Biological Terrorism: Understanding the Threat, Preparation, and Medical Response

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Biological Terrorism: Understanding the Threat, Preparation, and Medical Response

Abstract.—The thought of an outbreak of disease caused by the intentional release of a pathogen or toxin in an American city was alien just 10 years ago. Many people believed that biological warfare was only in the military’s imagination, perhaps to be faced by soldiers on a far-away battlefield, if at all. Political factors—and possibly biotechnology—have changed that. As we enter the new millennium, national, state, and local governments in the United States are preparing for what is now called “not if, but when” biological terrorism. In contrast to the acute onset and first-responder focus with a chemical attack, in a bioterrorist attack, the physician and the hospital will be at the center of the fray. Whether the attack is a hoax, a small food-borne outbreak, a lethal aerosol cloud moving silently through a city at night, or the introduction of contagious disease, the physician who understands threat agent characteristics and diagnostic and treatment options and who thinks like an epidemiologist will have the greatest success in limiting the impact of the attack. As individual health-care providers, we must add the exotic agents to our diagnostic differentials. Hospital administrators must consider augmenting diagnostic capabilities and surveillance programs and even making infrastructure modifications in preparation for the treatment of victims of bioterrorism. Above all, we must all educate ourselves. If done correctly, preparation for a biological attack will be as “dual use” as the facility that produced the weapon. A sound public health infrastructure, which includes all of us and our resources, will serve this nation well for the control of disease, no matter what the cause of the disease.
David R. Franz, DVM, PhD, served in the US Army Medical Research and Materiel Command for 23 of his 27 years of active duty. Dr Franz has served as both Deputy Commander and Commander of the US Army Medical Research Institute of Infectious Diseases (USAMRIID) and as Deputy Commander of the US Army Medical Research and Materiel Command. Before joining the Command, he served as Group Veterinarian for the 10th Special Forces Group (Airborne.)

Dr Franz served as Chief Inspector on three United Nations Special Commission biological warfare inspection missions to Iraq and as technical advisor on long-term monitoring. He also served as a member of the teams from the United States and the United Kingdom that visited Russia in support of the Trilateral Joint Statement on Biological Weapons, and he was a member of the Trilateral Experts’ Committee for biological weapons negotiations.

Dr Franz was the technical editor of the Textbook of Military Medicine on Chemical and Biological Defense, which was published in 1997. He currently holds appointments to national-level committees for the Department of Defense and the National Academy of Sciences. He has been a speaker at nationally and internationally recognized organizations in academia, industry, and government and teaches first-responders as a member of the faculty of the US Department of Justice’s Center for Domestic Preparedness.

In August 1998, he joined Southern Research Institute as a vice president for the Chemical and Biological Defense Division, where he pursues interests in medical biological defense, education, and cooperative threat reduction. Dr Franz, who resides with his wife, Pat, in Frederick, Maryland, holds a DVM from Kansas State University and a PhD in physiology from Baylor College of Medicine.

Dr Zajtchuk received all of his medical and postgraduate training at the University of Chicago. After he completed his training, he was appointed as Assistant Professor in the Department of Surgery at the University of Chicago. In July 1970, Dr Zajtchuk volunteered for service with the US Army. During his 26 years of service, he held numerous academic, staff, and command positions.

Dr Zajtchuk’s major contributions include the work he did in his position as the director of Task Force Aesculapius, during which time he was responsible for the redesign and restructuring of the Army Medical Department to increase operational effectiveness. He organized and initiated extensive humanitarian
assistance programs in Central and South America, which led to changes in doctrine and laws, and he directed numerous project initiatives in advanced telecommunication technologies for the reengineering of the practice of medicine in times of peace and war. Dr Zajtchuk’s work with telemedicine has made the Army Medical Department a world leader in this area.

From June 1991 to October 1993, Dr Zajtchuk served as Commanding General of Brooke Army Medical Center and its affiliated regional hospitals. In March 1994, he was appointed Commanding General of the US Army Medical Research and Materiel Command, where he served until his retirement from the Army. While serving in that position, Dr Zajtchuk aggressively redesigned the Command’s core competencies of research, materiel development, logistics, and technology assessment with an integrated acquisition management framework, which will ensure the timely and cost-effective availability of medical materiel products for the Army of the 21st century. In addition, he served as Commander of the Fort Detrick installation, as Special Assistant to the Assistant Secretary of Defense (Health Affairs) for Biological and Chemical Defense, and as Chief Operating Officer for the Department of Defense Telemedicine Testbed. Dr Zajtchuk has also served in numerous academic positions as a cardiothoracic surgeon, including the chair and program director at Walter Reed Army Medical Center and the National Naval Medical Center.

Dr Zajtchuk’s basic and clinical research and extensive publication of scientific articles and books resulted in the achievement of a full academic professorship at the Uniformed Services University of the Health Sciences and George Washington University. He is nationally and internationally recognized for his academic achievements and has received numerous awards, including the Distinguished Service Award from the University of Chicago, acceptance to the Russian Academy of Sciences, and an honorary doctorate degree from the Russian Military Academy of Medicine. Only 4 people who are not Russian have received this award in the 200-year history of the Academy.

Dr Zajtchuk’s initiative in the completion of a 20-volume series of military medicine textbooks as the Editor-in-Chief and author of the project is especially noteworthy. The published books are considered classics by national and international experts, and the volume in which conventional warfare is addressed was extensively used during Operation Desert Storm. The textbook in which chemical-biological defense is discussed is considered a classic around the world.

In June 1998, Dr Zajtchuk joined Rush–Presbyterian–St Luke’s Medical Center and Rush University as Vice President for Advanced Technologies and International Health. He also serves as Professor of Cardiovascular and Thoracic Surgery.
Before 1990, little thought was given to the possibility of a biological warfare or biological terrorist attack on US cities. Even as recently as 1997, the US Department of Defense spent approximately $137 million on biodefense to protect the deployed force, while academia, industry, local governments, and the rest of the federal government were oblivious—and in some cases doubtful—about the “threat” of biological warfare.¹ In fiscal year 2000, the US government has committed more than $1.5 billion to military biodefense and another $1 billion to domestic preparedness for a biological attack. The responsibility for research, development, policy, and planning is now spread among the Departments of Justice, Health and Human Services, Defense, and Energy. The Justice Department is responsible for crisis management (intelligence, law enforcement, and education of first responders) and the Health and Human Services Department is responsible for consequence management (surveillance, epidemiology, reference laboratory and field diagnostics, triage and postexposure prophylaxis, and therapy). Not since the cold war and our focus on the nuclear arms race has the US government so aggressively addressed a perceived threat to the lives and communities of US citizens or have US citizens been so bombarded by fact and fiction (which unfortunately are too frequently indistinguishable from each other) about such a threat. Biological terrorism, its agents, the preparation and use of the agents, and the human response to the agents stand apart when compared with other weapons of mass destruction for several reasons. One of these distinguishing factors is that the physician, whether in a private clinic, a hospital emergency room, or a major medical center, will probably be at the front line of defense and response if we ever face the horror of bacteria, viruses, or toxins used as weapons in our cities.

The Genesis of Today’s Bioterrorism Threat: The Cold-War Era

In the early 20th century, the goal of the developers of biological weaponry was to select agents and delivery methods that produced the
desired effect in a reasonably controlled manner without causing harm to their own troops or citizens. The first, and probably only, use of biological agents on a large scale against humans in this century was planned and executed by the Japanese against the Chinese during World War II.\(^2\)

There is also some evidence that the Soviets may have used a tularemia weapon against the Germans during the siege of Stalingrad.\(^3\) The United States, Canada, the United Kingdom, the Soviet Union, and other nations had major biological weapons programs after the war. The US program is best known because of the openness of the US government.\(^4\)

In 1969, the Soviet Union petitioned the United Nations to develop an international treaty to ban biological weapons. In that same year, President Nixon declared a unilateral ban on US development of biological weapons; the US offensive program was halted and all the stocks of biological weapons were destroyed. After several years of negotiations, the Biological Weapons Convention of 1972 was signed by the United States and more than 100 other countries; it was ratified in 1975.\(^5\) Ironically, among the signatories were Iraq and the Soviet Union. The United States has honored that treaty since it was ratified.

### The Massive Soviet Program

In April 1992, President Yeltsin announced on television that the Soviet Union had continued what is now known to be a massive offensive biological warfare program for more than 20 years after the United States and its allies stopped producing biological weapons. During this period, US intelligence knew much about the Soviet nuclear program and had a partial understanding of the Soviet chemical program but knew very little about the largest and deadliest biological warfare program in the history of mankind. The first Soviet defector to the United States, Colonel (Dr) Ken Alibek recently described this program, of which he was an integral part, in great detail.\(^3\) Dr Alibek told that more than 60 thousand people were involved in research, testing, production, and equipment design throughout the country. In 1990, there may have been as many institutes in the Soviet Union working on plague (\textit{Yersinia pestis}) to be used as a weapon as there were scientists in the United States Army working on medical countermeasures to the disease. At least 2 of the agents in the Soviet arsenal, \textit{Y pestis} and variola major (the causative agent of smallpox) were developed and apparently filled into intercontinental ballistic missiles that targeted civilian populations in the United States. Throughout these years, the US population was unaware of this threat.
The Dual-Use Nature of Biological Warfare Programs

The process of research, development, and production of biological weapons is an extremely difficult intelligence target because legitimate vaccine and agricultural production facilities can be used to make illegal biological weapon agents, as they were in both the Soviet Union and Iraq. Basic research can be done in academic, industrial, or government public health laboratories. The scale-up of agent lots can be done in pharmaceutical or agricultural facilities. Weaponization and field testing may be more difficult to disguise, but the Iraqis successfully tested aerosol dissemination equipment on aircraft by flying modified crop-dusting equipment out of a crop-dusting airfield. Although the Iraqis had successfully developed and field tested biological agents (*Bacillus anthracis*, botulinum toxin serotype A, and aflatoxin) in bombs, rockets, and agricultural sprayers on conventional aircraft, our best information suggests that their program was nothing more than high-level bioterrorism when compared with the massive Soviet program. To put this in perspective, the total bacterial fermentor and viral bioreactor capacities believed to have been used during the last half of the 1980s by Iraq is approximately 77,000 L (DRF, personal calculations, 1996). The standard bacterial fermentor—of which there were hundreds in the Soviet program—was approximately 64,000 L. Therefore, almost the entire Iraqi offensive biological warfare program would “fit inside” one of the standard fermentors. Most nations today have the capacity to produce biological agents in their legitimate pharmaceutical or agricultural industries. Few (eg, Iraq and Russia) also have the capability to use these facilities for the production of biological weapons agents.

The Political Turmoil of the 1990s

Until US and coalition forces were deployed to the Persian Gulf throughout the buildup for Desert Storm in 1990 and 1991, biological weapons defense was a relatively minor part of US military training or preparation. It was during this campaign, for the first time in the history of modern combat, that the US force was seriously threatened by chemical and biological weapons. Countermeasures available to our soldiers in 1990 were limited to primitive environmental detectors, effective chemical protective masks, specific vaccines for anthrax and botulinum toxin, and conventional antibiotics. Thousands of service members were immunized for anthrax and botulinum toxins. Critical educational programs were developed and taught in the theater of war to prepare soldiers and leaders for the perceived chemical and biological threats.
crash effort to acquire field detection capabilities and to produce more anthrax and botulinum vaccines and botulinum antitoxins began. Fortunately Saddam Hussein chose not to release his biological arsenal against the coalition, and the war was soon over. The decisive engagement, if not victory, by the predominantly US force was bittersweet. It was now clear to the world that we were unbeatable, at least for the next few years, by conventional means. However, did we have a soft underbelly that might be penetrated by the “great equalizer,” biological warfare?

Shortly after Desert Storm, in 1991, the economic and political situation in the Soviet Union reached crisis stage and the implosion began. Thousands of scientists and engineers had dedicated their productive lives to making biological weapons. Similar to the developers who worked in the US program in the 3 decades before 1969, the people involved in the development of biological weapons for the Soviet Union had families to support and bills to pay. Suddenly, these highly qualified and experienced scientists were without jobs—and without income. An overriding concern in the US Department of State was that these unemployed biological warfare experts could sell their expertise to less developed nations—some of them oil rich—who were looking for the great equalizer to the conventional military might of the United States.

After President Yeltsin admitted that the Soviet Union had ignored the Biological Weapons Convention from 1972 to 1992, the United States took the lead internationally with two major programs. Both programs were designed to reduce the likelihood that the Russians would use their still-massive capacity and capability to make biological weapons. The first was the Trilateral Agreement, which was signed in September of 1992 by the United States, the United Kingdom, and Russia. This agreement established a symmetrical relationship to deal with an asymmetrical problem. Of the 3 nations, only Russia had a biological warfare program; however, the agreement allowed the United States and the United Kingdom to send teams to visit Russian nonmilitary biological warfare facilities and allowed Russian teams to visit nonmilitary facilities in the United States and the United Kingdom. The visits took place in late 1993 and early 1994. Teams from the United States and the United Kingdom visited 4 biopreparete sites in the former Soviet Union, and a Russian team visited 1 pharmaceutical company site in the United Kingdom, 2 pharmaceutical sites in the United States, and 1 US Department of Agriculture laboratory. Governments of the United States and the United Kingdom made extensive disclosures of their former offensive activities, whereas the Russians either refused to disclose or denied much of what
they had done. After months of negotiations and discussions about the visits to military sites that were generally agreed to, negotiations broke down. The entire process was plagued by a lack of trust on both sides.

US Senators Sam Nunn and Richard Lugar championed another approach, generally in parallel with the Trilateral Agreement activities and negotiations, to reduce the likelihood of further proliferation of biological weapons by Russia and to attempt to limit “brain drain” to nations that might be seeking to kick-start or strengthen their programs. The legislation provided millions of dollars to support 3 programs. The goal of these programs was to build relationships between scientists in academia, industry, and government throughout the world and former weapons scientists in Russia. The US Department of State funds scientists directly, which bypasses Russian government taxation through the International Science and Technology Center, which is headquartered in Moscow. The Department of Defense has developed a Cooperative Threat Reduction program, which is associated closely with the International Science and Technology Center. The Cooperative Threat Reduction program for biological issues is monitored by a committee of the National Academy of Sciences and uses the available funds to establish collaborative projects between former Soviet biological warfare scientists and Department of Defense scientists. Finally, the Department of Energy has a similar program called Initiatives for Proliferation Prevention. Although there are no simple solutions to proliferation and we may never know if the Russian program has really ended, these scientist-to-scientist collaborations have shown promise through the building of true understanding and even trust—at least at the scientist and institute level—between former enemies.

**The Biotechnological Revolution**

Another factor that has made biological warfare and terrorism a reemerging problem is the enormous advances that have occurred in the field of biotechnology. Automated sequencing, cloning, transfection, and polymerase chain reaction (PCR) are tools that have made new vaccines, drugs, diagnostics, and genetic therapies possible. The Human Genome Project, which is ahead of schedule and under budget, will change the lives of future generations and holds the promise of the elimination of certain heritable diseases. However, even before these tools were available, the Soviets were using phenotypic characteristics to make multiple-antibiotic–resistant bacterial agents. The biodefense world was surprised, if not shocked, in 1997 when scientists from former Soviet weapons laboratories
published findings of studies in which they expressed the cereolysin AB genes from *Bacillus cereus* in virulent *B anthracis*. The results described “the modulation of immunopathogenic properties of *B anthracis* due to expression of cereolysin AB genes.” The Russians stated that their own live anthrax vaccine (STI-1) is ineffective in protecting against this new strain of bacteria. The new agent has apparently retained the extreme stability of *B anthracis*, which contributes to its potential as a weapon, and has been given a new toxin. The disease syndrome it produces, and its mechanism of causing death in animal models, is not like that of *B anthracis*; only its physical characteristics as a weapons agent remain the same.

