Articles

Feces, Dead Horses, and Fleas

Evolution of the Hostile Use of Biological Agents

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Selected events in the history of biological weapons are highlighted to increase physicians' awareness of the threat of biological weapons. The hostile use of biological substances originated in antiquity and pervades the history of human conflict. Although difficult to verify at times, the use of such weaponry has not been limited to national militaries. Disgruntled civilians and even physicians have used biological weapons to promote their interests. Their potency, cost-effectiveness, and the ability to manufacture and deploy them with little sophistication, or under the semblance of legitimate commercial endeavors, will ensure that biological weapons remain a constant threat to public health.

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The flea, though he kill none, he does all the harm he can.
Devotions Upon Emergent Occasions
JOHN DONNE, 1642

Biological weapons originated in antiquity and pervade the history of armed conflict (Figure 1). The deliberate contamination of food and water sources with animal carcasses, pioneered by the Greco-Romans during the Carthaginian Wars in the 5th century BC, marked the dawn of biological warfare.[1–3] Barbarossa used the bodies of dead soldiers to contaminate drinking wells during the Battle of Tortona in 1155.[1] When a Venetian expeditionary force attacked Ragusa in 1171 in an attempt to rescue imprisoned comrades, the Ragusans delayed negotiations for several months, knowing that the force would eventually require water from previously contaminated wells.[1] Most of the would-be rescuers became ill and returned sans prisoners.[1] During the American Revolutionary War, British and Colonial forces knowingly offered the American Indians blankets and handkerchiefs contaminated with variola from use at smallpox infirmaries.[1,2,4–6] Although fomite transmission of variola is less efficient than respiratory transmission,[5] the incidence of smallpox increased substantially among those who received the tainted garments.[1,4–6] During the US Civil War, it was common practice for the retreating forces to slaughter livestock in ponds and streams, attempting to deny the enemy potable water or hygienic living conditions.[1,2,7]

The use of biological agents was not limited to defensive or retrograde operations. Scythian archers in 400 BC and Hannibal in 190 BC were probably the first to "weaponize" biological agents. The former did it by dipping their arrowheads in feces or decaying cadavers; the latter, by launching pottery filled with poisonous snakes onto the ships of King Eumenes during the Second Macedonian War.[1–3] Plague-infected cadavers were hurled into the fortifications of adversaries during medieval battles and during the famous Mongol siege of the Ukrainian city of Kaffa (now Feodosiya) in 1347.[1–5] Later, the development of the trebuchet, an enhanced catapult, made it possible to accurately launch several-hundred-pound loads of manure or large piles of bodies that previously had been too heavy.[8] Although some authors believe cadavers were not competent plague vectors,[5] the prevailing scientific establishment of those times lacked the epidemiologic sophistication to realize this. Biological projectiles had some strategic value—if only psychological—because their use persisted into the 20th century during the Russian Revolution, various European conflicts, and the South African Boer wars.[1–5,7]

A more recent method of delivering a biological agent is through aerosolization. In the case of smallpox, aerosols generated from skin lesions represent an effective mode of transmission. Dried tissue from cattle, goats, and sheep infected with *Coxiella burnetii* can spread pathogenic aerosols as far as 1 km.[4,9] A Polish artillery officer might have been the first to recognize the strategic value of aerosolized infectious agents. In 1650, he suggested that projectiles be made of "hollow spheres filled with the slobber of rabid dogs and other

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substances that can poison the atmosphere and cause epidemics."[1] Today, researchers consider aerosolization of 5–10 μm particles one of the most effective means of delivering a biological agent.[4,9–12]

Role of Physicians

Soldiers were not the only ones who committed acts of biological aggression. Scientific and medical establishments also participated. Several physicians have played prominent roles in the history of biological warfare. In 1495 Cesalpino, an Italian physician, gave wine infused with blood from patients afflicted with leprosy to French forces during the Naples Campaign.[1] A Confederate surgeon, Dr Blackburn, was court-martialed for allegations of importing clothes infected with yellow fever during the US Civil War.[1] As the French retreated during the Battle for Paris in the Franco-Prussian War, another physician suggested that linens and clothes from smallpox victims be conspicuously left behind so that the advancing Prussian forces would find and use the tainted garments.[1,2,4–7]

