Chapter 1

HISTORY OF BIOLOGICAL WEAPONS: FROM POISONED DARTS TO INTENTIONAL EPIDEMICS

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INTRODUCTION

Since prehistoric times, humans have used available technologies for destructive and beneficial purposes. Aboriginal use of curare and amphibian-derived toxins as arrow poisons anticipated modern attempts to weaponize biological toxins such as botulinum and ricin. The derivation of the modern term "toxin" from the ancient Greek term for arrow poison, τωξικον φαρμακον (toxicon pharmicon; toxon = bow, arrow)[1,2] underscores the historical link between weaponry and biological agents.

Multiple factors confound the study of the history of biological weapons, including secrecy surrounding biological weapons programs, difficulties confirming allegations of biological attack, the lack of reliable microbiological and epidemiological data regarding alleged or attempted attacks, and the use of allegations of biological attack for propaganda and hoaxes. However, a review of historical sources and recent events in Iraq, Afghanistan, Great Britain, and the United States demonstrates that interest in biological weapons by state-sponsored programs, terrorist organizations, and criminal elements is likely to continue.

EARLY ATTEMPTS

The early use of biological weapons included the contamination of water with animal carcasses and filth. Another ancient tactic was to allow an enemy to take sanctuary in an area endemic for an infectious agent in anticipation that the enemy force would become infected, for example, allowing unimpeded access of opposing forces to areas where transmission of malaria was highly likely.

The Carthaginian leader, Hannibal, used early biological weapons (serpent toxins) in the naval battle of the Eurymedon against King Eumenes of Pergamum in 184 BCE. Hannibal ordered earthen pots filled with serpents to be hurled onto the decks of the Pergamene ships. The pots shattered on impact, releasing live serpents among the enemy sailors. The Carthaginians exploited the ensuing panic and chaos to win the battle.[3]

One of the most notorious early biological warfare methods was the hurling of cadavers over the walls of besieged cities, primarily as a terror tactic. De Mussis provided a dramatic record of the use of plague victims in biological warfare.[4,5] After war broke out between the Genoese and the Mongols in 1343 for control of the lucrative caravan trade route from the Black Sea to the Orient, the Mongols laid siege to Caffa, a Genoese colony in the Crimea. The plague, later known as the Black Death, was spreading from the Far East and reached the Crimea in 1346. The Mongols were severely afflicted and forced to lift their siege. As a parting shot, they hurled "mountains of dead" over the city wall, probably with the use of a trebuchet, in the hope that "the intolerable stench would kill everyone inside." An outbreak of plague in the city followed. A review of the incident by Wheelis[5] suggests that the introduction of plague into the city by the cadavers—as a result of a tactically successful biological attack—is the most biologically plausible of several competing hypotheses on the source of the outbreak. Although historically the predominant mode of human plague transmission has been attributed to bites from infected fleas, modern experience (United States 1970–1995)[6] has implicated direct transmission from contact with infected (animal) carcasses in 20% of instances in which the source of the infection could be attributed epidemiologically. Contact with tissue and blood would have been inevitable during the disposal of hundreds or possibly thousands of cadavers that had been smashed on impact. Typically, rats are sedentary and rarely venture far from their nests; it is unlikely that they would have traversed an open distance of several hundred meters between the Mongol front line and the city walls.[5] Transmission from sylvatic to urban rodents is infrequent, at least under current ecological conditions.[7] Alternatively, plague could have been introduced by imported human cases or infected rodents brought into the city through the maritime trade, which was maintained during the siege. Regardless of the portal of entry, the epidemic was likely amplified by an increase in the population of rats and fleas under siege conditions.

Smallpox was particularly devastating to Native Americans. The unintentional yet catastrophic introduction of smallpox to the Aztec empire during the Narváez expedition of 1520, and its subsequent spread to Peru in advance of Pizarro's invasion of the Inca empire, played a major role in the conquest of both empires.[8] At the conclusion of the French and Indian War in 1763, the Native Americans conducted a series of attacks against British forts along the western frontier in what is known as Pontiac's Rebellion. An outbreak of smallpox at Fort Pitt presented an opportunity to take advantage of the Native Americans' unique susceptibility to this disease.[9] On May 24, 1763, William Trent, the local militia leader, wrote of the actions of Captain Ecuyer, the Fort Pitt commander: "We gave them two Blankets and a Handkerchief from

the Smallpox Hospital. I hope it will have the desired effect."[10,11] Subsequently (in July 1763), Sir Jeffrey Amherst, British commander of forces in the American colonies, conceptualized a similar plan with Colonel Henry Bouquet, apparently unaware of the actions at Fort Pitt, thus sanctioning the concept of use of smallpox as a biological weapon.[12,13] An epidemic of smallpox occurred among the Native Americans of the Ohio River Valley that year. In retrospect, it is difficult to evaluate the tactical success of Captain Ecuyer's biological attack because smallpox may have been transmitted after other contacts with colonists, as had previously happened in New England and the South. Although scabs from smallpox patients are thought to be of low infectivity as a result of binding of the virus in fibrin matrix, and transmission by fomites has been considered inefficient compared with respiratory droplet transmission.[8]

THE EARLY ERA OF MODERN MICROBIOLOGY AND THE WORLD WARS

The birth of scientific bacteriology during the 19th century provided the scientific and technical basis for modern biological weapons programs. The Hague Conventions of 1899 and 1904 outlawed the use of "poison or poisoned arms," although the possible use of bacteriological weapons was not specifically identified or addressed.[14,15] Germany started the first known scientific, state-sponsored biological weapons program during World War I.[16] German espionage agents reportedly undertook a covert biological campaign in the United States before the United States entered the war. The Allies had purchased US draft animals for military use, and German operatives infected these animals with glanders and anthrax while they were awaiting shipment overseas.[17] The Germans also conducted similar operations in Romania, Russia, Norway, Mesopotamia, and Argentina, with varying levels of success. Attempts were also made to cripple grain production in Spain with wheat fungus, but without success.[18]

The German biowarfare program of World War I is of special interest for several reasons: it was the first national offensive program, the first program to have a scientific foundation, and the first confirmed instance of actual wartime use of biological agents. The German program was a large-scale (strategic) biological attack, which targeted neutrals rather than belligerents and targeted crops and animals as opposed to humans. It is impossible to determine the effectiveness of this program; although the German operatives involved thought it was a success, no documentary evidence supports this conclusion.[12]

In response to chemical warfare during World War I, the 1925 Geneva Protocol, an international protocol (for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare), was formulated. The protocol, developed by the League of Nations' Conference for the Supervision of the International Trade in Arms and Ammunition, addressed warfare methods of nation-states only. It had no verification mechanism and relied on voluntary compliance. Many of the original signatory states reserved the right to retaliatory use, making it effectively a no first-use protocol. Signatories that began basic research programs to develop biological weapons between World War I and II included Belgium, Canada, France, Great Britain, Italy, The Netherlands, Poland, and the Soviet Union.[19]

After the Japanese defeat of Russia in the 1905 Russo-Japanese War, Japan became the dominant foreign power in Manchuria. The Kwantung Army was created to maintain Japanese economic interests in the region. During the 15 months from September 1931 to the end of 1932, the Japanese military seized full control of Manchuria. In 1932 Major Shiro Ishii, a Japanese army physician with an established interest in biological agents, came to Harbin to conduct human research. He established his initial laboratory in the industrial sector of Harbin known as the Nangang District, but soon realized that his controversial involuntary human research could not be conducted freely there. Ishii moved to a secret facility at Beiyinhe, 100 km south of Harbin, and began experimenting on a more dramatic scale. No research study subjects survived; all died of either experimental infection or live vivisection. These studies continued until a prisoner riot and escape occurred, which resulted in the closing of the facility in 1937. However, larger and more extensive facilities were subsequently built.[19]

