaneously. The persistent oily agents generally have a longer latency before causing symptoms than do the volatile agents. Agents that are inhaled usually manifest symptoms of cardiopulmonary muscarinic toxicity first. On the other hand, agents absorbed via dermal exposure have a more gradual progression of symptoms beginning with neuromuscular nicotinic toxicity. The timing of onset, the sequence, and the severity of clinical signs and symptoms of nerve agent exposure are variable but depend on the dosage (concentration and duration [time] of inhalation exposure); this is referred to as the Ct.¹⁴ Therefore, exposed persons may manifest only a single symptom such as miosis and die within minutes, or they may be asymptomatic for up to 18 hours, and perhaps longer. In survivors, a complete recovery can take several months. In cases of exposure to a massive droplet aerosol or a concentrated gaseous vapor, survival depends on aggressive and antidote-specific interventions being initiated almost immediately.

Typically, the common signs of nerve agent exposure are miosis, rhinorrhea, salivation, bronchoconstriction and bronchorrhea, nausea and vomiting, diaphoresis, bradycardia with possible tachyarrhythmia, hypertension, loss of consciousness, convulsions, muscular fasciculations, and flaccid paralysis.¹⁵

The primary cause of death from nerve agents is usually respiratory failure resulting from muscle weakness or alveolar flooding. Alveolar flooding with secretions is similar to pulmonary edema or ARDS, which manifests by rapidly progressive and refractory hypoxemia. The bronchorrhea is precipitated by muscarinic autonomic hyperactivity.¹⁶ With alveolar flooding there is a progressive widening of the alveolar-arteriolar (A-a) gradient and an increased physiologic shunt fraction, with diminished oxygen delivery

Table 2. Clinical Signs and Symptoms of Exposure to Nerve Agents

Muscarinic

Pinpoint pupils: miosis
Blurred vision
Rhinorrhea
Headache
Salivation, lacrimation
Diaphoresis
Bradycardia
Abdominal cramps: nausea and vomiting
Bowel and bladder incontinence
Dyspnea and bronchospasm
Productive cough
Pulmonary edema and respiratory distress

Nicotinic

Hypertension
Tachycardia
Muscle fasciculations
Weakness
Flaccid paralysis

CNS

Seizures
Central respiratory depression
Apnea
Irritability
Coma

causing tissue hypoxia. Therefore, the airway must be immediately secured and positive airway pressure applied early. In situations where the patient is not profoundly hypovolemic and will tolerate the increased intrathoracic pressure associated with high alveolar pressures, the early application of positive end-expiratory pressure (PEEP) is helpful to improve oxygenation.

Cardiovascular abnormalities resulting from exposure to nerve agents include alterations in cardiac rate, rhythm, and conduction, which are aggravated by underlying cardiac disease, hyperkalemia, respiratory or metabolic acidosis, hypoxia, as well as the administration of antidotes such as 2-PAM. The initial response is cardiovascular overstimulation with hypertension and tachycardia resulting from a sympathetic discharge. Coronary vasospasm during this time is common and may be due directly to the nerve agent effect on coronary arteries, to a sympathetic-induced coronary vasospasm, or to rate-related ischemia. The second phase of cardiovascular instability manifests as severe cardiovascular depression with bradycardia and hypotension related to a predominant cardiodepressive muscarinic tone. Vasopressors and inotropes may be necessary to treat life-threatening hypotension and bradycardia during this period of shock.

The specific antidotes for nerve agents are anticholinergic medications that antagonize the effect of acetylcholine at the neuronal synapses (Table 3). Atropine, a tertiary amine and a potent muscarinic receptor antagonist, crosses the blood-brain barrier and inhibits peripheral autonomic transmission as well as central cholinergic transmission.¹⁷ The dose of atropine is not absolute and is titrated to the point where airway secretions and hypoxemia are controlled. Since atropine has short plasma half-life, it will need to be

Table 3. Treatment of Exposure to Nerve Agents (Adults)

| | |
|--------------------------------|--|
| Atropine | 1–2 mg IV or IM every 2–20 min, titrated to airway secretion management and oxygenation. Total dose may reach 5–15 mg. Pediatric dose: 0.02–0.10 mg/kg |
| Scopolamine | 0.25 mg IM, repeat in 30 min if needed; then 0.25 mg IM every 4–6 hr |
| 2-PAM | 15–25 mg/kg IV (1–2 g IV) over 30–40 min and 200–500 mg/hr infusion if needed. Alternatively, 600 mg IM or 5 g po. Pediatric dose 15–25 mg/kg IM. |
| Diazepam (Valium) | 5–10 mg IV/IM every 5–20 min titrated to seizure cessation. |
| Midazolam | 2–20 mg IV/IM. Titrate to effect. Alternatively, 0.5 mg/kg po. |
| Topicainamide eye drops | 1–2 gtt 0.5% solution, may repeat in 5 min |

readministered every few hours, and the total dose per day can reach 20–50 mg in adults. The pediatric dose of atropine is 0.02–0.10 mg/kg, which represents only an approximation, with the caveat that children can easily become hyperthermic and dehydrated in response to atropine administration. Hyperthermia will consequently increase the metabolic rate, may precipitate rhabdomyolysis, and can worsen the outcome from seizures, if they are present. Neither mydriasis nor tachycardia is a reliable indicator of adequate atropine administration. Glycopyrrolate, a quaternary amine, does not cross the blood–brain barrier; however, it weakly antagonizes cholinergic effects at peripheral nervous system muscarinic synapses and is a potent antisialagogue.

Central cholinergic crisis precipitates seizures, which need to be treated immediately with anticonvulsants such as benzodiazepines or barbiturates. It is unlikely that patients in shock will tolerate the cardiovascular depressive effects of diphenylhydantoin; therefore, the use of diazepam or midazolam to terminate seizures is favored.¹⁸ Midazolam may have neuroprotective effects in addition to its anticonvulsant effects and may in fact be the preferred benzodiazepine for the control of seizures.¹⁹ Whenever benzodiazepines or barbiturates are administered rapidly and in large doses in order to terminate seizures, the availability of definitive and immediate airway support is necessary, especially in these unstable patients. Scopolamine is a relatively weak anticholinergic agent and should not be used except as a last resort for its peripheral muscarinic antagonist effects; however, scopolamine has important synergistic central anticonvulsant effects.²⁰

Nerve agents also cause a failure of neuromuscular transmission and paralysis because of somatic cholinergic hyperactivity at nicotinic cholinergic synapses. Oximes are nucleophilic substances that reactivate AChE by cleaving the

organophosphoryl moiety. The oxime of choice in the United States is 2-PAM, the most effective antidote to progressive neuromuscular paralysis.²¹ If administered before “aging” occurs after exposure, 2-PAM can reactivate AChE by competitively uncoupling the phosphorylation reaction between the organophosphate compounds and AChE. Aging is that process whereby nerve agents become bound covalently and irreversibly to the AChE molecule. The time for somatic aging is approximately 2 minutes for soman but 5 hours for sarin. The dose of 2-PAM is likewise somewhat empirical and is frequently limited by hypotension,²² but the consensus is that it should be administered as soon as possible.

Most patients who were exposed to nerve agent will require adjunctive therapy: a secure airway and positive-pressure ventilation, aggressive suctioning of bronchial secretions, beta-2 agonists to treat bronchospasm, and inotropic and vasopressor support.²³

Pyridostigmine, in a dose of 30 mg by mouth, is not an antidote to nerve agent exposure but is commonly used prophylactically. Although the mechanism of action of pyridostigmine is similar to that of the nerve agents, it *only reversibly* binds to AChE, and thereby competitively prevents the irreversible binding of nerve agents to the active enzymatic site of the AChE molecule.²⁴ The use of pyridostigmine as a prophylactic agent is limited by its short half-life; it must be taken orally three times a day. Pyridostigmine also has systemic side effects similar to those of the nerve agents. Furthermore, it is hypothesized that pyridostigmine is a possible cause of Gulf War syndrome. Theoretically, pyridostigmine may cause a partial enzymatic blockade at the synaptic cleft and may locally increase the concentration of acetylcholine; this would result in transient muscarinic and nicotinic overstimulation.²⁵ The symptoms of hypercholinergic syndrome include weakness, diarrhea, nausea, restlessness, and hallucinations. However, paradoxically, pyridostigmine is a quaternary amine, does not cross the blood–brain barrier well, and therefore has limited prophylactic effect against the effects of nerve agents on the central nervous system.