Shiro Ishii, a Japanese Army physician who rose to the rank of general, epitomized physician involvement in the biological war effort. Ishii dreamt of "doctors in combat alongside the glorious infantry."[13] "Alongside" implied offensively using biological agents, not caring for the wounded. Dr Ishii is reported to have offered chocolates filled with anthrax bacteria to children in the Chinese town of Nanking (Nanjing).[7] In 1928, he secured generous funding for biological weapon programs and spearheaded the establishment of a colossal research facility that included a main complex of 150 buildings and 18 satellite facilities scattered from Manchuria on mainland China to Tokyo, the Dutch East Indies, and Celebes.[5–13] It employed a staff of more than 3,000, including entomologists, botanists, microbiologists, and at least 50 physicians.[1,5,7,13] Authors credit Dr Ishii with having launched perhaps the most gruesome series of biological weapon experiments in history.[2,3,7,13–15] As many as 10,000 prisoners died as a result of having been fed, sprayed, injected, or bombed with a long list of biological and chemical agents, including but not limited to plague, glanders, anthrax, dengue, cholera, and tularemia.[2,5,7,13–15] Prisoners were given seawater intravenously or horse blood in plasma exchange replacements or deliberately frozen to death to ascertain the effect of temperature on the various pathogens.[13] To determine the effects of barotrauma, they were pressurized until, as one eyewitness put it, "their eyes ruptured and bled."[13] At specifically designated research facilities under Ishii's purview, no prisoners were allowed to survive.[7,13] If they survived the initial series of experiments, they were then "sacrificed" to determine the progress of the iatrogenesis.[5,7,13]

Plague fascinated Ishii. He believed it held great strategic potential and so masterminded the flea bomb, a porcelain structure filled with plague-infected fleas and oxygen.[13,14] Oxygen sustained the fleas during high-altitude releases, whereas porcelain required less heat and force to shatter during detonation, allowing more fleas to survive. The brittleness of porcelain and a secondary charge ensured that the shell turned to dust, leaving no physical evidence of spent munitions.[13,14] About 15 million fleas were released per attack.[5] Previously classified documents revealed that at least 11 Chinese cities were attacked with plague, anthrax, and paratyphoid.[1,5,7] From 1940 to 1942, as many as 700 Chinese civilians died because of direct attacks.[5,7,13,14] More than 120 deaths resulted from the aerial dissemination of plague-infected fleas over the cities of Ch'ü-hsien (Qu Xian) and Ning-po (Ning-hsien).[7,13,14]

Because of the indiscriminate nature of biological weapons and the limited experience militaries had in using such weapons, aggressors occasionally succumbed to the diseases that they were trying to inflict on their enemy. During a Japanese assault on the Chinese city of Ch'ang-te in 1941, Japanese forces incurred 10,000 casualties and 1,700 deaths as a result of biological agents.[1,5,7]