In August 1936 Ishii, now promoted to Lieutenant Colonel, was made chief of the Kwantung Army water purification bureau. That autumn the Japanese appropriated 6 km^2 of farmland 24 km south of Harbin, which encompassed 10 villages and displaced 600 families from their ancestral homes. There Ishii built the massive research facility known as Unit 731, where a census of 200 prisoners was kept as expendable subjects of experimentation. Ultimately, more than 3,000 Chinese prisoners were killed and cremated after these experiments. Most of the evidence was destroyed at the end of the war, and in all likelihood the actual number was much greater.[19]

Major Wakamatsu Yujiro, a less flamboyant but equally ruthless veterinary officer, ran the Unit 100

facility at Changchun. In 1936 Japan appropriated 20 km^2 of land near Mokotan, a small village just 6 km south of Changchun, the capital of Japanese-occupied Manchuria. Predominantly a veterinary and agricultural biowarfare research unit (independent from Ishii's Unit 731), Unit 100 focused on developing biological weapons for sabotage operations. Although animals and crops were the focus of most of the research, numerous human studies were also conducted, similar to those conducted by Unit 731.[19]

In April 1939 a third major research facility, Unit Ei 1644, was established in an existing Chinese hospital in Nanking, under the command of one of Ishii's lieutenants, Lieutenant Colonel Masuda. Prisoners, including women and children, became the subjects of grisly experimentation, and were cremated in the camp incinerator usually late at night. Chemical warfare experiments were conducted in a gas chamber with an observation window. Unit Ei 1644 supported Unit 731's research efforts with bacterial agent production and flea cultivation.[19]

Eleven Chinese cities were allegedly attacked during "field trials" using infectious agents including *Yersinia pestis*, *Vibrio cholerae*, and *Shigella*. These attacks may have backfired because up to 10,000 Japanese soldiers reportedly contracted cholera after a biological attack on Changde in 1941.[20] As a result of the Japanese biowarfare program, 580,000 people are estimated to have died in China. The field trials were terminated in 1943, yet basic research and human experimentation at Unit 731 and elsewhere continued until the end of the war.[19,21]

Vaccine research and development was conducted at both Tokyo University and Unit 731. By the end of the war, the Japanese biowarfare program claimed to have effective vaccines for anthrax, cholera, dysentery, typhoid, and typhus. Unit 731 reportedly produced 20 million doses of vaccine per year, with millions more doses produced at satellite facilities in Manchuria and other parts of China. Use of biological warfare agents by Japanese forces may have given them an advantage over the Chinese, but results were erratic and prone to backfire. Despite the enormously expensive program (both in terms of national treasure and human lives) and the weaponization of many agents, Japan never developed a credible biowarfare capability, mainly because of the failure to develop an effective delivery system.[12]

In contrast to Japanese efforts during World War II, a German offensive biological weapons program never materialized. Studies of experimental infections using prisoners were done primarily to study pathogenesis and develop vaccines and sulfonamide antibiotics, rather than to develop biological weapons. Hitler reportedly issued orders prohibiting biological weapons development. With the support of high-ranking Nazi party officials, however, German scientists began biological weapons research, but their results lagged far behind those of other countries.[22]

Polish physicians used a vaccine and a serologic test during World War II in a brilliant example of "biological defense." Knowing that inoculation with killed Proteus OX-19 would cause a false-positive Weil-Felix typhus test, Polish physicians inoculated the local population with a preparation of formalin-killed Proteus OX-19 to create a serologic pseudoepidemic of typhus. Using serologic surveillance, the German army avoided areas that appeared to contain epidemic typhus; consequently, residents of these areas were spared deportation to concentration camps.[23] Several reported but unconfirmed allegations indicate that Polish resistance fighters conducted biological warfare against Nazi occupation forces, including using letters contaminated with *Bacillus anthracis* to cause cases of cutaneous anthrax among Gestapo officials[18,24] and using typhus against German soldiers.[18,25] Czechoslovakian agents reportedly used a grenade contaminated with botulinum toxin, supplied by British Special Operations, to assassinate Reinhard Heydrich, the Nazi governor of occupied Czechoslovakia[26]; however, the veracity of this reported incident has been challenged.[18]

The perceived threat of biological warfare before World War II prompted Great Britain to stockpile vaccines and antisera, establish an emergency public health laboratory system, and develop offensive biological weapons. "Cattle cakes" consisting of cattle feed contaminated with *B anthracis* spores were designed to be dropped from aircraft into Axis-occupied Europe to cause epizootic anthrax among livestock,[27,28] which would in turn induce famine. The cattle cakes were intended as a strategic economic weapon rather than as a direct cause of human anthrax. In addition, explosive munitions designed to aerosolize and disperse *B anthracis* spores as an antipersonnel weapon were tested on Gruinard Island near the coast of Scotland in 1942. These experiments successfully produced anthrax among targeted sheep.[29] The island was quarantined because of focal soil contamination by *B anthracis* spores. The antipersonnel weapons were not mass produced, and neither the cattle cakes nor the explosive munitions were used.[16] Great Britain continued research and development after the war in conjunction with the United States and Canada and performed secret open-air tests using pathogens in open ocean near the Bahamas and Scotland in 1948, 1952, 1953, 1954, and 1955. Simulant studies were performed off the coast of the United Kingdom in

1957, 1958, 1964, and 1965.[16] Great Britain's offensive program was ultimately terminated between 1955 and 1956[30] because of budgetary constraints and reliance on nuclear deterrence.[27,28] Gruinard Island was decontaminated in 1986 using 2,000 tons of seawater and 280 tons of formaldehyde.[31]

THE US PROGRAM

The US military recognized biological warfare as a potential threat after World War I. Major Leon Fox of the Army Medical Corps wrote an extensive report concluding that improvements in health and sanitation made biological weapons unfeasible and ineffective. In the fall of 1941, before the US entry into World War II, opinions differed about the threat of biological warfare. Consequently, the secretary of war asked the National Academy of Sciences to appoint a committee to study the issue. The committee concluded in February 1942 that biowarfare was feasible and that the United States should reduce its vulnerability.

President Roosevelt established the War Reserve Service (with George W Merck as director) to develop defensive measures against a biological attack. By November 1942 the War Reserve Service asked the Army's Chemical Warfare Service to assume responsibility for a secret large-scale research and development program, including the construction and operation of laboratories and pilot plants. The Army selected a small National Guard airfield at Camp Detrick in Frederick, Maryland, for the new facilities in April 1943. By summer of 1944, the Army had testing facilities in Horn Island, Mississippi (later moved to Dugway, Utah), and a production facility in Terre Haute, Indiana. Cattle cakes using *B anthracis* spores were produced at Camp Detrick and shipped to Great Britain but were never used. No agents were produced at the Terre Haute plant because of safety concerns; simulant tests had disclosed contamination after trial runs. The War Reserve Service was disbanded after the war, and the Terre Haute plant was leased for commercial pharmaceutical production.[26] In January 1946 Merck reported to the secretary of war that although the focus of the program was to defend against a biological threat, the United States clearly needed a credible capability to retaliate if attacked with biological weapons. Basic research and development continued at Camp Detrick.