In response to any incident in which nerve agents may have been released, only personnel trained in the use of protective gear such as mission-oriented, protective posture (MOPP) suits and positive-pressure, self-contained breathing apparatus (SCBA) should approach the hot zone. Latex gloves are completely ineffective as barriers to nerve agents. Health care providers receiving exposed victims who have not been decontaminated adequately are likely to become exposed to the agent themselves, either in the form of oil and liquid residue on clothes or skin, which will remain bioactive, or as vapor. However, it is important to realize that in an emergency, exposure to nerve agent *vapors* only does not require complete decontamination prior to initiating treatment. On the other hand, following exposure to liquid aerosol, frank liquid, or oils, therapy can be rendered safely only by personnel in full protective gear (MOPP 4). For the nonvolatile agents, immediate removal of contaminated clothing (with precautions) and dilution of any residual agent with large quantities of cool water are usually effective. On a cautionary note, vigorous scrubbing, hot water, and hypochlorite solution will cause cutaneous vasodilation and thereby increase absorption of the toxins.

Anesthetic Considerations in Patients Exposed to Nerve Agents. There are three primary issues regarding the anesthetic care of patients who have been exposed to nerve agents. First, the use of a depolarizing muscle relaxant such as succinylcholine for emergency intubation and airway

management is controversial.^{26,27} However, at least theoretically, it should probably be avoided because of an already hyperactive, stimulated, postsynaptic membrane.²⁸ In individuals in whom recent nerve agent exposure has caused muscular fasciculations, severe hyperkalemia related to extracellular release of intracellular potassium is a consideration. Hyperkalemia is further potentiated by metabolic or respiratory acidosis. Conversely, postsynaptic muscle membranes that have been fully depolarized by a cholinergic excess are likely to be completely resistant to succinylcholine; patients in such situations will be spasmodic and rigid. Prior treatment with 2-PAM and pyridostigmine may alter nicotinic receptor pharmacology unpredictably.²⁹ The use of neostigmine or edrophonium to reverse neuromuscular blockade at the conclusion of surgery is also controversial.³⁰ Since these agents are likely to worsen the muscarinic side effects of nerve agents, it is best to avoid them whenever possible.

A second consideration for anesthesia in the setting of exposure to a nerve agent is cardiovascular instability. The autonomic instability typically caused by anesthetic agents will be further compounded by the disrupted sympathetic–parasympathetic balance in the setting of nerve agent intoxication. Such instability is likely to be further exaggerated if there is concomitant therapy with pyridostigmine or 2-PAM. Therefore, anesthesia should be induced with agents least likely to exacerbate cardiovascular depression. Barbiturates and propofol are profound cardiovascular depressants; etomidate, fentanyl, and ketamine are better choices. However, ketamine increases salivary and airway secretions and may therefore be relatively contraindicated. Prolongation of the cardiac QTc interval increases mortality almost fourfold, mainly from lethal arrhythmias.³¹ Adjunctive medications that increase the QTc interval even further (such as droperidol and haloperidol) must be avoided.

A third important consideration, especially with the nonvolatile nerve agents, is that any break in the integrity of the skin increases the potential for more rapid absorption of any residual nerve agent.

Pulmonary Agents and Vesicants. The pulmonary irritant agents cause incapacitation and death by producing acute airway injury, laryngospasm and bronchospasm, interstitial and pulmonary edema, and systemic hypoxemia and tissue hypoxia (Table 3). These agents are absorbed by inhalation and their effect is dose related. The primary agents in this class are phosgene, diphosgene, chlorine, chloropicrin, ammonia, and also the heavy metal gases such as zinc oxide, phosphorus, and titanium tetrachloride. These agents are especially important because they are commonly used in the chemical industry and are commercially available – the United States produces over a billion pounds of phosgene, chlorine, and ammonia each year. Insidiously, because of exposure to home cleaning solutions and swimming pools, many people have become desensitized to the odor of chlorine gas and cannot detect its presence except in large concentrations.

Phosgene and chlorine are denser than air and thus settle near the ground, and they do not dissipate easily; therefore, unprotected persons are likely to have prolonged exposure to this agent. Since phosgene is water insoluble, it is inhaled deep into the lungs where it reacts with amino and thiol groups in cellular amino acids and causes a protein denaturation and similarly affects the polar head groups of pulmonary surfactant molecules.³² In addition, the vesicants are similar to chemotherapeutic agents in that they cause the alkylation of DNA, precipitating generalized protease

activation, tissue inflammation, and death. Since they inhibit DNA replication, they first injure the more rapidly dividing cells such as those in tissues such as marrow, epithelium, and endothelium; these agents are also therefore highly teratogenic.

The characteristic pulmonary toxicity of phosgene and chlorine gas manifests as an acute lung injury that rapidly progresses to ARDS and refractory hypoxemia.³³ The toxicity of phosgene and chlorine is enhanced by their electrophilic nature, which enables them to react with nucleophiles to form hydrochloric and other acids, adducts, and free radicals, which further worsen lung injury, and cause epithelial injury and airway necrosis.³⁴ Free-radical generation perpetuates the inflammatory cascade. Phosgene and chlorine decontamination with copious water must be followed immediately by standard supportive respiratory therapy aimed at improving oxygenation and minimizing further lung injury.³⁵ Mechanical ventilation with PEEP and employing a lung-protective mechanical ventilation strategy improves patient survival.

The vesicant agents, the mustards, and lewisite are characterized as gases or liquid aerosols that have extreme cutaneous persistence (Table 4). Once they contact the epithelium, they cause severe burns and necrotic sloughing of the skin, severe corneal injury and acute blindness, pancytopenia, and liver and kidney dysfunction.³⁶ The onset of symptoms following cutaneous exposure to lewisite occurs very rapidly, within 10–20 seconds after contact; thereafter, blistering follows within 5 minutes to 24 hours. Severe ocular damage with permanent corneal scarring may occur and cause both temporary and permanent blindness. Inhalational exposure is characterized by airway hyperreactivity, bronchospasm, bronchiectasis, necrotic sloughing of the pulmonary epithelium with pseudomembrane formation, airway obstruction, and eventual respiratory failure.³⁷ In survivors, the clinical picture is similar to that induced by pulmonary asphyxiants, i.e., acute and chronic bronchitis, pulmonary fibrosis, and bronchiolitis obliterans pneumonitis with severe long-term pulmonary damage. These agents are extremely irritating to tissues, are highly effective activators of cytokine-mediated inflammatory response syndrome, and produce a sepsis syndrome and shock. Mechanical ventilatory support is necessary in most patients.

Table 4. A Sampling of the Vesicant Agents

Mustards

Nitrogen mustards (HN-1, HN-2, HN-3)

Sulfur mustards (H, HD, HT)

Phosgene oxime (CX)

Lewisite (L)

Mustard-Lewisite (HL)

Vesicant exposure requires aggressive hazardous material decontamination with copious 0.5% hypochlorite solution, disinfection with povidone–iodine solution, systemic hydration and limitation of secondary end-organ injury, and mechanical ventilation when indicated. The effects of lewisite can be treated by rapid application of dimercaprol (2,3-dimercaptopropanol, British antilewisite [BAL]) to the skin or eyes. BAL reacts with lewisite to form a nontoxic substance; however, to prevent ocular injury, BAL must be applied within 2 minutes of exposure.

There is no specific antidote to the mustards, diphosgene, chlorine, chloropicrin, ammonia, zinc oxide, phosphorus, titanium tetrachloride, or phosgene. In patients with very large skin blisters, supportive burn-care protocols may be necessary, including irrigation, debridement, topical antibiotics, petroleum jelly, and pain relief. Morbidity and mortality following exposure to the pulmonary agents are usually caused by acute respiratory failure, secondary bacterial pneumonia, mechanical obstruction from airway edema or necrosis, and hypoxemia. Therefore, treatment is based on rapid decontamination and subsequent supportive pulmonary management. Bronchodilator and steroids may be necessary to treat bronchospasm. When steroids are used, an acceptable starting regimen is methylprednisolone, 1 mg/kg intravenously (IV) every 8 hours followed by a gradual taper, or transition to prednisone as needed. Nebulized sodium bicarbonate may have therapeutic potential after low-level chlorine gas exposure but should not be used in patients with large-dose inhalation exposures because the exothermic reaction of acid-base neutralization can burn the airway epithelium.³⁸ If sodium bicarbonate is used in an attempt to neutralize the effects of minor inhalational exposure, the bicarbonate can be administered via nebulizer or bronchoalveolar lavage. A reasonable nebulizer dose is 5 ml of 4.2% sodium bicarbonate solution prepared as 2.5 ml of standard 8.4% sodium bicarbonate solution diluted 1:1 with normal saline. In this fashion, the nebulized bicarbonate can be administered either by handheld nebulizer or by ventilator in-circuit nebulizer.

