Biological warfare and bioterrorism: a historical review

STEFAN RIEDEL, MD, PHD

Because of the increased threat of terrorism, the risk posed by various microorganisms as biological weapons needs to be evaluated and the historical development and use of biological agents better understood. Biological warfare agents may be more potent than conventional and chemical weapons. During the past century, the progress made in biotechnology and biochemistry has simplified the development and production of such weapons. In addition, genetic engineering holds perhaps the most dangerous potential. Ease of production and the broad availability of biological agents and technical know-how have led to a further spread of biological weapons and an increased desire among developing countries to have them. This article explains the concepts of biological warfare and its states of development, its utilization, and the attempts to control its proliferation throughout history. The threat of bioterrorism is real and significant; it is neither in the realm of science fiction nor confined to our nation.

EARLY USE OF BIOLOGICAL WARFARE

Infectious diseases were recognized for their potential impact on people and armies as early as 600 BC (1). The crude use of filth and cadavers, animal carcasses, and contagion had devastating effects and weakened the enemy (2). Polluting wells and other sources of water of the opposing army was a common strategy that continued to be used through the many European wars, during the American Civil War, and even into the 20th century.

Military leaders in the Middle Ages recognized that victims of infectious diseases could become weapons themselves (1). During the siege of Caffa, a well-fortified Genoese-controlled seaport (now Feodosia, Ukraine), in 1346, the attacking Tartar force experienced an epidemic of plague (3). The Tartars, however, converted their misfortune into an opportunity by hurling the cadavers of their deceased into the city, thus initiating a plague epidemic in the city. The outbreak of plague followed, forcing a retreat of the Genoese forces. The plague pandemic, also known as the Black Death, swept through Europe, the Near East, and North Africa in the 14th century and was probably the most devastating public health disaster in recorded history. The ultimate origin of the plague remains uncertain: several countries in the Far East, China, Mongolia, India, and central Asia have been suggested (4, 5).

The Caffa incident was described in 1348 or 1349 by Gabriel de Mussis, a notary born in Piacenza north of Genoa (6). De Mussis made two important claims: plague was transmitted to the citizens of Caffa by the hurling of diseased cadavers into the besieged city, and Italians fleeing from Caffa brought the plague into the Mediterranean seaports (4). In fact, ships carrying plague-infected refugees (and possibly rats) sailed to Constantinople, Genoa, Venice, and other Mediterranean seaports and are thought to have contributed to the second plague pandemic. However, given the complex ecology and epidemiology of plague, it may be an oversimplification to assume that a single biological attack was the sole cause of the plague epidemic in Caffa and even the 14th-century plague pandemic in Europe (3). Nonetheless, the account of a biological warfare attack in Caffa is plausible and consistent with the technology of that time, and despite its historical unimportance, the siege of Caffa is a powerful reminder of the terrible consequences when diseases are used as weapons.

During the same 14th-century plague pandemic, which killed more than 25 million Europeans in the 14th and 15th centuries, many other incidents indicate the various uses of disease and poisons during war. For example, bodies of dead soldiers were catapulted into the ranks of the enemy in Karolstein in 1422. A similar strategy using cadavers of plague victims was utilized in 1710 during the battle between Russian troops and Swedish forces in Reval. On numerous occasions during the past 2000 years, the use of biological agents in the form of disease, filth, and animal and human cadavers has been mentioned in historical recordings *(Table 1)*.

Another disease has been used as an effective biological weapon in the New World: smallpox. Pizarro is said to have presented South American natives with variola-contaminated clothing in the 15th century (1, 2, 7). In addition, during the French-Indian War (1754–1767), Sir Jeffrey Amherst, the commander of the British forces in North America, suggested the deliberate use of smallpox to diminish the native Indian population hostile to the British (7, 8). An outbreak of smallpox in Fort Pitt led to a significant generation of fomites and provided Amherst with the means to execute his plan. On June 24, 1763, Captain Ecuyer, one of Amherst's subordinate officers, provided the Native Americans with smallpox-laden blankets from the smallpox hospital. He recorded in his journal: "I hope it will have the desired effect" (2,

From the Department of Pathology, Baylor University Medical Center, Dallas, Texas.