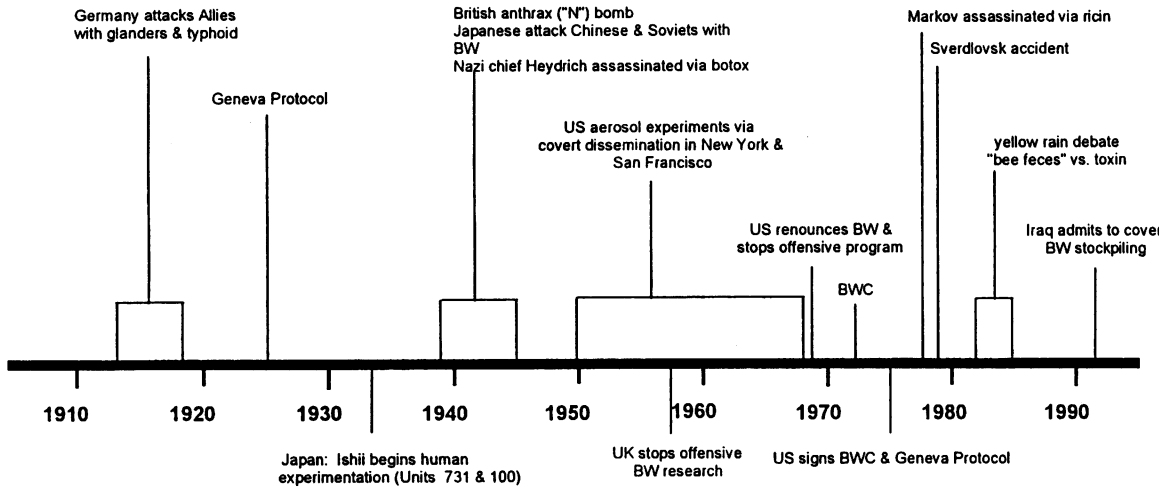
Biological Warfare

Besides Japan, other countries that possessed a viable of biological weapons program before World War II included France, Russia, Great Britain, and Germany. Germany used biological weapons as early as World War I. In 1917, Germany attempted to infect livestock destined for shipment to the United States and Russia with anthrax and glanders (*Pseudomonas mallei*).[5] By 1942, Britain developed strategic amounts of anthrax based on their experiments on Gruinard Island, which remained largely uninhabitable for the following four decades because of high-level anthrax contamination.[1,5,14] After manufacturing 5 million anthrax-impregnated cattle cakes and a 227-kg (500-lb) anthrax bomb, Britain later became one of the first nations to voluntarily halt research on offensive biological weapons in 1957.[1,5,13]

The United States began a full-fledged biological weapons program in the early 1940s based on the recommendation of Secretary of War Henry Stimson and subsequent approval by President Franklin Roosevelt. George Merck directed the War Research Service, which oversaw the development of Camp Detrick, Maryland; Dugway Proving Ground, Utah; and testing installations on Horn Island, Mississippi.[1,4,5] By 1946, the United States had strategic amounts of botulism toxin and anthrax.[1,4,5,14]

US Role in Biological Weapons Research

Research in the US on biological weapons climaxed during the period from 1950 to 1969 as Fort Detrick, Maryland, "became the world's leading consumer of guinea pigs."[7] Vigo, Indiana, became home to a biological weapons plant that, if it were put into use, would have been capable of producing 100 tons of anthrax spores per month.[5,14,15] During this period, the US vulnerability to biological attack was clandestinely demonstrated by the military as they released *Serratia marcescens* off the coast



Pre-modern Area:

400BC–Scythian archers 400BC
300BC–Roman/Greeks use cadavers for contamination
190BC–Hannibal uses snakes in earthen vessel as projectiles
1150–Barbarossa contaminates wells at Tortona
1347–Tartars catapult dead plague victims at siege of Caffa
1495–Italian soldiers give infected wine (leprosy) to French forces
1710–Russians catapult dead plague victims at siege of Reval
1763–British give smallpox blankets to Native Americans
1864–American Civil War, water supply contamination with carrion
1900–Boer War, water supply contamination with dead bodies

Figure 1.—Some of the highlights of the history of biological warfare are shown. BW = biological weapons, BWC = Biological Weapons Convention, UK = United Kingdom

of San Francisco, California, and dropped lightbulbs filled with *Bacillus globi* into the ventilator shafts of the New York City subway system.[1,5,7,14,15] Both field trials demonstrated that minute amounts of bacteria could rapidly and effectively cover large areas. Most of San Francisco's population had each inhaled particulate matter containing substantial amounts of *S marcescens*.[2,7,11,12,16] In the New York subway, *B globi* had been detected throughout the subway system within minutes of being released.[7,11,12] Although both strains of bacteria were thought to be harmless biological markers, following the San Francisco dissemination, the incidence of *S marcescens* infections increased, including the first reported fatality attributed to *S marcescens* endocarditis.[5,16] Following the covert dissemination of aerosolized *Serratia* species in Alabama and Florida, a record number of cases of pneumonia were reported in the respective communities. None of the outbreaks caused by *S marcescens* were due to the same serotype and biotype as those used in the military field experiments.[5,16]