Defense is always more difficult than offense. William C. Patrick, III, one of the last of the US developers of biological weapons of the 1960s, stated, “It’s a different world...Defense studies are so much more complicated. It takes 18 months to develop a weapons-grade agent and 10 more years to develop a good vaccine against it.” That principle is even more applicable to bioterrorism, in which intelligence collection and threat prediction are even more difficult and the threat agent spectrum is broader than it was during the cold war.

**Today’s (and Tomorrow’s) Threats to Our Cities**

**Classic Cold-War Agents**

During the cold war, which reached its peak in the 1980s, countries such as Japan, the Soviet Union, the German Democratic Republic, and the United States and its allies, the United Kingdom and Canada, developed biological weapons. Other than the US coalition, most of these programs were developed independently as highly classified endeavors. However, of the thousands of bacteria, viruses, and biological toxins available in nature, the developers typically selected fewer than 20 agents for weaponization—and their lists were strikingly similar. (There is evidence that the Iraqi program agent list was influenced by the previous work of others.) Anthrax, plague, and tularemia were commonly selected bacterial agents during the past 60 years. The easily grown and highly infectious encephalitic alphaviruses (eg, Venezuelan equine encephalitis) were favorites, and the botulinum toxins were always tried, at least in the beginning of developing programs. The Soviet program, because of its size, scope, and duration also included a highly contagious virus, variola (small pox), and the filoviruses Marburg and Ebola.

Why is there a similarity among the lists of favorites developed by competitors in a highly classified world? Undoubtedly, scientists and
engineers responsible for developing biological weapons in the past used similar screens when selecting agents. Because biological agents, unlike chemical agents, are neither volatile nor dermally active (see Table A1, Appendix 1), they must be released as a respirable aerosol (1-25 μ particles). The process of converting a bacterial slant or cell culture vial that contains a lethal agent to an invisible cloud of respirable particles that hover near the ground to be inhaled by intended victims is not a trivial undertaking. There are many opportunities to fail during production or to kill the organisms before they are adequately prepared for dissemination as a homogeneous liquid slurry or, preferably, a dry, talcumlike powder. The developers of the past selected their agents for pathogenicity or toxicity, ease of production into weapons, and stability during production, processing, storage, and dissemination. It is not surprising that anthrax came to the top of everyone’s list.

The would-be terrorist is constrained by most of the physical and biological rules that plagued the biological warfare developers of the past. To lethally infect 100,000 people in a city, the terrorist must lay down a cloud in a respirable particle size that will allow pulmonary or airway retention of the agent. The cloud must stay close to the ground and must not be dispersed and diluted in the atmosphere, as it would be on a warm, sunny day. Although some experts disagree, Dr Franz (one of the authors of this article) believes that to accomplish such a deed efficiently, the terrorist would be dependent on state sponsorship—by a state at least as accomplished as Iraq in 1999—and would have to use one of the “dirty dozen” agents selected by previous developers of biological weapons. For the infection of 500 to 1000 people through the air-handling system of a large office building, the meteorologic constraints would be eliminated, but many of the other constraints would remain. In addition, the terrorist would have to get past building security and dust the agent into the right part of the heating, ventilating, and air conditioning (HVAC) system.

The goals and modus operandi of the terrorist make it possible for him or her to accomplish the mission, however, without actually making 100,000 or even 100 people ill. The goals of terrorists have been clearly discussed.11,12 Whereas participants in the cold war in the 1960s, 1970s, and 1980s probably believed they had to affect thousands of troops to make a strategic difference, now bioterrorists only need to make us believe they have done that to succeed. It is possible that dissemination of a non–mass-casualty agent, such as that done successfully by the Rajneeshe in The Dalles, Oregon, in 1984, is
Seven hundred fifty-one people became ill when they ate food from one of the 10 salad bars in local restaurants that were contaminated with *Salmonella typhimurium* that was prepared in liquid culture. This kind of attack could be conducted by one unsophisticated microbiologist with less than $100 to spend. It is interesting to note that the Rajneesh attack was initially believed to be a natural food poisoning, and it was more than 1 year before enough evidence was collected to link the Rajneesh commune with the outbreak. If the same outbreak occurred today, it is probable that the Federal Bureau of Investigation would be involved within 24 hours. Although our increased awareness of the potential of bioterrorism in the United States has resulted in better preparedness, it has also heightened the awareness and, in many cases, fear of the citizenry.

The concern about and preparation for a response to bioterrorism in the United States has developed in measured and sometimes plodding steps. The stage was set in the early 1990s with our demonstrated conventional power and the collapse of the Soviet Union. The bombings of the World Trade Center in New York City and the federal building in Oklahoma City and the Aum Shinrikyo chemical attack were fueled by news hype, documentaries, novels, and movies. Much of the information distributed

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**TABLE A1. Comparison of toxins and chemical agents**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Toxins</th>
<th>Chemical Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin</td>
<td>Natural</td>
<td>Man-made</td>
</tr>
<tr>
<td>Production</td>
<td>Difficult, small-scale</td>
<td>Large-scale industrial</td>
</tr>
<tr>
<td>Volatility</td>
<td>None volatile</td>
<td>Many volatile</td>
</tr>
<tr>
<td>Relative Toxicity</td>
<td>Many are more toxic</td>
<td>Less toxic than many toxins</td>
</tr>
<tr>
<td>Dermal Activity</td>
<td>Not dermally active†</td>
<td>Dermal active</td>
</tr>
<tr>
<td>Use</td>
<td>Legitimate medical use</td>
<td>No use other than as weapons</td>
</tr>
<tr>
<td>Odor and Taste</td>
<td>Odorless and tasteless</td>
<td>Noticeable odor or taste</td>
</tr>
<tr>
<td>Toxic Effects</td>
<td>Diverse toxic effects</td>
<td>Fewer types of effects</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Many are effective immunogens†</td>
<td>Poor immunogens</td>
</tr>
<tr>
<td>Delivery</td>
<td>Aerosol delivery</td>
<td>Mist/droplet/aerosol delivery</td>
</tr>
</tbody>
</table>


In addition to the agent characteristics listed, an important difference from the standpoint of the health-care provider is the incubation period: minutes (chemical agents) to hours (toxins) to days or weeks (bacteria or viruses). Therefore victims will have signs of disease at the site of the attack with chemical agents and much later with biological agents.

*Exceptions are trichothecene mycotoxins, lyngbyatoxin, and some of the blue-green algal toxins. The latter 2 cause dermal injury to swimmers in contaminated waters but are generally unavailable in large quantities and have low toxicity, respectively.

†The human body recognizes them as foreign material and makes protective antibodies against them.
to the masses politicized the issue and led to the appropriation of money by the government for new programs for domestic preparedness and to the development of such programs. We are passing through a phase in which the populace is marginally informed and sufficiently frightened by what they have heard and read. Therefore a terrorist act, even a hoax, could have a significant impact and fulfill the terrorist’s goals. For this reason, education at all levels is critical now and can actually reduce the potential impact of an attack.

Non-Mass-casualty Agents

Salmonella on a salad bar, cryptosporidium introduced into the public water supply, and \textit{E. coli} contamination of a meat processing line would not kill 100 people—or even 10—but may make hundreds of people temporarily ill. If the act were done overtly or announced to the press after the first patients arrived at the emergency room, attacks such as these would probably serve the terrorist’s needs very well. Anyone with a basic understanding of microbiology could perpetrate such an attack, but a robust public health system can greatly blunt the impact of such an attack.

Hoaxes

Hoaxes can also have an impact far beyond their actual value. The best known biological hoax in the United States occurred in 1997 when a group called the Counter Holocaust Lobbyists of Hillel left a wet paper bag that contained a petri dish labeled “anthrix” and “Yersinia pesits” at a Washington, DC, B’nai B’rith center.\textsuperscript{14} This incident occurred early in the public’s learning curve about biological terrorism. First responders in Washington, DC, who were ahead of their peers in most other large cities, responded vigorously, tested the samples in the field with newly available chromatographic assays, decontaminated civilians in the street, quarantined others in an office building, and generally took control of several city blocks. While they worked in the streets, the sample was whisked off to a local government laboratory, where it was soon confirmed as negative for the 2 feared agents. In retrospect, the first responders of Washington, DC, overreacted greatly to a wet paper bag that contained a petri dish of innocuous red gelatin. The terrorists won the day. However, the extent and manner of the response should not be criticized. The police, firefighters, and paramedics did a commendable, although very conservative, job with the knowledge available to them. Consider how differently they could have responded if they had understood that even \textit{B. anthracis} and \textit{Y. pestis} are neither dermally active nor volatile. These agents, had they been
present, would not have “jumped” from the soggy paper bag to hurt anyone. Education is our best weapon against hoaxes.

We have concluded that the true mass-casualty attack could best be done with the assistance of a state sponsor and one of the classic cold-war biological agents. The non–mass-casualty attack can be greatly blunted by a robust public health infrastructure, and education at every level can be effective against the hoaxer. Because both hoaxes and use of biological agents to cause harm are criminal, a swift and vigorous response by law enforcement authorities is essential and will have a strong deterrent effect. Moderation by the press in the reporting of these events will also deter the would-be hoaxer.

**Highly Contagious Agents**

There is one type of attack for which a direct relationship between effort by the terrorist and result on the target may not apply. We have said that intent, access to agents, research and development, scale-up, weaponization, testing, and favorable meteorological conditions are necessary for the successful execution of an attack with a respirable biological agent. The highly contagious agents such as variola (smallpox) or an influenza strain similar to that which killed approximately 20 million people in the early 1900s may allow the terrorist to attack without actually developing a weapon. The simple introduction of a sick person into a crowd of travelers could start an epidemic. Fortunately, the world’s known stocks of variola are locked up in the high-security containment laboratories in Atlanta, Ga, and Novosibirsk, Russia. Highly lethal isolates of influenza are not readily available to the masses. Limited access to agents, and possibly concern for their own health and safety, may be the most important constraints on terrorists who would choose a highly contagious agent.

**Individual Disease Agents**

The sources listed below can also be found in the reference list of this article. However, we believe that these 2 works are extraordinarily useful and comprehensive as ready sources of essential information on disease agents and preparation for bioterrorist attack, and as such, they deserve special attention.

- Franz DR, Jahrling PB, Friedlander AM, et al. Clinical recognition and management of patients exposed to biological warfare agents
A summary of the individual disease agents is presented in Table 1.

**Anthrax**

**Clinical Presentation.** *B. anthracis*, the etiologic agent of anthrax, can cause 3 forms of disease: cutaneous anthrax, gastrointestinal anthrax, and inhalation anthrax. Only inhalation anthrax can lead to massive casualties, and it is the disease of concern for biological terrorism. After an incubation period of 24 hours to 6 days, exposed individuals have nonspecific symptoms of malaise, fatigue, myalgia, fever and, in some, nonproductive cough and mild chest pain. These prodromes may persist for 2 to 3 days, and the patient may actually improve slightly before the sudden onset of severe respiratory distress, dyspnea, stridor, cyanosis, increasing chest pain, and diaphoresis. Individuals may have edema of the neck and chest. Chest x-ray films often show the characteristic widening of the mediastinum and pleural effusions. Meningitis, often with subarachnoid hemorrhage, is present in approximately half of the cases. Bacteremia, septic shock, and death usually follow the onset of respiratory disease within 24 to 36 hours. Historically, treatment has been almost universally ineffective, but very few cases of inhalation anthrax have been treated since the advent of modern intensive care.

**Agent and Infective Dose.** *B. anthracis* and anthrax occur worldwide. In the infected host, the gram-positive bacillus exists in its vegetative form and sporulates only if it is exposed to air. Spores are typically the infective form. The spores are very hardy and may survive in the environment for decades in certain conditions. Animals become infected when they ingest spores while grazing on contaminated land or eating contaminated feed. There is typically an increased incidence of disease in animals in the southwest United States after periods of drought, which may promote trauma to the oral cavity during grazing and greater access for the spores, which settle and concentrate at the bottom of drying waterholes. Humans can become infected by inoculation of skin lesions through contact with infected animals or animal products, by ingesting contaminated meat from diseased animals, or by inhaling spores. Anthrax in humans is associated with agricultural or industrial exposure to infected or contaminated meat, hides, bones, or carcasses. In the United States, the annual incidence of human anthrax, of all types, has declined from more than 100 cases per year in the early 20th century to about 1 case per year in the past
10 years. The last cases of inhalation anthrax in humans in the United States occurred in the 1950s in the New England wool mills. The United States, during its offensive biological weapons program (1943-1969), Iraq, and the Soviet Union all chose anthrax as their premiere biological weapon. It is lethal, relatively easy to grow in culture, and above all, superbly stable. The most recent large outbreak of inhalation anthrax occurred in 1979 after an accident in a Soviet weapons facility in Sverdlvosk. It is believed that at least 66 people and many animals died as a result of the inadvertent release of dried anthrax spores. Estimates for the aerosol infective dose for humans are based on nonhuman primate studies and range from 8000 to 50,000 spores.

**Diagnosis and Patient Precautions.** Knowledge of a history of exposure or high index of suspicion is critical in the diagnosis of inhalation anthrax. Nonspecific flulike illness followed by the development of respiratory distress and widened mediastinum, as well as hemorrhagic pleural effusion or hemorrhagic meningitis, is suggestive of pulmonary anthrax. A sputum examination does not help physicians make a diagnosis because pneumonia is not a usual feature of inhalation anthrax. Anthrax-caused meningitis is clinically indistinguishable from meningitis caused by other etiologic agents. The cerebrospinal fluid shows evidence of hemorrhage in as many as 50% of the cases. The diagnosis of meningitis can be confirmed by identification of the organism in cerebrospinal fluid with microscopy or culture. In experimentally infected animals that are challenged by inhalation, bacilli and toxin appear in the blood on the second or third day. *B anthracis* can be seen by Wright or Gram stain in peripheral blood, but typically not until late in the course of the disease. Only the vegetative stage occurs in vivo. The organism grows well aerobically on sheep blood agar and is nonhemolytic in these conditions. The colonies are large, rough, and grayish-white, with irregular curving outgrowths from the margin. Toxin can be identified by enzyme-linked immunosorbent assay (ELISA). Serology is typically useful for only a retrospective diagnosis and primarily for cutaneous and oropharyngeal anthrax. The course of inhalation anthrax is too short to allow a serologic response. Patients with inhalation anthrax may be handled with standard precautions against contagion.

