As mankind hurtles along its self-destructive path, combat involving biological weapons may be the fastest way to hasten the journey. However, biological warfare is no new threat. For thousands of years, biological warfare has been used by innovative tacticians. With the discovery of microorganisms and genetic manipulation, coupled with advances in missile technology, this ancient art has become the masterpiece of many weapon arsenals. The roots of biological warfare can be traced back to dipping arrowheads in excrement to encourage wounds to fester, and it has progressed to the weaponization of deadly organisms stockpiled by many countries. This article focuses on several of the organisms that are currently considered a threat by the Atlanta-based Center for Disease Control (CDC) and provides a brief timeline highlighting some of the key points in the development of biological warfare (Figure 1).

Smallpox
For as long as man has roamed the earth, the smallpox virus has followed closely in his tracks. Claiming one third of those it infects, this virus has long been a human scourge. An incredibly potent microbial killer, it is credited with claiming 300 million lives in the 20th century alone. Yet, despite the international health triumph of worldwide vaccination accomplished in the 1970s, it could once again rear its menacing head - this time as a biological weapon of terror.

The earliest physical evidence of a smallpox infection is a pustular rash on the mummified body of Pharaoh Ramesses V of Egypt, who died in 1157 B.C.E. However, written references to the disease are as ancient as medical records themselves. For example, one of the most important and influential of all medieval Islamic physicians, Rhazes [864-930 C.E.], described sufferers of the disease as,

“The bodies most disposed to the Smallpox are in general such as are moist, pale, and fleshy; the well-coloured also, and ruddy, as likewise the swarthy when they are loaded with flesh; those who are frequently attacked by acute and continued fevers, bleeding at the nose, inflammation of the eyes, and white and red pustules, and vesicles.”

600 BCE  Assyrians contaminate enemy wells with Rye Ergot
184 BCE  Hannibal’s forces launch pots filled with serpents onto enemy decks during a naval battle against Pergamon.
1346  The Tartars catapult corpses of plague victims into the city during the siege of Caffa.
15th Century  Pizarro presents South American natives with clothing infected with the variola virus as gifts.
1767  During the French and Indian War, Sir Jeffrey Amherst, gives blankets laced with smallpox to Indians loyal to the French.
1797  Napoleon attempts to infect enemies with swamp fever during his Italian campaign.
1925  The Geneva Protocol bans biological weapons.
WW2  Japan experiments with biological weapons against Chinese forces and civilian population.
1972  The Biological Weapons Convention prohibits the research, development and proliferation of offensive biological weapons.
1979  In Sverdlovsk, Russia, around a hundred people are infected with Anthrax accidentally released from a nearby biowarfare facility.
1998  The US Defense Department starts an Anthrax vaccination program to immunize all personnel.

During the 10th century populations in both India and China developed a crude inoculation process. For the vast majority of people a mild course of disease would ensue, leaving the patient immune to subsequent infection. Unfortunately, this technique (known as Variolation), which required the pus of human smallpox vesicles to be rubbed into the open sores of otherwise healthy individuals, was not introduced to the Western world until 1721, when Lady Mary Wortley Montague observed the technique in

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Turkey and brought it home with her to the British aristocracy. The procedure was not accepted by the medical establishment of the time, and it was not until 1796, when Edward Jenner observed that milkmaids who caught cowpox never suffered from smallpox, that a proper vaccine was developed. In a congratulatory letter to Jenner, Thomas Jefferson declared: “Medicine has never before produced any single improvement of such utility. You have erased from the calendar of human afflictions one of its greatest.”

In 1959, the World Health Assembly passed an ambitious resolution to undertake a worldwide smallpox vaccination campaign, and completed the objective in 1977. This is undoubtedly one of the greatest international health care achievements of our time.

Despite this incredible accomplishment, smallpox has once again become an imminent threat. According to the testimony of defector scientist Ken Alibek, a former deputy director of the Soviet Union’s bioweapons program, the Russians, despite heading the global vaccination campaign, recognised that the virus would be an incredibly powerful weapon once it was eradicated and vaccination ended. To this end they stored particularly virulent strains of smallpox, while developing the technology to mass-produce and weaponize the virus. According to Alibek and confirmed by U.S. intelligence, it is highly likely that these stores were stolen by profiteering scientists following the disintegration of the U.S.S.R, and then sold to terrorist organisations and pseudo-states, as well as to countries such as Iraq, Iran and Pakistan.

