INFECTIOUS DISEASES IN HISTORY

Helsinki, Finland
January 8, 1996

Over recent decades, we have witnessed extraordinary changes in medicine ranging from organ transplantation, genetic engineering, pioneering advances in surgery and diagnostics, all manner of applications for biotechnology and bioengineering, wondrous new antibiotics and, last but not least, a growing cornucopia of effective vaccines.

For those of us living in the well-sanitized, temperate climate, industrialized world, infectious diseases became increasingly a rarity and for many of those that did occur, antibiotics were a quick and efficient solution. Indeed, it was during the 1960s and 1970s that many concerned with science policy declared that the victory over infectious diseases had essentially been won--at least in the industrialized countries. In the United States, Departments of Microbiology in Schools of Medicine withered, infectious disease residencies diminished in number and epidemiologists shifted their attention to the chronic diseases.

It is all too apparent that we acted prematurely. We have watched helplessly as the Human Immunodeficiency Virus (HIV) emerged and spread steadily across the globe. Our once misplaced self-confidence (or perhaps arrogance) is epitomized in the 1983 declaration by our U.S. Secretary of Health that, having isolated the HIV, a vaccine would be available within two years. Now, some 12 years later, and after mobilization of the best of basic and applied science and the expenditure of billions of dollars, we have only a few antiviral compounds of marginal efficacy, a handful of experimental vaccines which have yet to reach the point of phase III trials and a fatal epidemic which continues

to spread inexorably across the world. It has been a properly humbling experience for all in the medical community.

In the meantime, other previously unknown or unrecognized infections as well as a few, once controlled, have materialized. In our own country, Lyme disease, multiply antibiotic-resistant tubercle bacilli and enterococci, and Hanta virus infection have been identified. Dengue hemorrhagic fever, once localized to Southeast Asia, is now prevalent throughout the Caribbean and is spreading into Central and South America. New infections have emerged in Africa and some have spread to Europe--Llasa fever, Marburg and Ebola virus disease. Within the past two years, a new type of cholera has appeared in Asia, possibly the harbinger of the next global pandemic.

Should we, living in America or you, living in Finland be concerned about these problems? After all, as tragic a disease as AIDS may be, its threat to our own populace is less serious than once was feared. In fact, the numbers of new infections acquired annually in the United States have fallen to a level of about 40,000 persons per year. This is approximately the number of fatalities recorded annually for which firearms are responsible and one-tenth the number of deaths caused by tobacco. As for the other new infectious agents, only a few have so far exhibited an ability to spread, let alone spread widely in temperate climates. Is it not reasonable to view these new and emergent entities as biological curiosities, now being uncovered by virtue of more diligent science, rather than as potential harbingers of more serious, perhaps catastrophic biological events in the future?

We tend to forget--and, indeed, ignore at our peril--the potential destructiveness of the lowly microbe. As a comparative mark of destructiveness, I would offer the numbers of deaths resulting from armed conflict. Estimates have recently appeared in the popular press suggesting that between 100 and 140 million persons have lost their lives in this century either directly from the effects of armed conflict or indirectly, as, for example, from the effects of starvation or disease among refugee populations. This amounts to, on average, 1 to 1.4 million deaths per year. Many of those deaths are clustered, of course, during the 1914-1918 and 1939-1945 periods. What does the record reveal for microbes?

Smallpox deaths in 1967, at the time the global eradication campaign began, were estimated to number between 2.0 and 2.5 million (Table 1).[1] These numbers are the more impressive when it is appreciated that virtually all countries that were then already engaged in vaccination programs and, indeed, substantial areas of the world were smallpox-free, including Europe, all of the Western Hemisphere except Brazil and most of East Asia, including China. As of 1993, deaths due to tuberculosis, to measles and to diarrheal disease among children under five years accounted for 2.0 to 3.0 million deaths.[2] Measles deaths numbered 1.2 million, a decrease from 3.0 million only eight years before as vaccination programs burgeoned world-wide. Finally, it is important to recall that the severe influenza pandemic itself killed an estimated 21 million.[3]

As awesome as these figures are, most have forgotten or may not appreciate that there have been eras in the past when epidemic disease not only altered history but, indeed, threatened civilization. I would like today to refer to only two such periods--the

first is the period of the Black Death in Europe commencing in 1346; the second period encompasses 300 years following the introduction of smallpox and measles into the Americas beginning in 1520. Both of these chapters have relevance to the threat posed by new and emergent infections today.