**Treatment and Prophylaxis.** Large doses of penicillin have been the treatment of choice for inhalation anthrax. All naturally occurring isolates tested have been sensitive to erythromycin, chloramphenicol, gentamicin, and ciprofloxacin. Antibiotic therapy should be instituted as early as possible, and the patient should be supported with vigorous fluid
### TABLE 1. Summary of biological warfare agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Ineffective Dose (Aerosol)</th>
<th>Incubation Period</th>
<th>Diagnostic Samples (BSL)*</th>
<th>Diagnostic Assay</th>
<th>Patient Isolation Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td>8000 to 50,000 spores</td>
<td>1-5 d</td>
<td>Blood (BSL-2)</td>
<td>Gram stain, Ag-ELISA, Semig: ELISA</td>
<td>Standard precautions</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>10-100 organisms</td>
<td>3-60 d (occasionally months)</td>
<td>Blood, bone marrow, acute and convalescent sera (BSL-2)</td>
<td>Serology: agglutination Culture</td>
<td>Standard precautions: Contact isolation if drainage lesions present</td>
</tr>
<tr>
<td>Plague</td>
<td>100-500 organisms</td>
<td>2-3 d</td>
<td>Blood, sputum, lymph node aspirates (BSL-2)</td>
<td>Gram or Wright-Giemsa Stain, Ag-ELISA, Culture, Semig: ELISA, FA</td>
<td>Pneumonic: droplet precautions until patient tested for 3 d</td>
</tr>
<tr>
<td>Q fever</td>
<td>1-10 organisms</td>
<td>10-40 d</td>
<td>Serum (BSL-3)</td>
<td>Semig: ELISA, FA</td>
<td>Standard precautions</td>
</tr>
<tr>
<td>Tularemia</td>
<td>10-50 organisms</td>
<td>2-10 d</td>
<td>Blood, sputum, serum EM of issue (BSL-2)</td>
<td>Culture Semig: agglutination</td>
<td>Standard precautions</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Assumed low (10-100 organisms)</td>
<td>7-17 d</td>
<td>Pharyngeal swab, nasal material (BSL-4)</td>
<td>ELISA, PCR, virus isolation</td>
<td>Airborne precautions</td>
</tr>
<tr>
<td><em>Viral encephalitides</em></td>
<td>10-100 organisms</td>
<td>VEE, 2-4 d</td>
<td>Serum VEE (BSL-3) EEE (BSL-2) WEE (BSL-2)</td>
<td>Viral isolation Semig: ELISA or hemagglutination inhibition</td>
<td>Standard precautions: (mosquito control)</td>
</tr>
<tr>
<td><em>Viral hemorrhagic fevers</em></td>
<td>1-10 organisms</td>
<td>4-21 d</td>
<td>Serum, blood</td>
<td>Most viral hemorrhagic fevers (BSL-4) RVF, KNV, and YF (BSL-3)</td>
<td>Viral isolation Ag-ELISA RT-PCR</td>
</tr>
<tr>
<td>Botulism</td>
<td>0.001 μg/kg (typ A)</td>
<td>1-5 d</td>
<td>Nasal swab (possibly) (BSL-2)</td>
<td>Ag-ELISA, Mouse neutral</td>
<td>Standard precautions</td>
</tr>
<tr>
<td><em>Staphylococcal enterotoxin B</em></td>
<td>30 ng/person (intracutaneous)</td>
<td>1-6 h</td>
<td>Nasal swab, serum, urine (BSL-2)</td>
<td>Ag-ELISA Semig: ELISA</td>
<td>Standard precautions</td>
</tr>
</tbody>
</table>


BSL, Biosafety level; Rx, chemotherapy; Px, chemoprophylaxis; Ag, antigen; ELISA, enzyme-linked immunosorbent assay; IV, intravenously; q, every; IM, intramuscular; qd, each day; PO, by mouth; FA, immunofluorescent assay; IND, investigational new drug; SC, subcutaneous; EM, electron microscopy; PCR, polymerase chain reaction; VIG, vaccinia immune globulin; DOD, Department of Defense; VEE, Venezuelan equine encephalitis; EEE, eastern equine encephalitis; WEE, western equine encephalitis; NA, not available; RVF, Rift Valley fever; KNV, Korean hemorrhagic fever; YF, yellow fever; RT-PCR, reverse transcriptase polymerase chain reaction; Ab, antibody; CCHF, Congo-Crimean hemorrhagic fever; AHF, Argentine hemorrhagic fever; BHF, Bolivian hemorrhagic fever; CDC, Centers for Disease Control and Prevention.

*Information on diagnostics, medical management, and vaccines is available by contacting Commander, USAMRIID, at 301-619-2833 (phone) or 301-619-4625 (fax). Readers are advised to consult product literature before administering drugs or vaccines.

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and airway management, appropriate vasopressors, oxygen, and other supportive therapy. Data from studies of a nonhuman primate animal model of the use of ciprofloxacin, doxycycline, and penicillin show that treatment with antibiotics that begins 24 hours after exposure to a lethal aerosol challenge with anthrax spores prevents death. In these studies, optimal postexposure protection was provided by antibiotics administered for 30 days and by 2 doses of active immunization at 0 and 2 weeks after exposure.18
A licensed vaccine, which has also been proven to be very effective against inhalation challenge in animal models, is available. It is an aluminum hydroxide-adsorbed vaccine derived from culture fluid supernatant from an attenuated, unencapsulated, nonproteolytic strain of \textit{B\textsubscript{anthracis}}. The antigen in the filtrate is primarily protective antigen, a component of the protein toxins. The recommended schedule for preexposure immunization is 0.5 mL given subcutaneously at 0, 2, and 4 weeks followed by boosters at 6, 12, and 18 months. Although there have been no controlled clinical efficacy trials of the licensed vaccine in the United States, it has been shown to be efficacious, even on a reduced schedule, in inhalation-challenged nonhuman primates. The incidence of local and systemic reactions in two different studies has been low.\textsuperscript{19,20}

\textbf{Brucellosis}

\textit{Clinical Presentation.} Of the 6 species of \textit{Brucella}, 4 are pathogenic for humans, \textit{Brucella melitensis} usually infects goats, \textit{Brucella suis} infects swine, \textit{Brucella abortus} infects cattle, and \textit{Brucella canis} infects dogs. Unlike anthrax, the signs and symptoms are similar whether exposure is oral, aerosol, or cutaneous. The clinical manifestations of brucellosis are diverse, and the course of the disease is variable. The disease may be abrupt or insidious at the onset. After an incubation period of 3 days to 2 months or longer, patients have fever, chills, malaise, myalgia, and joint pain, and a small percentage have splenomegaly or hepatomegaly. Cough and pleuritic chest pain may also be noted. Chronic manifestations include sacroiliitis, infections of large joints, and vertebral osteomyelitis. Genitourinary infections and hepatitis may occur. Although endocarditis and central nervous system infections are rare, they account for nearly all fatalities (approximately 5\% of cases). The disease may last for weeks or months. Most patients recover within 1 year, but relapses are common.

\textit{Agent and Infective Dose.} Brucellae are small, slow-growing, pleomorphic, gram-negative, aerobic, non–spore-forming coccobacilli. In animals, they typically cause infertility and abortion. Although the 6 species of \textit{Brucella} are associated with certain animal hosts, they may also cause disease in other animals.\textsuperscript{21} Human cases occur after contact with infected animals or animal products. The order of severity of human disease ranked from greatest to least is \textit{B\textsubscript{melitensis}}, \textit{B\textsubscript{suis}}, \textit{B\textsubscript{abortus}}, and \textit{B\textsubscript{canis}}. Natural disease is most commonly seen in veterinarians, shepherds, cattlemen, and slaughterhouse workers. Person-to-person transmis-
sion normally does not occur in nature, although laboratory infections are common. The brucellae are highly infectious by aerosol; the estimated infectious dose is only 10 to 100 organisms. The United States made a \( B\) \textit{suis} weapon in its now-defunct biological warfare program. The agent was produced, placed in weapons, and tested in field trials during the 1940s. The brucella program ended in 1967, 2 years before the United States unilaterally stopped its biological warfare program.

\underline{Diagnosis and Patient Precautions.} The most important factors in the diagnosis of brucellosis are a nonspecific febrile illness and a thorough history of potential exposure. When the disease is considered as part of the differential, diagnosis is usually made by serology. Immunoglobulin M increases early in the course of the disease and may persist at low levels for months or years after treatment. The standard assay method is tube agglutination. Tube agglutination measures the ability of serum to agglutinate killed organisms, which reflects the presence of anti-O-polysaccharide antibody.\(^{22}\) The tube agglutination method does not work for \( B\) \textit{canis}, which lacks O-polysaccharide on its surface. ELISAs have been developed for \( B\) \textit{canis} and other species, but the ELISAs have generally not been widely validated or standardized. Diagnosis should be confirmed by culture of blood, body fluids, or bone marrow. The organism can grow very slowly; therefore cultures must be kept for at least 8 weeks with weekly subculture onto enriched agar plates. The infective dose for humans is believed to be 10 to 100 organisms inhaled. Because the agent is extremely infectious, it should be subcultured only in a biohazard hood. Patients may be handled with standard precautions, unless draining lesions are present. If lesions are present, contact isolation should be used.

\underline{Treatment and Prophylaxis.} Combinations of antibiotics provide the best therapeutic approach for this often chronic disease.\(^{23}\) Therapy with single drugs has resulted in high relapse rates. The treatment of choice is doxycycline and rifampin for at least 6 weeks. Trimethoprim-sulfamethoxazole has been substituted for rifampin. For joint infections, endocarditis, and central nervous system disease, an aminoglycoside such as streptomycin should be included and therapy should be prolonged. Treatment of endocarditis may necessitate heart valve replacement. Because any of the bacterial organisms produced for biological attack by a state-sponsored terrorist may have been made resistant to 1 or more antibiotics, it is important to collect samples for sensitivity studies early after the attack. There is no licensed human brucella vaccine in the United States.
Tularemia

Clinical Presentation. Tularemia, which is also known as rabbit fever or deerfly fever, may appear in either ulceroglandular or typhoidal forms, depending on the route of inoculation. Humans may acquire the disease in natural conditions through inoculation of skin or mucous membranes with blood or tissue fluids of animals or through bites of infected deerflies, mosquitoes, or ticks. The typhoidal form is seen after inhalation exposure which, in nature, may occur after the inhalation of contaminated dust. Typhoidal and septicemic tularemia manifest as fever, prostration, and weight loss without adenopathy (lymph nodes larger than 1 cm in diameter are common in the ulceroglandular form). Pharyngitis may occur in as many as 25% of patients with tularemia, often accompanied by pneumonia. More than 50% of patients with tularemia have lower respiratory involvement. Approximately 30% of patients with ulceroglandular tularemia and 80% of patients with typhoidal tularemia have pneumonia.24 Substernal discomfort and a nonproductive cough may occur as respiratory manifestations. Evidence of pneumonia and pleural effusion may be seen on radiographs. Without appropriate antibiotic treatment, patients may exhibit malaise, weakness, and weight loss for months. The case fatality rate of untreated typhoidal disease is approximately 35%, which is higher than that for the ulceroglandular form (4%), probably because of the pulmonary involvement with the former.

Agent and Infective Dose. Francisella tularensis is a small, nonmotile, aerobic, facultative intracellular gram-negative cocccobacillus. Biovar F tularensis is the most common isolate in the United States; it is highly virulent for rabbits and humans. Biovar F palearctica is seen in water mammals and mosquitoes outside the United States; it is nearly avirulent for rabbits and humans. The subspecies are indistinguishable serologically, but may be distinguished by 16S ribosomal RNA analysis.25 The organism is relatively stable and remains viable for weeks in water, soil, or carcasses of infected animals and for years in frozen rabbit meat. The infective human dose is 10 to 50 organisms inhaled or injected intradermally. The United States made F tularensis into a weapon in its biological weapons program that ended in 1969.

Diagnosis and Patient Precautions. Diagnosis of typhoidal tularemia is difficult because the signs and symptoms are nonspecific. In natural exposure, diagnosis may also be complicated by lack of an exposure history. Isolation of the organism from blood, sputum, skin, or mucous membrane lesions can be used; however, isolation is also difficult because of complex growth characteristics and overgrowth by common organisms.
The organism can often be recovered even after antibiotic therapy has begun. Because brucella species grows poorly on standard media, cysteine or other sulfhydryl compounds must be used. Growth appears as small, smooth, opaque colonies after 24 to 48 hours of incubation at 37°C. Most diagnoses are made serologically with the use of bacterial agglutination or ELISA. Antibodies that agglutinate *F. tularensis* appear within 1 week of infection, but titers high enough to make specific confirmatory diagnoses do not appear in less than 2 weeks. The serologic response may be blunted by previous use of antibiotics. Antibodies to *F. tularensis* may cross-react with *Brucella*, *Proteus*, and *Yersinia*. Although laboratory infections are common (the agent is highly infectious in aerosol) human-to-human transmission is rare; therefore respiratory isolation is not required. Patients may be cared for with standard precautions.

**Treatment and Prophylaxis.** With appropriate therapy, tularemia has an overall mortality rate of approximately 1% to 2.5%. Streptomycin or gentamicin given parenterally for 10 to 14 days is effective; patients usually respond favorably within 48 hours of the initiation of treatment. Tetracycline and chloramphenicol are also effective, but there have been reports of significant relapse rates with these drugs if they are given too early in the course of the disease or if they are not continued long enough. Postexposure prophylaxis is difficult; tetracycline that is begun 24 hours after aerosol exposure and continued for 2 weeks is recommended. Studies that were conducted during the US offensive program showed that a whole-cell killed vaccine was ineffective against aerosol challenge. A live attenuated tularemia vaccine is available as an investigational new drug (IND). This vaccine, which is called live vaccine strain and was adapted from a vaccine developed by the Soviets, protected human subjects from aerosol challenge.

**Plague**

**Clinical Presentation.** Similar to anthrax, plague may manifest in several forms: bubonic, primary septicemic, and pneumonic. After an incubation period of 2 to 3 days, patients with pneumonic plague have acute and fulminant pneumonia with malaise, high fever, chills, headache, and muscle pain. Often within 24 hours of onset, they develop a productive cough with blood-tinged sputum, a hallmark of pneumonic plague. Bilateral alveolar infiltrates are the most common radiographic findings. Clinical sepsis may develop quickly, then progress rapidly to dyspnea, stridor, and cyanosis, and then to shock, respiratory failure, and a bleeding diathesis. Large ecchymoses on the backs of patients in the
terminal stages of pneumonic and septicemic plague were probably the source of the medieval epithet, “Black Death.”

**Agent and Infective Dose.** The etiologic agent of plague, *Yersinia pestis*, is a gram-negative, non–acid-fast, nonmotile, nonsporulating, nonlactose-fermenting, bipolar coccobacillus from the family Enterbacteriaceae. It was the cause of many of the urban epidemics throughout history and typically spread from the black rat, *Rattus rattus*, to the oriental rat flea to humans as bubonic plague. It is maintained in nature in several rodent reservoirs in a stable enzootic rodent–flea life cycle. Most carnivores, except cats, are resistant to infection. Man is an accidental host and is not necessary for the agent’s persistence. Transmission to humans occurs by contact with fleas from rodents, respiratory droplets from animals, or infected humans. A plague weapon was developed by the Japanese and used against the Chinese during World War II. The Soviet Union also developed a plague weapon and the United States studied *Y pestis* as a potential biological warfare agent in the 1960s. It is believed that 100 to 500 organisms inhaled constitute an infective dose. Human-to-human transmission may occur. Primary pneumonic plague is more rapidly fatal than secondary pneumonic plague because the inhaled droplets contain phagocytosis-resistant bacilli as a result of organisms growing at 37°C in the human host.

**Diagnosis and Patient Precautions.** A presumptive diagnosis can be based on identification of gram-negative coccobacillus and of safety-pin bipolar-staining organisms in peripheral blood, lymph node needle aspirate, sputum, bubo aspirate, or other clinical specimens. The organism’s bipolar appearance is seen when Wright-Giemsa or Gram’s stains are used. Immunofluorescent staining for the capsule or a 4-fold rise in antibody titer are considered to be diagnostic. Most plague strains that occur naturally produce F1 capsular antigen in vivo, which may be identified by serology. Diagnosis can be confirmed by culture; the organism grows slowly at standard incubator temperatures and may be missed in an automated system. Small, 1- to 3-mm “beaten-copper” colonies can be seen on blood agar after 48 hours. For pneumonic plague, patient considerations must include droplet precautions until the patient has been treated with appropriate antibiotics for at least 3 days. Plague is recognized internationally as a disease that requires quarantine and, as such, must be reported to the World Health Organization.

**Treatment and Prophylaxis.** Streptomycin sulfate, tetracycline, chloramphenicol, and gentamicin sulfate are effective against bubonic plague. Pneumonic plague must be treated within 24 hours of the onset of symptoms. Intramuscular streptomycin (the antibiotic of choice), gentamicin, or
intravenous doxycycline are the drugs of choice for the treatment of pneu-
monic plague. Treatment should be continued for 10 days or for 3 to 4 days
after clinical recovery. Without treatment, the mortality rate is 100% for
pneumonic plague. Chloramphenicol that is given intravenously is the
choice for plague meningitis.