Corresponding author: Stefan Riedel, MD, PhD, Department of Pathology, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, Texas 75246 (e-mail: docriedel@aol.com).

Table 1. Examples of biological and chemical warfare use during the past 2000 years

Time	Event
600 BC	Solon uses the purgative herb hellebore during the siege of Krissa
1155	Emperor Barbarossa poisons water wells with human bodies in Tortona, Italy
1346	Tartar forces catapult bodies of plague victims over the city walls of Caffa, Crimean Peninsula (now Feodosia, Ukraine)
1495	Spanish mix wine with blood of leprosy patients to sell to their French foes in Naples, Italy
1675	German and French forces agree to not use "poisones bullets"
1710	Russian troops catapult human bodies of plague victims into Swedish cities
1763	British distribute blankets from smallpox patients to Native Americans
1797	Napoleon floods the plains around Mantua, Italy, to enhance the spread of malaria
1863	Confederates sell clothing from yellow fever and smallpox patients to Union troops during the US Civil War
World War I	German and French agents use glanders and anthrax
World War II	Japan uses plague, anthrax, and other diseases; several other countries experiment with and develop biological weapons programs
1980–1988	Iraq uses mustard gas, sarin, and tabun against Iran and ethnic groups inside Iraq during the Persian Gulf War
1995	Aum Shinrikyo uses sarin gas in the Tokyo subway system

9). As a result, a large outbreak of smallpox occurred among the Indian tribes in the Ohio River Valley. Again, it has to be recognized that several other contacts between European colonists and Native Americans contributed to such epidemics, which had been occurring for over 200 years. In addition, the transmission of smallpox by fomites was inefficient compared with respiratory droplet transmission.

The description of these historical attempts of using diseases in biological warfare illustrates the difficulty of differentiating between a naturally occurring epidemic and an alleged or attempted biological warfare attack—a problem that has continued into present times.

BIOLOGICAL WARFARE IN THE 19TH AND 20TH CENTURIES

The use of biological warfare became more sophisticated during the 19th century. The conception of Koch's postulates and the development of modern microbiology during the 19th century made possible the isolation and production of stocks of specific pathogens (2).

World War I

Substantial evidence suggests the existence of an ambitious biological warfare program in Germany during World War I. This program allegedly featured covert operations. During World War I, reports circulated of attempts by Germans to ship horses and cattle inoculated with disease-producing bacteria, such as *Bacillus anthracis* (anthrax) and *Pseudomonas pseudomallei* (glanders), to the USA and other countries (10, 11). The same agents were used to infect Romanian sheep that were designated for export to Russia. Other allegations of attempts by Germany to spread cholera in Italy and plague in St. Petersburg in Russia followed (10, 11). Germany denied all these allegations, including the accusation that biological bombs were dropped over British positions.

In 1924, a subcommittee of the Temporary Mixed Commission of the League of Nations, in support of Germany, found no hard evidence that the bacteriological arm of warfare had been employed in war (11). However, the document indicated evidence of use of the chemical arm of warfare. In response to the horror of chemical warfare during World War I, international diplomatic efforts were directed toward limiting the proliferation and use of weapons of mass destruction, i.e., biological and chemical weapons (12, 13). On June 17, 1925, the "Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases and of Bacteriological Methods of Warfare," commonly called the Geneva Protocol of 1925, was signed. Because viruses were not differentiated from bacteria at that time, they were not specifically mentioned in the protocol. A total of 108 nations, including eventually the 5 permanent members of the United Nations (UN) Security Council, signed the agreement. However, the Geneva Protocol did not address verification or compliance, making it a "toothless" and less meaningful document (13). Several countries that were parties to the Geneva Protocol of 1925 began to develop biological weapons soon after its ratification. These countries included Belgium, Canada, France, Great Britain, Italy, the Netherlands, Poland, Japan, and the Soviet Union. The USA did not ratify the Geneva Protocol until 1975 (13).