In 1969, President Richard Nixon championed the Biological Weapons Convention and Treaty, terminated offensive research in the United States, and destroyed stockpiles of such weapons. Since then, at least 158 nations have signed the treaty agreeing to halt research directed at the offensive use of biological weapons.[5,12]

Continuing Biological Weapons Research

Despite this, there did not appear to be a decrement in the overall research effort. Research for the detection and defense of biological weapons is not prohibited. The United States and former Soviet Union have interpreted the treaty in such a way as to allow ongoing research of more than 200 projects, with 41 devoted solely to recombinant DNA techniques.[17,18] During a five-year period, US funding of biological weapons research increased 400%.[18] Currently at least 18 viruses, 15 bacteria, and 3 fungi are thought to represent a threat serious enough to warrant the development of detection devices.[19]

In addition to robust research efforts, other evidence suggests that the treaty did not promote biological disarmament. In the spring of 1979, an outbreak of anthrax occurred 1,400 km east of Moscow in Sverdlovsk. Russia denied accusations by the US Department of Defense that the outbreak was the result of military activity. Russia claimed that it was the result of the sale of infected meat on the black market. Initially, civilian experts, including a prominent biochemist and biological weapons observer, along with anthrax specialists and epidemiologists from the Center for Disease Control, rejected the Department of Defense's hypothesis, believing it was a "sporadic food-borne outbreak in an anthrax endemic area."[20] In 1992, Russian President Boris

Yeltsin admitted that an accident at a biological weapons research facility was at fault.[7] Two years later, some of the original proponents of the contaminated meat theory concluded that the release of aerosolized anthrax under the daytime atmospheric conditions of April 2, 1979, at Military Compound 19 resulted in the largest documented outbreak of human inhalation anthrax.[21]

Sverdlovsk was not the only incident that polarized the experts and demonstrated the difficulty in distinguishing natural from artificial epidemics. It illustrates the difficulty in verifying biological weapons allegations. In 1982 the US State Department and the Department of Defense believed that they had sufficient physical evidence to prove ongoing biological weapons use by various countries.[22] The United States accused Soviet and Soviet-backed Laotian, Vietnamese, and Ethiopian forces of employing trichothecene mycotoxins ("yellow rain") against political resurgents in H'mong, Eritrean, Afghan, Cambodian, and Kampuchean villages from 1975 to 1981.[22] Trichothecene toxins inhibit DNA synthesis and are derived from the *Fusarium* genus of plant fungi. Several authorities claimed that the yellow rain, which might be linked to illnesses in these villages, was bee pollen because of the structural similarities between the two.[5,20,22] The yellow rain debate continued for years because of the paucity of both eyewitness reports and recovered aerosols, the inconsistent testimonials of survivors, and because, like anthrax and other biological weapons, trichothecenes occur naturally.[5,22,23]

Effectiveness of Treaties

The efficacy of treaties in preventing future development and the use of biological weapons is also debatable. As old as the weapons themselves, treaties appear ineffective at deterring biochemical armament. The ancient Greeks and Romans forbade their use in the *Ius gentium* or Law of Nations.[24] The Manus of India did the same in 500 BC, as did the Saracens in 500 AD and the Dutch in 1625.[24] In 1925 Poland spearheaded the Geneva Protocol, which also prohibited the use of biological weapons. Ironically, Poland was among the first to use biological weapons in sabotage operations against the Germans in World War II.[1,7,14] Since the Biological Weapons Convention of 1972, the number of countries with biological weapons continues to escalate and currently includes Iran, Iraq, Libya, Syria, North Korea, Taiwan, Israel, Egypt, Vietnam, Laos, Cuba, Bulgaria, India, South Korea, South Africa, China, and Russia.[2,24,25]