Smallpox, a DNA virus of the orthopoxvirus genus, is an ideal biological weapon. Considerable stability in ambient conditions, a silent two-week incubation period, and a propensity to spread by droplet nuclei, direct contact, or contaminated clothing and linens all contribute to the ability to widely disseminate the virus via aerosols. In fact, the first documented use of smallpox as a biological weapon occurred in 1754 when British commanders “donated” blankets laced with virus to North American Aboriginals. Many tribes were decimated by the ensuing epidemics, as they had never before been exposed to the virus, and lacked immunity. The smallpox virus is also widely believed to have killed off many of the Aztec and Inca tribes of Mexico during the 16th century, being brought there by Spanish conquistadors. Australia managed to escape the ravages of the virus until late in the 18th century. However, its arrival was a tragic death knell for the susceptible Aboriginal populations there as well.

As American health care officials and politicians presently debate the necessity to re-institute a broad based vaccination campaign, the population of the entire world can be likened to the unsuspecting and vulnerable indigenous peoples of the New World. The immunity acquired years ago by the adult population is no longer effective; treatment for this virus is severely limited to supportive therapy; and a reactionary vaccination campaign would be nearly impossible to organise amidst the widespread panic that would surely ensue following an attack of this nature.

**Botulinum Toxin**

*Clostridium botulinum* toxin joins plague, tularemia, smallpox, anthrax and viral hemorrhagic fevers at the top of the CDC list of deadliest biological organisms. This should come as no surprise because the toxin is the most poisonous substance known to man: 1 gram of crystalline toxin evenly dispersed and inhaled could kill more than one million people. Fortunately, the military uses of the toxin as a means to immobilize the opponent are currently restricted by technical difficulties in concentrating and stabilizing the agent for aerosol dissemination. However, deliberate release in the civilian population could produce large numbers of casualties and create a public health emergency.

The first known outbreak of the disease occurred in Germany in 1793. “Kerner’s disease,” named after the physician who compiled the death reports, was traced back to contaminated sausage. The condition was later renamed botulism, from the Latin *botulus* meaning “sausage”. Since naturally occurring botulism is most commonly related to contaminated food, public notices on food safety were issued by the German government in 1802. Nearly 90 years later, the gram positive, obligate anaerobic bacillus *Clostridium botulinum* was discovered by Emile van Ermengen, following an outbreak due to contaminated ham.

Clinically, botulism is characterized by acute, symmetric, descending, flaccid paralysis, with involvement of the cranial nerves causing diplopia, dysarthria, dysphonia, and dysphagia. These symptoms are the result of the blockage of acetylcholine release at the neuromuscular junction by botulinum toxin, which occurs 12 to 72 hours after exposure. The toxin, which exists in seven antigenic types, cleaves fusion proteins. This prevents acetylcholine-containing vesicles from fusing with the terminal membrane of the motor neuron. The disease can be categorized in three naturally occurring forms: foodborne, wound and intestinal. In the wound and intestinal types, the organisms are absorbed in the bloodstream or through gastric mucosa and produce the toxin *in vivo*. The most common form is foodborne botulism resulting from ingestion of toxin-contaminated food. A fourth form of the condition is the man-made “inhalational botulism” which would result following the release of aerosolized botulinum toxin.

There exist numerous attempts at using the lethal potential of *Clostridium botulinum* as a weapon. During World War II, Unit 731 of the Japanese Imperial Army was created in order to research the potential of microbial agents as weapons of mass destruction. The toxin was one of the agents actively researched by the infamous Unit and one of the many poisons forcibly fed to prisoners of war as part of the medical experiments. It is reported that the U.S. Office of Strategic Services developed a plan to assassinate high ranking Japanese officers using Chinese prostitutes armed with capsules containing botulinum toxin. The capsules “less then the size of a common pin head” could be slipped into the food of the unsuspecting officers. More recently, as a consequence of the U.N. inspections following the Persian Gulf War, Iraq admitted to stockpiling 19000L of concentrated toxin. Of these, 10000L were loaded onto weapons and constitute roughly three times the amount necessary to kill the entire world population (being introduced into the body by inhalation). Russian scientists who defected to the U.S.
gave evidence of attempts to splice the toxin-producing gene into other infectious agents.