World War II

During World War II, some of the mentioned countries began a rather ambitious biological warfare research program *(Table 2)*. Various allegations and countercharges clouded the events during and after World War II. Japan conducted biological weapons research from approximately 1932 until the end of World War II (1, 7, 12). The program was under the direction of Shiro Ishii (1932–1942) and Kitano Misaji (1942–1945). Several military units existed for research and development of biological warfare. The center of the Japanese biowarfare program was known as "Unit 731" and was located in Manchuria near the town of Pingfan (1). The Japanese program consisted of more than 150 buildings in Pingfan, 5 satellite camps, and a staff of more than 3000 scientists. Organisms and diseases of interest to the Japanese program were *B. anthracis*, *Neisseria meningitidis*, *Vibrio cholerae*, *Shigella* spp, and *Yersinia pestis* (1, 14). More than 10,000 prisoners are believed to have died as a result of experimental infection during the Japanese program between 1932 and 1945. At least 3000 of these victims were prisoners of war, including Korean, Chinese, Mongolian, Soviet, American, British, and Australian soldiers (14). Many of these prisoners died as a direct effect of experimental inoculation of agents causing gas gangrene, anthrax, meningococcal infection, cholera, dysentery, or plague. In addition, experiments with terodotoxin (an extremely poisonous fungal toxin) were conducted. In later years, Japanese officials

Table 2. Biological warfare programs during World War II

Nation	Numbers of workers (estimated)	Focus
Germany	100–200	Offense research forbidden
Canada	small	Animal and crop diseases, rinderpest, anthrax
United Kingdom	40–50	Animal and crop diseases, anthrax, foot and mouth disease
Japan	several thousand	Extensive; official information suppressed by a treaty with USA in which all charges for war crimes were dropped for exchange of information from experiments
Soviet Union	several thousand	Typhus, plague
USA	1500–3000	Chemical herbicides, anthrax (started too late to be important)

considered these experiments as "most regrettable from the view point of humanity" (14).

In addition to the experiments conducted on prisoners in the camps of Unit 731, the Japanese military developed plague as a biological weapon by allowing laboratory fleas to feed on plague-infected rats (14). On several occasions, the fleas were released from aircraft over Chinese cities to initiate plague epidemics. However, the Japanese had not adequately prepared, trained, or equipped their own military personnel for the hazards of biological weapons. An attack on the city of Changteh in 1941 reportedly led to approximately 10,000 casualties due to biological weapons. During this incident 1700 deaths were reported among Japanese troops. Thus, "field trials" were terminated in 1942.

In December 1949, a Soviet military tribunal in Khabarovsk tried 12 Japanese prisoners of war for preparing and using biological weapons (15). Major General Kawashima, former head of Unit 731's First, Third, and Fourth Sections, testified in this trial that no fewer than 600 prisoners were killed yearly at Unit 731. The Japanese government, in turn, accused the Soviet Union of experimentation with biological weapons, referring to examples of *B. anthracis*, *Shigella*, and *V. cholerae* organisms recovered from Russian spies.

Although German medical researchers infected prisoners with disease-producing organisms such as *Rickettsia prowazekii*, hepatitis A virus, and malaria, no charges were pressed against Germany regarding experimentation with agents of biological warfare (1, 7). Allegedly Hitler issued orders prohibiting the development of biological weapons, referring to his own devastating experience with the effects of chemical agents used during World War I. However, with the support of other high-ranking Nazi officials, German scientists began biological weapons research (16). Despite these efforts, which clearly lagged behind those of other countries, a German offensive biological weapons program never materialized.

On the other hand, German officials accused the Allies of using biological weapons: Joseph Goebbels accused the British of attempting to introduce yellow fever into India by importing infected mosquitoes from West Africa (1). This was in fact believable by many, because the British were actually experimenting with at least one organism of biological warfare: *B. anthracis*. Bomb experiments of weaponized spores of *B. anthracis* were conducted on Gruinard Island near the coast of Scotland (17). These experiments lead to heavy contamination of the island with persistence of viable spores. In 1986, the island was finally decontaminated by using formaldehyde and seawater.

