CHAPTER 1

Introduction: Pestilence, Plague, Bioterrorism

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Ring around the rosie,
Pocket full of posies,
a-tishoo, a-tishoo,
All fall down.

Old European nursery rhyme about smallpox and the bubonic plague

I have examined Man’s wonderful inventions. And I tell you that in the arts of life man invents nothing; but in the arts of death he outdoes Nature herself, and produces by chemistry and machinery all the slaughter of plague, pestilence, and famine.

The Devil speaking in Don Juan in Hell, Act III of Man and Superman by George Bernard Shaw, 1902

Human history has been shaped by virus infections. For instance, without the introduction of smallpox, measles, and yellow fever to the New World, it is likely that a significantly different natural, cultural, and governmental landscape may exist in the Americas. Not only are the factors that launched successful emerging viral diseases very much still with us, but modern societies have added multiple facilitating forces that ensure the continued role of viral infectious diseases in the future of Homo sapiens. Our response to this challenge will speak to the yet unanswered question: Are we deserving of our species name?

Humans have come to an exaggerated image of their role in the evolution of human history. While stacks of books narrate in detail human acts that molded the
fate of nation-states and civilizations, few admit the role of natural elements in shaping human destiny. Among such primal forces as volcanism, earthquakes, floods, drought, and climate change must be counted biogenic forces. Among the latter, infectious diseases of viral origin have writ large upon the chronicle of civilization’s development. The mummified remains of Egyptian royalty Ramses V documented his death from smallpox in 1158 BC. Smallpox imported from the East and known as the Plague of Antonius took the lives of millions of Romans in AD 165–180. Variola virus, as the causative agent of smallpox, likely was responsible for the decimation and subsequent defeat of Abyssinian troops in the attack upon the Arabic capital of Mecca in AD 570.

The accidental introduction of smallpox to the New World assumed a central role in the European conquest of Mexico, Peru, Brazil, North America, and Australia. Variola virus was imported to the Americas through the West African slave trade. The Spanish invaders under Hernan Cortes initially were appeased by Aztec Emperor Montezuma, who believed them the embodiment of the god Quetzalcoatl, the prophesized destroyer of the Aztec Empire. Later armed resistance by the Aztecs led by Montezuma’s brother Cuittlahuac drove the vastly outnumbered Spanish expeditionary troops to a last enclave, where annihilation would have seemed certain. Yet the arrival near Veracruz of a second expeditionary force that joined ranks with Cortes’ vastly diminished army perchance included a slave with smallpox. The disaster that followed was massive and world-shaping. The immunologically and genetically naïve native population of Veracruz was rapidly decimated, and the disease spread quickly to Tenochtitlán (now Mexico City), where it killed as many as half the population in some areas, and eventually took the lives of more than three million Aztecs. Because the disease spared the Spanish soldiers, who possessed both genetic and immunological resistance, but savagely destroyed the Aztecs, the native people came to accept this as punishment by an angry god. The Aztecs therefore accepted Spanish rule as their fate and no longer resisted. Conquest, subjugation, and Christianity followed hard on the heels of smallpox.

A similar fate befell the Inca of Peru. Smallpox’s arrival preceded Pizarro’s force of 168 men with whom he conquered an Empire of millions of Incas. Variola virus was Pizarro’s greatest ally, as it destroyed not only great numbers of Incas but led to social upheaval and civil war. Smallpox, measles, influenza, yellow fever, plague, tuberculosis, typhus, and other European imports effected a 95% decline in North American Indian populations, certainly preparing the path for domination and westward expansion.

The first recognized intentional use of smallpox as a biological weapon was by Sir Geoffrey Amherst who, as British Commander-in-Chief in North America during the French and Indian War, authorized provision of variola virus-contaminated blankets to hostile Indian tribes. During the American Revolution, George Washington greatly feared the use of smallpox as a bioweapon by the British. In fact, American troops under Benedict Arnold failed in their mission to conquer Quebec in 1776 when nearly half of the Continental forces died of smallpox, albeit an epidemic of natural origin.
By the conclusion of the eighteenth century, nearly 10% of all humans had been disfigured, crippled, or killed by smallpox. Cosmetics had come into being as a result of a need to hide the scars of smallpox. In the twentieth century alone, approximately 300 million people had perished from smallpox. For comparison, all the wars of the twentieth century killed just one-third the number of humans as did smallpox.

Variolation, the practice of rubbing smallpox pustule exudate into a needle scratch on the arm, provided protection against variola virus, but at a cost of 2 deaths per 100 variolations. Edward Jenner’s cowpox vaccination gave smallpox prophylaxis with a dramatic decrease in iatrogenic disease and death and further set the stage for the eradication of smallpox, a hope once advanced both by Jenner himself as well as Thomas Jefferson.

