THE BIRTH AND DEATH OF SMALLPOX

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Since the beginning of human existence, the evolution of disease has closely followed the evolution of culture. A complex feedback relationship exists between humans and the pathogenic organisms in their environment. Disease has been a powerful selective force, acting on human biology as well as culture. By the same token, human behaviors have been selective agents in disease evolution because cultural practices influence exposure to and transmission of all infectious diseases.

Smallpox is an excellent example of these interactions for several reasons. Its related high mortality rate imposes selection pressure on human biology. Its effect on culture and history is virtually immeasurable. The role of smallpox in decimating American Indian populations during conquest is one example of this effect (McNeill, 1976:209). Because smallpox is a uniquely human disease, the variola virus is viable only in the human organism, making it very sensitive to characteristics of human biology and behavior. Finally, its eradication graphically illustrates the power of human practices to be selective agents in the evolution of disease.

The origin of the community viruses is poorly understood. The community viruses include smallpox, measles, rubella, mumps and chicken pox. Because these diseases generally confer life-long immunity and require person to person transmission, large dense populations are necessary to sustain them. For instance, it is estimated that a population of one million is necessary to sustain measles as an endemic infection (Cockburn, 1967:99). For this reason theorists feel that the community viruses are a recent addition to the human repertoire of diseases, appearing sometime after the agricultural revolution allowed substantial increases in population size and density.

This simple picture is complicated by Cockburn's claim that non-human primates suffer from viruses very much like those of their human counterparts. They differ enough from those of humans and other animals to suggest that they occur naturally, and have mechanisms for survival in small populations (Cockburn, 1967:46). In spite of this, Cockburn feels that the community viruses arose in the recent past and began with accidental transmission from animal hosts. He supports this by stating that the nearest relatives of these viruses are those that affect domestic animals, and that man continues to be infected with zoonoses in such a manner (Cockburn, 1967:103). This interpretation, while plausible, is not conclusive. The same evidence could support an hypothesis that pathogens native to humans have infected various animal species. The possibility that human diseases can be transmitted to domestic animals, while almost a certainty, is often overlooked.

In viral taxonomy smallpox belongs to a group called the poxviruses, which includes cowpox, monkeypox, mousepox, and rabbitpox. The DNA double strand virus is carried in airborne droplets and enters the

body through the respiratory tract. After absorption through the mucous membrane there is an incubation period of from 7-17 days. With the onset of the disease high fever (102-105°F) and lower back pain are the major sysptoms, with nausea, vomitting and convulsions appearing in some victims. Three or four days later the temperature returns to normal and the patient feels much better for a couple of days. This period may be very important in transmitting the disease to new hosts.

With the eruption of the characteristic lesions comes a recurrence of fever as well as general restlessness and pain in the extremities. The papules develop in a centrifugal distribution (i.e., more on the face and extremities than on the trunk). As the rash develops into pustules burning and itching sensations are experienced. In severe cases pustules may develop on mucous membranes. The host's eyes may be swollen shut and swallowing may be difficult. It is not uncommon for an attack of smallpox to result in blindness. The death rate of variola major is from 20-40% (Henderson, 1976:26) and may be even higher in previously unexposed populations. If the infected individual survives the attack, the pustules form scabs which eventually fall off, leaving the disfiguring scars that have identified smallpox victims for centuries.

A good deal of variation exists in the way an attack of smallpox will be manifested in a particular individual. The 1980 WHO report on the eradication of smallpox lists four clinical types of the disease. These are ordinary, modified, flat, and hemorrhagic. Ordinary corresponds to the description presented above. Modified smallpox occurs in vaccinated individuals. Here the lesions may be superficial and fail to show the uniformity characteristic of ordinary smallpox. While modified smallpox is rarely fatal, the disease is transmitted in its typical virulent form to susceptible individuals. Flat smallpox is very severe with a high fatality rate. The defining characteristics of this clinical type is lesions that are slow to mature and resolve without pustulation in the survivors. Hemorrhagic smallpox is usually fatal and is characterized by bleeding and sudden death (World Health Organization, 1980:68). With the exception of modified smallpox, little is known of the determinants of these clinical types. A study of the characteristics of the victims who exhibit one form instead of another would be an interesting epidemiological problem.

The human response to an infectious disease such as smallpox can be divided into two components - biological and cultural. While these two are interrelated, it is useful to treat them separately. The evidence for a biological response to smallpox is circumstantial and inconclusive. It consists mainly of the demonstration that the disease has had different mortality rates in different populations. Variation in the pathogen can also produce such a phenomenon, and the separation of host resistance and virulence of the pathogen is problematic. However, it is not unreasonable to assume that the high mortality rates seen among the American Indians during the contact period were due to the 'virgin' status of these populations, and not to a new mutation of the variola virus.