In the USA, an offensive biological warfare program was begun in 1942 under the direction of a civilian agency, the War Reserve Service (1). The program included a research and development facility at Camp Detrick, Maryland (renamed Fort Detrick in 1956 and known today as the US Army Medical Research Institute of Infectious Diseases [USAMRIID]), testing sites in Mississippi and Utah, and a production facility in Terra Haute, Indiana. Initially, organisms of interest were *B. anthracis* and *Brucella suis*. Although about 5000 bombs filled with *B. anthracis* spores were produced at Camp Detrick, the production facility lacked adequate engineering safety measures, precluding a large-scale production of biological weapons during World War II (2, 7).

BIOWARFARE PROGRAMS AFTER WORLD WAR II

During the years immediately after World War II, newspapers were filled with articles about disease outbreaks caused by foreign agents armed with biological weapons (2, 18). During the Korean War, the Soviet Union, China, and North Korea accused the USA of using agents of biological warfare against North Korea (1, 18). In later years the USA admitted that it had the capability of producing such weapons, although it denied having used them. However, the credibility of the USA was undermined by its failure to ratify the Geneva Protocol of 1925, by public acknowledgment of its own offensive biological warfare program, and by suspicions of collaboration with former Unit 731 scientists (1, 18).

In fact, the US program expanded during the Korean War (1950–1953) with the establishment of a new production facility in Pine Bluff, Arkansas. In addition, a defensive program was launched in 1953 with the objective of developing countermeasures, including vaccines, antisera, and therapeutic agents, to protect troops from possible biological attacks. By the late 1960s, the US military had developed a biological arsenal that included numerous biological pathogens, toxins, and fungal plant pathogens that could be directed against crops to induce crop failure and famine (1).

At Fort Detrick, biological munitions were detonated inside a hollow 1-million-liter, metallic, spherical aerosolization chamber known as the "eight ball" (7). Volunteers inside this chamber were exposed to *Francisella tularensis* and *Coxiella burnetii*. The studies were conducted to determine the vulnerability of humans to certain aerosolized pathogens. Further testing was done to evaluate the efficacy of vaccines, prophylaxis, and therapy. During the offensive biological program (1942–1969), 456 cases of occupational infections acquired at Fort Detrick were reported at a rate of <10 infections per 1 million hours worked (7, 19). This rate of infection was well within the contemporary standards of the National Safety Council and below the rate reported from other laboratories. Three fatalities due to acquired infections were reported from Fort Detrick during this period: 2 cases of anthrax occurred in 1951 and 1958, and 1 case of viral encephalitis was

reported in 1964. In addition, 48 occupational infections were reported from the other testing and production sites, but no other fatalities occurred.

Between 1951 and 1954, several studies were conducted to demonstrate the vulnerability of US cities (20). Cities on both coasts were surreptitiously used as laboratories to test aerosolization and dispersal methods when simulants were released during covert experiments in New York City, San Francisco, and other sites. *Aspergillus fumigatus*, *Bacillus subtilis* var *globigii*, and *Serratia marcescens* were selected for these experiments (7, 20). Organisms were released over large geographic areas to study the effects of solar irradiation and climatic conditions on the viability of organisms. Concerns regarding potential public health hazards were raised after outbreaks of urinary tract infections caused by nosocomial *S. marcescens* at Stanford University Hospital between September 1950 and February 1951. The outbreak followed covert experiments using *S. marcescens* as a simulant in San Francisco.

In addition to these efforts in the USA, many other countries continued their biological weapons research, including Canada, Britain, France, and the Soviet Union. In the United Kingdom, the Microbiological Research Department was established in 1947 and expanded in 1951 (2, 21). Plans for pilot biological warfare were made, and research continued on the development of new biological agents and weapons design. Britain conducted several trials with biological warfare agents in the Bahamas, in the Isles of Lewis, and in Scottish waters to refine these weapons. However, in 1957, the British government decided to abandon the offensive biological warfare research and to destroy stockpiles. At that time, a new emphasis was put on further development of biological defensive research (21). At the same time, the Soviet Union increased its efforts in both offensive and defensive biological warfare research and development (1). Reports regarding offensive research repeatedly occurred in the 1960s and 1970s, although officially the Soviet Union claimed not to possess any biological or chemical weapons.

