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Suzanne M. Lutwick
Editors

Beyond Anthrax

The Weaponization of
Infectious Diseases

 Humana Press

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 Springer

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*Piglet sidled up to Pooh from behind.
“Pooh,” he whispered. “Yes, Piglet?”
“Nothing,” said Piglet, taking Pooh’s paw.
“I just wanted to be sure of you.”*

*This book is dedicated to those whom we
always want to be sure of:*

*Our parents and siblings and
Talora and Zev,
Rachel and Robert,
Zach and Mollie,
Arielle and Talal,
Nina and . . .*

*May all of you be able to spend playfully
exploring the world of Pooh without any
interference by the contents of this text.
And to a best friend who is looking down
upon us, still not a sports fan, Steve Straus.*

*Larry Lutwick
Suzanne Lutwick*

Preface

“If there is one thing the history of evolution has taught us it’s that life will not be contained. Life breaks free, expands to new territory, and crashes through barriers, painfully, maybe even dangerously.”

– Dr. Ian Malcolm, “*Jurassic Park*” (1993)

“The most merciful thing in the world, I think, is the inability of the human mind to correlate all its contents. We live on a placid island of ignorance in the midst of black seas of infinity, and it was not meant that we should voyage far. The sciences, each straining in its own direction, have hitherto harmed us little; but some day the piecing together of dissociated knowledge will open such terrifying vistas of reality, and of our own frightful position therein, that we shall either go mad from the revelation or flee from the deadly light into the peace and safety of a new dark age.”

– H.P. Lovecraft, “*The Call of Cthulhu*” (published 1928)

Howard Phillips Lovecraft was an American author of horror, fantasy, and science fiction. His major inspiration and invention was overt cosmic horror, and he is often regarded as one of the most influential horror writers of the twentieth century, exerting widespread and indirect influence, and frequently compared to Edgar Allan Poe. The above quotation begins the story and could be applied to more modern times, nearly 80 years since the story’s publication in “Weird Tales.” Of course, it is easy to argue that the sciences have no longer “harmed us little” with such developments of nuclear bombs and other weapons of mass destruction (WMDs). Among the WMDs (as the media enjoys calling them) are those of the biological variety. It is these agents that serve as the basis of this textbook.

“*Beyond Anthrax, The Weaponization of Infectious Diseases*” has been in development for a number of years and is meant as a primer for clinicians and epidemiologists on a variety of agents, organisms, or toxins, which are generally considered at the forefront of potential use in a biological attack from a rogue nation or radical group. In the aftermath of the September 11 World Trade Center attacks, a number of cases of inhalational anthrax were diagnosed in the eastern United States, specifically the New York City metropolitan area and Washington, DC, although the first case was diagnosed in Florida. The finding

of a disease such as anthrax outside of its general geographic area with an uncommon presentation (inhalation rather than cutaneous exposure) is the factor that raises the red flag of a possible bioterrorist attack. In this case, the spores of *Bacillus anthracis* were found to have been weaponized to increase infectivity and placed (by a person still unknown) in the mail. The letters, by processing in post office facilities or by opening at the final destination, delivered a deadly message producing inhalation anthrax in 11 individuals with a 45% case fatality rate [1]. Much information has been published regarding anthrax as a biological agent, and for reasons of space and minimizing repetition regarding this disease, the text will start beyond anthrax and discuss the remaining Category A agents as well as delve into a number of the diseases placed in Category B. It will suffice to say, however, that the anthrax incident has demonstrated what terrorism really does in getting a huge bang for its buck; that is, for a small number of cases, the outbreak caused major disruption to much of the fiber of this country changing some of it forever.

Before going forward, we must take stock of reality and not just jump, willy-nilly, on to the Lovecraftian slippery slope of the inevitability of something evil occurring fashioned by the hand of some bad person. No doubt, the possibility of the use of biological warfare has always existed millennia before the acceptance of the Germ Theory, a short century or so ago. Many of these events are discussed in Stuart Handysides' introductory chapter on the history of the topic. It is, to this point, useful to refer to the John Snow [2] Memorial Outbreak Scoreboard during the last decade or so. In doing so, our evil task doers are clearly trounced in overall numbers of cases and outbreaks by Mother Nature (MN), the world's most devious bioterrorist.

Although aided by humankind, MN has fashioned newly recognized diseases such as SARS (severe acute respiratory syndrome) [3] like a Golem out of the virtual molecular mud and has facilitated diseases such as monkey pox [4] and West Nile virus [5] unknown on a continent to appear there.