Bronchoalveolar lavage may be indicated immediately following exposure to remove both inhaled toxin and affected surface epithelium from the airways. This process may be used later to physically remove necrotic sloughed mucosa, which serves as a nidus for bacterial superinfection. The ability of patients to tolerate bronchoscopy and bronchoalveolar lavage may be limited in the setting of acute bronchospasm, pulmonary edema, and profound hypoxemia.

Experimentally, the systemic toxicity of vesicant and pulmonary agents has been treated successfully with anti-inflammatory agents and N-acetylcysteine. These agents are thought to limit oxidative and free-radical-induced oxidative stress by preserving intracellular thiol and glutathione concentration.

Cyanide. Cyanide is a domestically ubiquitous industrial agent, and toxic exposures are very common in residential fires as well as in industrial occupational settings. Exposure to cyanide can occur in its gaseous, solid, or dissolved forms. In its gaseous state, cyanide is colorless but has a characteristic odor of bitter almonds (which many people cannot detect). Cyanide gas is highly volatile and nonpersistent. Exposure is usually to either hydrogen cyanide, also known as hydrocyanic acid, or cyanogen chloride; the former is two to four times more toxic than the latter.

Cyanide is an asphyxiant. Following absorption, inhalation or ingestion, it is absorbed rapidly and diffuses quickly through tissues. The mechanism of cyanide action is the direct inhibition of the mitochondrial enzyme, cytochrome oxidase. Cytochrome oxidase inhibition uncouples oxidative phosphorylation, causing the effective cessation of tissue utilization of oxygen. Clinical manifestations of cyanide toxicity are dose dependent within very small differences in blood concentration; the dose-response curve is very steep. Following a large-dose exposure, hyperventilation occurs within 15 seconds, convulsions follow in another 15–30 seconds, apnea occurs within 2–3 minutes, and cardiac arrest occurs within 6–8 minutes. Smaller doses may have delayed

onset but may also be lethal.

The pathophysiology of cyanide toxicity is the precipitation of generalized cellular hypoxia, systemic lactic acidosis, and diffuse cell death. Rapidly progressive lactic acidosis ensues as oxygen extraction decreases and cells progress to anaerobic glycolysis. There is a decreased difference of arteriovenous oxygen partial pressures. The blood appears bright (“cherry”) red and fully oxygenated. The initial clinical signs of large-dose cyanide exposure are hyperpnea resulting from hypoxemia followed by loss of consciousness, apnea, cardiac arrest, and death. Cyanosis is a late sign. Exposure to lower doses of cyanide may cause only nonspecific symptoms such as hyperpnea, headache, generalized anxiety and central nervous system excitability, diaphoresis, mydriasis, arrhythmias, and emesis.³⁹

Decontamination is based on rapid evacuation, removal of contaminated clothing, and possibly gastric lavage and activated charcoal administration if the cyanide was ingested. General supportive measures include oxygen administration, control of seizures, and reversal of metabolic acidosis with IV bicarbonate; however, antidote therapy should not be delayed.⁴⁰

The specific treatment of cyanide poisoning⁴¹ is administration of sodium nitrite as either amyl nitrite, sodium nitrite, 4-dimethylaminophenol (4-DMAP), p-aminohexanoylphenone (PAHP), or (p-aminopropiophenone (PAPP), each of which causes the production of methemoglobin, which effectively binds cyanide to form cyanomethemoglobin.²⁰ Methemoglobin removes cyanide from the intracellular and extracellular fluid spaces and thereby limits concentration-dependent diffusion into the mitochondria, limiting the access of cyanide to its enzymatic site of action. Typically, amyl nitrate capsules are broken and inhaled for 30 seconds each minute, repeated every 3 minutes to administer treatment. These nitrate agents all cause significant peripheral vasodilation, flushing, and hypotension as side effects.

Intravenous sodium thiosulfate acts as a sulfur donor that specifically increases the clearance of cyanide as thiosulfate. Additionally, cobalt salts and hydroxycobalamin (vitamin B12) can be used to bind cyanide but are adjunctive, less effective therapies.

Incapacitating and Riot Control Agents. A large variety of agents have been used to produce temporary nonlethal incapacitation. These agents cause extreme discomfort through sensory stimulation of different sensory organs and pathways. Skatole derivatives are characterized by a highly offensive odor and are used to dissipate crowds. These agents are volatile and disperse rapidly but can precipitate allergic reactions in some victims. Sternutators are agents that primarily cause sneezing and upper respiratory tract symptoms. Irritants, or lacrimating agents such as CS and CN (Mace), precipitate severe tearing on exposure that usually lasts less than 30 minutes. Nauseants, or vomiting agents such as DM and apomorphine derivatives, are limited in civilian use because of their potential toxicity and the possibility of aspiration syndromes. Similarly, depressants such as aerosolized fentanyl or etorphine have severe respiratory depressant and nausea-producing effects that severely limit their safety. Anticholinergics such as BZ (QNB, or a 3-quinuclidinyl benzylate) and its analogs produce a temporary state of delirium and are increasingly used to incapacitate dangerous crowds but are by no means “safe.” Anticholinergic syndrome can be recognized by its characteristic features of “dry as a bone, red as a beet, hot as a hare, and mad as a

hatter." The primary riot control agents CS (o-chlorobenzal-malononitrile), CN (1-chloro-acetophenone), and DM (diphenylaminearsine chloride) all can cause severe medical complications, especially when used in confined spaces or in large quantities. Decontamination with water following extensive or protracted exposure should be considered, and facilities and personnel should be available to provide supportive treatment and life support where indicated in instances of symptomatic complications and idiosyncratic reactions.

Anesthesiologists are familiar with and should be ready to treat the toxic effects of riot control agents. Fentanyl is an opioid narcotic and can be easily and rapidly antagonized with naloxone (Narcan) in doses of 0.04–0.4 mg, supplemented as necessary and titrated to reversal of respiratory depression and narcosis. The need for rapid control of the airway with or without specific reversal of opiate toxicity is especially indicated in those instances where there is a combination of respiratory depression, loss of consciousness, and proemetic side effects. Indeed, the civilian mortality following the release of aerosolized fentanyl in Moscow could have been largely prevented/limited if the identity of the agent used been disclosed to health care providers in advance.

Furthermore, anesthesiologists regularly balance the cholinergic–anticholinergic effects of medications. Anticholinergic toxicity is frequently seen in the clinical setting; the clinical syndrome is similar to that seen with the toxicity of cholinergic riot control agents. Neostigmine (0.04–0.08 mg/kg) and edrophonium (0.5–1 mg/kg), pyridostigmine (0.1–0.4 mg/kg), or physostigmine (0.01–0.03 mg/kg) are all effective anticholinergic agents. Of these, neostigmine and edrophonium are routinely employed in the operative anesthesia setting to reverse neuromuscular blockade. Physostigmine, a tertiary amine, crosses the blood–brain barrier and is used to reverse central anticholinergic toxicity. On the other hand, if there is an excess level of cholinergic activity, the anticholinergics such as glycopyrrolate, atropine, or scopolamine are used, as in treatment of nerve agents.

Industrial Toxins. The possibility of an industrial release of toxic agent by accident or sabotage is a scenario that is perhaps more threatening than the use of conventional chemical or biological agents against the populations of developed industrial nations.⁴² In 1984, an inadvertent nighttime release of methylisocyanate and chlorine gases from a chemical plant in Bhopal, India,⁴³ resulted in 38,000 immediate inhalation casualties of whom 8,000 later died; the number of people left with permanent partial disabilities, especially pulmonary disease, is estimated to be close to 50,000.⁴⁴ The Bhopal incident underscores the potential lethality of domestic "civilian" industrial agents, a consideration that must be factored into any evaluation of chemical terrorist threat. Industrial chemical agents are generally extremely toxic, stored in large quantities, and often poorly protected; additionally, their release requires no special manufacturing or weaponization skills by terrorist groups. Industrial toxins can be released from existing storage or transport facilities such as manufacturing plants or storage tanks, or they may be hijacked while in transit in railway or tanker trucks, and targeted at vulnerable populations.⁴⁵ Since there are a very large number and variety of directly and indirectly toxic agents, agent identification will guide the response. The *Emergency Response Guidebook*⁴⁶ is an invaluable resource for identification, characterization, and response to industrial toxins.