People who have contact with patients with pneumonic plague and
anyone who is exposed during a biological terrorist attack should be
treated (postexposure prophylaxis) with tetracycline or doxycycline for 6
days. Individuals who have previously been vaccinated with the currently
licensed vaccine should also be given postexposure antibiotic prophylaxis.

A licensed, killed, whole-cell vaccine is available for individuals who
are at high risk. The vaccine was widely used during the Vietnam War,
with an attendant very low incidence of bubonic plague in soldiers who
served in an endemic area. Animal studies, however, suggest that this
vaccine is not effective against aerosol challenge. The US Army has
developed an experimental vaccine, which contains additional antigens,
that appears to be protective against aerosol exposure in animal models.

Q Fever

Clinical Presentation. After an inversely dose-related incubation period
of 10 to 40 days, Q fever may take many forms or simply be an asympto-
matic seroconversion in as many as 50% of infected individuals. The
onset of apparent disease may be acute or slow. Because fever, chills, and
severe frontal headache are the most common symptoms, Q fever has often
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basis of 16S ribosomal RNA analysis, is *Legionella*, which causes a different clinical syndrome. The *C. burnetii* infective dose by inhalation is believed to be only 1 to 10 organisms. A sporelike form that can withstand heat and drying for weeks, and the organism’s high infectivity, made it a natural selection as a biological weapon by early developers. The dried organism can persist on inanimate objects and can be carried for miles by the wind. Humans may be infected without direct contact with infected animals. *C. burnetii* was studied for weaponization by the United States before 1969.

**Diagnosis and Patient Precautions.** The diagnosis of Q fever is usually based on serologic testing by either antibody ELISA or indirect fluorescent antibody methods. Significant titers are usually not seen until 2 to 3 weeks after the onset of infection; several months after the onset of infection, convalescent titers often show a 4-fold increase. Measurable antibody may persist for years after acute infection, especially that measured by ELISA, the most sensitive of the antibody assay methods. Culture of *C. burnetii* is potentially hazardous to laboratory personnel and must be done in animals or cell culture. PCR will probably be useful in the future as a diagnostic tool but has not yet been validated for acute individual cases. Patients may be handled with standard precautions.

**Treatment and Prophylaxis.** Tetracyclines are the therapy of choice for acute disease, along with macrolide antibiotics such as erythromycin and azithromycin. When it is begun within the first few days of illness, tetracycline therapy shortens the course of disease. Initiation of postexposure prophylaxis within the first 24 hours of exposure only delays the onset of the disease; however, if the prophylaxis is started late in the 10 to 40 day incubation period, it precludes development of the disease. Endocarditis associated with chronic Q fever is treated with tetracycline combined with rifampin or a quinolone for 2 years; the mortality rate is 24%, even with therapy.

Q fever can be prevented by vaccination. Immunization with formalin-killed *C. burnetii* protected human volunteers from the disease after aerosol exposure. Protection primarily depends on cell-mediated immunity. A licensed vaccine (Q-Vax; CSL Ltd, Parkville, Australia) is available in Australia, and IND vaccines have been developed and produced by the US Army. The vaccination of immune individuals may lead to severe local reactions that result from a delayed hypersensitivity associated with previous infection; therefore recipients should be screened with an intradermal skin test before immunization.
Smallpox

Clinical Presentation. After aerosol exposure of humans to variola major, the virus is taken up by regional lymph nodes where it replicates, which results in a viremia quickly followed by a rash. The average incubation period of smallpox is 12 days. After replication in local nodes, the virus disseminates systemically to spleen, liver, bone marrow, and lung parenchyma. During this prodromal period, the virus can often be isolated from peripheral blood. The onset of clinical signs is abrupt; the signs include malaise, fever, rigors, vomiting, headache, backache, and, in a small percentage of cases, delirium. Two to 3 days after the onset of clinical illness, an enanthem appears with a discrete rash, typically on the face, hands, and forearms. Lesions on the mucous membranes shed infected epithelial cells, which results in infectious oropharyngeal secretions during the first few days of eruptive illness. These respiratory secretions are the most important means of viral aerosol transmission to people who the patient contacts. Cough and bronchitis occur occasionally, but pneumonia is rare. During the next week, the rash develops on the lower extremities and, finally, on the trunk. Lesions progress from macules to papules and then to pustular vesicles. A centrifugal distribution of lesions with concentration on the face and extremities is important in diagnosis and differentiates variola from varicella. During the second week after onset, scabs form on pustules and leave depressed scars when they heal. Virus can be recovered from scabs throughout convalescence. The mortality rate has historically been approximately 30% in unvaccinated individuals.35

Agent and Infective Dose. Although other biological agents that have been developed for weaponization in the past are lethal and stable, only variola is also extremely infective by aerosol, which makes it a threat to exposed individuals and to everyone with whom the exposed individuals may come into contact. Variola, a DNA virus with one of the largest genomes of any virus, can retain its infectivity for long periods outside the host.

In 1977, the World Health Organization declared that smallpox had been eradicated. Although the eradication campaign of the World Health Organization was based on the requirement of close person-to-person contact, hospital outbreaks during that era suggest the potential for high transmissibility.36 Approximately 30% of susceptible people who the patients contacted became infected.

The infective dose is assumed to be low, possibly 10 to 100 organisms. Monkeypox, a closely related orthopoxvirus found in Africa, causes a
Disease nearly indistinguishable from smallpox both clinically and by its lethality in humans. Fortunately, transmission of monkeypox from human to human does not appear to be nearly as effective as it is for smallpox.

**Diagnosis and Patient Precautions.** The diagnosis of smallpox will require that the clinician differentiate it from other vesicular exanthems such as chickenpox. Clinical diagnosis is based on observation of the distinctive rash with the accompanying symptoms, including malaise, fever, rigors, vomiting, headache, and backache. A definitive diagnosis will depend on one of several laboratory tests. Virions that can be seen with electron microscopy or Guarnieri bodies that can be seen on an exam with light microscopy do not discriminate variola from vaccinia, monkeypox, or cowpox. In the past, the differentiation among the orthopox viruses was done by viral isolation and observation of viral growth on the chorioallantoic membrane of eggs. Virions produced by variola are small and grayish-white. PCR methods now promise the relatively rapid, definitive identification of the agent in clinical or field samples. A diagnosis of smallpox should be considered an international emergency and should be reported immediately to public health authorities. Strict quarantine with respiratory isolation for 17 days is mandated for all people with whom the patient has had contact. Patients are infectious from the time of the onset of the eruptive exanthem, which typically occurs 3 to 6 days after the onset of fever. Airborne precautions must be implemented immediately.

**Therapy and Prophylaxis.** Methisazone was licensed for prophylaxis in susceptible patients during the eradication program, but its efficacy was questionable and it is no longer available. Cidofovir has been shown to be effective, in vitro and in vivo, against a broad range of poxviruses but is not licensed for the treatment of poxviruses. Other promising drugs are in preclinical trials. Data from the period during which smallpox was endemic suggest that vaccination given within a few days after exposure provides some protection and provides almost complete protection in patients who have previously been immunized. All people who are exposed through contact with an infected patient or a terrorist weapon release should immediately be immunized. A licensed vaccine (Dryvax, Wyeth Laboratories, Sanford, NC) prepared from calf lymph is available in limited supply in the United States. The vaccine must be given by scarification. Both cellular and humoral immune responses are important in protection and recovery from smallpox. During the World Health Organization eradication program, a clinical “take” after vaccination within the past 3 years was considered to provide protective immu-
Commercial distribution of smallpox vaccine in the United States was stopped in May 1983; immunization of military personnel was stopped in July 1988. Vaccination is contraindicated in immune-compromised individuals; however, most authorities state that vaccination after exposure is indicated in all patients except those who are severely immunosuppressed. Concurrent administration of vaccinia immunoglobulin is recommended for pregnant women and for individuals with eczema. Because smallpox is essentially the only relatively highly contagious human agent and vaccination is possible, immunization of the population may be considered. A number of technical and logistical barriers exist, not the least of which is the epidemic of human immunodeficiency virus and acquired immunodeficiency syndrome, which was not a factor during the initial smallpox eradication program.

**Viral Encephalitides**

**Clinical Presentation.** The most common presentation after infection with the agents for the genus Alphavirus is a systemic, viral febrile syndrome that consists of fever, headache, and myalgia, which may progress to encephalitis in some cases. Patients who are encephalitic may have fever, headache, confusion, obtundation, dysphasia, seizures, paresis, ataxia, myoclonus, and cranial nerve palsies. The occurrence and degree of neurologic disease depends on which of the 3 viruses—Venezuelan equine encephalitis (VEE), eastern equine encephalitis (EEE), or western equine encephalitis (WEE)—is involved. EEE and WEE are endemic to the United States and VEE is endemic to South and Central America.

VEE was probably selected by early developers of biological weapons because it is easy to produce and has a high infectivity and the ability to produce symptoms in essentially 100% of human infections. The incubation period is typically 2 to 6 days, although it may be shorter. In addition to the febrile syndrome (38°C-40.5°C), patients may experience photophobia, sore throat, myalgia, and vomiting. Although VEE is only incapacitating for most victims, a small percentage (0.5%-4.0%) progress to neurologic involvement. The virus can be lethal in children and in the elderly. Epidemics that involved 50,000 to 100,000 people were reported in South America and Central America.

EEE and WEE have similar signs and symptoms; EEE is typically the most severe. The human infection rate is much lower for EEE and WEE than it is for VEE during natural outbreaks. The incubation period for EEE is 5 to 15 days. After a febrile illness that lasts up to 11 days, neuro-
logic disease begins, which may progress to somnolence, delirium, and eventually coma over the next few days. EEE may have a case-mortality rate of 50% to 75%, and as many as 30% of survivors may be left with serious neurologic sequelae. The incubation period for WEE is 5 to 10 days, and the case-fatality rate is approximately 10%. Symptoms usually begin with malaise, headache, and fever, which are often followed by nausea and vomiting. Like VEE, WEE is less virulent for adults than for children. Most adults recover, but may have fatigue, headaches, and other chronic symptoms for months or years.

**Agent and Infective Dose.** Alphaviruses are naturally transmitted by mosquitoes but are also highly infectious by aerosol. There is no evidence that person-to-person transmission occurs. The viruses grow to exceptionally high titer in roller bottles or other simple production systems and are relatively stable during preparation and storage. There are 11 distinct subtypes of VEE, 3 of which are pathogenic for horses and can lead to human epidemics. The WEE complex is made up of 6 viruses; EEE comprises 2. VEE is maintained in nature in rodent-mosquito cycles, whereas EEE and WEE are maintained in passerine birds and mosquitoes. The infective dose of this family of viruses is believed to be 10 to 100 organisms.

**Diagnosis and Patient Precautions.** Because of the nonspecific nature of signs and symptoms early in the course of the disease, a history of possible exposure and epidemiologic findings may be most useful in the diagnosis of encephalitis. The challenge with naturally occurring cases is to include these agents in a diagnostic differential. Viral isolation, serologic testing, or both can be used for making a specific diagnosis. Virus may be recovered from a patient’s serum during the first few days of the febrile syndrome but typically not after the onset of encephalitic symptoms. Isolates have also been recovered from pharyngeal washes. Antibody is generally present by the second week of illness. Virus may often be isolated from postmortem brain-tissue samples. When PCR is widely available and validated for diagnostic use, it will probably be the most useful means for differentiation of the viral encephalitides.

**Treatment and Prophylaxis.** No specific therapeutics exist for the viral agents that cause these encephalitic syndromes. Patients should be treated symptomatically to control fever and neurologic and muscular signs and to maintain fluid balance and blood gases.

Vaccination is effective in the protection of animals, and apparently of humans, from natural inoculation by infected mosquitoes and by laboratory exposure. The US Army has developed live, attenuated (TC-83) and
inactivated (C-84) VEE vaccines and inactivated vaccines for EEE and WEE. TC-83 has proven to be somewhat reactogenic; approximately 20% of the recipients of TC-83 have experienced fever, malaise, and headache after the vaccination. All 4 vaccines are in IND status. Animal data suggests that protection from aerosol exposure may be more difficult to achieve than protection from natural exposure. Immunity after infection is probably lifelong to the homologous serotype, but cross-protection is weak for heterologous serotypes. The US Army has developed a series of recombinant (infectious clone) alphavirus vaccines, which are in preclinical trials. This approach may provide adequate protection against aerosol infection, but multiple or polyvalent vaccines may be necessary.

**Viral Hemorrhagic Fevers**

**Clinical Presentation.** The viral hemorrhagic fever (VHF) syndrome is characterized by febrile illness with vascular involvement. The incubation period for the various viral agents varies from 4 to 21 days. In addition to fever, malaise, and prostration, the agents cause a general increase in vascular permeability and abnormalities of circulatory regulation. Initial examination may show only conjunctival injection, mild hypotension, flushing, and petechial hemorrhages. Severe VHF syndrome progresses to shock and to generalized mucous membrane hemorrhage, often with neurologic, hematopoietic, or pulmonary involvement. Hepatic involvement is common, and renal failure is related to cardiovascular compromise.

Although there are marked similarities in the presentation of the VHFs, there are also distinguishing manifestations of the related viral agents. Jaundice is a regular event only with yellow fever. For Rift Valley fever (a hepatotropic virus similar to yellow fever), hemorrhagic fever is seen only rarely, whereas retinitis is common. Hemorrhagic manifestations are also not common with Lassa fever, and neurologic complications are infrequent. For Junin and Machupo, both South American viruses, hemorrhagic and neurologic manifestations are much more common. Likewise, Congo-Crimean hemorrhagic fever infection produces severe hemorrhagic disease with disseminated intravascular coagulation. Dengue hemorrhagic fever is usually seen only in individuals who have been previously exposed to other dengue serotypes.

**Agent and Infective Dose.** Viruses from the Arenaviridae (Lassa, Junin, Machupo, Guanarito, and Sabia), Bunyaviridae (Rift Valley fever and Congo-Crimean hemorrhagic fever viruses and hantaviruses),
Filoviridae (Marburg and Ebola), and Flaviviridae (yellow fever and Dengue) families are causative agents of VHF. VHF agents are all RNA viruses that are naturally transmitted to humans by animal reservoirs or insect vectors. Several of these viruses fit the definition of emerging diseases because changes in human demographics have resulted in outbreaks of disease. The mortality rates of the VHF syndrome typically range from 5% to 20%; however, the Filoviridae may produce mortality rates of up to 90%. Most of the viruses are highly infectious (infectious dose of 1-10 organisms) by aerosol and can be grown to high titers in cell culture or animal systems. Therefore all might be suitable candidates for malicious use. Although none of the VHF viruses were tested in weapons in the former US offensive program, the Filoviridae were tested for weaponization by the Soviets, and it has been reported in the media that Aum Shinrikyo sought to acquire a culture of Ebola during the Kikwit, Zaire, outbreak in 1995.