In spite of initial widespread opposition to a program of worldwide smallpox eradication, continued pressure by individuals such as Brock Chisholm of the World Health Organization (WHO), Victor Zhadnov of the Soviet Union, and Marcelino Candau of WHO, saw the worldwide eradication program eventually actualized and financed. Under the direction of Donald A. Henderson from 1966, the WHO smallpox eradication campaign achieved its remarkable goal of worldwide eradication when the last case of smallpox was reported in Somalia in 1977.

The yellow fever virus also has directed the course of human history. This flavivirus was introduced into the New World from Africa by means of the slave trade, which Europeans expanded to replace the human labor lost when smallpox and measles took their ghastly toll of Native American slaves. In a strange turn of fate, the yellow fever virus thwarted the ambitions of at least one European empire builder when it essentially destroyed Napoleon’s expeditionary force sent to put down the Haitian rebellion. Thus Haiti won its independence from France. Moreover, Napoleon was so rattled by this empire-defeating disaster wrought by a lowly virus that it was a key factor in his decision to execute the Louisiana Purchase with Jefferson, thereby abandoning France’s claims and avoiding a war with the United States. This sequence of events catalyzed the American westward expansion.

It was the yellow fever virus that forced France to abandon the Panama Canal Project. Subsequently, bolstered by the findings of the Yellow Fever Commission that revealed the mosquito as the vector for yellow fever, the United States was able to shoulder the Canal Project. For most people, measles invokes a childhood disease that, before vaccine was available, was an unpleasant but common occurrence albeit with rare sequelae of encephalitis and, even rarer, subacute sclerosing panencephalitis. Nonetheless, to a totally immunologically isolated and naïve population, measles is a deadly disease. To wit, its introduction to Fiji in 1875 resulted in widespread social disruption and a 40% decrease in the native population. Measles also collaborated with smallpox in the ravaging of the early Native Americans, thereby facilitating European domination. However, even in non-naïve populations, the effects of measles were devastating. Both Union and Confederate Armies in the American Civil War suffered extensively. Although the WHO has proposed steps toward eradication of measles, it remains a major source of morbidity and mortality in developing countries.
No one can debate the effects of influenza virus on the human condition. In recent times, the defeat of Germany in World War I was in part related to an influenza outbreak. At detailed by Oldstone, Germany’s spring 1918 offensive, after the withdrawal of Russia from the war, threatened the Allies with defeat. However, influenza brought about a massive loss of German troops and concurrent breakdown of logistics. German Commander Eric von Ludendorff blamed influenza for cessation of the German Army offensive. This in turn permitted time for the influx of the American Expeditionary Force, the accompanied regain of lost French soil, and an eventual armistice. Yet influenza, not the weapons of war, caused 80% of American casualties and 43,000 deaths. This experience was generalized expertly by Jared Diamond in Guns, Germs, and Steel: “All those military histories glorifying great generals oversimplify the ego-deflating truth: the winners of past wars were not always the armies with the best generals and weapons, but were often merely those bearing the nastiest germs to transmit to their enemies.”

Worldwide, the 1918–1919 influenza epidemic (termed the Spanish flu) infected a fifth of the total human population at that time and killed an estimated 20–50 million people.

Other RNA viruses evoke concern. Many of them have been the subject of press accounts over the past few decades and, in various modified embodiments, have become the stuff of novels and stars of films alike.

Presently, human immunodeficiency virus (HIV), with the resultant acquired immune deficiency syndrome (AIDS), is the most infamous example of a modern emerging infectious disease. There were 38 million HIV-infected humans in 2003, and nearly five million people became infected with HIV in 2003, more than any year before. Over 20 million already have died. Over 90% of people living with HIV/AIDS are in the developing world, with sub-Saharan Africa claiming the greatest number (25 million) and the greatest number of deaths (3 million) from AIDS. Nonetheless, Asia now has the fastest-growing HIV/AIDS epidemic on earth, and sadly the advent of antiretroviral drugs has led to an increase in high-risk behavior in high-income countries, resulting in an increase in the number of new HIV infections.

While only time will reveal the full impact of HIV/AIDS on the human story, it is already certain that it has altered the future of Africa. The pandemic has already reduced average national economic growth rates by 2–4% a year across Africa. Some predictions call for even greater impacts. Through increased mortality and morbidity, the HIV/AIDS pandemic impacts labor supply, causing loss of skills in key sectors of the labor market. In South Africa, for example, around 60% of the mining workforce is aged between 30 and 44 years; in 15 years this is predicted to fall to 10%. In the South African healthcare sector, 20% of student nurses are HIV positive. AIDS reduces labor productivity, thereby reducing competitiveness, profits, exports, and balance of payments.

And it must be remembered that HIV/AIDS has released a host of opportunistic infections caused by organisms ranging from other viruses to helminths, some of which are newly recognized taxa or organisms never before identified as serious
pathogens of humans. Thus HIV has provided a potential factory for the generation of even more novel emerging pathogens.

