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History of biological warfare and bioterrorism

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Abstract

Bioterrorism literally means using microorganisms or infected samples to cause terror and panic in populations. Bioterrorism had already started 14 centuries before Christ, when the Hittites sent infected rams to their enemies. However, apart from some rare well-documented events, it is often very difficult for historians and microbiologists to differentiate natural epidemics from alleged biological attacks, because: (i) little information is available for times before the advent of modern microbiology; (ii) truth may be manipulated for political reasons, especially for a hot topic such as a biological attack; and (iii) the passage of time may also have distorted the reality of the past. Nevertheless, we have tried to provide to clinical microbiologists an overview of some likely biological warfare that occurred before the 18th century and that included the intentional spread of epidemic diseases such as tularaemia, plague, malaria, smallpox, yellow fever, and leprosy. We also summarize the main events that occurred during the modern microbiology era, from World War I to the recent 'anthrax letters' that followed the World Trade Center attack of September 2001. Again, the political polemic surrounding the use of infectious agents as a weapon may distort the truth. This is nicely exemplified by the Sverdlovsk accident, which was initially attributed by the authorities to a natural foodborne outbreak, and was officially recognized as having a military cause only 13 years later.

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Introduction

The current definition of terrorism emphasizes that its main objective is to threaten and terrorize large groups of humans, governments, armies, or society as a whole. Thus, one may assume, in the context of a historical analysis of bioterrorism, that it involves the use of various biological agents by all kinds of actors or groups, including political or military actors and official states, motivated by different reasons (be they political, religious, or other ideological objectives), in order to attain such objectives. As expressed by a prominent expert on the topic, the 'transcendence of biological warfare—over medicine and public health, private criminal acts, terrorism, interstate warfare, and international law directed at the elimination of biological warfare—makes this one of the most intricate topics of discourses, poses very difficult problems, and open some novel challenges in the ethical domain. Biological warfare events (BW) is widely regarded as the absolute perversion of medical science' [1]. As well as this being perfectly true with regard to contemporary political and scientific concerns, the claim of the transcendence of biological warfare (BW) and bioterrorism also has historical pertinence, insofar as the fact of threatening one's neighbours' health by using biological technologies seems to be as old as humanity itself. However, the historical study of BW and bioterrorism is made extremely difficult, and any conclusions in this respect must be drawn with caution, because of several concomitant factors: first, the lack of reliable scientific data regarding alleged bioterrorist attacks, especially before the advent of modern microbiology; second, the polemical conditions surrounding any alleged biological attack, within which the available documents become susceptible to multiple political manipulations, and thus difficult

to interpret objectively; and third, the historical distance of ancient stories about biological attacks, and the possible misunderstanding of them if they are read with contemporary lenses [2]. Given such factors, it is easy to understand why it may become difficult for historians to differentiate natural epidemics from alleged biological attacks.

From an epistemological perspective, the advent of modern microbiology at the end of the 19th century undoubtedly marks the major turning point in the scientific history of BW long after its beginnings in remote antiquity. Thus, Louis Pasteur's and Robert Koch's advances in the theoretical understanding of microbiology, and the derived practical microbiological methods, suddenly offered scientists the possibility of systematically isolating and producing a huge number of specific pathogens, as well as, in the majority of cases, controlling their dissemination. From a socio-political perspective, however, one might consider other turning points: the major world conflicts of the 20th century constitute, in this respect, the main events that turned BW from a sporadic, if dangerous, mass weapon, to an almost standard, if not constantly used, weapon, in brief a classic tool of most of modern armies. From that period on, modern states felt compelled to mutually negotiate and agree on international regulations in order to try to master the threat of biological (as well as chemical) weapons. A crucial step in the history of BW and bioterrorism occurred after World War II, when small groups of activists acquired the ability to master the technologies involved in BW, and were suddenly able to threaten not only individuals but huge amounts of people, thus adding to the threat of the states' armies the more uncontrollable one of single individuals or small groups, and thus representing a major concern for state security.