The United States learned of the extent of Japanese biological weapons research after World War II. At the end of the war, in a move that has now become controversial, Ishii, then a lieutenant general, and his fellow scientists were given amnesty for providing information derived from years of biological warfare research.[19]

When war broke out on the Korean peninsula in June 1950, concerns about Soviet biological weapons development and the possibility that the North Koreans, Chinese, or the Soviets might resort to biological warfare resulted in expansion of the US program. A large-scale production facility in Pine Bluff, Arkansas, was established. The new plant featured advanced laboratory safety and engineering measures enabling large-scale fermentation, concentration, storage, and weaponization of microorganisms. In 1951, the first biological weapons, anticrop bombs, were produced. The first antipersonnel munitions were produced in 1954, using *Brucella suis*. The United States weaponized seven antipersonnel agents and stockpiled three anticrop agents (see Table 1-1) in 26 years.[32] However, the US military has never used biological weapons. The Central Intelligence Agency developed weapons using toxins including cobra venom and saxitoxin for covert operations; all records regarding their development and deployment were destroyed in 1972.[33]

Field tests were done in the United States between 1949 and 1968, in which the general public and test subjects were uninformed. At least 239 open-air tests were conducted at several locations including the Dugway

TABLE 1-1

BIOLOGICAL AGENTS PRODUCED BY THE US MILITARY (DESTROYED 1971–1973)*

Lethal Agents	Incapacitating Agents	Anticrop Agents
Bacillus anthracis	*Brucella suis*	Rice blast
Francisella tularensis	*Coxiella burnetii*	Rye stem rust
Botulinum toxin	Venezuelan equine encephalitis virus	Wheat stem rust
	Staphylococcal enterotoxin B	

*Lethal and incapacitating agents were produced and weaponized. Anticrop agents were produced but not weaponized.

Proving Ground, Utah; remote Pacific Ocean sites; and populated areas including Minneapolis, Minnesota; St. Louis, Missouri; Eglin Air Force Base, Florida; New York, New York; and San Francisco, California. These studies tainted the history of the offensive biological warfare program. The Special Operations Division at Camp Detrick conducted most of the field tests as studies on possible methods of covert attack to examine aerosolization methods, the behavior of aerosols over large geographic areas, and the infectivity and rates of decay of aerosolized microbes subjected to solar irradiation and climatic conditions. Most tests used simulants thought to be nonpathogenic, including *Bacillus globigii*, *Serratia marcescens*, and particulates of zinc cadmium sulfide.[32,34] In conjunction with the US Department of Agriculture, several open-air tests were conducted using anticrop agents at sites selected for safety.[34,16] Open-air releases of human pathogens (*Coxiella burnetii*, *Francisella [Pasturella] tularensis*) were performed at the Dugway Proving Ground, Eglin Air Force Base, and remote Pacific Ocean sites to study viability and infectivity using animal challenge models.[35,34,16] Controversial studies included environmental tests to determine whether African Americans were more susceptible to *Aspergillus fumigatus*, as had been observed with *Coccidioides immitis*. These studies included the 1951 exposure of uninformed workers at Norfolk Supply Center in Norfolk, Virginia, to crates contaminated with *Aspergillus* spores. In 1966 the US Army conducted covert experiments in the New York City subways. Light bulbs filled with *Bacillus subtilis var niger* were dropped from subway platforms onto the tracks to study the distribution of the simulant through the subway system.[36] Similar tests were conducted using the ventilation system of the New York City subway and the Pentagon.

The first large-scale aerosol vulnerability test conducted in San Francisco Bay in September 1950 using *B globigii* and *S marcescens* demonstrated the public health issues of such testing.[32] An outbreak of 11 cases of nosocomial *S marcescens* (*Chromobacterium prodigiosum*) urinary tract infection occurred at the nearby Stanford University Hospital; one case was complicated by fatal endocarditis. Risk factors included urinary tract instrumentation and antibiotic exposures.[37] No similar outbreaks were reported by other San Francisco area hospitals. A panel of civilian and academic public health experts secretly convened by the Army in 1952 failed to reach a conclusion regarding the possible link between the Stanford outbreak and the testing program, but recommended that other microbes be used as simulants.[32] Public disclosure of the testing program in the *Washington Post* on December 22, 1976, and in US Senate hearings in 1977[38] resulted in harsh criticism of the continued use of *S marcescens* as a simulant after the Stanford epidemic.[39] However, a 1977 report from the Centers for Disease Control and Prevention (CDC) concluded that in 100 outbreaks of *S marcescens* infection, none was caused by the 8UK strain (biotype A6, serotype O8:H3, phage type 678) used by the Army testing program. Other reports from the 1970s postulated a link between *S marcescens* infection and the testing program; however, all clinical isolates available for strain typing were antigenically distinct from the Army test strain. In all likelihood, the 1950 Stanford *S marcescens* epidemic represents an early example of nosocomial outbreaks resulting from opportunistic pathogens of low virulence complicating the use of medical devices and surgical procedures in the setting of antibiotic selection pressure.[39]

The US program developed and incorporated modern biosafety technology and procedures such as protective equipment, engineering and safety measures, and medical countermeasures, including new vaccines. There were 456 occupational infections and three fatalities (two cases of anthrax in 1951 and 1958 and a case of viral encephalitis in 1964) reported at Fort Detrick during the offensive program (1943–1969). The infection rate of fewer than 10 infections per million hours of work was within the contemporary National Safety Council standards; the morbidity and mortality rates were below those reported by other laboratories. There were 48 infections and no fatalities at the production and testing sites.[32]

After 1954, the newly formed Medical Research Unit at Fort Detrick conducted studies independent of those done by the Chemical Corps to develop vaccines and therapy to protect against biological agents. Researchers began using human volunteers in 1956 as part of a congressionally approved program referred to as "Operation Whitecoat." This use of volunteers set the standard for ethics and human use in research. Active-duty soldiers with conscientious objector status served as research volunteers, and participation was voluntary with the informed consent of the volunteer. The program concluded with the end of conscription in 1973.

KOREAN WAR AND COLD WAR ALLEGATIONS

During the Korean War (1950–1953), North Korean, Chinese, and Soviet officials made numerous allegations of US biowarfare use. The descriptions of biowarfare in many of the allegations appear to be based on Chinese experiences during World War II with "field testing" conducted by the Japanese Unit

731. Polish medical personnel were sent to China to support the Communist war effort, accompanied by Eastern European correspondents, who made numerous accusations based on anecdotal accounts of patients. These allegations, however, were not supported by scientific evidence. Some stories, such as the use of insect vectors to spread cholera, had dubious scientific plausibility. The North Korean and Chinese governments ignored or dismissed offers from the International Committee of the Red Cross and World Health Organization to conduct impartial investigations. The Soviet Union thwarted a proposal from the United States and 15 other nations to the United Nations (UN) requesting the establishment of a neutral commission for investigation. The United States admitted to having biological weapons but denied using them. The credibility of the United States may have been undermined by the knowledge of its biological weapons program and its failure to ratify the 1925 Geneva Protocol until 1975. Although unsubstantiated, these accusations resulted in a loss of international goodwill toward the United States and demonstrated the propaganda value of biological warfare allegations, regardless of veracity.[40] Reviews of documents from former Soviet archives published by a Japanese newspaper in 1998 provide evidence that the allegations were deliberate and fictitious propaganda.[41,42]

Numerous unsubstantiated allegations were made during the Cold War era. The Soviet Union accused the United States of testing biological weapons on Canadian Eskimos, resulting in a plague epidemic,[43] and of collaborating with Colombia in a biological attack on Colombian and Bolivian peasants.[44] The United States was also accused of planning to initiate an epidemic of cholera in southeastern China[45] and of the covert release of dengue in Cuba.[46]

Similarly, the US allegations that Soviet armed forces and their proxies had used "yellow rain," aerosolized trichothecene mycotoxins (inhibitors of DNA and protein synthesis derived from fungi of the genus *Fusarium*) in Laos (1975–1981), Kampuchea (1979–1981), and Afghanistan (1979–1981) are widely regarded as unsubstantiated. The remote location of the alleged attacks made intelligence investigations extremely difficult. Attacks were never witnessed by Western intelligence operatives, and no samples of the aerosols were recovered. Confounding factors included:

- contradictory testimonies from survivors of alleged attacks;
- discrepancies in reported symptoms;
- low disease rates in the allegedly attacked populations;
- the recovery of mycotoxin in fewer than 10% of the clinical and environmental samples submitted;
- the presence of *Fusarium* organisms as environmental commensals;
- the possible decay of toxin under prevailing environmental conditions;
- conflicting results of toxin assays from different laboratories;
- the similarity of alleged yellow rain deposits recovered from environmental surfaces to bee feces in ultrastructural appearance and pollen and mold content; and
- the natural occurrence of showers of bee feces from swarms of honey bees in the rain forests of southeast Asia.[47]

DISARMAMENT

In July 1969 Great Britain issued a statement to the UN Conference of the Committee on Disarmament calling for the prohibition of development, production, and stockpiling of bacteriological and toxin weapons. That September the Soviet Union unexpectedly recommended a disarmament convention to the UN General Assembly. In November 1969 the World Health Organization issued a report on biological weapons, after an earlier report by the 18-nation Committee on Disarmament, describing the unpredictable nature, lack of control, and other attendant risks of biological weapons use. On November 25, 1969, when visiting Fort Detrick, President Nixon announced a new US policy on biological warfare, unilaterally renouncing the development, production, stockpiling, and use of biological weapons. Research was strictly directed to the development of vaccines, drugs, and diagnostics as defensive measures. The UN then developed the 1972 Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological and Toxin Weapons and on their Destruction (1972 Biological Weapons Convention [BWC]), which prohibited any malicious research, production, or use of biological agents. Among the 103 initial cosignatory nations, agreement was reached to "never develop, produce, stockpile, or otherwise acquire or retain microbiological agents or toxins, whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes; and weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict." The United States ratified both the 1925 Geneva Convention and the 1972 BWC in 1975. Signatory states suspecting

others of treaty violations may file a complaint with the UN Security Council, which, in turn, may order an investigation. However, mandatory measures for verification and enforcement are lacking[48]; numerous attempts to formulate such measures have been unsuccessful because of numerous political, security, and proprietary issues.[49,16] Only one allegation has been formally registered under the BWC: in July 1997 Cuba accused the United States of a biological attack with a crop pest insect, *Trips palmi*. The allegations were unsubstantiated in a BWC consultation that was concluded in December 1997.[16] Other attempts at biological arms control have been conducted outside of the context of the BWC; for example, inspections and sanctions against Iraq from 1991 to 1998 and 2002 to 2003 were accomplished under separate UN Security Council Resolutions, 681 and 1441, respectively.

Although many welcomed the termination of the US offensive program for moral reasons, the decision was partly motivated by pragmatic considerations. Biological weapons were unnecessary for national security because of a formidable arsenal of conventional, chemical, and nuclear weapons. Although open-air simulant studies suggested that biological weapons would be effective, the potential effects of aerosols of virulent agent on targeted populations were still conjectural and for ethical and public health reasons could not be empirically validated. Biological weapons were considered untried, unpredictable, and potentially hazardous for the users. Field commanders and troops were unfamiliar with their use. Most importantly, the United States and allied countries had a strategic interest in outlawing biological weapons programs to prevent the proliferation of relatively low-cost weapons of mass destruction. Outlawing biological weapons made the arms race for weapons of mass destruction prohibitively expensive, given the cost of nuclear programs.[50,16]

The US Army, in response to the 1969 presidential directive, did not await the BWC or its ratification. By May 1972 all personnel-targeted agents had been destroyed, and the production facility at Pine Bluff, Arkansas, was converted into a research facility. By February 1973 all agriculture-targeted biological agents had been destroyed. Biological weapons have never been used by the US military. The Central Intelligence Agency destroyed its toxin samples per presidential orders after a US Senate investigation.[33] Fort Detrick and other installations involved in the offensive weapons program were redirected. In 1969 the US Army Medical Research Institute of Infectious Diseases (USAMRIID) was created with biosafety level 3 and 4 laboratories dedicated to developing medical defensive countermeasures. USAMRIID replaced the US Army Medical Unit.

THE SOVIET PROGRAM

Although a signatory to the 1925 Geneva Convention, the Soviet Union began its weapons development program at the Leningrad Military Academy in Moscow under the control of the state security apparatus, GPU (the Unified State Political Administration of the Committee of People's Commissars of the USSR). Work was initially done with typhus, reportedly with experimentation on political prisoners during the pre-World War II era at Slovetsky Island in the Baltic Sea and nearby concentration camps. The program subsequently expanded to include work with Q fever, glanders, and melioidosis, and possibly tularemia and plague. Outbreaks of Q fever among German troops in the Crimea and tularemia among the German siege forces of Stalingrad are two suspected, but unconfirmed, Soviet uses of biological warfare during World War II. [51]

During World War II Stalin was forced to move his biological warfare operations out of the path of advancing German forces. Laboratories were moved to Kirov in eastern European Russia, and testing facilities were eventually established on Vozrozhdeniya Island on the Aral Sea between the Soviet Republics of Kazakhstan and Uzbekistan. At the conclusion of the war, Soviet troops invading Manchuria captured many Unit 731 Japanese scientists and learned of their extensive human experimentation through captured documents and prisoner interrogations. Emboldened by the Japanese findings, Stalin put KGB (Committee of State Security) chief Lavrenty Beria in charge of a new biowarfare program. The production facility at Sverdlovsk was constructed with Japanese plans. When Stalin died in 1953, a struggle ensued for control of the Soviet Union. Beria was executed during the power struggle, and Khruschev, the new Kremlin leader, transferred the biological warfare program to the Fifteenth Directorate of the Red Army. Colonel General Yefim Smirnov, who had been the chief of army medical services during the war, became the director.[51]

Smirnov, who had also been Stalin's minister of health, was a strong advocate of biological weapons. In 1956 Defense Minister Marshall Georgi Zhukov announced that Moscow would be capable of deploying biological and chemical weapons in the next war. By 1960 numerous research facilities existed in the Soviet Union. Although the Soviet Union signed the 1972 BWC, the Soviets appeared to have subsequently in-

creased their biowarfare efforts.[52] The Soviets doubted US compliance with the convention, which further motivated their program.[51] The Soviet biological weapons effort became an extensive program, comprising various institutions under different ministries and the commercial facilities collectively known as Biopreparat. The Soviet Politburo had formed and funded Biopreparat to carry out offensive research, development, and production under the label of legitimate civil biotechnology research. Biopreparat conducted its clandestine activities at 52 sites and employed over 50,000 people. Annualized production capacity for weaponized smallpox was 90 to 100 tons.[50]

The former Soviet Union was an active participant in the World Health Organization's 1964 to 1979 smallpox eradication program. Soviet physicians participating in the program sent specimens to Soviet research facilities. For the Soviets, the program presented an opportunity not only to rid the world of naturally occurring smallpox, but also, reportedly, to obtain virulent strains of smallpox virus that could be used to develop a biological weapon. The World Health Organization announced the eradication of smallpox in 1980, and the world rejoiced at the elimination of a disease that had caused more human deaths than any other infection. The bioweapon developers in the former Soviet Union had a more cynical reason to celebrate. Smallpox eradication would result in the termination of vaccination programs; eventually the world's population would again become vulnerable. It was this vulnerability that would inspire the former Soviet Union to develop smallpox as part of a strategic weapons system, with production of the virus on a massive scale and delivery using intercontinental missiles.[51]

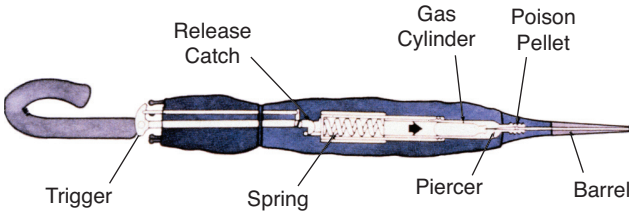

Fig. 1-1. An umbrella gun of this type was the clandestine weapon used to assassinate Bulgarian exile Georgi Markov in London in 1978. The weapon consisted of a spring-loaded piston, which would drive a carbon dioxide cartridge forward into a firing pin. The gas would then propel a poison projectile out of the hollow tip of the umbrella gun, through the clothing, and into the flesh of the intended victim. Reproduced from van Keuren RT. *Chemical and Biological Warfare, An Investigative Guide*. Washington, DC: Office of Enforcement, Strategic Investigations Division, US Customs Service; October 1990: 89.