Ease of Use

The appeal of biological weapons extends beyond national militaries. Terrorists, spies, and frustrated citizens resorted to biological weapons to promote their interests.[2,7,14,24–28] During the World War II, Reinhard Heydrich, a high-ranking Nazi secret agent, succumbed to wounds incurred during an assassination attempt with botulinum toxin.[7,14] In 1978, two Bulgarian exiles were assassinated with ricin, a toxic protein derived from the castor bean.[1,7] In the mid 1980s, an outbreak of *Giardia lamblia*, confined to a single apartment block in Edinburgh, Scotland, was attributed to the deliberate contamination of a water tank with feces.[7] In 1984, members of the Rajneeshpuram cult contaminated the salad bars of four restaurants in The Dalles, Oregon, with *Salmonella* species they cultured in a laboratory on their compound.[26] The result was 751 cases of enteritis and 45 hospital admissions.[26] In 1989, the mayor of Los Angeles, California, received letters from an organization known as the "breeders," who claimed to be spreading Mediterranean fruit flies in protest of prevailing agricultural policies.[7] The US Department of Agriculture later confirmed these claims based on the pattern of infestation.[7] Wanting "to purge the U.S. of Iraqis super-germs," a laboratory technician who was a member of a white supremacist organization, using a false letterhead, successfully ordered three vials of *Yersinia pestis* from the American Type Culture Collection in Rockville, Maryland, on May 5, 1995.[24] Had he not become impatient and complained about a delay in the shipment, the incident would have gone unnoticed.[24] In the fall of 1996, someone intentionally contaminated pastries in a break room of a Texas medical center with *Shigella dysenteriae* from the laboratory's stock strain.[27] Twelve people had severe diarrheal illness, and four required admission to a hospital.[27]

Several characteristics of biological weapons will continue to ensure their popularity. The most potent and cost-effective type of weapon to produce, a major biological weapon requires only $10,000 worth of equipment and a 5×5-m (16×16-ft) room to manufacture.[9,10,12,24] The infectious dose of Coxiella burnetii can be as little as one organism.[4,9] Botulinum toxin has the smallest mean lethal dose of any biochemical compound.[4,9,29] The production of mass casualties requires approximately $2,000 per square kilometer using conventional weapons, $800 per square kilometer using nuclear weapons, $600 per square kilometer using chemical weapons, and $1 per square kilometer for biological weapons.[9,10,12,23,24] Ten grams of anthrax can kill as many people as 900 kg (1,984 lb) of the chemical nerve agent sarin.[2,9] (Had biological weapons been used in the terrorist attack on the Tokyo, Japan, subway in 1995 instead of sarin, the death toll might have been much higher.) Under ideal weather conditions, 900 kg of sarin would cover about 7 km^2 and, if used over a city like Washington, DC, would cause an estimated 2,000 to 8,000 deaths.[2,24,28] A similar attack using anthrax would cover 300 km^2 and result in 1 to 3 million deaths.[2,5,24] In a conflict, the side that uses biological weapons offensively can protect itself by using agents they have developed specific drugs or vaccines against. If direct person-to-person contact is anticipated or required, the aggressor can use agents that are not transmissible by that manner.[30] Such agents include Histoplasma capsulatum, Venezuelan equine encephalitis, and C burnetii.[30]

Biological weapons attacks using agents that have a delayed onset or longer incubation period can go unnoticed until casualties occur.[30] They can also penetrate armored defenses and leave equipment intact.

These unique properties, along with their ability to defy antiproliferation attempts and their historical reputation, will ensure that biological weapons remain a threat to the military and civilian public health. As Dr Ishii observed, "If it's important enough to be included in a treaty, it must be worth having in your arsenal."[7]

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