Other allegations occurred during the post–World War II period (11):

- The Eastern European press stated that Great Britain had used biological weapons in Oman in 1957.
- The Chinese alleged that the USA caused a cholera epidemic in Hong Kong in 1961.
- In July 1964, the Soviet newspaper *Pravda* asserted that the US Military Commission in Columbia and Colombian troops had used biological agents against peasants in Colombia and Bolivia.
- In 1969, Egypt accused the "imperialistic aggressors" of using biological weapons in the Middle East, specifically causing an epidemic of cholera in Iraq in 1966.

THE 1972 BIOLOGICAL WEAPONS CONVENTION

During the late 1960s, public and expert concerns were raised internationally regarding the indiscriminate nature of, unpredictability of, epidemiologic risks of, and lack of epidemiologic control measures for biological weapons (11, 13). In addition, more information on various nations' biological weapons programs became evident, and it was obvious that the 1925 Geneva Protocol was ineffective in controlling the proliferation of biological weapons. In July 1969, Great Britain submitted a proposal to the UN Committee on Disarmament outlining the need to prohibit the development, production, and stockpiling of biological weapons (22). Furthermore, the proposal provided for measures for control and inspections, as well as procedures to be followed in case of violation. Shortly after submission of the British proposal, in September 1969, the Warsaw Pact nations under the lead of the Soviet Union submitted a similar proposal to the UN. However, this proposal lacked provisions for inspections. Two months later, in November 1969, the World Health Organization issued a report regarding the possible consequences of the use of biological warfare agents *(Table 3)*.

Table 3. Estimates of casualties produced by a hypothetical biological attack*

Agent	Downwind reach (km)	Number killed	Number incapacitated
Rift Valley fever	1	400	35,000
Tickborne encephalitis	1	9500	35,000
Typhus	5	19,000	85,000
Brucellosis	10	500	125,000
Q-fever	>20	150	125,000
Tularemia	>20	30,000	125,000
Anthrax	>20	95,000	125,000

*Release of 50 kg of agent (aerosolized) by aircraft along a 2-km line upwind of a population center of 500,000 (23).

Subsequently, the 1972 "Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction," known as the BWC, was developed. This treaty prohibits the development, production, and stockpiling of pathogens or toxins in "quantities that have no justification for prophylactic, protective or other peaceful purposes" (22). Under the BWC, the development of delivery systems and the transfer of biological warfare technology or expertise to other countries are also prohibited. It further required the parties to the BWC to destroy stockpiles, delivery systems, and production equipment within 9 months of ratifying the treaty. This agreement was reached among 103 cosigning nations, and the treaty was ratified in April 1972. The BWC went into effect in March 1975 (1). Signatories that have not yet ratified the BWC are obliged to refrain from activities that would defeat the purpose of the treaty until they specifically communicate to the UN their intention not to ratify the treaty. Review conferences to the BWC were held in 1981, 1986, 1991, and 1996. Signatories to the BWC are required to submit the following information to the UN on an annual basis: facilities where biological defense research is being conducted, scientific conferences that are held at specified facilities, exchange of scientists or information, and disease outbreaks (1, 24).

However, like the 1925 Geneva Protocol, the BWC does not provide firm guidelines for inspections and control of disarmament and adherence to the protocol. In addition, there are no guidelines on enforcement and how to deal with violations. Furthermore, there are unresolved controversies about the definition of "defensive research" and the quantities of pathogens necessary for benevolent research (24, 25). Alleged violations of the BWC

were to be reported to the UN Security Council, which may in turn initiate inspections of accused parties, as well as modalities of correction. The right of permanent members of the Security Council to veto proposed inspections, however, undermines this provision. More recent events in 2003 and 2004 again illustrated the complexity and the enormous difficulties the UN faces in enforcing the statutes of the BWC.