Furthermore, she has assisted in the production of multidrug resistant organisms [6,7] in a healthcare arena where fully sensitive ones had been present. Additionally, and certainly last but not least, MN continues to percolate new strains of influenza A including the current H5N1 avian strain [8] that threaten to win the primary race for next pandemic candidate. Although the diseases forthcoming in this text may be formidable opponents in the future, it remains a solid wager that infectious disease clinicians, epidemiologists, and public health personnel will have their hands soiled with many more threats than that are contained here.

Following the Stuart Handysides (former Medical Editor of Communicable Disease and Public Health) chapter on the history of biological warfare, the text has five chapters regarding the Category A diseases that are (true to the title, beyond anthrax), namely, smallpox, plague, tularemia, botulism, and the viral hemorrhagic fevers. The chapters are written by some of the foremost experts of each field including representatives of the National Institutes of Health, the

Centers for Disease Control and Prevention, and UK's Defense Science and Technology Laboratory at Porton Down. The chapters for the most part contain similar sections including outbreak scenarios, a historical perspective, microbiologic considerations, natural infection with its epidemiology and diagnostic considerations, as well as specific biowarfare issues. Additionally, the chapters discuss both therapeutic and preventative measures and may include infection control, prophylactic drugs, reservoir controls, and vaccinations.

The next part of the text contains chapters dealing with many, but not all, of the Category B agents, selected for overall interest. This includes a chapter on the intentional contamination of food and water as well as ones dealing with melioidosis, epidemic typhus, and some of the biotoxins such as ricin and staphylococcal enterotoxin B. Overall, the organization of these chapters parallel that in those of the Category A diseases. With much more emphasis on the "A" diseases, the inclusion of these entities provides a good source of information for the clinician and epidemiologist.

Following the "B" list are a number of chapters that concentrate on a variety of issues that are important in any contribution in the biowarfare arena. All of these have direct applications to natural outbreaks and epidemics, and they include Public Health Infrastructure, Public Health Law, Public Health Surveillance, Mental Health Management, as well as a chapter regarding the role of the media in outbreaks written by David Brown, a physician who has written regularly for the *Washington Post*. The text ends with an overview of rapid detection of pathogens and a final chapter discussing agroterrorism, that is, biological attacks on the potentially very vulnerable food-producing systems of the world. Biowarfare aimed at flora and fauna rather than on humankind, although not as often written about, are ripe areas for further discussions and protective measures.

In several of the original versions of the "Table of Contents," several other chapters were envisioned, but as the text matured, they were not included. The editors thank those who contributed additional but unused material.

We hope that the topics contained here, as biowarfare events, remain purely didactic exercises and not issues that interject themselves into clinical medicine.

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Contents

1 The History of Bioterrorism: Old Idea, New Word, Continuing Taboo	1
Stuart Handysides	
2 Smallpox and Bioterrorism	17
Daniel R. Lucey, Joel G. Breman and Donald A. Henderson	
3 Plague	55
Petra C. F. Oyston and Richard W. Titball	
4 Tularemia	77
Daniel S. Shapiro	
5 Botulism	85
Jeremy Sobel	
6 The Viral Hemorrhagic Fevers	107
Daniel G. Bausch and C. J. Peters	
7 Melioidosis	145
Pooja Tolaney and Larry I. Lutwick	
8 Epidemic Typhus Fever	159
Mohammad Mooty and Larry I. Lutwick	
9 Category B Biotoxins	181
Larry I. Lutwick, Jeremy Gradon and Jonathan Zellen	
10 Intentional Terrorist Contamination of Food and Water	207
Jeremy Sobel and John C. Watson	
11 Public Health Infrastructure	219
Isaac B. Weisfuse	

12 Public Health Law and Biological Terrorism 239
Lance Gable and James G. Hodge, Jr.

13 Public Health Surveillance for Bioterrorism. 253
Peter N. Wenger, William Halperin and Edward Ziga

14 Psychosocial Management of Bioterrorism Events. 279
David M. Benedek and Thomas A. Grieger

15 The Role of the Media in Bioterrorism. 295
David Brown

16 Rapid Detection of Bioterrorism Pathogens. 317
David Perlin

17 Plant Pathogens as Biological Weapons Against Agriculture. 335
Forrest W. Nutter and Lawrence V. Madden

Index 365

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Chapter 1

The History of Bioterrorism: Old Idea, New Word, Continuing Taboo

Stuart Handysides

1.1 Definitions

The word “bioterrorism” first appeared in a book called *Killing Winds*, by Jeanne McDermott, in 1987 [1], and took another 9 years to reach a biomedical publication [2]. It appears in only the post-2003 editions of large dictionaries in my local bookshop and the *Oxford English Dictionary* online [3]. A Medline search yielded 2,018 entries on the topic—none before 1996, only 50 before 2000, and then an exponential increase (70 in 2000, 445 in 2001, 862 in 2002, and 3,998 by November 13, 2007) [4]. The history of bioterrorism would be rather short if written to consider events only since the word was coined. From a historical perspective it will be better, I think, to consider the phenomenon itself and take a longer view. Nevertheless, the word itself needs defining.