Use of Biological Weapons During Antiquities, Middle Ages and Colonial Period

Contagious diseases and other biological weapons were recognized for their potential impact on armies or people as early as the 14th century BC (Table 1). The Hittites might have produced the first documented example of BW by sending diseased rams (possibly infected with tularaemia) to their enemies to weaken them [3]. In the fourth century BC, the Greek historian Herodotus relates that Scythian archers used to infect their arrows by dipping them in a mixture of decomposing cadavers of adders and human blood. According to our modern interpretation, this mixture might have contained *Clostridium perfringens* and *Clostridium tetani*, as well as the snakes' venom [4]. In the third century BC, the military commander Hannibal of Cartagena set fire to the enemy's fleet

TABLE 1. Examples of biological warfare before the microbiology era [13])

Year	Event
14th century BC	The Hittites send rams infected with tularaemia to their enemies
4th century BC	According to Herodotus, Scythian archers infect their arrows by dipping them into decomposing cadavers
1155	Barbarossa poisons water wells with human bodies, Tortona (Italy)
1346	Mongols hurl bodies of plague victims over the walls of the besieged city of Caffa (Crimea)
1422	Lithuanian army hurls manure made of infected victims into the town of Carolstein (Bohemia)
1495	Spanish mix wine with blood of leprosy patients to sell to their French foes, Naples (Italy)
1650	Polish army fires saliva from rabid dogs towards their enemies
1710	Russian army catapult plague cadavers over the Swedish troops in Reval (Estonia)
1763	British officers distribute blankets from smallpox hospital to Native Americans
1797	The Napoleonic armies flood the plains around Mantua (Italy), to enhance the spread of malaria among the enemy
1863	Confederates sell clothing from yellow fever and smallpox patients to Union troops during the American Civil War

(belonging to King Eumenes II of Pergamon) with pots full of venomous snakes. Similar examples are reported by historians or, for cases closer to our epoch, by anthropologists of the use of arrows or other vessels infected with different products extracted from animal parts or plants in order to attack the human enemy [5,6]. Similarly, the use of arrows for the transmission of plague is suggested by some allegoric documents, such as the drawing painted in 1437 by an anonymous artist on a wood cover used by the government of Siena to protect official documents (Fig. 1). In the Middle Ages, a famous although controversial example is offered by the siege of Caffa (now Feodossia in Ukraine/Crimea), a Genovese outpost on the Black Sea coast, by the Mongols. In 1346, the attacking army experienced an epidemic of bubonic plague. The Italian chronicler Gabriele de' Mussi, in his *Istoria de Morbo sive Mortalitate quae fuit Anno Domini 1348*, describes quite plausibly how the plague was transmitted by the Mongols by throwing diseased cadavers with catapults into the besieged city, and how ships transporting Genovese soldiers, fleas and rats fleeing from there brought it to the Mediterranean ports. Given the highly complex epidemiology of plague, this interpretation of the Black Death (which might have killed >25 million people in the following years throughout Europe) as stemming from a specific and localized origin of the Black Death remains controversial. Similarly, it remains doubtful whether the effect of throwing infected cadavers could have been the sole cause of the outburst of an epidemic in the besieged city. However, this episode of the use of cadavers in order to infect a population remains a landmark in the history of BW [7–9]. Similar examples of the use of the technique of catapulting infected cadavers can be found throughout the

FIG. 1. Allegory of the plague: *Biccherna*, a wood cover (used to protect official documents of the civic government of Siena), painted around 1437 by an anonymous artist (possibly Giovanni di Paolo). This allegory is considered to be a representation of the plague and its high contagiousness, and suggests that, in addition to the catapulting of cadavers into besieged cities, plague may also be transmitted by using inoculated arrows. Copyright: ©bpk/Kunstgewerbemuseum, SMB/ Saturia Linke.

modern period, from the siege of the Bohemian city of Carolstein by Lithuanian troops in 1422 to the siege of the Swedish army in Reval (Estonia) in 1710 by the Russians [10–13].