In the USA, the offensive biological weapons program was terminated by President Nixon by executive orders in 1969 and 1970 (7). The USA adopted a policy to never use biological weapons, including toxins, under any circumstances. National Security Decisions 35 and 44, issued in November 1969 (microorganisms) and February 1970 (toxins), mandated the cessation of offensive biological weapons research and production and the destruction of the biological weapons arsenal. However, research efforts continued to be allowed for the purpose of developing countermeasures, including vaccines and antisera. The entire arsenal of biological weapons was destroyed between May 1971 and February 1973 under the auspices of the US Department of Agriculture, the US Department of Health, Education, and Welfare, and the Departments of Nature Resources of Arkansas, Colorado, and Maryland. After the termination of the offensive program, USAMRIID was established to continue research for development of medical defense for the US military against a potential attack with biological weapons. The USAMRIID is an open research institution, and none of the research is classified.

THE TIME AFTER THE BWC

Despite the agreement reached in 1972, several of the signatory nations of the BWC participated in activities outlawed by the convention (1). These events clearly demonstrate the ineffectiveness of the convention as the exclusive approach for eradicating biological weapons and preventing further proliferation. The number and identity of countries that have engaged in offensive biological weapons research is largely still classified information. However, it can be accurately stated that the number of state-sponsored programs of this type has increased significantly during the past 30 years. In addition, several assassination attempts and attacks, as well as non–state-sponsored terrorist attacks, have been documented.

During the 1970s, biological weapons were used for covert assassinations. In 1978 a Bulgarian exile named Georgi Markov was attacked and killed in London, England. This assassination later became known as the "umbrella killing," because the weapon used was a device disguised as an umbrella (26). This weapon discharged a tiny pellet into the subcutaneous tissue of Markov's leg while he was waiting at a bus stop in London. The following day, he became severely ill, and he died only 3 days after the attack. On autopsy, the pellet, cross-drilled as if it was designed to contain another material, was retrieved. As it was revealed in later years, this assassination was carried out by the communist Bulgarian secret service, and the technology to commit the crime was supplied to the Bulgarians by the Soviet Union (1, 26). Only 10 days before the assassination of Markov, an attempt to kill another Bulgarian exile, Vladimir Kostov, had occurred in Paris, France. Kostov said that one day when he was leaving a metro stop in Paris, he had felt a sharp pain in his back. When he turned around, he saw a man with an umbrella running away. Two weeks later, after he had learned of Markov's death, Kostov was examined by French doctors. They removed a similar pellet, which was made from an exotic alloy of iridium and platinum and contained the toxin ricin.

In the late 1970s, allegations were made that planes and helicopters delivering aerosols of different colors may have attacked the inhabitants of Laos and Kampuchea (1, 7). People who were exposed became disoriented and ill. These attacks were commonly described as "yellow rain." In fact it was highly controversial whether these clouds truly represented biological warfare agents. Some of these clouds were believed to comprise trichothecene toxins (e.g., T-2 mycotoxin). Some scientists believed that the yellow rains were most likely the fecal matter of wild honeybees dropped during their "cleansing flights." The controversy over the yellow rain incidents remains unresolved.

During April 1979, an epidemic of anthrax occurred among the citizens of Sverdlovsk (now Ekaterinburg), Russia. The epidemic occurred among people who lived and worked near a Soviet military microbiology facility (Compound 19) in Sverdlovsk. In addition, many livestock died of anthrax in the same area, out to a distance of 50 km (27). European and US intelligence suspected that this facility conducted biological warfare research and attributed the epidemic to an accidental release of anthrax spores. Early in February 1980, the widely distributed German newspaper *Bild Zeitung* carried a story about an accident in a Soviet military settlement in Sverdlovsk in which an anthrax cloud had resulted (28). When this story was published, other major Western newspapers and magazines began to take an interest in the anthrax outbreak in Sverdlovsk, a city of 1.2 million people, 1400 km east of Moscow. Later that year several articles occurred in Soviet medical, veterinary, and legal journals reporting an anthrax outbreak among livestock. Human cases of anthrax were attributed to the ingestion of contaminated meat.