The current treatment for botulism is supportive care — the paralysis can persist for months — and passive immunization with equine antitoxin. Prophylaxis is also possible as circulating antibodies to the toxin provide protection against the disease. Passive immunity can be achieved using equine or specific human hyperimmune globulin; endogenous immunity results following inoculation with botulinum toxin.11 Neither option is without side effects, making botulism a highly dangerous disease and an ideal “incapacitating agent” among the bioweapons. Ironically, this feared pathogen is also historically the first biological toxin licensed for treatment of human disease. Strabismus, cervical torticollis, blepharospasm associated with dystonia are but a few of the conditions that benefit from use of Botulinum toxin, not to mention the multiple cosmetic uses of Botox® injections.11

Anthrax

The terrorist assaults on New York and Washington in 2001 forever changed the world. Yet even as America came to grips with these tragedies, another perhaps more frightening threat was already in the air. In the months following the World Trade Centre and Pentagon attacks, America was subjected to a sustained terror campaign via the dissemination of Anthrax-laced mail, distributed unknowingly by the U.S. Postal Service. In total, 22 confirmed or expected cases of Anthrax developed across the country, with 5 people succumbing to their infections.14

Bacillus anthracis is the aerobic, gram positive, spore forming bacteria causing Anthrax. It takes its name from the Greek anthrax, meaning “coal”. This is in reference to the dark black skin lesions that are associated with cutaneous infection.

Anthrax has been used as a biological weapon since WWI. Charges from this era include the intentional infection of livestock intended for export to Allied forces by Germany, as well as U.S. operations to contaminate animal feed and infect horses intended for export to Europe.15 During WWII, America is known to have produced 5000 bombs filled with B. anthracis spores at a pilot plant at Camp Detrick, the U.S. Army base for biological research, although none of them were ever deployed.15

Despite widespread acceptance of the Biological Weapons Convention in the early 1970s, some nations persisted with their development of offensive biological weapons. The former Soviet Union is known to have developed a large B. anthracis production program. In 1979, an accident at a biological weapon plant in Sverdlovsk, Russia (now Ekaterinburg, Russia) resulted in the release of spores leading to an epidemic of Anthrax that killed at least 66 people.15 In 1995 Iraq admitted to producing and weaponizing B. anthracis to a UN special commission.16 Also in 1995, the Japanese cult Aum Shinrikyo was implicated in spreading aerosols of anthrax and botulism in Tokyo on at least 8 separate occasions.17 Fortunately the strain they released was a variant of an animal vaccine that did not pose a threat to humans.18

B. anthracis is a particularly frightening bacterium. Its virulence factors include an antiphagocytic capsule and several different toxins. The lethal toxin leads to the perpetual release of pyrogenic cytokines, and the edema toxin causes pulmonary edema by impairing neutrophil function and water homeostasis. Inhalation anthrax can have a variable dormancy period, but clinical symptoms rapidly follow germination. At this point treatment hinges upon the appropriate diagnosis and aggressive antibiotic therapy. A vaccine is available, but will not help once the infection has spread.

Anthrax infection can follow one of three routes: cutaneous, gastrointestinal or inhalation. The primary route of human infection is through contact with infected animals that have ingested spores from the soil while feeding. These spores can survive for decades in ambient conditions. Cutaneous infection is the most common route, with about 2000 cases annually worldwide.19 Gastrointestinal infection is uncommon, but occasional outbreaks in Asia and Africa occur from consumption of undercooked contaminated meats. Inhalation anthrax is by far the most deadly, and would logically be the route of choice for delivery as a biological weapon.