In addition to military biological weapons programs, the Soviets developed toxin weapons for use by Warsaw Pact intelligence services. Perhaps the most dramatic example of assassination using a biological weapon occurred in September 1978 when Georgi Markov, a Bulgarian exile living in London, was attacked by a member of the Bulgarian secret service. A device concealed in the mechanism of an umbrella (Figure 1-1) surreptitiously discharged a tiny pellet into the subcutaneous tissue of his leg. He died mysteriously several days later with fever, hypotension, and clinical sepsis. The pellet (Figure 1-2), which had been drilled to hold a toxic material, was found at autopsy. No toxin was identified, but ricin was postulated as the only toxin with the potency to kill after such a small dose.[53] That August in Paris, Vladimir Kostov, a Bulgarian defector living in Paris, had been attacked in a similar manner. He experienced pain and bleeding at the wound site and a fever, yet had no further complications. After hearing of Markov's death in September, he sought medical evaluation; X-ray radiographs disclosed a small metallic pellet in the skin. The pellet was surgically recovered from subcutaneous fat. Kostov then

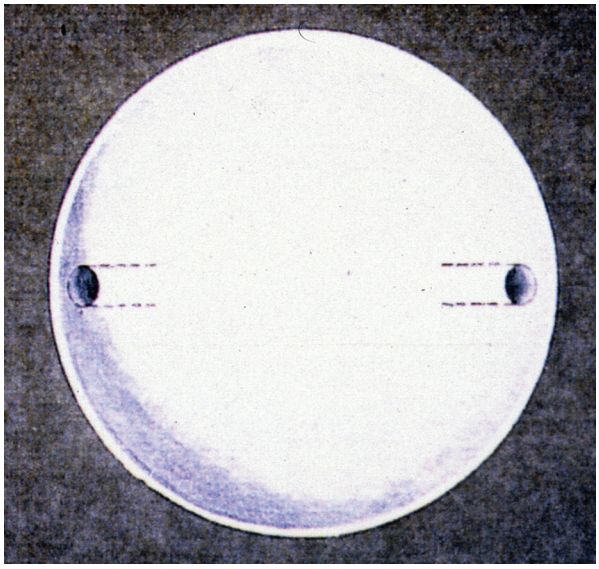

Fig. 1-2. A pellet of this type, designed to contain ricin toxin, was used to assassinate Georgi Markov in London and in the attempt on the life of Vladimir Kostov in Paris. The tiny, platinum-iridium pellet—the size of the head of a pin (0.068 in. diameter)—was cross-drilled with 0.016-in. holes in which ricin (or another toxin) could be placed. Reproduced from van Keuren RT. *Chemical and Biological Warfare, An Investigative Guide.* Washington, DC: Office of Enforcement, Strategic Investigations Division, US Customs Service; October 1990: 90.

tested positive for antiricin antibodies, supporting the probable use of ricin in these attacks.[18]

In October 1979 a Russian emigrant newspaper published in Frankfurt, Germany, reported a sketchy story of a mysterious anthrax epidemic in the Russian city of Sverdlovsk (now Yekaterinburg). The military reportedly moved into the hospitals in Sverdlovsk and took control of the care of thousands of patients with a highly fatal form of anthrax. Suspicions emerged about an accidental release of anthrax agent into the urban area in the vicinity of a Soviet military installation, Compound 17.[54] The Central Intelligence Agency sought the opinion of Harvard biologist Matthew Meselson on the situation. Meselson had been a strong proponent of the Nixon ban on the US biological warfare program, and he attempted to refute the Soviet weapon release hypothesis. Other observers reviewing the same evidence reached different conclusions, however, and satellite imagery from the late spring of 1979 showed a flurry of activity at and around the Sverdlovsk installation consistent with a massive decontamination effort. The event generated enough concern within the Reagan administration and the Department of Defense to increase military biopreparedness.[54]

Debate about the incident raged for the next 12 years. Meselson testified before the US Senate that the burden of evidence was that the anthrax outbreak resulted from the Soviets' failure to keep anthrax-infected animals out of the civilian meat supply, and not the consequence of an accident at a military weapons facility, as maintained by many US officials. Meselson asserted his opinion that the 1972 BWC had been a total success and no nation possessed a stockpile of biological weapons. In June 1992, during a brief but open period of detente, Meselson was allowed to take a team of scientists to review autopsy material and other evidence from the Sverdlovsk incident. After examining autopsy specimens of mediastinal tissue, team pathologist David Walker determined the disease had been contracted from inhalation of anthrax spores, not from ingestion of tainted meat as the Soviets continued to allege.[54] The team's attempts to review hospital records of cases from the outbreak were unsuccessful because the records had been confiscated by the KGB. However, the team acquired an administrative list of 68 of the deceased, obtained information from grave markers in a cemetery designated for the anthrax casualties, obtained epidemiological data by interviewing nine survivors and relatives and friends of 43 deceased, and determined that the cases occurred among people who had either lived or worked in a narrow zone southeast of a Soviet military microbiology facility during the first week of April 1979. A review of archived weather reports at the city's airport disclosed that the wind direction on April 2, 1979, correlated with the geographic distribution of cases. Meselson and his team concluded that the outbreak resulted from the escape of aerosolized spores from the facility on April 2, 1979, with downwind transmission.[55]

Russian leader Boris Yeltsin admitted in private conversations with President George H. Bush early in 1992 that the KGB and military had misrepresented the anthrax deaths. Subsequently, in a press release, Yeltsin admitted to the offensive program and the true nature of the Sverdlovsk biological weapons accident.[54] Additionally, retired Soviet general Andrey Mironyuk disclosed that safety filters had not been activated on the fateful morning in early April 1979, resulting in the escape of aerosolized *B anthracis* and the ensuing Sverdlovsk epidemic.[56] Soviet defectors, including Ken Alibek, first deputy chief of Biopreparat from 1988 to 1992, confirmed that not only was the Sverdlovsk anthrax epidemic caused by an accidental release of spores from a biological weapons production plant, but also that the Soviet biological warfare program had been massive. In September 1992 Russia signed an agreement with the United States and Great Britain promising to end its weapons program and to convert its facilities for benevolent scientific and medical purposes.[16,51,57]

SOUTH AFRICA

The South African Defense Force is alleged to have begun a small-scale biological weapons program in the early 1980s, primarily investigating *B anthracis* and *V cholerae*. The agents allegedly were used, but details are not available. The program was closed in 1993 after diplomatic interventions by the United States and the United Kingdom, coincident with the demise of the apartheid regime.[16]

THE SPECIAL CASE OF IRAQ

The most ominous threat of biological warfare that US military forces have faced came during Operations Desert Shield and Desert Storm in 1990 and 1991. Intelligence reports suggested that Iraq had operated a biological weapons program. Coalition troops trained in protective gear and stockpiled ciprofloxacin for use as postexposure prophylaxis against anthrax. Approximately 150,000 US troops received the Food and Drug

TABLE 1-2

BIOLOGICAL AGENTS PRODUCED BY IRAQ*

Agent	Produced (L)	Weaponized (L)
Botulinum	19,000	10,000
Bacillus anthracis	8,500	6,500
Aflatoxin	2,200	1,580