Summary and Conclusions

It is aptly stated that "chance favors the prepared mind." Only through education, training, rehearsal, and the development of a coordinated response network can countries marshal effective domestic responses to war, terrorist threat or attack, industrial catastrophes, and natural disasters. Never before has the threat of domestic deployment of weapons of mass destruction been so great; never before have the stakes been as high. The principles of critical care medical management are grounded in basic biochemistry, anatomy, physiology, and pharmacology. Therefore, physicians should already be familiar with the mechanics of triage, resuscitation, and life support; by extension, with appropriate specialized training in disaster response, physicians should be ready to provide the highest quality medical care under the most adverse circumstances.

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Nerve Agent Intoxication: What You Don't Know Can Hurt You

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Learning Objectives:

1. To understand the basic pharmacology and pathophysiology of nerve agents.
2. To recognize the signs and symptoms of nerve agent exposure.
3. To appreciate the time course of acetylcholinesterase inhibition after exposure.
4. To understand the need for and the fundamental principles of patient decontamination and self-protection.
5. To know the general treatment principles and the role of anticholinergics and oximes in casualty management.

Abstract

Lack of preparedness on the part of the health care community in the event of mass casualty poses a great challenge to the outcome of such an event. Proper training and preparation can mitigate the human costs of a chemical attack. This paper presents a discussion of the basic types of weapons of mass destruction and how to recognize and treat them.

There is an increasing likelihood that individuals or groups with hostile intentions have in their possession weapons of mass destruction. These may include chemical (nerve and blister agents), biologic (anthrax, smallpox, botulinum toxin, plague, or others), or radiologic (fission device or “dirty” bombs) weapons. The current state of preparedness of civilian health care providers and facilities is suboptimal.

The modern era of chemical warfare began in Ypres, France, on April 22, 1915, with the use of chlorine gas by the Germans. The resultant bombardment caused 15,000 Allied casualties, with 5000 dead.¹ During the 1930s in Nazi Germany, the chemist Gerhard Schrader discovered the highly toxic effects of the pesticide tabun (NATO: GA) on mammalian tissue. This was quickly followed by the discovery of several more nerve agents. Although these highly toxic compounds have been in existence for almost 70 years, the vast majority of civilian health professionals have received little, if any, education or training on the medical management of victims of nerve agent intoxication. The goal of this case presentation is to introduce the participant to the fundamental principles of the diagnosis, treatment, and decontamination of victims of nerve agent poisoning.

Stem Case

It's 5 p.m. on a beautiful spring afternoon and you're enjoying a break between cases. A news flash breaks into the afternoon market wrap-up. A reporter at the central city subway station approximately 7 miles away from your hospital is describing an explosion with the release of some form of toxic chemicals on the subway platform. A second explosion occurred 5 minutes later. The scene on television is chaotic. The camera pans toward the subway entrance, where there are numerous dead bodies. Several individuals stagger out the subway entrance and collapse on the sidewalk. One victim vomits, collapses, and begins seizing. The chemical is tentatively identified as a "nerve agent." Absolute chaos is an appropriate description for the scene at the trauma center closest to the disaster. The press is estimating as many as 1000 casualties, with more than 100 dead at the scene. You hear over the public address system that the hospital is implementing the mass casualty disaster plan.

You have just been informed that your hospital can expect more than 100 casualties. Among them are numerous police, fire, and emergency medical services personnel. In an effort to rapidly evacuate the site, some victims may not have received adequate decontamination.

Approximately 30 minutes later, you receive your first victim from the scene. While attempting to flee the scene, a 37-year-old woman was struck by a motorcycle as she ran into the street. She now presents with multiple contusions and abrasions as well as indications for the need for a laparotomy and possible splenectomy. Her medical history is significant for tobacco abuse of ~20 pack years, no known drug allergies, and no current use of medications. She had her last meal approximately 4 hours ago. Prehospital interventions included 1000 ml of lactated Ringer's solution via peripheral intravenous (IV) line and cervical spine precautions. The patient is awake and alert but appears very anxious, tremulous, and tearful. Her vital signs are as follows: blood pressure, 164/80 mm Hg; pulse, 108 beats/min; and respirations, 30/min with mild dyspnea. During a brief focused physical examination, she vomits and voids on the stretcher.

The patient's clinical condition begins to deteriorate. She is brought promptly to the operating room. You are informed that the agent has been identified as sarin (NATO: GB).

General endotracheal anesthesia is induced. You notice that the airway pressure at 7 ml/kg tidal volume is 60 cm H₂O. Copious secretions are noted in the no. 8 endotracheal tube. The surgeons are asking to begin. Now her blood pressure is 154/78 mm Hg, her pulse is 107 beats/min, and SaO₂ is 90% by pulse oximetry on 100% inspired oxygen. Approximately 1 hour after induction, your assistant begins to complain of blurry vision, rhinorrhea, and mild nausea.

The surgical procedure, an exploratory laparotomy and splenectomy, requires 1½ hours to complete. No significant surgical complications occurred. The patient is brought to the postanesthesia care unit (PACU). In the PACU, secretions are noted in the endotracheal tube. You are advised that ventilators are in very short supply. You give more antidote and suction the airway. After a few more minutes, her spontaneous respirations appear much less labored and the secretions are improving.

The nurse in pre-op holding calls you to come quickly. Your next patient is apenic and seizing.

Discussion

Chemical warfare agents are chemicals that have direct toxic effects on humans, plants, and animals. Due to the recent tragic events, these agents have attracted much media attention. Memories of World War I, when chemical weapons were used to kill or injure millions, are again fresh in people's minds.

Many physicians and other health care providers caring for chemical casualties in recent conflicts lacked any formal training in this area. There are case reports of casualties contaminated with mustard agent in the Iraq-Iran war having been evacuated as far as hospitals in Europe without adequate decontamination.¹ Lack of adequate knowledge and confidence to deal with the problem under the stress of a mass casualty situation will have a serious negative impact on survivability. There is nothing unique about the pathophysiology of chemical injury that is beyond the understanding of properly trained clinicians. The principles of rapid thorough decontamination, self-protection, and an understanding of the actions of antidotes are the keys to effective chemical casualty care.

Nerve agents are among the most toxic chemicals known. They exert their biologic effect by inhibiting the enzyme acetylcholinesterase (AChE).¹ There are two major categories of nerve agents: the carbamates and the organophosphates (OPs). Among the former are neostigmine, physostigmine, pyridostigmine (recently fielded by the military as a pretreatment medication), and several commercially available insecticides. The OPs include the "military" nerve agents and several insecticides. Five OP AChE inhibitors are recognized as military nerve agents. They are commonly known as tabun (North Atlantic Treaty Organization [NATO] designation: GA), sarin (NATO: GB), soman (GD), GF, and VX. The agents GF and VX have no common name. The "G" agents were developed in Nazi Germany by Gerhard Schrader and associates while researching insecticides for the conglomerate Internationale Gesellschaft Farbenindustrie A.G. (I.G. Farben) between 1936 and 1944. The "V" allegedly stands for "venomous" and was discovered by the British in 1954 while searching for a replacement for the insecticide DDT.

A nerve agent, given adequate time, will irreversibly bind all three forms of AChE in tissue, blood, and plasma. The binding of a nerve agent to AChE prevents the degradation of acetylcholine (ACh). The toxic effects of nerve agents are a result of massive excess of ACh.² The symptoms are related to both the dose and the route of exposure. Inhalation of vapor causes immediate symptoms. If the vapor concentration (mg/m³) and exposure time are significantly high, then the onset will be immediate and death may occur in minutes (the LC₅₀ in mg-min/m³ is the vapor exposure that will kill 50% of the exposed population).¹ Nerve agents penetrate clothing and are readily absorbed through intact skin. The onset of symptoms after skin exposure to a liquid agent can be delayed. It is dependent on the amount, the promptness of decontamination, temperature, moisture, and location on the body. It can range from several minutes for large exposures to 12 to 18 hours for doses much less than the LD₅₀.¹

All nerve agents are liquid at standard atmospheric conditions. The G-agents are more volatile than VX and constitute a significant vapor hazard, whereas VX presents predominately a liquid hazard. Sarin (GB) is the most volatile of the G-agents and has a vapor pressure (2.1 mm Hg at 20°C)² close to that of water (17.4 mm Hg at 20°C). By

comparison, the vapor pressure of isoflurane is 238 mm Hg at 20°C. Generally, nerve agents are colorless, odorless, and tasteless liquids. The G-agents are less persistent than VX, with a $T_{1/2}$ of several hours to a few days. The $T_{1/2}$ of VX can be a week or longer. Nerve agents may be dispersed via explosive devices, from spray tanks, or by other types of delivery systems.¹

Nerve agents can be identified by several detection systems available to the military. These detectors may not be immediately available to the initial civilian responders. Identification will likely be made by knowledge of the clinical toxicity until the arrival of civilian or military HAZMAT teams.