**Diagnosis and Patient Precautions.** Viral hemorrhagic fever should be suspected in any patient with a severe febrile illness and evidence of vascular involvement. Because of the restricted geographic distribution of these viruses, obtainment of the patient’s history of travel to areas where the viruses occur naturally is critical for a diagnosis to be made. History of biological warfare attack would, of course, be further reason to include this group of viruses in a differential diagnosis. With the exception of Hantavirus infections, most patients have a detectable viremia when they are first seen for treatment. Definitive diagnosis requires viral identification through antigen-capture ELISA or reverse-transcriptase PCR, which is possible early in disease, or identification of immunoglobulin-M, which can also be done by ELISA, sometimes during the course of the disease. ELISA can be conducted safely with B-propiolactone inactivated sera, and PCR can be performed with samples that have been extracted with chloroform and methanol. Definitive viral isolation may take 3 to 10 days for most VHF agents and longer for the hantaviruses and should be done in biological containment (biosafety level-4 [BSL-4]) laboratories. The combination of cell culture, electron microscopy, and immunohistochemistry may be useful when other methods fail. Until the nucleic acid–based assays become widely available and validated for individual case diagnosis, government facilities such as the Centers for Disease Control and Prevention/National Centers for Infectious Disease (CDC) or the US Army Medical Research Institute of Infectious Diseases should be used as reference laboratories for the VHF's.
Treatment and Prophylaxis. Patients should be hospitalized with minimal transportation to prevent further trauma to the already-compromised peripheral vascular system. Intravenous access should be avoided unless absolutely necessary, and replacement therapy (fresh frozen plasma, clotting factor concentrates, and platelets) should be used with more severe hemorrhage. Transportation by air may be contraindicated because of the potential negative effect of rapid changes in ambient pressures on fragile pulmonary capillary beds. The management of hypotension in patients with VHF is difficult. The patients often respond poorly to fluid infusions and are at risk for pulmonary edema. Dopamine and α-adrenergic agents have been suggested, but not widely tested, as therapies for the VHF s. Anticoagulant therapy is indicated in response to disseminated intravascular coagulation. The diffuse nature of the assault on the vascular tree may necessitate multiple organ system support.

The antiviral drug ribavirin, a nucleoside analog, is useful as therapy for Lassa fever and as an adjunct to immune therapy for Junin infection. There are some data that suggest that ribavirin may be of value for Bolivian hemorrhagic fever, Congo-Crimean hemorrhagic fever, and Rift Valley fever. Convalescent plasma that contains adequate neutralizing antibody has been effective in the treatment of Argentine hemorrhagic fever (causal agent, Junin virus) and Bolivian hemorrhagic fever. Neither ribavirin or passive immune therapy has demonstrated effectiveness against Ebola virus in nonhuman primates.

A licensed, highly effective vaccine has greatly reduced the risk of yellow fever. Likewise, an effective IND vaccine for Argentine hemorrhagic fever that was developed by the US Army has been widely used in Argentina and has effectively reduced the incidence of that disease.

Biological Toxins

Biological toxins merit our consideration not because they are especially effective biological warfare agents but criminals and would-be terrorists have used biological toxins more commonly than replicating agents. Toxins are biological poisons produced by living organisms (animals, plants, or microorganisms). They differ significantly from replicating agents (bacteria or viruses) and from chemical agents. They do not replicate in the human body, as do microorganisms, and they are not typically manmade, as are chemical agents. Although toxins have been relegated to second-class status in most military offensive biological warfare programs over the years, assassins have often selected toxins. The selection of toxins by marginally funded terrorists is prob-
ably related to the ease of access and ease of production or extraction of toxins and to the perception that toxins are less dangerous to work with than the replicating agents. As aerosol weapons, toxins must meet many of the same requirements as bacteria or viruses. Because they are neither dermally active or volatile, they must be presented to the victim as respirable aerosols that will allow contact with the more vulnerable inner surfaces of the lung. Fortunately, this complicates an aggressor’s task because it limits the number of toxins that are potent enough to be effective. Similar to toxic chemicals, toxin doses can be evaluated as lethal or incapacitating; there is no “infective” dose.

Of the hundreds of biological toxins in nature, only a very small number are potent enough to be used as biological weapons. Because toxins must be delivered as respirable aerosols, the use of a toxin as a battlefield—or urban—weapon is limited by its potency and ease of production. A theoretical calculation of the approximate quantities of toxins of varying potencies that would intoxicate people exposed to the toxin in large open areas under optimal meteorologic conditions is shown in Figure 1. The figure is based on a mathematical model that has been field tested and found to be valid. For a toxin with an aerosol toxicity of $0.025 \, \mu g/kg$, 80 kg of toxin would be needed to cover 100 km$^2$ with a cloud, which would expose individuals to an approximate lethal dose of 50 (LD$_{50}$). LD$_{50}$ means, for example, that a person who weighs 70 kg would have a 50% chance of surviving after receiving a 70 µg dose of a toxin with an LD$_{50}$ of 1.0 µg/kg. Note that for toxins less potent than botulinum or the staphylococcal enterotoxins, hundreds of kilograms, or even tons, would be needed to cover an area of $10 \times 10$ km ($100$ km$^2$) with an effective aerosol. If this is true, the number of toxins that could be used to blanket a city is very limited; most less potent agents cannot be produced and delivered with current technology in the quantity needed to cover large areas. Ease-of-production is another limiting factor, and stability after the toxin is made into an aerosol further limits the effectiveness of toxin weapons.

If other characteristics of toxins are ignored, it is apparent that if a toxin is not adequately potent, sufficient quantities cannot be produced to make even 1 weapon. Because of low potency, hundreds of toxins can be eliminated because they would be ineffective for use as mass-casualty weapons in our cities. Certain plant toxins with marginal potency, such as ricin, could be produced in large quantities (tons). These toxins could possibly be made into weapons by a very competent organization. At the other extreme, several bacterial toxins are so lethal that mass-casualty...
quantities are measured not in tons, but in kilograms, which are quantities that can be produced more easily. Such toxins are potential threats to our cities. Some toxins are adequately potent and can be produced in sufficient quantities to be used as weapons but are too unstable in the atmosphere to be candidates for weaponization. Although stabilization of naturally unstable toxins and enhanced production of those toxins (which are now difficult to produce) may be possible, there is no evidence at this time for successful amplification of the potency of a naturally occurring toxin.

The incapacitation of humans caused by toxins, as well as the lethality of toxins, must be considered. A few toxins cause illness at levels that are many times less than the concentration needed to kill. For example, toxins that directly affect membranes or fluid balance within the lung may greatly reduce gas transport without causing death. Less potent toxins could also be significant threats as aerosols in a confined space, such as in the air-handling system of a building. Breakthroughs in delivery vehicle efficiency or toxin “packaging” by an aggressor may alter the relationship between toxicity and quantity, as shown in Figure 1 but, even at best, the quantities needed could be reduced by only one half for a given potency.

Figure 1. Toxicity, in mouse LD$_{50}$, plotted against the quantity of toxin required to provide a theoretically effective open-air aerosol exposure, under ideal meteorological conditions, to an area of 100 km$^2$. Although the toxicity is based on studies with mice, it is believed to be very similar in humans. The mathematical model corrects for human parameters such as respiration. Ricin, saxitoxin, and botulinum, and trichothecene mycotoxins (T-2) kill at the concentrations depicted. (From Franz DR. Defense against toxin weapons. In: Zajtchuk R, editor. Textbook of military medicine: medical aspects of chemical and biological warfare. Bethesda (MD): Borden Institute; 1997. p. 603-19; adapted from Spertzel RO, Wannemacher RW, Patrick WC, Linden CD, Franz DR. Technical ramifications of inclusion of toxins in the chemical weapons convention (CWC). Alexandria (VA): Defense Nuclear Agency; 1992. p. 18. DNA Technical Report 92-116.)
**Classes of Toxins.** The most potent biological materials known are protein toxins produced by bacteria. They are generally more difficult to produce on a large scale than the plant toxins are but are many, many times more toxic. Diphtheria, tetanus toxins, botulinum toxins (7 toxins closely related to tetanus toxin), and the staphylococcal enterotoxins (also 7 different toxins) are well-known examples of bacterial toxins. The botulinum toxins are so potent that lethal aerosol weapons could be produced with quantities of toxin that are attainable relatively easily with present technology, but they have not been proven to be very stable in the atmosphere. The botulinum toxins cause death through the paralysis of respiratory muscles. Staphylococcal enterotoxins, when inhaled, cause fever, headache, diarrhea, nausea, vomiting, myalgias, shortness of breath, and a nonproductive cough within 2 to 12 hours after exposure; they can also kill, but only at much higher doses. Staphylococcal enterotoxin B can incapacitate at levels at least 100 times lower than the lethal level. These levels would also most likely be delivered as respiratory aerosols.

Other bacterial toxins, which are classified generally as membrane-damaging, are derived from *Escherichia coli* (hemolysins), *Aeromonas, Pseudomonas,* and *Staphylococcus* alpha, (cytolycins and phospholipases) and are moderately easy to produce but vary a great deal in stability. Many of these toxins affect bodily functions, or even kill, by forming pores in cell membranes. In general, their lower potencies make them less likely to be mass-casualty threats used by terrorists.

A number of the toxins produced by marine organisms or by bacteria that live in marine organisms could be used to produce terrorist biological weapons. Saxitoxin, the best known representative of this group, is a sodium-channel blocker and is more potent by inhalation than by other routes of exposure. Unlike oral intoxication with saxitoxin (paralytic shellfish poisoning), which has a relatively slow onset, intoxication with inhaled saxitoxin can be lethal in a few minutes. Saxitoxin could be used as an antipersonnel weapon; however, because it cannot currently be chemically synthesized efficiently or produced easily in large quantities from natural sources, it is unlikely to be used as an area aerosol. Tetrodotoxin is similar to saxitoxin in mechanism of action, potency, and physical characteristics. Palytoxin, which comes from a soft coral, is extremely potent and quite stable in impure form, but the difficulty of production or harvest from nature reduces the likelihood that palytoxin will used as a mass-casualty weapon. The brevetoxins, which are produced by dinoflagellates, and the blue-green algal toxins such as the hepatotoxin microcystin have limited potencies. Either difficulty of
production or lack of sufficient toxicity limits the likelihood of the use of many of these toxins as mass-casualty weapons.

The trichothecene mycotoxins, which are produced by various species of fungi, are also examples of low–molecular weight toxins (molecular weight, 400-700 d). The unproven Yellow Rain incidents in Southeast Asia in the early 1980s suggest the danger of T-2 mycotoxin as a biological warfare agent. T-2 is one of the more stable toxins; it retains its bioactivity even when it is heated to a high temperature. High concentrations of sodium hydroxide and sodium hypochlorite are required to neutralize T-2. Aerosol toxicities are generally too low to make this class of toxins useful to an aggressor as a mass-casualty weapon as defined in Figure 1; however, unlike most toxins, these are dermally active. The clinical presentation of T-2 includes nausea, vomiting, weakness, low blood pressure, and burns in exposed areas.

Toxins derived from plants are generally easy to produce in large quantities at minimal cost in a low-technology environment. For this reason, they are more likely to be choices of the would-be terrorist, and ricin has actually been used in recent years. Ricin is a protein toxin derived from the bean of the castor plant. Approximately 1 million tons of castor beans are processed annually worldwide in the production of castor oil. The resulting waste mash is 3% to 5% ricin by weight. Because of its marginal toxicity, at least 1 ton of the toxin would be necessary to produce an effective mass-casualty weapon. Unfortunately, the precursor raw materials are available in those quantities throughout the world.

Animal venoms often contain a number of toxic proteins, as well as nontoxic proteins. Until recently, it would have been practically impossible to collect enough of these materials to develop them as biological weapons. However, many of the venom toxins have now been sequenced and some have been cloned and expressed (produced by molecular biology techniques). Some of the smaller venom toxins could also be produced by relatively simple chemical synthesis methods. Examples of the venom toxins are (1) the ion channel (cationic) toxins, such as those found in the venoms of the rattlesnake, scorpion, and cone snail; (2) the presynaptic phospholipase A2 neurotoxins of the banded krait, Mojave rattler, and Australian taipan snakes; (3) the postsynaptic (curarelike) alpha neurotoxins of the coral, mamba, cobra, and sea snakes and of the cone snail; (4) the membrane-damaging toxins of the Formosan cobra and the rattlesnake; and (5) the coagulation-anticoagulation toxins of the Malayan pit viper and the carpet viper. Some of the toxins in this group must be considered to be potential future terrorist threats as large-scale
production of peptides becomes more efficient; however, the current difficulty in production of venom toxins in a large quantity may limit the threat potential of many of these toxins.

**How Toxins Work.** Unlike chemical agents, there are many classes of toxins and they differ widely in their mechanisms of action. This makes the job of medically protecting victims difficult because there are seldom instances where 1 vaccine or therapy would be effective against more than 1 toxin. The time from exposure to the onset of clinical signs may also vary greatly among toxins.

Some neurotoxins, such as saxitoxin, can kill within minutes after the inhalation of a lethal dose. This toxin acts by directly blocking nerve conduction, and it causes death by paralyzing the muscles of respiration. Yet, at just less than a lethal dose, the exposed individual may not even feel ill or may just feel dizzy. Because of the rapid onset of signs after inhalation, prophylaxis (immunization or pretreatment with drugs) would be required to protect individuals from these rapidly acting neurotoxins. Unprotected individuals who inhale a lethal dose would probably die before they could be helped, unless they could immediately be intubated and artificially ventilated. Although the mechanism of death after inhalation of saxitoxin is believed to be the same as when the toxin is administered intravenously, it is more potent if it is inhaled.

Other neurotoxins, such as the botulinum toxins, must enter nerve terminals before they can block the release of neurotransmitters that normally cause muscle contraction. Botulinum neurotoxins generally kill by the relatively slow onset of respiratory failure (hours to days). The intoxicated individual may not have signs of disease for 24 to 72 hours. The toxin blocks biochemical action in the nerves that activate the muscles that are necessary for respiration, which leads to suffocation. Intoxications such as this can be treated with antitoxin (passive immunotherapy) that can be injected hours (up to 24 hours in monkeys and probably also in humans) after exposure to a lethal dose of toxin, and the antitoxin can still prevent illness and death. Although the mechanisms of toxicity of the botulinum toxins appear to be the same after any route of exposure, the actual potency is less by inhalation (ie, the lethal dose of botulinum toxin is slightly greater by inhalation).

Neurotoxins effectively stop nerve and muscle function without causing microscopic damage to the tissues, but other toxins destroy or damage tissue directly. For these toxins, prophylaxis is important because the point at which the pathologic change becomes irreversible often occurs within minutes or a few hours after exposure. An example
of this type of toxin is microcystin, which is produced by blue-green algae and binds very specifically to an important enzyme inside liver cells; this toxin does not damage other cells of the body. Unless uptake of the toxin by the liver is blocked, irreversible damage to the organ occurs within 15 to 60 minutes after exposure to a lethal dose. In this case, the tissue damage to a critical organ, the liver, is so severe that therapy may have little or no value. For this toxin, unlike most, the potency is the same no matter what the route of exposure is.

The consequences of intoxication may vary widely with the route of exposure, even with the same toxin. The plant toxin ricin kills by blocking protein synthesis in many cells of the body, but no lung damage occurs with any exposure route except inhalation. If ricin is inhaled, as might be expected during a biological attack, microscopic damage is limited primarily to the lung and that damage may be caused by a mechanism that is different from that which occurs if the toxin is injected. Furthermore, when equivalent doses of toxin are used, much more protective antibody must be injected to protect from inhalation exposure than that needed to protect from intravenous injection of the toxin. Finally, although signs of intoxication may not be noted for 12 to 24 hours, microscopic damage to lung tissue begins within 8 to 12 hours or less. Irreversible biochemical changes may occur within 60 to 90 minutes after exposure, which also makes therapy difficult.

The potencies of some bacterial toxins are too low to make the toxins effective lethal mass-casualty weapons, according to the standards described in Figure 1. However, extremely low levels of some of the toxins cause incapacitating illness. Therefore lethality alone is not an appropriate criterion on which to base the potential of a toxin as a threat. The staphylococcal enterotoxins are examples. They can cause illness at extremely low doses, but relatively high doses are required to kill. These toxins are unusual because they act by causing the body to release abnormally high levels of its own cytokines, which are beneficial and necessary for life in very small amounts but are harmful at higher levels.