In 1986, Matthew Meselson (Department of Molecular and Cellular Biology, Harvard University, Cambridge, Massachusetts) renewed previously unsuccessful requests to Soviet officials to bring independent scientists to Sverdlovsk to investigate the incident (1, 28). This request finally resulted in the invitation to come to Moscow to discuss the incident with 4 Soviet physicians who had gone to Sverdlovsk to deal with the outbreak. The impression after these meetings was that a plausible case had been made, and further investigation of the epidemiologic and pathoanatomical data was needed. The Soviet Union maintained that the anthrax outbreak was caused by consumption of contaminated meat that was purchased on the black market (28). However, after the collapse of the Soviet Union, Boris Yeltsin, then the president of Russia, directed his counselor for ecology and health to determine the origin of the epidemic in Sverdlovsk. In May 1992, Yeltsin admitted that the facility had been part of an offensive biological weapons program and that the epidemic was caused by an accidental release of anthrax spores. He was quoted as saying, "The KGB admitted that our military developments were the cause." Meselson and his team returned to Russia to aid in these further investigations (1, 28). Among the evidence reviewed were a private pathologist's notes from 42 autopsies that resulted in the diagnosis of anthrax (29). Demographic, ecologic, and atmospheric data were also reviewed. The conclusion was that the pattern of these 42 cases of fatal anthrax bacteremia and

toxemia were typical of inhalational anthrax as seen in experimentally infected nonhuman primates. In summary, the narrow zone of human and animal anthrax cases extending downwind from Compound 19 indicated that the outbreak resulted from an aerosol that originated there (27, 29).

A 1995 report stated that the Russian program continued to exist after the 1979 incident and had temporarily increased during the 1980s. In 1995, the program was still in existence and employed 25,000 to 30,000 people (1). At the same time, several high-ranking officials in the former Soviet military and Biopreparat had defected to Western countries. The information provided by these former employees gave further insight into the biological weapons program of the former Soviet Union. After the anthrax incident in Sverdlovsk, the research was continued at a remote military facility in the isolated city of Stepnogorsk in Kazakhstan, producing an even more virulent strain of anthrax (1, 28). In 1980, the former Soviet Union expanded its bioweapons research program and was eventually able to weaponize smallpox. This research was conducted at remote facilities in Siberia, and very little information is available about the extent and outcome of this research and where it was conducted (1).

During Operation Desert Shield, the build-up phase of the Persian Gulf War (Operation Desert Storm) after Iraq had invaded and occupied Kuwait in the fall and winter of 1990, the USA and the coalition of allied countries faced the threat of biological and chemical warfare (2, 30). The experience gained from observations during the first Persian Gulf War in the late 1980s supported the information on biological and chemical weapons available to the Western intelligence community. In fact, Iraq had used chemical warfare against its own people on many occasions in the 1980s (1). Intelligence reports from that time suggested that the Iraqi regime had sponsored a very ambitious biological and chemical warfare program.

Coalition forces prepared in 1990–1991 for potential biological and chemical warfare by training in protective masks and equipment, exercising decontamination procedures, receiving extensive education on possible detection procedures, and immunizing troops against potential biological warfare threats. Approximately 150,000 US troops received a Food and Drug Administration–licensed toxoid vaccine against anthrax, and 8000 received a new botulinum toxoid vaccine (7). For further protection against anthrax spores, 30 million 500-mg oral doses of ciprofloxacin were stockpiled to provide a 1-month course of chemoprophylaxis for the 500,000 US troops that were involved in the operation.