Mechanisms of Action. The toxic effects of cholinergic poisoning occur in the central, autonomic, and peripheral nervous systems. The massive excess of ACh causes a wide variety of symptoms. The most immediately life-threatening is respiratory compromise due to increased airway resistance, central nervous-system-mediated respiration depression, and paralysis. At higher exposures, apnea, seizures, and coma occur. Of particular concern to health care providers are the ophthalmic symptoms of miosis, blurred vision, diminished visual acuity, and loss of accommodation. This can occur after minimal exposure to vapor and can severely hamper patient care. In the 1995 Sarin attack on the Tokyo subway, miosis was the most common symptom, being reported by over 90% of victims.

Protection of Medical Personnel. Toxin identification may not occur in the early phase of response; therefore, secondary contamination may be a serious concern. This poses a significant risk to emergency response personnel. Decontamination should occur as close to the site of exposure as possible to limit the spread of contamination and reduce the time to initial treatment. A hospital receiving potentially contaminated casualties should establish a "hot zone" where casualties will receive adequate decontamination before being permitted entry into the facility. This area is best located in a well-ventilated open area outside the hospital. A "dirty dump" site must be established downwind from the treatment facility, where all contaminated clothing and equipment is located. Victims' personal effects must be tagged, double-bagged, and secured in an appropriate manner. Contaminated patients may find their way to operating rooms, intensive care units, or any other hospital location if not controlled. Contaminated medical electronic equipment may not be recoverable. Secondary injury to health care providers will seriously degrade medical capabilities and add to the casualty numbers. Institutional and individual self-protection is of critical importance. Latex gloves, surgical masks, and gowns are not protective apparel.³ Appropriate protective garments and equipment must be provided. Butyl rubber gloves and gowns or chemical protective overgarments must be worn by all personnel caring for all casualties whose contamination status is unknown. "Off gassing" of volatile nerve agent from clothing and, to a much lesser extent, skin, poses a vapor threat, so appropriate respiratory protection must be worn.

Decontamination Procedures. Decontamination begins with the removal of the victim's clothing. It is critical that decontamination begins as soon as possible after exposure. The goal is the physical removal and chemical degradation of the chemical agent. Casualties should be decontaminated with copious amounts of tepid water and soap. The victim's hair may become a source of contamination and may require

cutting to facilitate decontamination. Hot water, harsh chemicals, strong soaps, and stiff brushes should not be used. Care should be taken to avoid causing vasodilation or mechanical damage to the skin, as this may enhance nerve agent absorption. Mild alkaline solutions and chlorine releasing agents such as diluted (0.5% hypochlorite) household bleach will neutralize nerve agents more quickly than plain soap and water. This solution is contraindicated in patients with eye, abdominal, or brain injuries and therefore may be of limited utility for the nerve agent-intoxicated patient who has also sustained penetrating or blunt trauma.²

For chemically injured patients, the fundamental principles of resuscitation do not change. An airway should be established and adequate gas exchange and circulatory support provided. However, to this must be added termination of the exposure and decontamination of the victim.¹ The exact sequence in which these occur can be greatly influenced by the situation.

Pharmacologic Management. The cornerstones of pharmacologic management consist of three classes of drugs: the anticholinergic atropine; the pyridinium oxime, pralidoxime (2-PAMCl); and the benzodiazepines. The actions of atropine and the oximes may be synergistic.⁴ Atropine is extremely effective at blocking the effects of excess ACh at peripheral muscarinic sites. Atropine will improve the bronchoconstriction, bronchorrhea, nausea, vomiting, diarrhea, and bradycardia. Atropine will not alleviate many of the ocular disturbances or prevent skeletal muscle paralysis.

The oxime 2-PAMCl reactivates AChE by breaking the AchE-NA bond. The nerve agent bound to 2-PAMCl is unable to attack and bind AChE. Reactivation of AChE is most apparent in improved skeletal muscle strength. It should be noted that reactivation of AChE by oximes will occur only if the victim receives this treatment prior to the chemical process of aging of the AchE-NA bond. Once the AchE-NA bond has aged, the oxime cannot reactivate the enzyme. Thereafter, recovery of function depends on synthesis of new AChE. The aging half-time varies from a few minutes for soman (NATO: GD) to 48 hours for the poorly volatile, highly persistent agent VX. The aging half-time for sarin (NATO: GB) is 5 hours.¹

Benzodiazepines are used to decrease convulsant activity associated with severe exposure.

As with all treatment protocols designed for mass casualty events, simplicity is a key goal. The US Army Chemical Casualty Care Division of the Medical Research Institute of Chemical Defense (USAMRICD) offers a practical approach to medical management, which was initially developed for battlefield use.^{1,2}

Civilian physicians may see military-style Atro-Pen® MARK I kits in a nerve agent attack. Some municipalities are acquiring them for emergency responders and other providers as part of the Chemical Stockpile Preparedness Program. The current kits contain two autoinjectors: one with 2 mg of atropine and another with 600 mg of pralidoxime chloride. It has been approved for civilian use by the U.S. Food and Drug Administration. Auto-injectors are a superior delivery method for intramuscular antidotes. Instead of creating a small pool of medication, they discharge the medication as the needle pierces the tissues. Activated auto-injectors deploy in all-or-nothing fashion and can quickly achieve high serum concentrations.³ Using this dosing method, casualties would receive one, two, or three MARK I kits intramuscularly with or without diazepam, based on the severity of the exposure.

Additional atropine would then be titrated to clinical response at 10- to 15-minute intervals.

Levels of Exposure. Nerve agent exposure generally occurs via three routes: inhalation of vapor, liquid on skin, or ingestion. In most potential scenarios, the likely routes of exposure will be inhalation and liquid on skin. This will occur with or without concomitant direct physical trauma. Because of the large absorptive capacity of the respiratory system, exposure to vapor rapidly produces symptoms. Exposed patients present with acute-onset miosis, copious rhinorrhea, dyspnea, apnea, and ultimately convulsions and death. Depending on the severity of the exposure (LCt in mg-min/m³), the time course of events may vary from a few seconds to a few minutes. Victims exposed to high concentrations of vapor are unlikely to survive. Casualties with vapor exposure alone do not require decontamination. The time to onset of symptoms following dermal exposure may be highly variable.

In broad terms, exposure can be broken down to the route of exposure and severity of exposure. Intoxication can be mild to moderate or severe. A mild vapor exposure might present with miosis, dim vision, rhinorrhea, salivation, anxiety, and mild dyspnea. The presence of severe respiratory distress, loss of bowel or bladder control, generalized muscle fasciculation, convulsions, or apnea implies severe intoxication. Mild-to-moderate dermal exposure may present with localized muscle twitching and sweating at the exposure site, anxiety, nausea, vomiting, and a feeling of weakness. Severe liquid exposure would include all of the aforementioned symptoms plus severe dyspnea, generalized muscle twitching, seizures, loss of consciousness, apnea, and loss of bowel and bladder control.

For mild-to-moderate intoxication, 2 to 4 mg of atropine IV bolus plus 600 to 1200 mg of pralidoxime IV over 30 minutes would be the initial therapy. For severe intoxication, 6 mg of atropine with 1800 mg pralidoxime plus 10 mg diazepam IV is the recommended initial therapy. Atropine is titrated to an improvement in symptoms, as generally indicated by a reduction in secretions and the ability to oxygenate and ventilate the victim. Nebulized beta-agonists should be administered to help treat nerve agent-induced bronchoconstriction. It should be noted that nerve-agent-induced miosis is resistant to parenterally administered atropine and therefore is not a good indicator of full atropinization. If IV access is unavailable, then both antidotes may be given intramuscularly.