*Disclosed by the Iraq government after 1995
L=Liter

TABLE 1-3

DELIVERY SYSTEMS FOR BIOLOGICAL AGENTS DEVELOPED BY IRAQ*

Aerial Bombs		Missile Warheads	
Botulinum	100	Botulinum	13
Bacillus anthracis	50	*Bacillus anthracis*	10
Aflatoxin	16	Aflatoxin	2

*Disclosed by the Iraq government in 1995

Administration–licensed anthrax vaccine, and 8,000 received a botulinum toxoid vaccine approved by the Food and Drug Administration as an investigational new drug. Postwar inspections by the UN Special Commission on Iraq (UNSCOM) were confounded by misinformation and obfuscation. After General Hussein Kammal defected in 1995, the Iraqi government disclosed that it had operated a robust biological weapons program at six major sites since the 1980s. The Iraqi program conducted basic research on *B anthracis*, rotavirus, camelpox virus, aflatoxin, botulinum toxins, mycotoxins, and an anticrop agent (wheat cover rust), and it tested several delivery systems including aerial spray tanks and drone aircraft. Furthermore, the Iraqi government had weaponized 6,000 L of B anthracis spores and 12,000 L of botulinum toxin in aerial bombs, rockets, and missile warheads before the 1991 Persian Gulf War (Table 1-2 and Table 1-3). These weapons were deployed but not used.[58,59] The reasons behind Saddam Hussein's decision not to use these weapons are unclear; perhaps he was concerned about provoking massive retaliation. Alternately, factors may have included the possible ineffectiveness of untested delivery and dispersal systems, the probable ineffectiveness of liquid slurries resulting from poor aerosolization, and the potential hazards to Iraqi troops, who lacked the protective equipment and training available to coalition forces.[59,60]

The Iraqis claimed to have destroyed their biological arsenal immediately after the war but were unable to provide confirmatory evidence. A covert military research and development program continued for another 4 years, with the intent of resuming agent production and weapons manufacture after the end of UN sanctions. Infrastructure was preserved, and research on producing dried agent was conducted under the guise of biopesticide production at the Al Hakam Single Cell Protein Plant until its destruction by UNSCOM inspectors in 1996. The UNSCOM inspectors never received full cooperation from the Saddam Hussein regime, and they were ejected from Iraq in 1998. International concern lead to renewed inspections in 2002 under UN Security Council Resolution 1441. The Iraqi government failed to cooperate fully with the inspections, and coalition forces invaded Iraq in 2003. In 2005, the Iraq Survey Group (an international group composed of civilian and military persons) concluded that the Iraqi military biological weapons program had been abandoned from 1995 through 1996 because the potential discovery of continued activity would risk severe political repercussions including the extension of UN sanctions. However, Hussein had perpetuated ambiguity regarding a possible program as a strategic deterrent against Iran.[57] The Iraqi Intelligence Service continued to investigate toxins as tools of assassination, concealed its program from UNSCOM inspectors after the 1991 Persian Gulf War, and reportedly conducted lethal human experimentation until 1994. Small-scale covert laboratories were maintained until 2003.[61]

BIOLOGICAL TERRORISM

Bioterrorism refers to use of biological agents by a political or religious group or cult (a group not otherwise recognized as an extension of the government of a state) to achieve a political or ideological objective. Bioterrorist incidents have increased markedly since 1985, with two peaks in 1998 and 2001. The 1998 peak followed publicity of the anthrax threat posed by Larry Wayne Harris; the 2001 peak followed the September through October anthrax mailings. Successfully executed attacks have been few but high in impact; the 1984 Rajneeshee Salmonella attack resulted in 751 cases of infection; the 2001 anthrax mailings resulted in 22 cases of infection, five deaths, and approximately 10,000 individuals being offered postexposure prophylaxis. The vast majority of incidents (at least 98% during 2000–2002) have been

hoaxes, which have nonetheless produced considerable social disruption.[62,63]

The first large-scale bioterrorism attack in the United States occurred in 1984. In the 1960s an Indian guru named Bhagwan Shree Rajneesh founded the Rajneeshee cult. Rajneesh succeeded in attracting followers from the upper middle class and collecting significant donations and proceeds from book and tape sales. Rajneesh acquired the Big Muddy Ranch near The Dalles, Oregon, and built a community for his followers named Rajneeshpuram, which became an incorporated community. Within a few years, the Rajneeshees came into conflict with the local population regarding development and land use. The Rajneeshees attempted to gain control of the Wasco County government by bringing in thousands of homeless people from cities around the country, counting on their votes in the upcoming elections. The Rajneeshees also plotted to sicken the local population to prevent them from voting.[18]

The first documented incident of Rajneeshee use of a biological agent occurred on August 29, 1984. Two Wasco County commissioners visiting Rajneeshpuram were given drinking water contaminated with *Salmonella typhimurium*; both became ill and one was hospitalized. In trial runs in the months leading up to the November 1984 elections, several attempts at environmental, public water, and supermarket food contamination were unsuccessful. In September Rajneeshees began contaminating food at local restaurants by pouring slurries of *S typhimurium* into salad bars, salad dressing, and coffee creamers at 10 restaurants. As a consequence of this attack, 751 cases of enteritis resulted in at least 45 hospitalizations.[18,64]

In 1995 in Japan, the Aum Shinrikyo cult released sarin gas in the Tokyo subway system, resulting in 12 deaths and thousands seeking emergency care. The cult, founded by Shoko Asahara, had amassed approximately 10,000 members and $300,000,000 in financial assets. Aum Shinrikyo mimicked the organization of the Japanese government with "ministries and departments." "Health and welfare" was headed by Seiichi Endo, who had worked in genetic engineering at Kyoto University's viral research center. "Science and technology" was headed by Hideo Murai, who had an advanced degree in astrophysics and had worked in research and development for Kobe Steel Corporation. Endo attempted to derive botulinum toxin from environmental isolates of *Clostridium botulinum* at the cult's Mount Fuji property. A production facility was built and horses were stabled for developing a horse serum antitoxin. It is uncertain whether Endo successfully produced potent botulinum toxin.[18]

In 1993 Aum Shinrikyo built a new research facility on the eighth floor of an office building owned by the cult in eastern Tokyo. The cult grew *B anthracis* and installed a large industrial sprayer to disseminate the anthrax. The cult is also believed to have worked with *C burnetii* and poisonous mushrooms, and it sent a team to Zaire in the midst of an Ebola epidemic to acquire Ebola virus, which the cult claimed to have cultivated. According to press accounts from 1990 to 1995, the cult attempted to use aerosolized biological agents against nine targets. Three attacks were attempted with *B anthracis* and six with botulinum toxin. In April 1990 the cult equipped three vehicles with sprayers containing botulinum toxin targeting Japan's parliamentary Diet Building in central Tokyo, the city of Yokahama, Yosuka US Navy Base, and Nairta International Airport. In June 1993 the cult targeted the wedding of Japan's crown prince by spraying botulinum toxin from a vehicle in downtown Tokyo. Later that same month, the cult spread anthrax using the roof-mounted sprayer on its eight-story building. In July 1993 the cult targeted the Diet in central Tokyo again by using a truck spraying anthrax, and later that month it targeted the Imperial Palace in Tokyo. On March 15, 1995, the cult planted three briefcases designed to release botulinum toxin in the Tokyo subway. Ultimately Aum Shinrikyo gave up on its biological weapons and released sarin in the Tokyo subway on March 20, 1995.[18]

Reasons given for the cult's failure include its use of a nontoxin-producing (or low yield) strain of *C botulinum*, use of a low-virulence vaccine strain of *B anthracis*, ineffective spraying equipment, and perhaps subversion on the part of some cult members who were reluctant to execute the planned operation.[18]

Meanwhile in the United States, two members of the Minnesota Patriots Council, an antigovernment extremist group, were arrested for producing ricin and planning to attack federal agents by contaminating doorknobs. Larry Wayne Harris, a clinical microbiologist with ties to racist groups, was arrested in 1995 for using fraudulent information to obtain a culture of *Y pestis* from the American Type Culture Collection. He was arrested a second time in 1998 after making threatening remarks to US federal officials and violating his parole. Harris had constructed a covert laboratory in Nevada and was conducting experiments with the Sterne strain of *B anthracis*, a nonencapsulated but toxigenic live attenuated veterinary vaccine,[65] and he threatened to attack Las Vegas with the *B anthracis*. His case led to the development of stringent regulations for the procurement and shipping of select microbes.