At the end of the Persian Gulf War in August 1991, the first UN inspection of Iraq's biological warfare capabilities was carried out. Representatives of the Iraqi government announced to representatives from the UN Special Commissions Team 7 that Iraq had conducted research into the offensive use of *B. anthracis*, botulinum toxins, and *Clostridium perfringens* (30). Iraq had extensive and redundant research facilities at Salman Pak, Al Hakam, and other sites, only some of which were destroyed during the war (1, 30). Despite these elaborate efforts by the UN, the struggle with enforcement of the BWC continued throughout the late 1990s and into the 21st century. As the recent developments in Iraq have shown, development of biological and chemical weapons is a real threat, and efforts to control its proliferation are limited by logistical and political problems. As long as there are no concrete provisions for enforcement, the BWC will remain a toothless instrument in the hands of the UN Security Council.

In addition to these state-sponsored and military-related biowarfare programs, private and civilian groups have attempted to develop, distribute, and use biological and chemical weapons. One incident was the intentional contamination of salad bars in restaurants in Oregon by the Rajneeshee cult during late September 1984 (7, 28). A total of 751 cases of severe enteritis were reported, and *Salmonella typhimurium* was identified as the causative organism. Forty-five victims were hospitalized during this outbreak. Although the Rajneeshees were suspected, the extensive research and investigation conducted by the Oregon Health Department and the Centers for Disease Control could not conclusively identify the origin of the epidemic. However, in 1985, a member of the cult confirmed the attack and identified the epidemic as a deliberate biological attack (28).

Unfortunately, recent examples of the intentional use of biological weapons are not difficult to find. In the mid 1990s, large amounts of botulinum toxin were found in a laboratory in a safe house of the Red Army Faction in Paris, France. Apparently, the toxin was never used (28). The bioterrorism threat resurfaced then on March 18, 1995, after the Aum Shinrikyo attacked the Tokyo subway system with sarin gas. The investigations after this incident disclosed evidence of a rudimentary biological weapons program. Allegedly before March 1995, the cult had attempted 3 unsuccessful biological attacks in Japan using anthrax and botulinum toxin. In addition, cult members had attempted to acquire Ebola virus in Zaire during 1992 (7, 28). However, only a small portion of the entire program was discovered by Japanese police and intelligence, and only fragments of evidence have been made available to the public. Until the present time, the full extent of the biological weapons program by the Aum Shinrikyo, as well as its present condition, remains unknown.

CONCLUSIONS

Biological weapons are unique in their invisibility and their delayed effects. These factors allow those who use them to inculcate fear and cause confusion among their victims and to escape undetected. A biowarfare attack would not only cause sickness and death in a large number of victims but would also aim to create fear, panic, and paralyzing uncertainty. Its goal is disruption of social and economic activity, the breakdown of government authority, and the impairment of military responses. As demonstrated by the "anthrax letters" in the aftermath of the World Trade Center attack in September 2001, the occurrence of only a small number of infections can create an enormous psychological impact—everyone feels threatened and nobody knows what will happen next.

The choice of the biowarfare agent depends on the economic, technical, and financial capabilities of the state or organization. Smallpox, Ebola, and Marburg virus might be chosen because they have a reputation for causing a more horrifying illness. Images on the nightly news of doctors, nurses, and law enforcement personnel in full protective gear could cause widespread public distraction and anxiety.

Biowarfare attacks are now a possibility. The medical community as well as the public should become familiar with epide-

miology and control measures to increase the likelihood of a calm and reasoned response if an outbreak should occur. In fact, the principles that help clinicians develop strategies against diseases are relevant as the medical community considers the problem of biological weapons proliferation. For the medical community, further education focusing on recognition of this threat is both timely and necessary.

Primary prevention rests on creating a strong global norm that rejects development of such weapons. Secondary prevention implies early detection and prompt treatment of disease. The medical community plays an important role in secondary prevention by participating in disease surveillance and reporting and thus providing the first indication of biological weapons use. In addition, continued research to improve surveillance and the search for improved diagnostic capabilities, therapeutic agents, and effective response plans will further strengthen secondary prevention measures. Finally, the role of tertiary prevention, which limits the disability from disease, shall not be forgotten. Unfortunately, the tools of primary and secondary prevention are imperfect. While the BWC is prepared to assist those nations that have been targets of biological weapons, the medical community must be prepared to face the sequelae should the unthinkable happen.

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