During the three centuries prior to the beginning of the epidemic, best known as the Black Death, populations in Europe had grown steadily, bringing ever more land under cultivation; cities grew; and trade prospered.[4] It was also during that period, that Genghis Khan and his successors established the Mongol Empire which eventually extended from eastern Europe across Eurasia and deep into China. The rapid and extensive movement of Mongol armies and messengers, coupled with increasingly numerous caravans which traversed the great Silk Route, linked closely together for the first time the previously remote population centers of China and the Indus Valley with those of Europe. One early traveler on that route was the black rat, originally native to Asia, and an ideal host for the plague bacillus, pasteurella pestis. Later, plague followed.

The Black Death arrived in Europe in 1346. It broke out among the armies of a Mongol prince who was then laying siege to the trading city of Caffa in the Crimea. Historical accounts indicate that nothing resembling plague had visited Europe for at least 350 years. The epidemic, spread via rodents carried by trading vessels, moved into the Mediterranean in 1347 and thereafter traversed much of Europe over the next three years.

What began as bubonic plague, transmitted from infected rats to man by fleas, was soon transformed into pneumonic plague with spread by droplet infection directly from

person to person. Without antibiotics (and there were none, of course), fewer than 25% survived. Some escaped infection simply by not being exposed and indeed some villages were spared altogether. Historians estimate that overall between one-third and one-half of Europe's 80 million residents died. Priests, scholars, farmers and the gentry alike succumbed. The social disruption was profound. Agricultural production declined and food shortages and starvation followed. Construction came to a virtual standstill and the European world lapsed into a lethargy from which recovery was slow to come.

The plague continued to recur at intervals over the next century and more. Populations declined irregularly but persistently over the following 100 years, reaching a low point sometime in the mid- to late 1400s. Indeed, nearly 300 years were to elapse before the population of Europe regained the numbers present in 1346.[5]

The Black Death is a classic example of an emergent infection, long endemic in a remote area along the Burma-Yunan border but devastating when introduced into new areas--first in China and then Europe. With population losses such as these and numerous deaths among productive adults as well as children, the very fabric of civilization was tested.

Gradually, control of the plague was achieved, in part by the application of quarantine measures; in part through greater use of better housing materials which discouraged rodents. Still, the potential remained for localized, devastating epidemics. As recently as 1898, for example, more than six million persons died in an epidemic in Bombay.

As grim as was this chapter in history, a far more disastrous chapter was that written in the Americas following the introduction of smallpox in 1516 and later measles.[6] The Amerindian population then numbered some 30 to 40 million persons, about half the population of Europe at that time. Most resided in middle and south America.[7]

After Columbus' discovery of the Americas in 1492, settlements had followed quickly--and soon thereafter, smallpox. In the earliest settlements of Hispaniola, Puerto Rico and Cuba, smallpox spread rapidly through native populations killing such large numbers that many such populations disappeared altogether. In the spring of 1520, Cortez sailed from Hispaniola for Mexico, in part to try to find additional natives who could be conscripted for labor. He was accompanied by fewer than 500 men, but one was infected with smallpox. In Mexico, the disease began to spread soon after Cortez' arrival and by early September, it had invaded the Aztecs' great capital (now Mexico City) lying high on the inland plateau. The Aztecs at first sought to expel the Spaniards but smallpox soon prevailed causing tens of thousands of deaths and claiming the lives of the emperor as well as other prominent rulers. The Spaniards who were all survivors of the disease in infancy were unaffected and this the Aztecs took as a sign of the Spaniards' divinity. Within years, Cortez had subjugated both the Aztec and Mayan empires and within a decade, Pizzaro conquered the Mayas. Thus, more than 30 million Amerindians were subjugated by two Spanish conquistadors each with less than 500 men. The subjugation, however, was the product of epidemic disease rather than warfare--and

the devastation was unbelievable. One outbreak in Peru during the 16th century was poignantly described as follows:

> **"They died by scores and hundreds. Villages were depopulated. Corpses were scattered over the fields or piled up in the houses or huts. All branches of industrial activity were paralysed. The fields were uncultivated; the herds were untended; and the workshops and mines were without laborers. It was only with difficulty that the ships could be manned. The price of food rose to such an extent that many persons found it beyond their reach. They escaped the foul disease, but only to be wasted by famine."[8]**

As wave after wave of smallpox continued to sweep across the Americas and other previously unknown diseases, principally measles, assaulted the natives, populations plummeted. Most authors concur that over a period of 75 years following the introduction of smallpox into the Americas, native populations had declined by between 70 and 95%.

North American Indians, many of whom were hunter-gatherers living in smaller tribal groups, experienced a similar fate. Records indicate that epidemics in the early 17th century wiped out 90% of the Indian population along the Massachusetts coast and over the next three centuries, countless tribes throughout the country, disappeared one by one as decimating disease was followed by starvation. The last destructive epidemics,

from 1836-1840, effectively pacified the western frontier. The impact is summarized in a letter dated 1838.

> **"We have, from the trading posts on the western frontier of the Missouri, the most frightful accounts of the ravages of smallpox among the Indians....The number of the victims within a few months is estimated at 30,000 and the pestilence is still spreading....The vast preparations for the protection of the western frontier are superfluous....Every thought of war was dispelled and the few (Indians) that are left are as humble as famished dogs....No language can picture the scene of desolation which this country presents."**[9]

During these two chapters in history, one shaped by plague and the other primarily by smallpox, it is apparent that the fabric of civilization for native residents was severely tested before adaptations could be effected and control measures implemented. Indeed, generations rather than years were required for European recovery; the outcome for native Americans was never ultimately a happy one.

The effects of new but lethal microbes on a virgin population are not to be underestimated. Of course, these two events occurred several centuries ago and, as we know, we are certainly today better equipped to deal with infectious disease than they were then. But a word of caution is in order. In the case of smallpox, for example, there is even today no effective treatment other than nursing care. Deaths are caused primarily by the virus itself, not secondary bacterial infection. Without a vaccine, the

saga of smallpox would have been far different than what it was. The fact that throughout this period, smallpox persisted in Europe with less devastating consequences reflects the fact that it had become endemic, i.e., constantly present, and that most individuals contracted the disease in childhood. Society could deal with death rates among children of 25 to 40% by higher fertility rates. Comparable rates in adults, however, seriously disrupted the social fabric. However, the impact even of endemic smallpox is not to be underestimated as the population of Europe, in fact, grew very slowly until the contemporaneous beginning of smallpox control and the Industrial Revolution.

But there is one further chapter which I would like to share with you which illustrates the enormous potential and challenge which microbial agents may pose to mammalian survival. This deals with a cousin of smallpox, an orthopoxvirus known as myxomatosis, which infects rabbits.[10]

Myxomatosis virus has long been known as a poxvirus native to the Americas where it produces a benign infection in native wild rabbits. However, when the myxomatosis virus is inoculated into the European hare, a different species, it is almost uniformly fatal. The European hare had been introduced into Australia in the 19th century and, with few natural predators, it had so propagated that destruction of crops became a serious problem. Australians attempted all manner of approaches in efforts to control the burgeoning rabbit population but all proved costly and none were markedly successful. Finally, they proposed to infect wild rabbits with myxomatosis hoping that the disease might spread naturally and destroy large numbers. After extensive testing to

assure that the virus was specific only to rabbits, a number were infected and released in 1950. And, indeed, the virus spread with dramatic rapidity.