Only one class of easily produced toxins, the trichothecene mycotoxins, is dermally active. Therefore trichotheccenes must be considered by different standards than all other toxins. They can cause skin lesions and systemic illness without being inhaled or absorbed through the respiratory system. Skin exposure or ingestion of contaminated food are the two most likely routes of exposure. Nanogram quantities per square centimeter of skin cause irritation, and microgram quantities cause
necrosis. If the eye is exposed, microgram doses can cause irreversible injury to the cornea. The aerosol potency of even the most toxic member of this group is low enough that large-quantity production (approximately 80 metric tons to expose a 100 km² area with respirable aerosol) makes an inhalation threat unlikely on the battlefield. These toxins, therefore, might be dispersed as larger particles, probably visible in the air and on the ground and foliage. In contrast to treatment for exposure to any of the other toxins, simply washing the skin with soap and water within 1 to 3 hours after an exposure will eliminate or greatly reduce the risk of illness or injury.

The concept in Figure 1 is amplified by classes of toxins in Table 2. All known toxins are categorized by potency into most potent, highly potent, or moderately potent. Only the most toxic toxins could be used in a weapon to produce mass casualties—and then only if the toxins were producible and stable enough to deploy. Highly potent toxins could probably be used in closed spaces such as the air-handling system of a building or as a relatively ineffective terror weapon in the open; collective filtration would be effective against these toxin aerosols in closed spaces. The moderately potent toxins would most likely be useful only as assassination weapons.

**Botulinum Toxin**

**Clinical Presentation.** Botulinum toxin serotype A is 10,000 to 100,000 times more potent than most of the well-known chemical warfare agents. The onset of signs of botulinum intoxication is dose-dependent and may vary from 24 hours to several days after exposure. Bulbar palsies are prominent early, with ocular symptoms such as blurred vision caused by mydriasis, diplopia, ptosis, and photophobia and other bulbar signs such as dysartria, dysphonia, and dysphagia. Skeletal muscle paralysis follows, manifested as a symmetrical, descending, and progressive weakness that may culminate abruptly in respiratory failure. Progression from the onset of symptoms to respiratory failure has occurred in as few as 24 hours in cases of food-borne botulism.

**Agent and Toxic Dose.** Botulinum toxins are proteins with a molecular weight of approximately 150,000 d that are produced by the anaerobic bacterium *Clostridium botulinum*. There are 7 immunologically distinct but related toxins that are produced by different strains of the bacterium. All serotypes act with similar mechanisms and result in similar pathology. The estimated toxic dose for serotype A, the most common serotype studied for weaponization, is only 0.001 µg/kg of body weight.
The toxins act by binding to the presynaptic nerve terminal at the neuromuscular junction and cholinergic autonomic sites. After internalization, the toxins prevent the release of acetylcholine presynaptically and thus block neurotransmission. This interruption of neurotransmission causes the bulbar palsies and skeletal muscle weakness associated with clinical botulism. Iraqi government officials admitted to a United Nations Special Commission that they had conducted research to develop offensive botulinum weapons before the Gulf War. They later admitted that they had also filled and deployed botulinum munitions immediately before the start of hostilities. The United States and the Soviet Union studied this family of toxins during development of their biological weapons programs, but botulinum was never considered to be an ideal weapons agent, probably because of its relative instability in the environment and resultant relatively low effectiveness.

**Diagnosis and Patient Precautions.** Before the onset of ventilatory effects, a physical examination usually shows an alert and oriented afebrile patient. Postural hypotension may be present. Mucous membranes may be dry and crusted, and the patient may complain of a dry mouth or sore throat. Ptosis is often an early clinical sign, and extraocular muscle palsies may be observed. Later in intoxication, pupils may be dilated and even fixed. Variable degrees of skeletal muscle weakness occur, which often manifest as a “heavy head” before ventilatory difficulty begins. Deep tendon reflexes may be present or absent. In the final stages of severe

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<td>Total</td>
<td>17</td>
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<td>&gt;305</td>
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*Most toxic (LD$_{50}$ < 0.025 µg/kg), highly toxic (LD$_{50}$ 0.025-2.5 µg/kg), and moderately toxic (LD$_{50}$ > 2.5 µg/kg).*

<table>
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intoxication, the patient may become cyanotic or have narcosis from carbon dioxide retention. An epidemic of cases of descending and progressive bulbar and skeletal paralysis in afebrile patients may suggest a release of a botulinum toxin weapon. Differentials may include Guillain-Barré syndrome, myasthenia gravis, or tick paralysis. The edrophonium test may be transiently positive for botulism, so it may not be possible to distinguish botulinum intoxication from myasthenia. Laboratory tests are of limited value in the diagnosis of botulism. Toxin may be found in the serum or stool after food poisoning, but studies in nonhuman primates suggest that toxin is not often found in these samples after aerosol intoxication. Seroconversion is seldom seen for survivors of intoxication, probably because of the high potency and thus subimmunogenic dose in a nonlethal exposure. Toxin may be present on nasal mucous membranes, and identifiable with ELISA, for 24 hours after inhalation exposure. Patients may be handled with standard isolation precautions.

**Treatment and Prophylaxis.** Respiratory failure is the most serious complication and necessitates tracheostomy, endotracheal intubation, and ventilatory assistance. Intensive and prolonged nursing care may be required for recovery; for serotype A, support may be necessary for months. Nonhuman primate studies have shown that after aerosol exposure, botulinum antitoxin can be effective and can prevent all signs of intoxication if it is given before the onset of symptoms. Data from infant botulinum cases also suggest that administration of antitoxin is of value if the disease has not progressed to a stable state.

A trivalent equine antitoxin is available from the CDC for food poisoning. The US Army has developed a despeciated [F(ab’)2] equine heptavalent antitoxin which is in IND status; preclinical trials and compassionate use in infant botulinum intoxication suggest that it is effective. Use of either antitoxin requires skin testing for horse serum sensitivity before administration. A pentavalent toxoid that was also effective against inhalation challenge in preclinical trials is available as an IND.

**Staphylococcal Enterotoxins**

**Clinical presentation.** Intoxication with the *Staphylococcus aureus* enterotoxin B begins 3 to 12 hours after inhalation of the toxin. Patients may experience the sudden onset of fever, headache, chills, myalgia, and nonproductive cough. In more severe cases, dyspnea and retrosternal chest pain may develop. Nausea, vomiting, and diarrhea typically occur as a result of inadvertent swallowing of toxin; fluid loss can be significant. A fever of 39.4°C to 41.1°C, with chills and prostration, may persist for 5 days, and the cough may persist for as long as 1 month.45
Agent and Toxic Dose. S. aureus produces a number of exotoxins. Staphylococcal enterotoxin B (SEB) was made into a weapon and tested by the United States during the US offensive program. The extreme potency and stability of SEB, along with its low incapacitating-lethality ratio, made it a likely candidate as an incapacitating biological warfare agent. It proved to be stable and effective in field tests. SEB, staphylococcal enterotoxin C, and other staphylococcal enterotoxins might also be used as weapons agents. The toxins are exotoxins because they are excreted from the organism; however, they are called enterotoxins because they normally exert their pathogenic effects on the gastrointestinal tract. SEB is heat-stable and commonly causes food poisoning in humans after the toxin is produced in improperly handled foods and subsequently ingested. Many of the effects of these toxins are mediated by interactions with the host’s immune system. Toxins bind directly to the major histocompatibility complex, which stimulates a large proliferation of T cells. This activity of the toxins is referred to as a superantigen effect and results in the secretion of various cytokines, which mediate most of the toxic effects of SEB. The aerosol-incapacitating dose is 30 nanograms per person, and the lethal dose is believed to be approximately 1.7 micrograms per person.

Diagnosis and Patient Precautions. As with the botulinum toxins, intoxication caused by SEB inhalation is a clinical and epidemiologic diagnosis. Differential diagnostic considerations must include a number of respiratory pathogens such as influenza, adenovirus, and mycoplasma, all of which present as a flulike syndrome. After a terrorist attack with SEB, large numbers of patients would be seen within a relatively short time, as opposed to the usual transmission pattern during an influenza epidemic. Intoxication with SEB tends to progress rapidly to a fairly stable but nonlethal state, whereas pulmonary anthrax or pneumonic plague would both progress to death if untreated. SEB is not associated with pulmonary infiltrates seen on chest radiographs, as are tularemia, plague, and Q fever. The ventilatory dyspnea associated with botulinum intoxication is obviously neuromuscular in origin and is not accompanied by fever, as is the early onset respiratory syndrome in SEB intoxication. Patients may be handled with standard isolation precautions.

As with botulinum poisoning, laboratory findings are not very helpful in the diagnosis of SEB intoxication. A nonspecific neutrophilic leukocytosis and elevated erythrocyte sedimentation rate may be seen 12 to 24 hours after exposure. The toxin is difficult to detect in serum when symptoms occur. Data from animal studies, however, show that SEB in the serum is transient and metabolites accumulate in the urine and can be
_detected for several hours after exposure. The toxin can be detected in nasal swabs for at least 24 hours after exposure, and antibody can be detected in serum after recovery.

**Treatment and Prophylaxis.** Therapy is limited to supportive care. Attention must be paid to oxygenation and hydration, and positive end-expiratory pressure ventilation may be necessary in severe cases with pulmonary edema. The value of steroids is controversial. Most patients would recover from inhalation exposure and could return to normal function within 1 to 2 weeks, although cough may persist longer than that.

Vaccine and passive antibody preparations are not available. The US Army has developed a toxoid and several recombinant vaccines for the enterotoxins that are in preclinical trials and good manufacturing practices production.

**Ricin**

**Clinical Presentation.** Ricin toxin, although it lacks the characteristics of a mass-casualty–weapons agent, has been a favorite of would-be terrorists or assassins. The appeal of ricin is probably related to availability, relative ease of extraction, and popularization by the press. Unlike with botulinum intoxication, the pathogenesis of disease with ricin is dependent on the route of intoxication. Oral intoxication with castor beans is less severe than generally believed. Of 751 cases of castor bean ingestion described by Rauber and Heard in an article published in 1985, there were 14 deaths, 12 of which occurred before 1930. That is a death rate of only 1.9%, which is much lower than traditionally believed. Only 2 lethal cases have been documented since 1930; one involved a 24-year-old man who ate 15 to 20 beans and the other involved a 15-year-old boy who ate 10 to 12 beans. Oral ingestion, if serious or lethal, results in the following classic clinical course: rapid (less than a few hours) onset of nausea, vomiting, and abdominal pain followed by diarrhea, rectal hemorrhage, anuria, cramps, dilation of the pupils, fever, thirst, sore throat, headache, vascular collapse, and shock. Death occurs on the third day or later.

In a large clinical trial, ricin was used as an injectable anticancer drug and was well tolerated at the dose of 18 to 20 µg/m². Flulike symptoms, fatigue, muscular pain, and sometimes nausea and vomiting were reported. Georgi Markov, a Bulgarian defector who was working for the British Broadcasting Corporation in London, was assassinated by intramuscular injection of what is believed to be as much as 500 µg of ricin. Markov had immediate local pain that progressed to weakness within 5 hours. Fifteen to 24 hours later, he had a high temperature, nausea, and
vomiting, and he was admitted to the hospital at 36 hours after the injection. When he was admitted to the hospital, he had fever, tachycardia, and local lymphadenopathy. Two days after the attack he suddenly became hypotensive and tachycardic and then went into shock. Early on the third day, Markov became anuric and began vomiting blood and died shortly after. His white blood cell count was 33,200/mm³ when he died.

In a study by Wilhelmsen and Pitt,⁴⁹ the clinical picture after ricin aerosol was inhaled by laboratory animals was characterized by a dose-dependent preclinical period of 8 to 24 hours, followed by anorexia and progressive decrease in physical activity. Death occurred 36 to 48 hours after the challenge. Gross and histopathologic changes were confined to the thoracic cavity and included acute marked pneumonia to severe fibrinopurulent pneumonia, with variable degrees of diffuse necrosis and acute inflammation of airways. There was also diffuse, severe alveolar flooding and peribronchovascular edema, acute tracheitis, and purulent mediastinal lymphadenitis. The cause of death after inhalation intoxication appears to be pulmonary damage and resultant pulmonary edema, alveolar flooding, and hypoxemia.

**Agent and Toxic Dose.** Ricin is a globular protein with a molecular weight of 66,000 d that makes up, by weight, 1% to 5% of the castor bean, which is the fruit of the plant *Ricinis communis*. The 2 glycoprotein chains that make up the protein must be associated for toxicity. The B-chain, a lectin, binds to galactosides of cell-surface carbohydrates, and the wholotoxin is internalized by means of endocytosis. After it is transported through the Golgi complex, the A-chain enzymatically stops protein synthesis by blocking elongation factor-2 and binding to the 28S ribosomal subunit. The LD₅₀ varies greatly by route and species. In the mouse, the LD₅₀ is 3 to 5 µg/kg by inhalation, 5 µg/kg by intravenous injection, 22 µg/kg by intraperitoneal injection, 24 µg/kg by subcutaneous injection, and 20 mg/kg by intragastric administration. There was no dermal toxicity at 50 µg/spot in mice (Dr Robert W. Wannemacher, personal communication, September, 1994).

**Diagnosis, Samples, and Assay and Patient Precautions.** As with other potential terrorist intoxication agents, epidemiologic findings will probably play a central role in the diagnosis of ricin intoxication. Relatively rapid onset of severe pulmonary and systemic distress in a previously normal population would be suggestive of ricin inhalation. A differential diagnosis should include SEB and exposure to pyrolysis by-products of organofluorine polymers or other organohalides, oxides of nitrogen, and phosgene. In rats, 70% of radiolabeled ricin injected intra-
venously was excreted in the urine as low–molecular weight metabolites within approximately 24 hours. Standard isolation precautions are appropriate. Clinical samples may be handled at BSL-2. Nasal swab collection and analysis by antigen-ELISA may be useful for early diagnosis. Ricin is very immunogenic; antibody-ELISA serology may be useful for the identification of exposed individuals.

**Treatment and Prophylaxis.** For oral intoxication, supportive therapy includes activated charcoal administration and intravenous fluid and electrolyte replacement. For inhalation intoxication, supportive therapy to counteract acute pulmonary edema and respiratory distress is indicated. Symptomatic care is the only intervention currently available to clinicians for the treatment of incapacitating or lethal doses of inhaled ricin. Positive end-expiratory ventilatory therapy, fluid and electrolyte replacement, anti-inflammatory agents, and analgesics would probably be of benefit in the treatment of aerosol-intoxicated humans.

There are no licensed vaccines or passive immune products available for human use. The US Army has demonstrated that active immunization is effective against inhalation therapy and that immunization or passive antibody therapy protects against intravenous or intraperitoneal intoxication with ricin.

**The Terrorist Spectrum**

Many of the agents discussed in detail above are the classic, cold-war biological agents selected by proliferators for the past 60 years. As described in the “Introduction,” terrorists may be hard pressed to (1) obtain cultures of these agents, (2) grow them in adequate quantities, (3) prepare them for weaponization, and (4) release them in the form necessary to cause disease in large numbers of people without either getting caught or infecting or intoxicating themselves.

Because of the complexities and dangerous nature of the work, it is possible that the would-be terrorist might turn to other agents and methods rejected by developers in the past. Therefore the spectrum of terrorist agents may be much broader—although not necessarily more lethal—than what our forces faced from the Soviet threat during the cold war.

A hypothetical terrorist spectrum and summarization of the threat are shown in Figure 2. The ordinate represents “ease of accomplishment” of a terrorist attack of a given type and the abscissa represents the “number of casualties” or impact that such an attack might have on a population or on our society. We propose that, to kill thousands, the terrorist will have to rely on the classic agents and on state sponsorship for the prepa-
ration of a weapon. For these reasons, and others, the mass-casualty attack is probably the least likely to occur. Recent history supports the idea that hoaxes will be the most likely attacks in the future. Of intermediate impact—and probable likelihood—is the non-mass-casualty attack. Almost anyone with the most basic knowledge of microbiology or a willingness to search the Internet or a library for information can culture sufficient biological agent and contaminate public food or water to cause illness and discomfort in tens or hundreds of our citizens. The psychologic impact of any of these classes of attacks could increase their impact; education can reduce it.