Pediatric Patients. Children are more susceptible than adults to the effects of nerve agents. Resuscitation of pediatric victims after nerve agent exposure poses a great challenge.⁵ Dosing is weight based, and intravascular access may be difficult to attain. The current recommendations are atropine, 0.05–0.1 mg/kg; pralidoxime, 25–50 mg/kg; and diazepam, 0.05–0.3 mg/kg IV/IM.⁶

Multitrauma. Victims who have sustained both nerve agent exposure and physical trauma are at higher risk of mortality. Nerve agent intoxication reduces the cardiopulmonary response to physical trauma.⁷ Penetrating trauma provides a direct portal of entry for a nerve agent. Examination and evaluation of a toxic, traumatized patient may be a particular challenge.

Anesthetic management of the nerve agent toxic, traumatized patient is based on a very small number of cases and therefore not well understood. The safest technique of

anesthetic management may well be general endotracheal anesthesia.⁷ Inhaled volatile anesthetics are potent bronchodilators and relax skeletal muscle. This would facilitate ventilation and provide acceptable surgical conditions. The nausea and vomiting associated with nerve agent exposure may require airway protection during the induction of anesthesia.

Selection of induction agents can be a challenge. Sodium thiopental or propofol may augment the hemodynamic instability of the nerve-agent-intoxicated patient. Ketamine may offer some advantages. It is commonly used to induce anesthesia in the hemodynamically compromised patient and is a potent analgesic. The bronchodilation and mild increase in heart rate may be beneficial. The choices for skeletal muscle relaxation may also be restricted. Nerve-agent-induced inhibition of plasma cholinesterase and the unique structure of succinylcholine may cause its duration of action to become unpredictable. The positive chronotropic effect of pancuronium may make it a better choice. Using neostigmine to reverse the effects of the neuromuscular blockade may prove problematic. Careful monitoring of the neuromuscular blockade is recommended. Perioperative pain management may require opioids. The histamine-releasing potential of morphine may make it a poor selection. Histamine release can exacerbate the bronchoconstriction and hypotension associated with nerve agents. Fentanyl has potential vagotonic effects and may worsen the bradycardia. The use of meperidine as an analgesic has been suggested, owing to its lack of histamine release and tendency to increase heart rate.⁷

Conclusion

The medical management of mass casualty events poses some of the greatest challenges to the health care delivery system. Mass casualty situations involving chemical, biologic, or radiologic weapons present an even greater threat. One fact is certainly undebatable: lack of preparedness on the part of the health care community will not improve the outcome of such an event. With proper training and preparation, the human costs of a chemical attack can be mitigated.

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Pain Management in Mass Casualty Incidents

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Learning Objectives:

After completion of this article, the participant will be able to

1. Delineate the meaning of the colored tag system used in triage.
2. Define the use of other analgesics in mass casualty situations.
3. Delineate the steps necessary to prepare for an attack.

Abstract

To be prepared for action in a crisis requires physical and mental readiness; one never knows when to expect a terror attack. Preparation should begin with a proper and thorough inventory of supplies and the assessment of capabilities; it should continue with training that simulates various terror scenarios and follow with repeated drilling of the training exercises. It is important that physicians know the agents and devices expected in a chemical and radiologic attack. This paper gives an overview of what to expect and what to use in a crisis situation.

Asymmetric warfare (also known as terrorism) may start without any heralding event at virtually any time and any place. The start may be appreciated by an increased number of hospital admissions for fever, shortness of breath, unexplained rashes, or mucosal irritations or an increased number of consultations for airway management because of bulbar palsies. There may be unusual temporal and geographic clustering of illnesses (e.g., patients who attended the same ball game, live in the same part of town, or work at the same hospital). Because of this lack of warning time, it is incumbent upon pain management specialists to prepare their clinics or departments to meet the sequelae of an attack, which may occur at any time. The nature and timing of any future strike is extremely unpredictable and a flexible plan, rather than a rigid set of instructions, is essential.

Proper planning and preparation can markedly change the mortality and morbidity of these events.

Dr. Gevirtz has no material conflict of interest to disclose. Off-label use: Ketamine, morphine, transdermal fentanyl, transdermal clonidine, and dexamorphan are discussed in off-label uses. Unconventional uses of MS Contin and OxyContin, proscribed by the U.S. Food and Drug Administration, are described as options in extreme emergencies.

We should consider the awful but very real probability of an attack and how to prepare ourselves for it. Planning starts with a candid assessment of available resources and capabilities. If the practitioner is hospital based, effective preparation also requires the running of multiple detailed drills and candid critiquing of the results. Once-a-quarter drills to meet the Joint Commission on Accreditation of Healthcare Institutions (JCAHO) requirements will not produce the learned responses necessary to deal effectively with a sudden attack.

Defining Mass Casualty Incidents

In contrast to disasters, which are commonly ecological in nature, multiple casualty incidents (MCIs) have as their primary effects morbidity and mortality to individuals, while the community infrastructure remains relatively intact. A passenger train accident with 500 injured or dead occupants is considered an MCI. Similarly, 9/11 was an MCI. However, if this morbidity and mortality were the result of the release of persistent nerve gas attack, a much higher potential for additional casualties would exist. Normal operations and activities of daily living in the surrounding area would be disrupted for a longer period and this sort of event might cross over into a "disaster."

Triage

The concept of triage involves providing the most help for as many patients as possible. A complete description of triage is beyond the scope of this review, but there is a marked difference in the style of medical care provided. Medical personnel are accustomed to providing extensive, definitive care to every patient. When confronted by a number of patients simultaneously in an MCI situation, it is easy to become overwhelmed, even for the most experienced trauma worker. The goal is to provide an acceptable minimum level of care to the maximum number of patients. This is a very different approach from providing the very best care for each individual.

Medical triage developed from the need to prioritize the care of injured soldiers in battlefield settings. The concept of prioritizing patients and providing immediate care to the most seriously injured was practiced in France in the early 1800s (triage is derived from the French *trier*, meaning "to sort"). Over the next century, this practice was further developed in armies throughout the world. As a result, many injured persons whose surgery heretofore might have been delayed received critical care earlier. During World War I, improved outcomes of some battle injuries were credited to appropriate triage. Thus, triage is one of the first applications of medical care after first aid on site.

MCI medical triage is a dynamic process occurring at several levels in the health care system to rapidly identify patients with critical injuries from the total number of presenting casualties. Traditionally, triage systems have attempted to sort victims into categories (*vide infra*) to determine treatment and transport priorities. Triage in an MCI is neither perfect nor democratic. It lacks sensitivity and specificity; however, triage improves outcome for the overall population of the injured. Simple triage and rapid treatment categorize victims based on their ability to walk, their mental status, and the presence or absence of ventilation or capillary perfusion.

Patients generally are tagged at the scene or upon entry to an emergency department. The tags are color-coded as follows:

- Red - emergent
- Yellow - urgent
- Green - nonurgent
- Black - dead or very severely injured and not expected to survive

Black tags are the most difficult to assign because of the obvious individual ominous implications. The patients placed in this category clearly are so severely injured that no degree of medical help relieves them. Where heroic efforts might be made if there was just a single casualty, here it would be considered a waste of precious limited resources. Palliation should be the goal, and the use of strong opiates is the first choice.

The green-tag patients are easily sorted just by asking patients who can walk by themselves to go to a separate area, e.g., one part of the emergency department. If they are self-ambulating, usually the pain can be managed by Step I of the WHO ladder,¹ specifically, acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). Yellow- and red-tagged patients may require WHO Step II or Step III interventions such as strong opiates. A patient-controlled analgesic (PCA) machine is ideal here, since once initiated, it can provide continuous analgesia with little additional oversight until the crisis becomes more manageable. However, most facilities have only a limited number of machines and opiate cassettes.

MCI Preparation

Various methods have been developed to assist planners in MCI preparation. The potential injury-creating event (PICE) system is designed to identify common aspects of a disaster and of response capabilities.² This system is a valuable tool in planning for mitigation.

The PICE system uses four modifiers to describe a particular disaster (Table 1). The first modifier describes the potential for additional casualties, e.g., is this a single event like an airplane crash or is this opening salvo in a series of events? The second modifier identifies the degree to which local resources are disrupted, e.g., is this controllable by local resources or are they overwhelmed with the rescue resources themselves in jeopardy? The third modifier identifies the geographic boundaries of involvement. The final modifier, crisis staging, indicates the likelihood of needing outside assistance to augment or replace local resources. Stage 0 means no outside help is needed. Stage I means there is a small chance that outside help will be required and nearby resources should go on alert. Stage II means there is a reasonable probability that help and

resources should stand by for deployment. Stage III means local resources are clearly overwhelmed and immediate dispatch is required. These descriptors can change for identical disasters, depending on the location of the event and the availability of resources. For example, the events of 9/11 would have been categorized as dynamic (at least during the first hours), paralytic, international, and stage III.