Initial strains of the virus killed more than 99% of those infected. These, I would remind you, were naturally occurring strains in Latin America. Not all rabbit populations were in sufficiently close contact with others to permit virus spread throughout the country and so some rabbit burrows escaped initial infection--much as in the 14th century, not all villages were exposed to plague. However, the population of rabbits shrank dramatically to a level of perhaps 20% of the original population. Over the years, the strains of the virus and the rabbit population continued to be monitored. With time, the virus gradually became less virulent. While this may seem reassuring, as we contemplate the question of other new or emergent viruses, it is to be noted (Table 2) that ten years after the first release, 10% of the strains recovered were as virulent as ever; 53% killed "only" 80% of animals; while a handful of strains caused death in less than 30%.[11] If one translates this episode into human terms, can one imagine the devastation wrought by a virus disease exhibiting a case-fatality rate of 99% or even one which on average killed "only" 60%? Such could essentially end human civilization as we know it.

The myxomatosis chapter is but one more illustration of a microbial infection invading a virgin population with devastating effect. Is it reasonable in the present era to anticipate new or emergent infections which could so threaten the fabric of civilization itself as did plague and smallpox in an earlier era?

Suppose, for example, that HIV was successful in acquiring the ability to be transmitted by aerosol, much like influenza. A preposterous supposition you would suggest. However, bear in mind that the retroviruses are among the least stable of all viruses and, suppose that one mutant did acquire the property of being transmitted by aerosol. Certainly, it would have an enormous advantage in propagating itself. And, as you may know, there is indeed accumulating evidence that certain strains (or clades) of HIV do appear better able to propagate themselves through heterosexual transfer and that, in areas where such strains are now found, the incidence of HIV infections has been rising sharply.[12]

There are good reasons to question the complacency and confidence with which we have, until recently, viewed the infectious disease world. We need to remind ourselves that the world is populated by countless varieties of microbes, and that those microbes, multiplying at astronomical rates and in astronomical numbers, are continually mutating, adapting, changing to assure their own survival and niche in nature. Of special concern are the viruses which by their very nature become fundamentally entangled with the genetic and metabolic machinery of the host as they propagate themselves.

We are beginning to appreciate the fact that new and emerging microbes, new diseases and new manifestations of old diseases are to be expected for the indefinite future. To paraphrase Dr. Josh Lederberg:

> **It is clear that man's only competitors for dominion of the planet are the viruses--and the ultimate outcome is by no means fore-ordained.**[13]

The number, diversity and severity of such infections appear from reports to have increased over the past decade or so. Some have suggested that this reflects improved surveillance and better science and perhaps this is so. There are, however, reasons for such infections to be increasing in number and to increase further over the years ahead.

First and foremost is the rapid growth of enormous, densely populated, poorly sanitized urban areas such as have never existed before in history. In 1950, there were only two cities with populations of over 7.5 million persons, the largest--New York City--being 12 million. Now there are 28 urban centers with more than 7.5 million persons (Figure 1), seven of which have populations which are each larger than the total population of Scandinavia.[14] Many are in tropical or subtropical areas with minimal sanitation and all are growing at two to three times the rate of their national populations. What better place for a bacterial mutant to gain a foothold and to begin spreading from person to person.

But there are other factors as well. International travel is growing exponentially making it ever more likely that whatever illnesses are seen in one continent will soon be occurring on other continents. Civil disorders are more common and refugee populations are now the largest in history. Such populations provide especially fertile soil for the occurrence of explosive epidemics of all types. Hospitals, especially in developing countries, are proving to be unique amplifiers of infection, and these have burgeoned in number over recent decades. Contaminated needles and other instruments as well as crowded patient wards provide exceptionally dangerous environments for disease transmission. Finally, opportunities have greatly expanded for new microbes to

emerge from previously inaccessible areas such as rain forests as man increasingly penetrates these and other regions around the world.