The World Health Organisation has estimated that the release of 50 kilograms of B. anthracis spores over a city the size of Toronto would likely infect 350 000 people, and leave about 100 000 dead.20 A similar analysis conducted by the U.S. Congressional Office of Technology estimated that between 130 thousand to 3 million deaths could follow the release of 150 kilograms of bacterial spores;21 a lethality matching that of the H-bomb.22 Furthermore, an aerosol release of B. anthracis would be totally undetectable, and have a range of many kilometres from the release point.

Plague

Of the many infectious diseases that have afflicted mankind, plague has earned the most sinister reputation. The three great plague pandemics shaped the course of history by disrupting social and economic patterns, as all large scale deadly epidemics do. Plague even impacted on the very core of human values by influencing religion, literature and art. Today, in the age of antibiotics and sophisticated medical care, Yersinia pestis, the causative bacteria of plague, is still at the top of the Critical Biological Agents list compiled by the CDC. Presently the cause of panic is not the mystery of the “Black Death”, but the full understanding of the devastating potential of this disease that has become yet another weapon in the dreadful arsenal of biological warfare.

The first record of a plague outbreak is described in the Bible, and occurred among the Philistines. From then on, vivid descriptions appear in the works of great historians, such as Thucydides’ eye witness account of the plague in Athens: “no human art was of any avail …and at last men were overpowered by the calamity and gave them all up”.22 The most infamous plague epidemic was the great European pandemic of the Late Middle Ages, which started in Northern Italy in 1347 and continued until 1351. During the 1346 siege of Caffa – a port of the Crimean peninsula to the Black Sea – the Tatar armies experienced an outbreak of plague. Skilled
warriors, they managed to turn their misfortune into a tactical advantage by catapulting the dead bodies of the victims over the city walls. This rudimentary biological weapon won them the victory but may have inadvertently caused the future deaths of one third of Europe’s population. The Italian sailors fled the city of Caffa and brought the plague to the many ports of the Mediterranean and, from there, to the mainland.

Plague is primarily a disease of rodents that can be transmitted to humans through flea bites. If left untreated it has an estimated 50-60% fatality rate. Great improvements in living conditions and the advent of antibiotics have made plague an uncommon occurrence, but the disease still exists in localized foci. The World Health Organization reports that 1000 to 3000 cases occur per year. Three different forms of the disease exist. In bubonic plague the bacillus is deposited in the network of cutaneous lymphatics, which carry it to regional lymph nodes. Swollen, tender lymph nodes, known as “bubo”, appear in the axillary, inguinal and cervical regions. Bacteremia, followed by sepsis, is the natural course of the disease. Sometimes necrosis and gangrene of digits and nose occur in advanced stages of the disease, so the plague became commonly known as “Black Death”. Septicemic plague occurs when the flea deposits the bacillus directly into the blood. Pneumonic plague is by far the most worrisome manifestation of the disease: it is the only form of plague that is transmissible from person to person, via respiratory droplets. It has 100% mortality if untreated, with death following soon after the onset of symptoms reminiscent of a respiratory infection.

The first account of the use of plague as an agent of biological warfare seven centuries ago in Caffa was by no means the last. During World War II, Unit 731 of the Japanese Imperial Army used prisoners of war to test the lethality of typhoid fever, anthrax and plague. In 1940 active military campaigns by the Japanese dropped paper bags filled with plague-infested fleas over the Chinese province of Zhejiang. Yersinia pestis was one of the choice pathogens that was the subject of intense research both at Fort Detrick as well as its Soviet counterpart during the early stages of the Cold War. According to Dr. William C. Patrick in an interview with The New York Times, when the U.S. terminated its biological weapons development program in 1969, the plague was not successfully weaponized. Scientists deficient from the Soviet program brought chilling news of the successful development of weapons capable of disseminating contagious lethal agents like plague and smallpox rather than incapacitating agents, like anthrax and tularemia. Even more astounding is the deliberate creation of antibiotic resistant strains of plague or “superbugs.” These are genetically engineered hybrids of viruses such as Ebola or encephalomyelitis and the bacterial host.

It appears that history has failed to teach its lesson. Despite incredible advances in science and technology, today’s biowarriors would have no more control over the lethal potential of their bioweapons than the 14th century assailants of Caffa.

References