**The Epidemiology of Bioterrorism**

**The Attack**

The likelihood of a strategic attack by Russian intercontinental ballistic missiles carrying *Yersinia pestis* or variola is much lower than it was 10 years ago. However, the likelihood of a biological terrorist attack on our
cities is believed by most experts to be higher than it was when the Soviets were the major threat. There are numerous potential scenarios for attack, but the simplest terms, the covert and overt approaches, will be considered here. 

**Covert Approach.** Assume that an individual or group is able to obtain a high quality, talcum powder–like dry agent with adequate viability and release it in one of our cities in the right meteorologic conditions and at the right time of day without notice. In this scenario, the terrorists decide not to announce their actions at all, or at least not until the effects of the attack are widely known. The result would be a “footprint” of potential exposure, with high and low concentration eddies caused by buildings and city effect. The extent of exposure would be greatly dependent on time of day, season, weather, and chance. The dose received by those exposed would follow a broad distribution, and for many agents the onset of clinical disease would vary directly with dose and possibly with age and physical condition of the patients. Many of the diseases associated with the agents we have discussed present as a flulike illness. In our society, many individuals would attempt self-medication and the first few who visit their physicians might be sent home with analgesics and forced fluids and told to get bed rest. In prepared cities with surveillance systems in place, case numbers or pharmacy sales would probably first trigger suspicion, depending on the time of year. Local physicians might meet casually or call a friend to describe an unusual grouping of patients. Because of education and press coverage, once suspicion was triggered, local and state and then national public health authorities would be notified. Law enforcement would be called in quickly, and a formal response would begin.

**Overt Approach.** It is the third quarter of major sporting event. The crowd is still talking about the fireworks and rock stars of the half-time show. A man in a team sweatshirt taps on the window of the press box and hands the announcer an envelope marked “prediction” before disappearing into the crowd. Because he is busy interviewing the hero from the last decade, the announcer lays the envelope on the desk and forgets about it until just before the start of the final quarter. Then, intrigued by the word on the envelope, he opens it to find a typed note: “During the half-time fireworks show, we released aerosol cans of [pick a bug] throughout the stadium. Everyone is exposed and you are all going to die. Have a good day.” The announcer shows the note to the color person to his right. Their minds race as they try to continue working while deciding what to do. One wrong word could cause the 35,000 fans to panic. Is this a hoax? What shall they do? Who do they call? In 30 minutes, the crowd will leave the stadium for parties and highways and airplanes and will disperse across the nation.
Although both of the above scenarios are horrific, the second, because of the many uncertainties and the possibility of panic, has the potential of being enormously difficult to handle. The psychologic impact of a real attack or a successful hoax could be enormous. In an attack that involves firearms or explosives, or even chemical agents, the physical impact on the target can be evaluated in seconds or minutes. The result may be terrible and many lives may be lost, but the victims can be identified, the magnitude of the problem can be evaluated, and an efficient response can be mounted. By contrast, with the aerosol release of a biological agent, none of those things take place. The weapon may be silent, invisible, and odorless. Triage is extremely difficult and may be impossible before the onset of illness. In a chemical attack, victims will be ill in a few minutes; victims of a biological attack may not know for a week that they have been exposed. In addition to these technical difficulties, we have a population that has a limited understanding of infectious diseases and that has been prepared with a mix of good and not-so-good information by novels, movies, and television.

Israel, which is probably the best-prepared and best-disciplined society in the world at this time, provides an interesting case study. From January 18 to February 28, 1991, 39 Iraqi-modified SCUD (Soviet 55-1 series) missiles reached Israel. Although many malfunctioned or were off target, some of the missiles landed in and around Tel Aviv. Approximately 1000 people were treated as a result of the missile attacks, but only 2 died. Five hundred forty-four patients were admitted to hospitals with diagnoses of anxiety, and 230 patients were hospitalized for atropine overdose. Approximately 75% of the casualties resulted from inappropriate actions or reactions on the part of the victims. If one of the warheads had contained a biological agent that infected or intoxicated even a few people, the terror effect would have been far greater. However, the likelihood that a hoax or real attack will cause terror in a population decreases when individuals, health-care providers, and leaders become better educated about the nature of biological agents and the threat of such agents.

Response: How Difficult Is It?

It is much more difficult to protect civilians than it is to protect a military force. For the military force, we can use countermeasures such as (1) active immunization for some agents, (2) passive immunoprophylaxis and chemoprophylaxis for other agents, (3) battlefield detection systems, (4) physical protection (masks), (5) identification and diagnosis tools and
methods, (6) decontamination procedures, (7) passive immunotherapy, and (8) chemotherapy. For an attack on our citizens, our useful countermeasures are probably limited to identification and diagnostics, chemotherapy, and possibly decontamination for some people. Furthermore, our free civilian society is much less disciplined and their movements are relatively uncontrolled. In many ways, we are an extremely vulnerable society. Countering our vulnerability, however are an excellent law enforcement infrastructure and probably the world’s finest public health system.

It may not be immediately obvious that there has been a biological attack. We may have to differentiate such an attack from a spontaneous outbreak in an endemic area or a spontaneous epidemic of an emerging or unknown disease. With a spontaneous outbreak, there may be seasonal clues and a gradual increase in incidence and traditional cycles of transmission. With a biological attack, whether aerosol or foodborne, there may be a compressed epidemic curve, even when varying exposure dose and differing states of health of the exposed population are considered.

Identification of the Agent

Kauffman et al. calculated the potential long-term cost of bioterrorism. They estimated it to be nearly $5 million per 100,000 people effectively exposed to brucellosis species and $26 billion per 100,000 people exposed to inhalation anthrax. They concluded, “Rapid implementation of a post-attack prophylaxis program is the single most important means of reducing these losses.”

Identification of the agent may be difficult and is of critical importance. Without identification of the agent, rational postexposure prophylaxis will be impossible. If a weapon or container is found, samples may be taken directly and delivered to a reference laboratory for analysis. If the attack was covert, as in the hypothetical example, the obtainment of one of the aerosol dispersal cans would be of highest priority. If the dispersal systems cannot be obtained, swab samples from the ground or from objects within a few yards of the release point should be taken. Such samples should be placed in sealed glass or polytetrafluoroethylene containers and kept dry and as cold as possible. It can be very dangerous to handle a dry or powdered biological agent because material may adhere to skin and clothing and could be easily inhaled.

Case Definition

The formulation of a case definition is important for several reasons. During epidemiologic investigation, the case definition provides investi-
gators who are widely separated geographically with the same criteria to use in evaluating the extent of the outbreak and the attack rate. It allows the outbreak to be described, and the clinically based definition supports diagnostic and triage efforts even if definitive diagnostic tools are not widely available. The case definition is even more important for the investigation of a potential biological attack because of the increased likelihood of hysteria and confusion caused by rumor, misinformation, and fear of the unknown. In the city in which good, seasonally adjusted background rates for influenza, gastrointestinal disease, and other common public health threats are collected, responders will be better prepared to identify and describe the unusual outbreak.

Description of the Outbreak

The outbreak must be described to assist in the identification and care of victims and also for forensic purposes. It will be necessary to circumscribe the footprint of an aerosol attack to assist in the notification, testing, and treatment of people who are potentially exposed. The aerosol attack differs from traditional insect-borne or patient-contact exposure and disease spread. Onset data would be compressed and exposure data, especially for a noncontiguous aerosol, would reflect a snapshot-in-time location map of the victims. Therefore knowledge of whether the release occurred during rush hour or at 2:00 AM would greatly change the exposure footprint, if not the actual cloud footprint. An attack on a city would be complicated by complex wind patterns that prevail among buildings with multiple stories and by the microenvironment produced by unique temperature gradients. Meteorologic information from local airports or weather stations can be helpful. Several government agencies now have computer plume-prediction models, which can also be helpful if some source and routine meteorologic data are available. The investigation of the Sverdlovsk accident, even 20 years after it occurred, benefited from historical meteorologic data and airport weather station data were useful in the confirmation that the spores had been wind-borne.16

Historically, in a disaster a relatively large percentage of any population leave their homes and flee.52 Flight after a biological aerosol attack is, of course, the wrong thing to do. Not only does movement from the area complicate the investigation, it also takes patients away from help and, in the case of contagious agents, may facilitate the spread of the outbreak. Knowledgeable, respected medical leadership in the city will be needed to appeal to members of the population for their trust and cooperation with the response personnel.
Identification of Exposed Individuals

Humans who are exposed to biological agents, even to replicating agents, will not have measurable amounts of the agent in their blood or serum for several days at the earliest, and they will not have a measurable immune response. However, after inhalation exposure of replicating agents or toxins, nasal mucosal swab samples may contain sufficient agent to allow identification by PCR or ELISA. In this sense, humans—or domestic animals—may be the only “collectors” at the site of the aerosol attack. Although there are currently no commercially available field assays designed for this purpose, the concept has been demonstrated in the laboratory with experimental animals, and nasal swab assays are being studied. This method of triage of those who are potentially exposed to an aerosol is not very practical for agents of high infectivity or toxicity for which the effective dose is very low (Table 1). Nasal swab analysis may be useful for anthrax, for example, but not for the alphaviruses or for some of the viral hemorrhagic fevers with extremely low infective doses. According to Dr Steve Morse, the Defense Advanced Research Projects Agency is also evaluating nonspecific means of detection of preclinical disease (personal communication, November 1998). For example, exhaled nitric oxide, produced by activated pulmonary macrophages, has shown promise as a marker of early pulmonary disease.

Treatment and Patient Management

When the agent has been identified, decisions can be made about triage and postexposure prophylaxis. Is specific therapy available? How much time do we have to treat primary exposures? Is there a chance of secondary spread? If the causative agent of inhalation anthrax, pneumonic plague, or possibly tularemia with its 35% case fatality rate, is identified from field or nasal swab samples, a very rapid response becomes the first priority. With these agents, postexposure prophylaxis within the first 24 to 48 hours can mean the difference between life and death. If the agent were VEE, less could be done for individual victims, but mosquito control and equine immunization might be critical. The appropriate response may range from door-to-door treatment teams to simply the provision of good information to the public by means of the media. If the decision is made to treat the population within the cloud’s footprint, it may be done door to door, at central collection points such as schools, churches or civic centers, or with both approaches. If the agent is highly contagious, the use of central collection points may be counterproductive.
In the aftermath of a terrorist attack, many victims may go to the hospital. City hospitals may have overwhelming admissions and emergency room visits after the attack. If the agent used was not life-threatening, crowd control procedures may suffice for large numbers of hospital visits. If the agent causes severe illness or death, hospital administrators must be prepared to increase capacities by adding beds and reducing routine patient load.

**Preparation for Biological Attack: What Can a Medical Facility Do?**

The physician and the medical facility, and not necessarily the paramedics, police, and fire service, will take the brunt of a biological terrorist attack. The prepared physician, hospital, and medical center have the potential of making an enormous difference in the outcome after an attack. Therefore preparation at this level is critical. Fortunately, much of what should be done in anticipation of a biological terrorist attack is also applicable to any public health disaster or infectious disease outbreak. Sound preparation, similar to the production of biological weapons, is truly dual-use.

**Education and Training**

Education and training are at the top of the list of priorities. Much of what is needed in a hospital or medical center where there is a spike in the patient load after an attack is simple application of the standard principles of medicine with which the professional and support staffs are already intimately familiar. But if the disease is not in the doctor’s differential or if he is unaccustomed to thinking about “herd health,” the way ahead may seem as fraught with danger as a twisting road on a rainy night. Education and training must include the general characteristics of biological agents versus chemical agents; of clinical presentation, diagnosis, prophylaxis, and therapy for the most important diseases; and of sample handling, decontamination, and barrier patient care. Training, planning, and drills must prepare the physicians and staff for mass-casualty patient management, respiratory support for unusual numbers of patients, distribution of medications, or support of the local government in vaccination programs. The engineering staff must be taught to establish improvised containment in patient rooms or suites. Applying the knowledge we already have and using the facilities already in place in a mass-casualty situation that results from a biological terrorist attack are
the least difficult, least expensive, and probably the most important things we can do to prepare.

Diagnostic Capabilities

During the cold war, diagnostic research and diagnostic capabilities for the agents used as biological weapons were relegated to second place in the all-important vaccine research and development program. Although this was appropriate in the context of protecting a military force, the importance of diagnostic capabilities greatly increases as we face the threat of a biological attack against civilians. We may never be able to immunize the population because of cost, logistical, and technical constraints; therefore we must be able to identify the agents and triage people who are exposed as quickly as possible. The standard hospital clinical lab, although typically prepared for only BSL-2 containment, can provide a significant amount of support with the use of staining, culture, and sensitivity capabilities. This is primarily true for the bacterial agents; in contrast, identification of exotic viral disease agents may require reference lab support at the state or national level.

Hospital and city administrators may take several approaches to assure that they will have a more in-depth diagnostic capability when needed. A few of our larger cities are fortunate to have government, academic, or private enterprise reference laboratories in which researchers routinely work with the more exotic agents, with the use of antibody- and nucleic acid–based assays. Some city administrators have partnered with these reference laboratories and have supplied pagers to key scientists, which has extended the capabilities of the laboratories. The CDC has been charged with upgrading the diagnostic capabilities of state-level public health laboratories. Hospital and medical center staffs should assure that they could communicate with their state public health laboratories and with the local Federal Bureau of Investigation office if necessary. The Federal Bureau of Investigation will most likely be involved in initial identification of the agent in their laboratories at Quantico, Va, or by serving to coordinate shipment to Department of Defense or Department of Health and Human Services reference laboratories. Finally, there has been a flurry of activity in the development and sales of ELISA-based chromatographic assays for use by law enforcement and first responders. Although these assays may be helpful, the first or second generation of these simple assays should not be considered to be definitive tools. Clinical or reference laboratories must still be used as quickly as possible. An appropriate operating procedure might be to split samples as soon as
possible and attempt identification locally while submitting samples to a
definitive reference lab by the most expedient means. Early information
obtained locally (although it is not perfect), in combination with epidemi-
ologic and law enforcement information, may make an enormous differ-
ence in patients’ outcome because the in-depth level of forensic analysis
used by national authorities is sometimes time-consuming.

Someone in the hospital should be aware of federal requirements for
the packaging and shipping of etiologic agents, and the appropriate ship-
ingen containers should be stocked. If weapons agent containers or muni-
tions are found, the law enforcement authorities will want to conduct
forensic analysis, including fingerprint analysis. Therefore all materials
should be handled with gloves or forceps and, of course, with all appro-
priate safety precautions.

Stockpiles

Although the stockpiling of medical countermeasures may be coordi-
nated at the national or state level, hospital or medical centers in high-risk
cities may consider several options. By increasing the pharmacy stocks of
some of the antibiotics that are effective against anthrax, pneumonic
plague, and tularemia and by continuing to dispense the drugs with the
earliest expiration dates first, a hospital staff will be better prepared.
Hospital administrators may also consider establishing agreements with
pharmaceutical distributors for “just-in-time” delivery of antibiotics.
Today, neither antiviral drugs or vaccines for the 2 agents (smallpox and
anthrax) for which they might be needed after an attack are available in
sufficient quantities to allow hospital-level stockpiling. Most experts
believe that ventilators would probably also be in short supply after an
attack on a city with some of the most important classic agents. Hospital
administrators should consider obtaining additional ventilators or making
arrangements with suppliers or sister institutions for rapid additional
acquisition or loan when needed. The Health and Human Services Office
of Emergency Preparedness and the CDC have developed lists of drugs
and material to be stockpiled for given population sizes. As national
domestic preparedness programs mature, there may be options for sharing
resources to reduce the financial burden of stockpiling.