During the subsequent centuries, smallpox represented the most effective, if purposefully used, biological weapon of Occidental war and colonial history. Introduced in the American continent by the European colonizers, it was explicitly used several times as a way to infect Native Americans during the so-called 'Conquest of the West'. To quote but only one anecdote, Captain Ecuyer, of the British forces, after offering blankets from a smallpox hospital to Native Americans, noted in his journal: 'I hope it will have the desired effect' [2]. However, in the light of contemporary knowledge, it remains doubtful whether his hopes were fulfilled, given the fact that the transmission of smallpox through this kind of vector is much less efficient than respiratory transmission, and that Native Americans had been in contact with smallpox >200 years before Ecuyer's trickery, notably during Pizarro's conquest of South America in the 16th century. As a whole, the analysis of the various 'pre-microbiological" attempts at BW illustrate the difficulty of differentiating attempted biological attack from naturally occurring epidemics [2].

Biological Warfare: A Classic Tool of Armies During the Modern Era

The truly modern era of BW starts with the foundation of microbiology at the end of the 19th century by Louis Pasteur, Robert Koch, and their followers. By identifying and controlling, in a rational and systematic way, many agents of human and animal disease, they gave scientists the possibility of systematically isolating and producing specific pathogens on a large scale, as well as, in a majority of cases, at least theoretically, controlling their dissemination. Until a few decades after being established, the new scientific paradigm does not seem to have been used as a new way to threaten or terrorize groups of human. Evidence has been produced that nations involved in World War I, especially Germany, but also France on a more limited scale, developed secret BW programmes, such as the infection of animal feed with *Bacillus anthracis* or *Burkholderia mallei* in order to infect the enemy [10,14]. Whatever the effectiveness of these programmes might have been, the threat of BW (Table 2), combined with the horror of chemical warfare being used on the battlefield, became, for the first time in history, a major political concern at the international level. As a consequence, the *Geneva Protocol for the Prohibition of the Use in War of Asphyxiating,*

TABLE 2. Crucial biological agents as defined by the CDC, and likely use as biological weapons [13]

Disease	Pathogen	Used[a]
Category A (major public health hazards)		
Anthrax	Bacillus anthracis	World War I; World War II; Soviet Union, 1979; Japan, 1995; USA, 2001
Botulism	Clostridium botulinum[b]	–
Haemorrhagic fever	Marburg virus	Soviet bioweapons programme
	Ebola virus	–
	Arenaviruses	–
Plague	Yersinia pestis	Fourteenth-century Europe; World War II
Smallpox	Variola major	Eighteenth-century North America
Tularaemia	Francisella tularensis	World War II
Category B (public health hazards)		
Brucellosis	Brucella	–
Cholera	Vibrio cholerae	World War II
Encephalitis	Alphaviruses	World War II
Food poisoning	Salmonella species, Shigella species	World War II; USA, 1990s
Glanders	Burkholderia mallei	World War I; World War II
Psittacosis	Chlamydia psittaci	–
Q-fever	Coxiella burnetti	–
Typhus	Rickettsia prowazekii	World War II
Various toxic syndromes	Various bacteria	World War II

Only a selected number of examples are provided in this table. Please note that Category C agents are not listed. Category C agents include emerging pathogens and pathogens that are made more pathogenic by genetic engineering. Category C agents include, for example, hantavirus, Nipah virus, tick-borne encephalitis virus, haemorrhagic fever viruses, yellow fever virus, and multidrug-resistant bacteria.
[a]Does not include time and place of production, but only indicates where agents were applied and probably resulted in casualties, and were used in war, in research, or as terror agents.
[b]In that case, only the toxin would be used.

Poisonous or Other Gases, and of Bacteriological Methods of Warfare was ratified in 1925, and prohibited the use of biological weapons, but not their research and production. Thus, states that had ratified the Geneva Protocol, such as France, the UK, Italy, Canada, Belgium, Poland, and the Soviet Union, began research on biological weapons; so did the USA, which did not ratify the Geneva Protocol until 1975 [2].