The changes in sources for our food supply and in its distribution deserve special comment.[15] Reflecting the smaller world we occupy, foodstuffs are now being produced, processed and packaged at all manner of farms and facilities across the world and shipped everywhere. In the United States, the average grocery store stocked 300 items in the 1950s; today, 25,000 different items is the norm, a great many from other countries, some produced under very marginal conditions. Seasonally now, 75% of U.S. fresh fruits and vegetables come from other countries. Thus, the prospects for all manner of organisms to be rapidly and widely disseminated are more prevalent than ever before. And, finally, the assembly-line processing of prepared foods uniquely opens the way to major epidemics. Illustrative is a Shigella outbreak which resulted from the breakdown in sandwich preparation in a U.S. airline flight kitchen--240 cases were identified on 219 flights in 24 states in four foreign countries. In total, it is estimated that some 1900 cases resulted from just this one brief sanitary breakdown. Clearly, the potential for widespread dissemination is beyond imagination.

In concluding this all too brief overview of microbes and history, I hope I have persuaded you that we declared victory over the infectious diseases somewhat prematurely. It is even more evident as we realize now that infectious agents can be carcinogenic and are responsible at least in part for cancers of the liver and cervix--and could well be responsible for more.

It is imperative, I believe, that we return to the basics and prepare ourselves thoroughly for a range of new microbial challenges which are as certain as death and taxes. World-wide, we need far greater clinical expertise in the infectious diseases, better surveillance and epidemiology, improved diagnostic capabilities, and a more comprehensive program of basic research both with respect to molecular biology as well as genetics and immunology. This is an ambitious agenda but how else can one possibly deal with the complex array of new problems now being posed by existing and emerging infections in a rapidly changing world? Faced with the not unrealistic prospect that we may one day face a latter day version of the Black Death or America's disastrous encounter with smallpox, can we afford not to invest in the manpower and weapons necessary to deal with a potential problem far more ominous and certain than mere armed conflict?

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1. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID (1988) Smallpox and its eradication. World Health Organization, Geneva

2. World Health Organization (1955) The world health report, 1955. World Health Organization, Geneva

3. Crosby AW Jr (1976) Epidemic and peace, 1918. Greenwood Press, Westport CT

4. McNeill WH (1976) Plagues and peoples. Anchor Press/Doubleday, Garden City, NY

5. Durand JD (1977) Historical estimates of world populations. Pop and Develop Review 3:253-296

6. Hopkins DR (1983) Princes and peasants: smallpox in history. U Chicago Press, Chicago

7. Durand JD (1977) Historical estimates of world populations. Pop and Develop Review 3:253-296

8. Hopkins DR (1983) Princes and peasants: smallpox in history. U Chicago Press, Chicago

9. ibid

10. Fenner F, Ratcliffe FN (1965) Myxomatosis. Cambridge U Press, Cambridge

11. Marshall ID, Fenner F (1960) Studies in the epidemiology of infectious myxomatosis of rabbits. VII The virulence of strains of myxoma virus recovered from Australian wild rabbints between 1951 and 1959. J Hyg Camb 58:485-494

12. Burke DS, McCutchan FE (1966) Global distribution of HIV-1 clades, in AIDS, 4th edn (in press)

13. Lederberg J (1993) Viruses and humankind: intracellular symbiosis and evolutionary competition, in Emerging viruses (SS Morse, ed). Oxford U Press, New York

14. United Nations (1990) World urbanization prospects--1900. United Nations Press, New York

15. Hedberg CW, MacDonald KL, Osterholm MT (1994) Changing epidemiology of food-borne disease: a Minnesota perspective. Clin Inf Dis 18:671-682

Table 1 Deaths per year (Millions) (1,2,3)

	Year	No.of deaths
Armed conflict (Aver. per year)		1 -1.4
Smallpox	1967	2.0
Diarrhea (<5 years)	1993	3.0
Tuberculosis	1993	2.7
Malaria	1993	2.0
Measles	1985	3.0
Measles	1993	1.2
Influenza	1918	21.0

Table 2 Strains of Myxomatosis: Virulence of Field Specimens (11)

(Case-fatality Rates--%)

	99	90	60	0-30
1950-51	100	0	0	0
1951-52	83	17	0	0
1952-53	17	74	9	0
1953-54	41	50	9	0
1954-55	32	42	26	0
1955-56	3	55	25	17
1956-57	6	55	24	15
1957-58	10	54	22	14
958-59	10	53	16	14

Fig 1