Routine Surveillance

Although most surveillance programs may be initiated at the national
or state level, the administrators of hospitals and medical centers should
consider establishing their own programs. This is more easily done today
than in the past because of automation. For example, large numbers of
flu-like illnesses seen at emergency rooms, severe gastrointestinal
syndromes, or evidence of an increased caseload of communicable
disease, non-trauma admissions, or even deaths should cause hospital
staffs to take a second look with an epidemiologic eye. The pharmacy
service might consider monitoring selected antibiotics or anti-diarrheal
medications and flagging dispensing levels that are greater than the
normal levels. In the case of a covert attack, surveillance may provide the
first indication of an attack. For either a covert or an overt attack, a sound
surveillance system may help circumscribe the geographic extent of the
attack and may provide essential information about where post-exposure
prophylaxis and therapy should be initiated.

Infrastructure Modifications

For a biological attack, two categories of modification to the hospital
building may be required. The first, which is related to decontamination
and segregation of patients, is probably less important for a biological
attack than for a chemical attack. As described above, patients exposed
to a true respirable aerosol may have little or no external contamination.
For most of the agents that are not highly infectious, simple surface
decontamination of the face and nares may be sufficient. In the past few
years, hospitals have developed portable shower systems and have
established “hot” and “cold” lines and patient traffic patterns within the
buildings. Others have added permanent showers and drains into an
appropriate entry hallway or parking garage, which allows all-weather
decontamination of greater numbers of patients.

The second modification that should be considered is some sort of pre-
paration for dealing with patients with highly contagious or dangerous,
infectious diseases. Fortunately, this might not be necessary with many
of the agents that might be selected by the bioterrorist.

High-efficiency particulate air (HEPA) filters are not expensive but do
increase resistance in HVAC systems and often require more powerful
blower systems and modifications to ductwork. This potential need
should be considered during new construction. Modification of existing
HVAC systems to allow HEPA filters to be temporarily placed in line in
a time of need might also be considered. Improvised filtration systems
with heavy plastic sheeting, portable blowers, and commercially avail-
able HEPA filters might be an option in some facilities. Finally, commer-
cially available “electret” type air filters and positive-pressure ventilation
might be considered for certain zones within the hospital (Table 3).53
### TABLE 3. Isolation procedures for patient care at USAMRIID, by disease agent or type of exposure

<table>
<thead>
<tr>
<th>Disease Agent or Type of Exposure</th>
<th>Biosafety Level 4 (BL-4) Isolation Suite Admission; Care Providers in Positive-Pressure Protective Suits</th>
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</thead>
<tbody>
<tr>
<td><strong>Ebola virus</strong></td>
<td><strong>Biosafety Level 4 (BL-4) isolation suite admission; care providers in positive-pressure protective suits</strong></td>
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<tr>
<td><strong>Marburg virus</strong></td>
<td><strong>Ebola virus</strong></td>
</tr>
<tr>
<td><strong>Crimean-Congo hemorrhagic fever virus</strong></td>
<td><strong>Marburg virus</strong></td>
</tr>
<tr>
<td><strong>Variola (smallpox) and monkeypox viruses</strong></td>
<td><strong>Crimean-Congo hemorrhagic fever virus</strong></td>
</tr>
<tr>
<td><strong>The patient is presumed to be a victim of biological agent attack until definitive diagnosis is made</strong></td>
<td><strong>Variola (smallpox) and monkeypox viruses</strong></td>
</tr>
<tr>
<td><strong>Biosafety Level 4 (BL-4) isolation suite admission; barrier nursing procedures</strong></td>
<td><strong>The patient is presumed to be a victim of biological agent attack until definitive diagnosis is made</strong></td>
</tr>
<tr>
<td><strong>Yersinia pestis (pneumonic form)</strong>†</td>
<td><strong>Yersinia pestis (pneumonic form)</strong>†</td>
</tr>
<tr>
<td><strong>Lassa fever virus</strong></td>
<td><strong>Lassa fever virus</strong></td>
</tr>
<tr>
<td><strong>Argentine hemorrhagic fever (Junin) virus</strong></td>
<td><strong>Yersinia pestis (pneumonic form)</strong>†</td>
</tr>
<tr>
<td><strong>Bolivian hemorrhagic fever (Machupo) virus</strong></td>
<td><strong>Lassa fever virus</strong></td>
</tr>
<tr>
<td><strong>Venezuelan hemorrhagic fever (Guanarito) virus</strong></td>
<td><strong>Argentine hemorrhagic fever (Junin) virus</strong></td>
</tr>
<tr>
<td><em><em>Normal hospital room; barrier nursing procedures</em> or secretion precautions,‡ depending on the agent</em>*</td>
<td><strong>Bolivian hemorrhagic fever (Machupo) virus</strong></td>
</tr>
<tr>
<td><strong>Tick-borne encephalitis complex</strong></td>
<td><strong>Venezuelan hemorrhagic fever (Guanarito) virus</strong></td>
</tr>
<tr>
<td><strong>Yellow fever virus§</strong></td>
<td><strong>Normal hospital room; no special precautions</strong></td>
</tr>
<tr>
<td><strong>Venezuelan equine encephalitis virus§</strong></td>
<td><strong>Tick-borne encephalitis complex</strong></td>
</tr>
<tr>
<td><strong>Rift Valley fever virus§</strong></td>
<td><strong>Yellow fever virus§</strong></td>
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<tr>
<td><strong>Chikungunya virus§</strong></td>
<td><strong>Venezuelan equine encephalitis virus§</strong></td>
</tr>
<tr>
<td><strong>Dengue virus§</strong></td>
<td><strong>Rift Valley fever virus§</strong></td>
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<tr>
<td><strong>Brucella species</strong></td>
<td><strong>Chikungunya virus§</strong></td>
</tr>
<tr>
<td><strong>Vibrio cholerae</strong></td>
<td><strong>Dengue virus§</strong></td>
</tr>
<tr>
<td><strong>Bacillus anthracis (pulmonary or cutaneous forms)</strong></td>
<td><strong>Brucella species</strong></td>
</tr>
<tr>
<td><strong>Francisella tularensis (pulmonary form)</strong></td>
<td><strong>Vibrio cholerae</strong></td>
</tr>
<tr>
<td><strong>Yersinia pestis (bubonic or septicemic form)</strong></td>
<td><strong>Bacillus anthracis (pulmonary or cutaneous forms)</strong></td>
</tr>
<tr>
<td><em><em>Normal hospital room; barrier nursing procedures</em> or secretion precautions,† depending on the agent</em>*</td>
<td><strong>Francisella tularensis (pulmonary form)</strong></td>
</tr>
<tr>
<td><strong>Eastern equine encephalitis virus</strong></td>
<td><strong>Yersinia pestis (bubonic or septicemic form)</strong></td>
</tr>
<tr>
<td><strong>Western equine encephalitis virus</strong></td>
<td><strong>Normal hospital room; no special precautions</strong></td>
</tr>
<tr>
<td><strong>Hemorrhagic fever with renal syndrome (Hantaan, Seoul, Puumala viruses)</strong></td>
<td><strong>Eastern equine encephalitis virus</strong></td>
</tr>
<tr>
<td><strong>Japanese encephalitis virus</strong></td>
<td><strong>Western equine encephalitis virus</strong></td>
</tr>
<tr>
<td><strong>Sandfly fever viruses</strong></td>
<td><strong>Hemorrhagic fever with renal syndrome (Hantaan, Seoul, Puumala viruses)</strong></td>
</tr>
<tr>
<td><strong>Coxiella burnetii (Q fever)</strong></td>
<td><strong>Japanese encephalitis virus</strong></td>
</tr>
<tr>
<td><strong>Chlamydia psittaci</strong></td>
<td><strong>Sandfly fever viruses</strong></td>
</tr>
<tr>
<td><strong>Botulinum toxin</strong></td>
<td><strong>Coxiella burnetii (Q fever)</strong></td>
</tr>
<tr>
<td><strong>Staphylococcal enterotoxin B</strong></td>
<td><strong>Chlamydia psittaci</strong></td>
</tr>
<tr>
<td><strong>Ricin toxin</strong></td>
<td><strong>Botulinum toxin</strong></td>
</tr>
<tr>
<td><strong>Saxitoxin</strong></td>
<td><strong>Staphylococcal enterotoxin B</strong></td>
</tr>
<tr>
<td><strong>Trichothecene mycotoxins</strong></td>
<td><strong>Ricin toxin</strong></td>
</tr>
</tbody>
</table>


†Barrier nursing procedures: wearing gown, gloves, and surgical mask, but caring for patients in isolation suites.

‡Secretion precautions: wearing gown and gloves; special handling of potentially infectious dressings, drainage, and/or excreta.

§The patient must be protected from potential arthropod vectors: windows should be screened and/or closed.
Management of Contaminated Remains

The contaminated remains of victims of biological agent exposure would typically be of less risk to health-care providers than the bodies of individuals exposed to chemical agents would be. By the time an individual became ill and died of most biological agents, it would be unlikely that significant surface contamination would remain. Simple decontamination of the body surface with bleach (sodium hypochlorite, 5%) should be adequate for all toxin- and bacterial agent–related casualties. Animals or humans who die of anthrax would have very high concentrations of vegetative bacilli in their blood and organs, which could constitute a risk of cutaneous exposure but probably not of inhalation exposure. Cadavers contaminated with some viral disease agents (eg, hemorrhagic fever viruses or smallpox) may pose serious risk; BSL-4 containment may be required for an autopsy.

Coordination for Reporting and Assistance

Members of the hospital or medical center staff should consider both their in-house response to evidence of a biological attack and how they will communicate their tentative or definitive evidence—or simply concern—to local, state, and possibly national authorities. It is important that the local and state authorities are not overlooked because they would be the primary source of support in the early hours after an attack, before federal assistance can arrive. Inside the hospital, standard procedures for notification and command structure must be carefully considered and established. Who will coordinate the center’s response? Who will serve as spokesman for the hospital? A thoughtful, coordinated, rational announcement to the community that demonstrates collaboration among health-care providers, law enforcement, and city authorities will facilitate the response and will serve to provide psychologic support and to reduce panic. Television camera crews will probably gather at the front and emergency room entrances of hospitals very quickly. Evidence of disorganization in the hospital or the staff’s lack of knowledge of the appropriate medical response will only increase the level of concern and panic in the community. An organized, rational response will calm the public and actually reduce the impact of the attack.

We thank Cheryl Parrott for assistance with the technical editorial review, Lori West for help with research, and Pat Franz for reading the near-final manuscript twice on a rainy Sunday in autumn.

REFERENCES

1. United States Department of State. Report of the United States of America to the
Appendix 1: Chemical Terrorism Defense

Chemical terrorism differs from biological terrorism in many ways (Table A1). From the standpoint of the physician and the hospital (and the victim), one of the most important differences is the rapid onset of clinical signs after exposure to a chemical agent. Individuals who have a lethal exposure may not reach the hospital. A terrorist attack with chemical warfare agents will result in a true medical emergency in the street; however, the impact of the attack will also greatly affect the hospitals in the area. Because of the acute nature of chemical intoxication, the “epidemic curve” will be extremely compressed. There will be less time to prepare the hospital and the staff for a mass-casualty event.

The other major difference between the biological and chemical agents is that the chemical agents may be volatile and dermally active. Therefore they do not need to be aerosolized to be effective. They can be splashed or sprayed onto humans or, if the agent has a high enough vapor pressure, it can simply be spilled in a crowded room or a container can be punctured as in the Tokyo subway.1 These characteristics make a terrorist chemical attack a much easier task to orchestrate and execute, and consequently this type of attack is more likely to occur than an effective biological attack. State sponsorship is less important to the chemical terrorist. Extremely toxic chemicals (eg, cyanide, phosgene, and organophosphate pesticides) are available commercially.
Because chemicals may be delivered as liquid droplets, chemical agent left on a patient’s skin or clothing may be a vapor risk for health-care providers, and it may be necessary to decontaminate the patient or for staff members to wear personal protective gear. The hospital decontamination showers may be even more necessary for dealing with a chemical attack than a biological attack. High-efficiency particulate air filters used in biological containment laboratories or wards will not stop the spread of chemical vapors; activated charcoal filters are necessary.

The diagnosis of chemical agent intoxication may be easier than that of biological infection or intoxication, and the successful therapeutic regimen will be recognized instantly. Therapy of chemical agent intoxication is generally better known, and fewer drugs are needed to cover classes of agents such as atropine and oximes for organophosphate intoxication. Large numbers of respirators may be required, as for chemical attacks and for certain biological attacks.

**Appendix 2: Agricultural Terrorism and Implications for Public Health**

For almost all human diseases and zoonotic disease agents that might be used against humans, the risk of transmission from an individual with a disease to another individual is relatively low. The exceptions to this are smallpox and influenza of the type encountered in the early 20th century. The relatively low transmissibility of most human agents makes production of a mass-casualty event dependent on presentation of the agent to the target as a respirable aerosol cloud. A major difference between human and agricultural (animal) terrorism is that there are more highly contagious agricultural agents, most of which have been eradicated from the US mainland but are endemic and available in other parts of the world. Examples of agricultural agents are hog cholera, avian influenza, African swine fever, foot and mouth disease, and vesicular stomatitis of cloven-hoofed animals and rinderpest of cattle. Our livestock populations are immunologically vulnerable. Furthermore, modern high-density husbandry methods, livestock sale and transportation practices, and centralized feed supply and distribution systems only add to the potential of animal-to-animal or fomite transmission. The foot-and-mouth disease outbreak that occurred in the swine population of Taiwan in 1996 showed the extreme vulnerability of such an industry to contagious disease.\(^2,3\)

Outbreaks of this type could devastate our livestock markets, and even our economy. Fortunately, the agents that are highly contagious to agri-
cultural livestock are not zoonotic. Even eating the meat of an animal infected with many of these agents is not harmful. During an outbreak, however, the people would most likely seek information from their healthcare providers about the risk of contracting the animal disease. Secondary risks to human health would be of concern, especially in rural areas, because agricultural officials would attempt to dispose of thousands or even millions of carcasses. Ground-water contamination related to burial and air pollution from incineration could become important issues.

There is little doubt that terrorists or nation-states exist who seek to cause us harm. An outbreak of a contagious foreign animal disease in our commercial livestock herds would have enormous economic consequences but little direct public health significance. A significant attack on a major species of livestock could, however, have secondary public health implications. Similar to human disease terrorism, awareness of the risk, education, effective veterinary preventive programs, and a strong technical research base prepare us for the unexpected and serve as a deterrent by raising the stakes for the would-be terrorist who may use foreign animal disease.

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Appendix 3: National Information Resources
Health and Human Services/Centers for Disease Control/National Centers for Infectious Diseases (domestic preparedness)
www.bt.cdc.gov/
Health and Human Services/Office of Emergency Preparedness (consequence management)
www.ndms.dhhs.gov
Department of Defense/US Army Medical Research Institute of Infectious Diseases (reference laboratory and education)
www.usamriid.army.mil
US Department of Transportation (shipping etiologic agents)
www.dot.gov/rules
Federal Bureau of Investigation/National Domestic Preparedness Office (crisis management)
www.fbi.gov/programs/ndpo/default.htm
Federal Emergency Management Agency (consequence management)
www.fema.gov
American College of Emergency Physicians (physician education)
www.acep.org
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<td>Official publication of the American Society for Aesthetic Plastic Surgery</td>
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<td>AirMed</td>
<td>Official publications of the five leading associations in air medical and critical care transport</td>
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<td>Clinical Pharmacology &amp; Therapeutics</td>
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