The word “terrorism” goes back only as far as the French Revolution. “The reign of terror” was a 2-year period of mob rule and bloodshed, led by the Jacobin government of Robespierre and the so-called Committee of Public Safety that followed the September massacres of 1792. Edmund Burke was one of the first persons to use the word “terrorist” to describe agents of the Jacobin government, in 1795, and the word “terrorism” was first used, in the same context, the same year.

Robespierre, translated from the original French by J. M. Thompson, explained the need for harsh measures: “If the basis of popular government in time of peace is virtue, its basis in time of revolution is both virtue and intimidation—virtue, without which intimidation is disastrous, and intimidation, without which virtue has no power . . . Intimidation is merely justice—prompt, severe and inflexible. It is therefore an emanation of virtue, and results from the application of democracy to the most pressing needs of the country” [5]. Thompson, commenting on these words, noted that intimidation was generally the weapon of tyrants. The new despotism of postrevolutionary France took this weapon out of the tyrant’s hand and turned it against

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him in the name of the people, but ended up turning it against anyone who disagreed with the current “party line”.

The word terrorist today is usually applied to a nongovernmental agent, an agent without state sponsorship, but this usage goes back only to the second half of the nineteenth century. The word was used in 1866 to describe the dissident Irish, and in 1883 Russian revolutionaries who were prepared to use violence received the same appellation. *Webster's New International Dictionary* (1913) defined terrorism as “a mode of governing, or opposing government, by intimidation” and a terrorist as “one who administers or coerces a government or community by intimidation” [6], thus covering the actions of established governments and those with grievances against them.

The word terrorist is often given a negative connotation, but history sometimes changes our perspective on people and events. As an example, the South African government imprisoned Nelson Mandela as a terrorist, but many saw his fight against oppression and demand for human rights and the end of apartheid as the just desires of a freedom fighter. The latter appear to have been right.

Central to the meaning of terrorism is the fear experienced by those being terrorized. The acts of violence or warfare themselves kill or injure, but the terror is experienced by those who wonder where it will end and whether they or their loved ones will be the next victims of pain, injury, or death. Perhaps, the greatest act of terrorism the world has seen was the unleashing of atomic bombs on Japan. Terror belonged not only to the survivors in Japan, but to the world in general in the following 40 years of the “Cold War” and the uncertainty of the deterrent power of mutually assured destruction.

The prefix “bio” denotes the use or threat of biological agents to terrorize. Human beings themselves are biological agents, whose fists, feet, and teeth may be used as weapons. Various large and/or fierce animals have been used to intimidate enemies—Hannibal’s elephants must have been an awesome sight, and the pots of snakes hurled by his men onto the ships of King Eumenes of Pergamon spread fear and distracted his enemies [7, 8]; Nero’s lions in the Coliseum were an attempt to reduce the attraction of Christianity; the Romans also catapulted bees and hornets at their enemies; and the horses of the Spanish conquistadors menaced the Incas and Aztecs [7]. The word bioterrorism is usually used, however, to describe the threat or deployment of microorganisms or the use of contagion or infection, as weapons. The *Oxford English Dictionary* defines bioterrorism as “the use of infectious agents or biologically active substances as weapons of terrorism” [3].

Does the term bioterrorism deserve to exist? Do we speak of ballistic, explosive, or chemical terrorism? Is the use of biological weaponry different from other methods of attack? Roman jurists protested when their attempt to conquer Germanic tribes was thwarted by the poisoning of wells: *armis bella non venenis geri*—war is fought with weapons, not with poisons [8]. Commanders might see their armies decimated by outbreaks of plague, typhoid, cholera, smallpox, or

influenza, but these were misfortunes rather than potential tools. Why is the use of a biological weapon seen as “fighting dirty” or “not cricket”?

This chapter, on the history of bioterrorism, will take an inclusive approach. It will draw little distinction between those who practice “warfare” and those who practice “terrorism.” It will also use the term bioterrorism to describe actions taken before the existence of microorganisms was discovered.