Other RNA viruses, emergent or reemergent, already are determining regional futures and may write even more upon the annals of human history. For instance, yellow fever has reemerged to constitute a major public health problem in Africa. Dengue virus and its associated DHF (dengue hemorrhagic fever) is an emergent disease in India and has spread from Asia to most of the tropics. Although rotaviruses already are the cause of extensive morbidity and mortality in children in developing countries, it appears that G serotype 5 is of emerging epidemiological importance in Brazil. West Nile (WN) virus invaded the Western Hemisphere in the summer of 1999 and represented the first introduction in recent history of an Old World flavivirus into the New World. Japanese encephalitis (JE) virus has recently encroached on the northern shores of Australia. As this manuscript is being prepared, another lethal outbreak of Ebola hemorrhagic fever has been reported in southern Sudan. Human-induced landscape alterations and/or climatic changes have caused emerging Hantavirus infections in rodents with resulting lethal spread to humans. Rabies is undergoing geographic expansion due to natural and anthropogenic movements of wild animals. Other emerging viruses, recognized now even by laypeople, include human monkeypox, Nipah virus, Hendra virus, and the coronavirus that causes SARS (severe acute respiratory syndrome).

Of course, at one time during human development, diseases such as smallpox, measles, and influenza were themselves emergent. Their emergence was facilitated greatly by the growing human populations, higher population densities, and domesticated animals. Just as variola arose from cattle poxvirus, measles from rinderpest from pigs, and influenza from ducks and chickens, today’s emerging diseases often have their roots in animals. The most infamous example would be HIV origination from chimpanzees. Yet, like our ancestors, we have introduced novel conditions for the emergence of new diseases. This emergence is the result of shifts in human demographics and behavior, changes in technology and industry, economic development, habitat invasion and destruction, increasing and facile international travel and commerce, microbial adaptation, alterations in human immune response and viral evasion, social and governmental disruptions, wars and the generation of great numbers of refugees, and the deterioration of public health measures.

Added to this multifactorial equation are the unknowns of microbial resistance development (as with HIV), insufficient political commitment to control by governments of countries where the disease is endemic and high-income countries where it may not seem a present threat, poor or inadequate disease surveillance, inappropriate disease control measures, and preventable poverty and living conditions that facilitate disease. At least from a purely selfish viewpoint, high-income governments need to educate their populace that emerging microbial infectious diseases, so long as uncontrolled elsewhere on earth, provide an ongoing potential source of new and perhaps even deadlier organisms. This would seem a special threat in the case of RNA viruses, which exist as genetic swarms and can easily mutate.
Finally, added into this witch’s cauldron is the unthinkable threat of biological terrorism. The threat was realized in the United States with the anthrax attacks in 2001. Although smallpox was declared to be eradicated on 8 May 1980, during the Thirty-third World Health Assembly, concerns about the possible use of the virus in bioterrorism have grown in the past few years. Other viruses, such as those that cause hemorrhagic fevers, have been identified as possible bioterrorism agents by the Centers for Disease Control and Prevention. They have been so designated because large amounts can be generated in cell culture, they are transmissible in aerosol form, and there are limited or nonexistent vaccine and drug strategies for either prevention or treatment of established infection. In addition, these viruses could be modified genetically to enhance their virulence or to promote resistance to vaccines or antivirals.

The purposeful manipulation, introduction, and/or reintroduction of these viruses would represent a wildcard in our future struggle with emerging infectious diseases. Almost certainly, the greatest damage would be borne in developing countries (say, by the reintroduction of smallpox). Imagine the horrific consequences of the added burden of reestablished smallpox in Africa on the existing pandemic of HIV/AIDS, yellow fever, and a host of other microbial and parasitic infections.

A new variant of mousepox virus with increased virulence for mice has been reported. This was created by splicing a gene for interleukin-4 into mousepox virus. Addition of the IL-4 gene apparently suppressed the normal immunological response against the mousepox virus infection, and the new poxvirus was able to evade vaccine-induced protection. Moreover, cidofovir, the only available drug thought to be effective against smallpox, did not protect mice against challenge with the IL-4 mousepox virus.

The threat from emerging diseases, whether of “natural” origin or the introduction of terrorists, cannot be underestimated. There is much that needs to be done in this fertile area for drug discovery. This volume deals with approaches to drug discovery and development for a number of emerging viruses and some of those of bioterrorism interest. HIV, although still emerging, is not included because of the enormous volume of research that has been well described in many other venues. We trust that the contributions herein will illuminate the path for an increasing number of able investigators to follow.

REFERENCES

1. Material in this introduction has drawn heavily upon the following resources.
REFERENCES

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10 INTRODUCTION: PESTILENCE, PLAGUE, BIOTERRORISM


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