During the interwar period, the Japanese government began to develop one of the most systematic and ambitious BW programmes known to date. The famous Unit 731 (whose official name was the Army Epidemic Prevention Research Laboratory) was set up in 1932 (Fig. 2). Inspired by the German use of gases during the World War I, Japanese scientists subjected prisoners to different kinds of experimentation, including vivisection, weapons tests, and germ warfare attacks. Human subjects were inoculated with organisms causing cholera, smallpox, botulism, bubonic plague, anthrax, tularaemia, and various venereal diseases, and then left untreated, in order to study the various effects of the diseases. The research of Unit 731 led the Japanese army to conduct large-scale trials of biological weapons, such as the development of bombs used to spread pathogens, the infection of reservoirs and wells with deadly pathogens (notably *B. anthracis*, *Vibrio cholerae*, *Yersina pestis*, *Shigella* species, and *Salmonella* species), and the dropping of plague-infected fleas, infected food and clothing by aircraft into areas of China that were not occupied by Japanese soldiers. It is now estimated that several thousands of people (including several Japanese soldiers, victims of the difficulty of strictly controlling the dissemination of biological weapons) died as the result of these attacks [15–17]. The Japanese army was also accused of using BW against the Soviet Union and Mongolia [17].

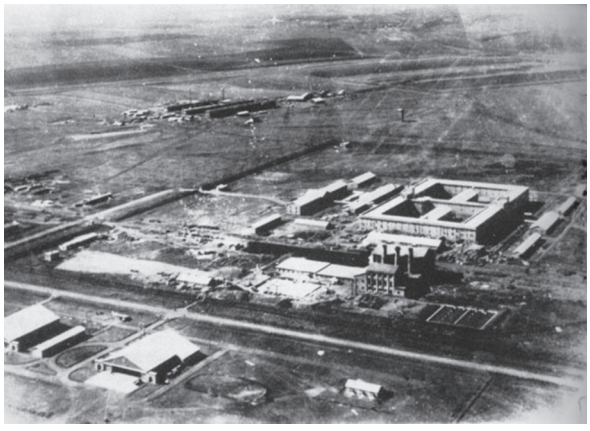

FIG. 2. View of the Unit 731 complex at Pingfan, China. Copyright: Despite all our efforts, we have not succeeded in identifying the authors and rights holders for this widely disseminated image. If you believe that you may be a rights holder, we invite you to contact Wiley, the publisher of this Journal.

The Nazis performed some research on the effects of various vaccinations and drugs on prisoners infected with *Rickettsia prowazekii*, hepatitis A virus, or *Plasmodium* species, but they apparently never considered using biological weapons during Word War II. In contrast, the USA was pushed to perform BW research by their allies, who feared that the Germans might attack with biological weapons [2,18,19]. In 1942, the US War Research Service was created to set up a BW programme. This included the creation of a laboratory research facility in Maryland (later renamed Fort Detrick), and various production facilities and testing places elsewhere in the country. After the end of World War II, the US government granted immunity against prosecution for war crimes to the Japanese Unit 731 leaders in exchange for the knowledge gained through their experiments. Many similarities can, indeed, be found between the scientific research interests of Unit 731 and the US BW programme, including the types of biological agent studied, and the use of simulations, such as tests using non-lethal forms of bacteria in order to test their dispersion properties as weapons. Samples from these tests were then collected by Soviet spies, and helped the Soviet Union to further develop its own biological weapons programme [19].

Typically for the Cold War era, many (mostly unsubstantiated) allegations of BW attacks were made between the 1950s and 1980s, in the context of the Korean and Vietnam wars, the Afghanistan invasion, and the Kampuchea dictatorship. However, they were never witnessed, nor were samples of the alleged products used found. They are now regarded as resulting from the ferocious propaganda arising from both sides.

In parallel with this aggressive development of BW programmes and counter-propaganda, there was an increasing concern among the nations regarding the epidemiological risks and the ineffectiveness of the Geneva Protocol of 1925. Under pressure from the WHO, the new *Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction* (better known under the abbreviation BWC) was signed in 1972 by the US, UK and Soviet governments, as well as by >100 other nations. Entering into force in March 1975, and having been continuously reviewed since, it prohibits: (i) the possession of biological agents except for 'prophylactic, protective, or other peaceful purposes'; (ii) the development of technologies intended for the dispersal of biological agents for offensive military purposes; and (iii) the destruction of existing stocks [20].