1.2 Acts of God

Several of the Biblical plagues meted out to the Egyptians when Pharaoh refused to allow the children of Israel their freedom could be regarded as bioterrorist acts [9]. In the first plague, the rivers turned to blood and the fish died and stank. The plague of frogs was unwelcome, as was their smell when they died and rotted in heaps. Plagues of lice and flies and a die-off of cattle, which spared the livestock of the Israelites, followed the plague of frogs. Pharaoh continued to take a hard line, refusing to bargain with the terrorists, and the next visitation was a plague of boils and blains on the skin of men and beasts. At this point, the Lord diversified, using hail and fire to destroy the ripening crops, but then again returned to a biological plague, employing locusts to finish off whatever the hail had left. The penultimate plague was a period of darkness, lasting 3 days. In the last plague, the firstborn of all families, human and animal, were slain in households where a prescribed sacrifice had not been made. At this point, Pharaoh hollered “nough” and sent the Israelites on their way.

The exact nature and factual existence of the plagues have been debated. The boils have been attributed to both plague and anthrax, but it all happened a long time ago. At the very least, however, the biblical report indicates that the potential for bioterrorism had been realized when the book of Exodus was written (about 1500 BC). If the book is taken as a literal historical report, it could be argued that God, as well as creator, was also the first bioterrorist.

The Bible also describes an outbreak—possibly plague—that befell the Philistines, when they captured the Ark of the Covenant from the Israelites [8, 10].

Another early reference to possible bioterrorism is found in Homer’s *Iliad*, which tells how the city of Troy came under siege of the Greeks, after the beautiful Helen (married to the Greek Menelaus) ran off with Paris, one of the sons of the Trojan king, Priam [11]. The tale, written perhaps 7–10 centuries before the birth of Christ, starts with a description of a plague on mules, dogs, and men meted out by Apollo, after his priest, Chryses, was sent away rudely by Agamemnon when he asked for the return of his daughter.

Thus, the earliest descriptions of what might be called bioterrorism were plagues attributed to the God of the Hebrews and the Greek god Apollo. Gods, unlike men, could not be fought. They had to be appeased. Pharaoh and Agamemnon capitulated.

1.3 Poisoning Water Supplies

A little later, in the fifth century BC, Hippocrates said that impurities in the air (Greek: *miasmata*) were the cause of plagues [12]. At much the same time, Thucydides noted that the people of Athens, suffering from plague (or was it measles? [13]), believed that the city's water supply had been poisoned by the Spartans. Although the Romans had declared that poisoning was not an appropriate way to wage war, they poisoned the wells of the remnants of the army of Aristonicus, who kept fighting despite being, to a large extent, defeated [8]. Many years later the Black Death spread from Constantinople to the whole of western Europe, following trade routes both on land and on sea. Jewish communities in some of the plague-affected cities were accused of well poisoning and were exterminated [12]. The practice of poisoning water supplies has continued: It occurred in the American Civil War, the Boer War, and, allegedly, in Turkish Kurdistan as recently as 1997 [8].

1.4 Ballistic Biological Weapons

The archers of Scythia, in about 400 BC, are said to have dipped their arrow tips in blood mixed with manure [8]. Other early instances of the ballistic distribution of biological weapons are arrow tips and darts from blowpipes poisoned with curare by native Amazonians and with batrachotoxin from frogs by Hawaiian islanders [8, 14]. A book published in 1777 suggested to dip "arrows in matter of smallpox and twang them at the American rebels" [8]. More recently, grenade shrapnel was contaminated with botulinum toxin in the Second World War [8].

Sometimes the missiles were rather larger. The original catapult and ballista, as used by the Romans, could hurl rocks of approximately 30 kg at and over the walls of castles [15]. Later developments, such as the trebuchet, could project missiles of 150 kg and even as much as 1,500 kg. When the rocks ran out, other objects could be used as ammunition. Gabriel de Mussis provided an eyewitness account of the siege of Caffa (now Feodosiya), on the Black Sea, from 1344 to 1346 [15]. The Genoese-occupied city held out for 3 years. Suddenly, the besieging Tartars and Saracens fell victim to plague: "the humors coagulated in the groins, they developed a subsequent putrid fever and died." Mountains of cadavers were "placed on their hurling machines and thrown into the city of Caffa ... soon all the air was infected and the water poisoned, corrupt and putrefied, and such a great odor increased." The Genoese took to their ships and fled, taking plague with them to Italy, Sicily, and Sardinia. It has been argued that the fleas responsible for transmission of plague would have left the dead to occupy living hosts and the cadaver missiles, therefore, may not have carried the vectors into the city [14]. But how dead were the dead, and how quickly would the fleas have fled?