During the late 1990s the US government launched an ambitious program to enhance biological preparedness at local, state, and federal levels,[66] including measures such as the Presidential Decision Directive-39 (1995),

Presidential Decision Directive-62 (1998), and Presidential Decision Directive-63 (1998). The Federal Response Plan (now called the National Response Plan) coordinates federal agencies responding to disasters. The Select Agent List was created to regulate the purchase, shipment, and research of designated microbial agents. The Department of Health and Human Services (DHHS) was given oversight of health and medical services, and its Office of Emergency Preparedness organized local medical response teams in 125 jurisdictions. Preparations in New York City and other locations included plans and exercises for local incident command; coordinated clinical response; surveillance; and massive distribution of postexposure prophylaxis at multiple distribution centers designed for efficient screening, triage, distribution, and documentation. Federal response teams were organized, staffed, and deployed to large official and public gatherings. CDC established a center for bioterrorism response to enhance state public health laboratories, improve surveillance systems, and improve rapid communication and coordination. A national stockpile of key pharmaceutical agents and vaccines, now called the Strategic National Stockpile, was prepared. The Laboratory Response Network for Bioterrorism, also managed by CDC, provided coordination of testing, sample shipment, and communication between designated local, regional, and reference laboratories. Department of Defense assets integrated into the National Response Plan included USAMRIID for emergency medical consultation and reference laboratory support; the Naval Medical Research Center for laboratory support; the US Marine Corps Chemical and Biological Incident Response Force for reconnaissance, initial triage, and the decontamination of casualties; and the Army Technical Escort Unit for sampling, transport, and disposal of dissemination devices. The Army Medical Department also fielded six regionally based Chemical/Biological Special Medical Augmentation Response Teams to deploy within 12 hours to assist local civilian authorities. The National Guard Bureau, under legislative direction from Congress, fielded regional biological response teams initially called Rapid Agent Identification Teams, and later renamed Civil Support Teams. Many of these new response mechanisms and agencies were tested in the autumn of 2001.

On October 4, 2001, just 3 weeks after the September 11th attacks on the World Trade Center and the Pentagon had made the nation acutely aware of its vulnerability to international terrorism, health officials in Florida reported a case of inhalational anthrax. During the first week of September, American Media, Inc, received a letter addressed to Jennifer Lopez containing a fan letter and a "powdery substance." The letter was passed among its employees, including Robert Stevens. Retrospectively, investigators would consider not this letter, but perhaps a subsequent letter, as the source of his infection.[67]

Stevens was admitted to a Palm Beach, Florida, hospital with high fever and disorientation on October 2, 2001. By October 5, 2001, Stevens was dead from inhalational anthrax, the first such case in the United States in over 20 years. An autopsy revealed hemorrhagic pleural effusions and mediastinal necrosis. Soon afterward anthrax mailings were received at civilian news media operations in New York City and in the Hart Senate Office Building in Washington, DC. US postal facilities in the national capital area and in Trenton, New Jersey, were also contaminated.

At least five letters (four recovered) and, possibly, as many as seven letters containing anthrax spores had been mailed, possibly in two mailings, on September 18, 2001, and October 9, 2001. Twenty-two people contracted anthrax, with 11 inhalational cases resulting in five deaths. Screening and postexposure prophylaxis resulted in significant disruption of operations at the Hart US Senate Office Building and in US postal facilities. Millions of dollars were spent on environmental decontamination. Public alarm was compounded by numerous "white powder" hoaxes.

A significant lesson learned from this incident was the importance of effective and accurate communication regarding the nature of the threat and response efforts. Farsighted emergency planning and training, in addition to the integration of federal and local medical, public health, and law enforcement agencies, were essential in the response to the 2001 anthrax mailings. These preparations in New York City and other cities enabled an unprecedented public health response. The Laboratory Response Network and military laboratories such as USAMRIID processed over 125,000 clinical specimens and 1 million environmental samples. USAMRIID ran over 260,000 assays on over 30,000 samples in 9 months. Prophylaxis supplied from the national stockpile was offered to nearly 10,000 individuals at risk. There were no cases among prophylaxis recipients.[68,69] Anthrax treatment guidelines advocating multidrug antibiotic combinations and aggressive intensive care were disseminated,[70] and the case fatality rate for inhalational anthrax, historically exceeding 90%, was reduced to 45%.[71,72] Bioterrorism response has since been strengthened with additional infrastructure and linkages among the emergency response, public health, clinical, and laboratory sectors.[68,69]

Since the fall of 2001, much has been accomplished to better prepare the nation for the threat of bioterrorism. In April 2004 President George W Bush signed Homeland Security Presidential Decision Directive-10, Biodefense for the 21st Century, which outlined a

national strategy for combating biological terrorism and mandated an interagency approach using strengths of various executive branch departments, including the Department of Homeland Security, DHHS, and the Department of Defense. Subsequently, the Homeland Security Council and the National Security Council formed an interagency steering committee called the Weapons of Mass Destruction Medical Countermeasures Subcommittee, whose principals were at the assistant secretary level; the group coordinates the various departmental efforts to prevent and respond to weapons of mass destruction attacks. The Department of Homeland Security took the lead on biological threat assessments, and DHHS took the lead on medical countermeasures.

The Office of Public Health Emergency Preparedness at DHHS, formed after the 2001 anthrax attacks, began to coordinate civilian medical countermeasure development by the National Institute of Allergy and Infectious Diseases, CDC, and the Department of Defense, under the leadership of eminent scientists and physicians such as DA Henderson and Philip K Russell. On July 21, 2004, President Bush signed legislation creating Project Bioshield, a $6 billion, 10-year program for acquiring new medical countermeasures for the Strategic National Stockpile. This legislation provided a significant funding boost to the Office of Public Health Emergency Preparedness. In the past 4 years, new medical countermeasures added to the Strategic National Stockpile include a new cell culture-derived smallpox vaccine; vaccinia immune globulin to counteract smallpox vaccine side effects; significantly increased doses of botulinum antitoxins to treat casualties of botulinum poisoning; antibiotic stocks for anthrax, tularemia, and plague treatment; and ventilators for respiratory support. Furthermore, DHHS has planned for the stockpiling of the licensed anthrax vaccine, a new recombinant anthrax vaccine, more doses of botulinum antitoxins, a safer smallpox vaccine that can be given to immunocompromised individuals, and anthrax adjunctive therapies.