The practical clinical importance of this system (Table 1) is that, in disruptive or paralytic settings as well as national and international emergencies, the cavalry may not be riding over the hill anytime soon and when supplies start to dwindle (a threshold of 20% is not unreasonable), rationing and ingenuity may be required to provide pain relief.

Initial Preparations

In preparing for an attack, the concept of “just in time” inventory is the antithesis of “reserve in depth,” which is required to effectively deal with these situations. Questions to be asked include the following:

1. What is the total number of PCA machines available?
2. How many doses of morphine, meperidine, and other injectable opiates are available?
3. How many equivalent dosing charts do you have available (for multiple personnel who don’t usually administer opiates personally)?
4. Do you have injectable or transdermal clonidine? How many doses?
5. How much dextromorphan is available?
6. How many doses of acetaminophen and NSAIDs are available?

These “excess” supplies are obviously not revenue producing and they lower profitability. A balance has to be struck between the ability to provide help in a disaster and to maintain financial viability.

The Centers for Disease Control (CDC) maintains “push packs” containing tens of thousands of doses of broad-spectrum antibiotics and other emergency drugs for dealing with attacks from weapons of mass destruction. While these packs are readily transported by cargo aircraft and can be delivered anywhere in the United States within 12 hours, hospitals near the disaster site may have to support large numbers of patients prior to the arrival of these supplies.

There are three major variables to consider in planning.

First, time to relief or re-supply. In the United States and Europe, relief should arrive within 24 hours unless there are physical barriers to overcome such as radiation or persistent nerve gas.

Second, the total number of analgesic doses available. You need to make a candid guess as to the total overall number of doses available as well as the number of personnel who can administer medications. Equal analgesic tables are also helpful when dealing with medications that are infrequently used (e.g., levorphanol, hydromorphone).

Finally, the distribution of patients within a disaster is often uneven. In the immediate aftermath of the World Trade Center, St. Vincent’s Hospital in Greenwich Village received several hundred patients, while Bellevue Hospital Center, which has a much larger emergency department, received fewer than 100. It may be necessary at some point to turn patients away or arrange for transfer if supplies of analgesics become limited.

Table 1. PICE Nomenclature

| A | B | C | Stage | |
|---------|------------|---------------|-------|-----|
| Static | Controlled | Local | P | 0 |
| Dynamic | Disruptive | Regional | I | I |
| | | National | C | II |
| | Paralytic | International | E | III |

End Game, or the Cavalry Isn't Coming Soon

When you have drawn down your supplies to 20% of the total supply and re-supply is not imminent, it is time to organize a scavenging party. You need to empty every closet and every drawer where analgesic medications may be stored. Unusual medications including mixed agonist-antagonist drugs, partial agonist, the full range of NSAIDs as well sustained-release opiates should be gathered and utilized. Referring back to the PICE guide, you need to make a guess as to when help will arrive. During the 9/11 disaster in New York City, emergency relief arrived within hours. Similarly, during a recent blackout in the northeastern United States, power was restored within 24 to 36 hours in most locations. The key question is to be answered (or guessed at) is, how long will the paralysis last? In a dirty bomb attack or chemical and biologic attack, it can be more than 48 hours, since specialized decontamination units will have to arrive on the scene to assist.

There may come a point in any crisis where the hospital is overwhelmed and supplies are becoming quite limited. Here the pain management specialist may be called upon to minister to the dying in less than ideal conditions and ingenuity may be required to bring comfort. Clearly, the concept of administering a drug, evaluating its effect, and monitoring for further complications and then redosing may not be possible.

Only in the most extreme situations should consideration of converting sustained-release to immediate-release use be entertained. Grinding MS Contin (The Purdue Frederick Company, Stamford, Connecticut), OxyContin (The Purdue Frederick Company), and Kadian (Alpharma Branded Products, Inc., Piscataway, New Jersey) into a powder will defeat the sustained-release mechanism. When orally consumed or nasally inhaled, these compounds will provide rapid relief. However, the effect in an opiate-naïve patient can be very unpredictable. This last resort will find its best use in palliation situations.

It is suggested that, absent a chart or other clear documentation, the drug, dose, and time be written directly on the patient's forehead or arm with a pen or magic marker. Usually there will be a triage tag (as referenced earlier) tied to an extremity where this information can also be recorded, but in mass casualty situations this may not also occur or the data may be incomplete.

Opiates and benzodiazepines remain the first line of therapy, but when these are depleted, other unusual and "off-label" approaches include the use of dextromethorphan, clonidine, and transdermal fentanyl. Dextromethorphan is an NMDA receptor antagonist that will potentiate the analgesia produced by small amounts of opiates. It is commonly available in over-the-counter cough syrup. An orally administered 30-mg dose will reduce by 50% the opiates required over a 6-hour period. Similarly, clonidine, either orally or transdermally (Catapres, Boehringer Ingheim Corporation, Ridgefield, Connecticut) administered, will reduce the opiate requirements of these patients. Injectable clonidine (Duraclon, Roxane Laboratories, Inc., Columbus, Ohio) in a dosage of 0.1 to 0.3 mg intravenously will reduce opiate requirements by more than 50%. But sedation and bradycardia are frequent side effects. Finally, while the FDA label specifically warns against the use of transdermal fentanyl (Duragesic, Janssen Pharmaceutica Products, LP, Titusville, New Jersey) for acute pain situations, in a crisis where other opiates are in short supply, the application of transdermal

fentanyl to an area of skin that first has been rubbed vigorously with alcohol pads will allow rapid uptake of fentanyl, and when transdermal clonidine is added to the area, potent analgesia will be obtained.³

The classic drug to provide both analgesia and anesthesia in the field without supplemental oxygen is ketamine.⁴ As a sole analgesic, it is administered at a dosage of 0.5 to 2 mg/kg intramuscularly every 30 minutes. It should be noted that if the patient is already suffering from mild exposure to nerve agents such as VX or sarin gas, the amount of salivation might actually increase. The major advantage is that this drug will not lower blood pressure unless the patient is at the end stage of hemodynamic shock. It is contraindicated in patients with head injury (possible increased intracranial pressure), open eye injuries, and poorly controlled hypertension.

Ketamine produces a state of dissociative anesthesia in intramuscular doses above 5 mg/kg, with wide-open wandering eyes and nystagmus. The patient is unconscious, amnesic, and deeply analgesic. The airway reflexes are usually preserved and end-tidal CO₂ is usually only minimally affected. The head may be placed in almost any position but turning to the side allows the secretions that may form to drain by gravity. Although ketamine is remarkably safe and is certainly the safest anesthetic in inexperienced hands, vigilance is still required. Intramuscular ketamine acts rapidly, usually within 5 minutes, and while it is irritating upon injection, the profound analgesia that results usually takes care of any complaint.

The large therapeutic index (LD₅₀ to ED₅₀) of ketamine makes it one of the safest sedative agents for most emergency clinical situations. Patients have recovered uneventfully after receiving 10 times the normal dose. The median lethal dose (LD₅₀) observed in animals is approximately 100 times the average human intravenous dose and 20 times the average human intramuscular dose.

Ketamine is both water and lipid soluble, allowing it to be administered conveniently by a variety of routes while still rapidly crossing the blood-brain barrier. This agent has been administered via intramuscular and intravenous injection, intranasal solution, rectal (PR) solution, and oral (PO) elixir. The latter routes are especially useful when running short on syringes.

Personal Readiness

A brief list of supplies that should be kept by every physician is presented in Table 2.

Table 2. Personal Readiness

1. Keep several changes of clothes in your locker.
2. Personal toiletries: toothbrush, toothpaste, mouthwash, soap, shampoo, comb, etc.
3. If you are taking any medications, keep an extra 30-day supply.
4. Keep the emergency backup list on a wallet card or preprogrammed into your cell phone.
5. Cell phone with backup battery.
6. Flash light with a set of backup batteries.
7. Food with a long shelf life, such as foils of tuna or beef jerky. (Although you are unlikely to run out of food in a hospital, long stretches without proper relief may occur.)

Psychiatric Trauma

Freud defined trauma as the experience of having the ego rendered helpless by overstimulation. Physicians within a disaster zone need to be aware of the psychiatric trauma that accompanies mass casualty situations and its impact on pain states. Patients who have pre-existing chronic pain conditions may experience an increase in Visual Analogue Scale scores and may develop new anxieties.