Other similar incidents have been documented. A few years earlier, in 1340, dead horses and other animals were hurled mechanically at the castle of Thun L'Veque in northern France. The reporter of this incident, Jean Froissart, wrote, "the stink and the air were so abominable . . . they could not long endure" [16]. Less successful was the siege of Carolstein, or Karlstein, in Bohemia in 1422. Despite a barrage of soldiers' bodies and 2,000 cartloads of excrement, and an outbreak of fever attributed to the stench, the siege was abandoned after 5 months [8, 15–17]. The Hippocratic idea of miasma as the means by which illness was transmitted was still commonly held at the time. A rain of mutilated, rotting corpses within the city walls might well have induced terror of contagion as well as spreading disease.

1.5 Fomites

It appears that the development of gunpowder and the ways of using it occupied the minds of militarists for the next few hundred years [8]. In the early eighteenth century, almost a 100 years before Edward Jenner showed that inoculation with cowpox offered protection against smallpox, the practice of variolation—inoculation with fluid from smallpox pustules—was recognized as a means of protecting against severe infection with smallpox [8]. Variolation had a mortality rate of 2–3%, one-tenth that of natural infection, and became popular. It offered the protection needed by an aggressor to contemplate the potential of using an infectious disease as a weapon.

British forces in North America, whether through natural infection or through variolation, probably had more immunity to smallpox than the Native Americans. In a well-documented incident from the Pontiac Rebellion in 1763, Captain Ecuyer (under the command of General Jeffrey Amherst) gave blankets and a handkerchief from the smallpox hospital at Fort Pitt to Delaware Indians, with the hope that they would "have the desired effect" [18]. An epidemic of smallpox among the Native American tribes in the area followed, although it is not clear whether it was the blankets or other contacts with colonists that introduced the virus into the Native American population [14]. The intention to harm was clear, and letters expressing genocidal intent have been preserved [18]. The attempt was made, however, in a way intended to cause harm without, necessarily, intimidation. Both British and American troops were variolated during the American War of Independence [8], and the British are said to have used smallpox against the Americans in both Quebec and Boston [16]. Fomites are said to have been used by "land speculators and corrupt agents of the Brazilian Indian Protective Service" to spread smallpox among native American tribes of the Amazonian basin between 1957 and 1965 [16].

1.6 Living Human Carriers

The traditional image of people with leprosy is of their being herded into colonies, being cut off from their healthy fellows, and having to carry a bell and ring it to warn people of their arrival and enable them to get out of the way [13, 19]. The potential for transmission was clearly known: Spaniards are said to have spiked French wine with blood from people with leprosy in 1495. The potential for using infectious people to spread disease was at least discussed in the American War of Independence. A letter from General Alexander Leslie to General Cornwallis in 1781 talks of distributing a cohort of 700 Negroes suffering from smallpox in the rebel plantations [8].

1.7 Economic Sabotage Through Biological Weapons

The work of Robert Koch and Louis Pasteur in the 1870s identified specific infectious agents as the causes of contagion rather than the “bad air” hypothesis that had held since the days of Hippocrates [13]. Bacteria could be grown in a laboratory and, presumably, released among or dispatched to your enemies. Germany tried it out in the First World War. The targets were not humans, however, but animals, which perhaps reflects persistence of the Roman sensitivity about the rules of engagement. The attacks were made, in general, on nonaligned countries that were supplying Germany’s enemies with animals for transport and food [14]. Romanian sheep to be exported to Russia, mules from Mesopotamia, horses from the United States destined for the allied forces, livestock from Argentina, and reindeer and horses from Norway were all attacked. The organisms used were *Bacillus anthracis* and *Pseudomonas mallei*, the pathogens associated with anthrax and glanders, respectively. Several methods were used: injections using needles that had been dipped in cultures, infected solutions poured onto feed, and capillary tubes embedded in sugar lumps [16]. The effectiveness of the campaign is not clear [16], but the intention was plain. In Mesopotamia, 4,500 mules were inoculated, and in Argentina over 200 mules died after infection with *B. anthracis* and *P. mallei* [14].

1.8 Biological Warfare and Terrorism by Established Powers Since the Geneva Protocol

Although biological weapons had not been used against humans in the First World War, their potential use and the need to control them were recognized in the 1925 Geneva Protocol for the Prohibition of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare [14]. The treaty banned the use of biological weapons, but did not outlaw research, production, or possession, and made no provision for inspection [14]. Several countries that