CDC launched a comprehensive smallpox preparedness program in 2002 as a result of concern about the potential use of Variola as a biological agent. The program integrated community, regional, state, and federal healthcare and public healthcare organizations and featured logistical preparation; training and education; risk communication; surveillance; and local preparations for mass vaccination, isolation, quarantine, and humane treatment of patients in designated facilities.[73] A strategy was adopted based on preexposure vaccination of carefully screened and trained members of first-response teams, epidemiological response teams, and clinical teams at designated facilities. Over 400,000 selected military personnel and 38,000 civilian emergency responders and healthcare workers in designated smallpox response teams were vaccinated. The program calls for a "ring vaccination" strategy: identifying and isolating cases, with postexposure vaccination and active surveillance of those potentially exposed by the initial release. Vaccinated individuals are to be monitored under active surveillance. Patients with suspected or confirmed smallpox are to be grouped together and quarantined in designated buildings (Category X for suspected cases, Category C for confirmed cases) with independent ventilation systems.[73] Researchers studied the immunogenicity of diluted vaccine because of shortages of vaccine supplies (approximately 15 million doses). A 10-fold dilution was found to be immunogenic; diluting the existing vaccine by 5-fold to 10-fold was considered an emergency measure.[74] Contracts for the production of a new cell culture-derived vaccine were awarded in 2000; CDC now holds sufficient cell culture-derived vaccine for the entire US population.[73] Severe adverse reactions have been rare during the smallpox preparedness program. However, cases of myocarditis and sporadic cardiovascular events among patients with vascular risk factors led to additional exclusion criteria.[75] The search for a less reactogenic vaccine has rekindled interest in a highly attenuated vaccinia strain (Modified Vaccinia Ankara)[76] and has led to the development of a DNA subunit vaccine candidate.[77]

The threat of bioterrorism continues. Al Qaeda initiated a biological weapons program in Afghanistan before the overthrow of the Taliban regime. Investigations after the US military intervention of 2001 uncovered two Al Qaeda laboratories for biological weapons development, supplied with commercially acquired microbiology equipment and staffed by trained personnel. Fortunately, a deployable weapon had not been constructed.[78]

US forces operating in northern Iraq in 2003 seized a camp linked to Al Qaeda reportedly containing instructions and equipment for ricin extraction.[79,80] Meanwhile, a raid on a London apartment yielded a written formula for ricin production, its natural source (castor beans), and a suitable solvent (acetone) for its extraction. Although tests for ricin were negative,[81] one of the tenants, an Al Qaeda-trained operative, was convicted of plotting a ricin attack. He planned to contaminate hand rails in the railway system connecting London and Heathrow Airport.[82] In March 2003 two flasks containing ricin were discovered in a railway station in Paris.[83] Ricin-containing packages mailed to officials in South Carolina, the White House, and the US Senate were intercepted during 2003 and 2004.[84,85] No casualties or significant environmental contamination were related to these incidents.

BIOCRIMES

Biocrime refers to the malevolent use of biological agents when the perpetrator's motivation is personal, as opposed to a broader ideological, political, or religious objective. Although biocrimes constitute only a small fraction of criminal assaults and are usually unsuccessful,[86] a well-executed attempt may be deadly; the resulting disease may pose clinical and forensic challenges. Biocrimes have generally been more successful than bioterrorist attacks; 8 of 66 biocrimes reviewed by Tucker[65] produced 29 deaths and 31 injuries.

Biocrimes are typically attempted by perpetrators with scientific or medical expertise or who have recruited suitably trained accomplices. Criminals without a technical background have successfully extracted ricin from castor beans but have generally been unable to obtain or produce other agents. In a review of 14 episodes in which agent was used,[86] the biological agents were usually obtained from a legitimate source or stolen; the perpetrators produced agent in only two cases. Preferred agents have been bacteria and toxins (eg, ricin). Food contamination has been preferred over direct injection or topical application as a means of attack.

Numerous and highly varied biocrimes have been reported; only several representative examples can be included in this chapter. The works of Tucker, [65] Carus,[18,86] and Leitenberg[16] provide comprehensive descriptions and analysis.

One of the most striking examples of foodborne biocrime occurred in Japan between 1964 and 1966. Dr Mitsuru Suzuki allegedly contaminated food items, medications, barium contrast, and a tongue depressor with *Salmonella typhi* and agents of dysentery on numerous occasions; these crimes resulted in over 120 cases of infection and four deaths. Dr Suzuki was reportedly motivated by his dissatisfaction with the medical training system and a desire to further his research on typhoid fever.[18]

In 1995 Dr Debra Green pleaded no contest to charges of murder and attempted murder. The murder charges stemmed from the deaths of two of her children in a fire thought to have been caused by arson. The attempted murder charges stemmed from the poisoning of her estranged husband with ricin. Green was sentenced to life imprisonment.[18]

A variation on the Suzuki crime occurred in 1996 when Diane Thompson, a hospital microbiologist, deliberately infected 12 coworkers with *Shigella dysenteriae*. She sent an email to her coworkers inviting them to eat pastries she had left in the laboratory break room. Eight of the 12 casualties and an uneaten muffin tested positive for *S dysenteriae* type 2, identical to the laboratory's stock strain by pulsed-field electrophoresis.[87] Police learned that her boyfriend had previously suffered similar symptoms and had been hospitalized at the same facility, and that Thompson had falsified his laboratory test results. Thompson was sentenced to 20 years in prison.[18]

Murders by direct injection included the use of diphtheria toxin in Russia in 1910 and *Y pestis* in India in 1933. The director of a Norwegian nursing home was convicted in 1983 of murdering 22 patients by injecting them with a curare derivative. Biocriminals have also harnessed the most lethal emerging pathogen of the 20th century; there have been at least four murder attempts by injecting victims with human immunodeficiency virus-infected blood.[18]

SUMMARY

The history of state-sponsored biological weapons programs is obscured by secrecy, propaganda, and a lack of rigorous microbiologic or epidemiological data to confirm allegations of use. With the exceptions of German sabotage during World War I, the Japanese field trials during World War II, and state-sponsored assassination by espionage agents, there are no well-documented or confirmed biological attacks by nation-states. In retrospect, the public health disaster at Sverdlovsk and political consequences after disclosures suggest that the liabilities resulting from state-sponsored biological weapons programs have outweighed potential strategic advantages. Biological weapons programs have been renounced by over 140 signatory states to the 1972 BWC for numerous political and strategic considerations. However, recent disclosures regarding the former Soviet program and findings by UNSCOM and the Iraq Survey Group underscore the ambitious intent and potential realization of covert state-sponsored programs. Furthermore, the Sverdlovsk accident provided a lethal "proof of concept" of what follows an airborne release of highly refined agent. According to an unclassified US Department of State report in 2005, nations suspected of continued offensive biological warfare programs in violation of the BWC include China, Iran, North Korea, Russia, Syria, and possibly Cuba. Counter-proliferation efforts, including verification of compliance of signatory states to the convention, remain an ongoing challenge.

The threat of bioterrorism reached paramount

importance in October 2001 and continues to present a formidable challenge. Increasingly, these terrorist organizations have taken an interest in biological agents.[88] One of the more alarming recent trends has been the increased motivation of terrorist groups to inflict mass casualties. Most biological incidents have been hoaxes, which have nonetheless resulted in considerable mayhem. Attacks with agent have usually been unsuccessful. Even the technically advanced program of the Aum Shinrikyo was a failure, most likely because of technical challenges posed by constructing an effective aerosol generator or other delivery devices. The likelihood of amateurs using homemade equipment to successfully launch a biological weapon of mass destruction is remote. Terrorists still rely on simple yet effective explosives as their weapon of choice. However, events in Iraq, the United Kingdom, and the United States reveal continued intent. The discovery of Al Qaeda laboratories in Afghanistan demonstrates a concerted effort to harness modern technology for malicious purposes. The possibility of a major bioterrorist attack resulting in massive casualties cannot be ignored. Medical personnel, public health officials, and government agencies that deal with emergency response must be prepared.

A coordinated response integrating local and federal intelligence, law enforcement, public health, and medical assets affords a measured response based on risk analysis (credibility of the attack, results of rapid identification tests); postexposure surveillance; prophylaxis; treatment of casualties; and risk communication. This coordinated response confers a capability to mitigate the clinical public health consequences of attacks and rapidly defuse hoaxes and obviate social mayhem. The response to the anthrax mailings of 2001 demonstrated that although it is impossible to prevent all biological casualties, much can be done to minimize the morbidity, mortality, and social disruption of an intentional epidemic.

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