However, the existence of the BWC did not prevent various states from developing BW research programmes

(with the notable difficulty of defining precisely what the limits of 'offensive' and 'defensive' are in this context). In fact, Iraq, under the dictatorship of Saddam Hussein, initiated a BW programme that included research on *B. anthracis* and various viruses, but these potential weapons were not used during the Gulf War. Some accidents resulting from manipulation also occurred during the same period. One of the most discussed examples is the case of the town of Sverdlovsk (now Ekatarinburg, Russia), which became famous in April 1979 after the outbreak of an epidemic of anthrax. Western specialists thought that Soviet workers, while transferring huge amounts of anthrax bacteria (they were said to be large enough to destroy the world's population) into containers, let some potentially deadly spores contaminate the environment. The epidemic of anthrax occurred within a distance of 4 km around the suspected BW research laboratory. However, the Soviet officials attributed it to unintentional consumption of contaminated meat, and it was only in 1992 that President Boris Yelstin admitted officially that 'our military developments were the cause' [2,21,22].

Bioterrorism during the Contemporary Period

Among the main concerns during the contemporary period is undoubtedly the possibility of the use of biological weapons in the context of bioterrorism in a strict sense, i.e. the use of biological weapons by non-state-sponsored individuals or groups. From the 1980s on, one striking example is offered by the Rajneesh cult, a religious group who, in 1984, intentionally contaminated salad bars with *Salmonella typhimurium* in various restaurants in Dalles, Oregon. This attack, which resulted in 751 cases, 45 of whom had to be hospitalized, seems to be one of the very few confirmed instances of biological terrorism after World War II, with a few exceptions such as the 'anthrax letters case' [19]. Another religious cult, known as Aum Shinrikyo, besides launching its famous attack with sarin gas in the Tokyo metro in March 1995, was also developing, during the same period, a programme on rudimentary biological weapons containing *Clostridium botulinum* and *B. anthracis*, but with no proof of effectiveness.

The case of the 'anthrax letters' in the aftermath of the World Trade Center attack of 9 September 2001 in New York represents one of the latest examples of bioterrorism, with a huge impact at a psychological and political level as compared with the small number of effective infections. Several letters were sent during the autumn to government officials or journalists. Overall, 22 people were infected with anthrax, and five of them died from anthrax or complications resulting from it. The particular strain used was traced to the US army's laboratory at Fort Detrick, but the perpetrators of the attacks remain unknown. This example shows that BW remains a threat in the public sphere that has to be taken seriously and responded to without overreaction at the both individual and political levels. It also shows the importance of an adequate level of preparedness of clinical microbiologists to identify agents of BW [23].

Conclusions

Despite the advances in scientific research on bacteriology and, more generally, in biology and medicine, definitive conclusions regarding the effective use of biological attacks in the history of humankind remain difficult to draw, even since the advent of state-sponsored programmes of BW: the lack of microbiological and epidemiological data, the weight of political propaganda and issues about military secrecy make the problem particularly difficult to solve for the historical researcher. However, the recurring use of biological weapons (be it speculative or real), which emerged long before the scientific revolution of microbiology at the end of the 19th century, is a striking characteristic of that history. BW, as a 'common aspect of the human behavioural repertoire' [24], is not a thing of the past, and remains a serious concern, at a local level and at a global level, notably in the light of the recent rise in the use (or possible use) of non-state-sponsored BW. The question remains open of whether, in the period in which we live, we have become more humane than our predecessors concerning BW, and what are the best ways of preventing similar threats in the future. In the final analysis, what the history of BW and bioterrorism suggests is that the most effective prevention measure rests on the creation and preservation of strong cultural norms at the individual, social and political levels that prohibit the development and use of such weapons. More broadly, although the problem of BW is undoubtedly important, it should not cause us to overreact, and obfuscate the reality of real and important preventable infections.

Transparency Declaration

The authors declare no conflicts of interest.

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