Posttraumatic stress disorder (PTSD) involves a combination of a conditioned fear response to trauma-related stimuli, altered neurobiological processes leading to increased arousal, altered cognitive processing, and social apprehension.

Psychiatric trauma occurs when an individual is faced with an overwhelming and negative experience that is incongruent within his or her existing social framework. The individual repeatedly recollects the event in an attempt to integrate it and to accommodate it into the existing cognitive schema. Meanwhile, numbing and psychological withdrawal arise in an attempt to cope with the pain of the memories. The psychological trauma of the event may interfere with effective pain management or complicate it by making the patient less compliant.

The emotional response to disaster, in both patients and health care providers, tends to follow a sequence of phases:

1. **Impact phase:** During the first few days, individuals often feel stunned. In the first week, disbelief, numbness, fear, and even confusion to the point of disorientation can occur.
2. **Crisis phase:** After the initial impact has been absorbed, individuals may experience a number of feelings. Persons may experience somatic symptoms (fatigue, dizziness, headaches, nausea) as well as anger, irritability, apathy, and social withdrawal. Individuals may be extremely angry with caregivers who fail to solve problems or who are unable to respond in a fully organized way in the chaos of the crisis.
3. **Resolution phase:** Grief, guilt at surviving while others have been harmed or died, and depression are often prominent during the first year, as individuals continue to cope with their losses. When the patients have a chronic pain state, their actions may manifest in a marked decrease in the ability to do the activities of daily living.
4. **Reconstruction phase:** During this phase, reappraisal and understanding of the meaning of the event may occur.

Potential Psychological Outcomes of Traumatic Events

Traumatic events can lead to a wide variety of emotional reactions. The pain physician must understand that underneath

the individual's reaction is an attempt to cope with the traumatic event. The first six symptoms are particularly common. Most individuals will have some symptoms following a significant traumatic event. A minority will have sufficient symptoms to fulfill the diagnostic criteria for acute stress disorder or PTSD. Relatively common symptoms following traumatic events include those listed below:

- Emotional reactions - Shock, daze, grief, anxiety, guilt, anger, numbness, helplessness, shame, emptiness, decreased ability to feel pleasure/interest/love; children may regress in physical and mental development.
- Cognitive reactions - Nightmares, poor concentration, unwanted repeated memories of the disaster, self-blame at not being able to prevent casualties, and increased worry.
- Physical reactions - Difficulty sleeping, exaggerated startle response, tension, fatigue, an overlay of new aches and worsening of pre-existing pain, change in appetite, and a change in libido.
- Interpersonal reactions - Distrust of physicians and nurses, withdrawal from stable friendships, problems at work, problems at school, decreased intimacy between stable partners; and children may become clingy or oppositional.

Rescue workers may develop the same symptoms as victims, including PTSD. As many as one in three rescue workers will develop PTSD.

Conclusion

Preparing for action in a crisis starts well before any actual terror attack. It should begin with a thorough inventory of supplies and assessment of capabilities and continue with training designed to simulate various terror scenarios. Each individual physician needs to prepare by familiarizing himself or herself with the agents and devices that may be used in chemical and radiologic attack. Quality improvement exercises that replicate various disaster drills should be run frequently and then critiqued for deficiencies. As one of my professors once said: "Proper prior preparation prevents pitifully poor performance." Only by drilling repeatedly will the challenge of a terror attack be met.

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The International Chief Emergency Physician Training Course on Command Incident Management and Mass Casualty Disasters

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Education and training are essential in preparation for response to mass casualty incidents and disasters. It is an obligation of any medical system in the world to meet these challenges. Guidelines for education and training in disaster medicine have been proposed in numerous publications. Key elements of preparing health care providers to function under such extreme circumstances include basic knowledge of techniques, tactics, and resources¹; simulations such as interactive case discussions, triage, and tabletop simulations to train specific capabilities^{2,3}; as well as full-scale disaster exercises.⁴

The idea of presenting a specific training course dedicated to the management of mass casualty incidents and disasters originates from the devastating experiences of the air show disaster at Ramstein Airbase in Germany in 1988 (Fig. 1). After a mid-air collision of two fighter planes, one dropped into the crowd, killing more than 100 and injuring several hundred spectators.⁵

In 1997, on the occasion of the 10th World Congress on Emergency and Disaster Medicine in Mainz, the first International Chief Emergency Physician (ICEP) course was presented by the International Trauma Anesthesia and Critical Care Society (ITACCS) and the Department of Anesthesiology, University of Mainz, Germany.⁶ The course was based on the experiences of the national German Chief Emergency Physician (Leitender Notarzt) curriculum published by the German Interdisciplinary Society of Intensive Care and Emergency Medicine as well as experiences gained in courses held in Mainz.⁷⁻⁹

Since that time, the basic curriculum has been expanded and adapted continuously to meet the requirements of the participants and to adapt to changes in emergency medicine and disaster management. The ICEP course has been approved by the Accreditation Council for Continuing Medical Education for 30 credits in Category 1 of the Physician Recognition Award of the American Medical Association as well as other national health authorities.



Figure 1. Air show disaster, Ramstein, Germany, 1988.

Throughout the ICEP course, participants are trained to function as a leader within a local command structure in order to manage all medical aspects of mass casualty incidents and disasters – both manmade (e.g., traffic crashes, industrial incidents, terrorist attacks) and natural (e.g., earthquakes, floods, fires). The participants learn how to define medical priorities and analyze and organize key problems, such as triage of victims, limitations of medical care, treatment, and transportation. The chief emergency physician is responsible for managing the medical aspects of the following response components:

- Overall assessment of the situation
- Cooperation with the dispatch center
- Coordination of medical treatment
- Allocation of patients to appropriate hospitals
- Documentation of medical treatment and transport

The extended and approved 45-hour curriculum imparts detailed knowledge on the following topics:

- Epidemiology of mass casualty incidents and disasters
- Chief emergency physician: definitions, duties, responsibilities
- Personnel protection and equipment
- Triage concepts
- Command and control
- In-field treatment
- Cooperation with other services
- Communications
- Supply
- Transportation in mass casualty incidents and disasters
- Mass casualty incident and disaster management in hospitals
- Preparation for mass gatherings
- Hazardous materials
- Mental health/management of physical and mental stress
- Public relations/media interactions/politics
- Law enforcement and special tasks
- Case reports
- Excursions/familiarization training
- In-field triage training
- Radio communication training
- Tabletop training (Fig. 2)
- Multiple patient simulator
- Mass casualty incident and disaster exercises (Fig. 3)



Figure 2. Tabletop scenario: fire in residential area.

After the beginning of the ICEP course in Mainz, Germany, the idea of presenting such extensive training gained international interest. The concepts of the ICEP course can be implemented into local emergency medical system structures because educational elements are flexible and the faculty includes international as well as local authorities.

More than 165 physicians from all continents have participated in the ICEP courses offered since 1997 (Table 1). They come to the course with experience in prehospital and trauma care, emergency medicine, and command incident management. In order to have homogeneous knowledge among participants, participants should be able to prove their knowledge of emergency medicine and a basic knowledge of disaster medicine prior to attending the course.

Table 1. Locations of International Chief Emergency Physician Training Courses

| Year | Location |
|------|---------------------|
| 1997 | Mainz, Germany |
| 1998 | Mainz, Germany |
| 1999 | Mainz, Germany |
| 2000 | Mainz, Germany |
| 2001 | Copenhagen, Denmark |
| 2002 | Athens, Greece |
| 2003 | Graz, Austria |
| 2004 | Rumania |

The faculty consists of experienced multinational chief emergency physicians and experts in the respective fields. Faculty members come from many countries, including Denmark, Germany, Greece, New Zealand, Qatar, Rumania, United Kingdom, and United States.

This constellation facilitates the exchange of concepts and ideas because every faculty member has extensive personal experience in managing medical resources in mass casualty incidents and disasters. Both the faculty and the participants



Figure 3. Disaster exercise involving coach and freight train, with more than 100 casualties.

are able to combine their specific knowledge and experience from different national and international disaster management strategies and emergency medicine systems in order to improve individual knowledge and qualification, even in uncommon topics.

Furthermore, the course is held in locations such as emergency medical services training centers, where participants and faculty members can spend their free time together discussing questions raised during the lectures and working together beyond the official course hours.

For further information about future courses, please visit www.itaccs.com/programs/index.htm or contact the authors directly.

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