A disease with a high mortality and high communicability rate has a good potential to produce some sort of adaptive biological response on

the part of its hosts. When smallpox enters a virgin community, it spreads rapidly, infecting virtually every susceptible host. Those who are most susceptible to its pathogenic effect die. Those who survive may do so because of some kind of biological advantage. Because life-long immunity follows the disease attack, the epidemic subsides as the susceptible hosts disappear. Only when new hosts in the form of infants and young children are available does the disease reach epidemic proportions again, having attained the status of a 'childhood' disease. Since these new hosts are the descendants of individuals who survived the initial epidemic, they may share the biological advantage of their parents. Hence mortality rates are lower in the second generation, and the disease appears to become milder over time.

The actual mechanisms of any such resistance are a complete mystery. 'Resistance' in this case refers to lower mortality rates, since all human populations are susceptible to smallpox. Attempts to correlate the severity of smallpox attacks with ABO blood type have been made, but the results are inconclusive. Mourant et al. (1978) tabulate some of the data that have been collected, but a look at the original works reveals a great deal of variation in methodology, which makes comparison difficult. Some authors look at ratios of survivors, others at mortality, and others at the severity of vaccination scars. Vogel and Chakravartti (1966) present evidence from India that strongly supports their hypothesis that individuals with type A are more severely affected by smallpox, and that those with types B and O have an immunological advantage. However, this does not fit well with the historical facts. American Indians are predominantly type O, and these populations did not exhibit an immunological advantage when compared with their European conquerors. If any type of biological adaptation to smallpox exists, it does not seem likely that it is exclusively related to ABO blood type.

It is the cultural response to disease that has been most important in determining the incidence and severity of smallpox. Deliberate exposure continues to be the most important human defense against many epidemic diseases. This practice has a long history, having persisted for at least three millenia. Variolation as performed in China around 1000 B.C. (Benenson, 1981:577) operated on the same principle as modern vaccination. A powder was prepared from the scabs of an infected individual and was inhaled by a susceptible one, who would usually get a milder form of the disease followed by lifelong immunity. Unfortunately the variolated individual was contagious and could pass the disease to others in its more severe form. Variolation practices in the near east and Africa were more similar to Western vaccination. A scratch would be made on the individual's body and fresh material from the pustules of an infected person rubbed into the wound (Langer, 1976:112).

In 1717 Lady Mary Wortley Montagu returned from Turkey and introduced smallpox inoculation into Europe. During that century English physicians showed that the death rate from variolation was about one tenth of the mortality rate from naturally acquired smallpox (Henderson, 1976:27).

In the late eighteenth century, Edward Jenner, who had himself been variolated at age eight (Rains, 1974:52) is said to have heard a country girl remark that she couldn't get smallpox since she had already had cowpox. The idea that those who developed infected hands from milking cows with cowpox acquired immunity to smallpox had existed in England as a folk belief for decades (World Health Organization, 1980: 17). In 1796 Jenner performed an experiment which many epidemiologists see as a hallmark in experimental medicine. Using material from the hand of a dairymaid infected with cowpox, he inoculated a susceptible individual. To prove that immunity had been achieved, he subsequently variolated the person, who failed to develop smallpox, demonstrating the efficacy of vaccination (Henderson, 1976:28). The origin of vaccinia, the substance currently used to vaccinate against smallpox, is unclear. Some feel that it is derived from cowpox (Springer and Weiner, 1962:444) and others see it as a lineal descendant of smallpox (Burnet and White, 1972:166).

Vaccination's superiority over variolation lies in the fact that the immunized individual does not generally suffer from the disease or transmit it to susceptible hosts. However, the immunity conferred by vaccination is not lifelong. The generally accepted length of time that effective immunity from vaccination lasts is three years (MMWR, 5-12-78:157) and revaccination is recommended yearly during an epidemic (Netter, 1970:432). Doubts about efficacy were among the points of controversy in the 19th century debate over vaccination. In spite of this initial resistance, the practice eventually came to be generally accepted.

By the end of the 19th century, smallpox rates in the United States had declined dramatically as a result of the practice. By the middle of the 20th century, the U.S. had seen its last case of smallpox (Benenson, 1981:578). Universal vaccination continued to be practiced in infancy until 1971 when the high rate of complications(fever, generalized vaccinia, eczema vaccinatum, vaccinia necrosum and post-vaccinal encephalitis with death rate estimated at one per million vaccinations as reported by the World Health Organization 1980:29) was no longer seen as justifiable in the absence of the disease in the country. Even at this time the immunity level was quite low because vaccination was usually only performed once or twice during a person's lifetime. The absence of the disease was due mainly to the fact that no importations occurred.

In 1967 smallpox was endemic in 33 countries around the world. It was in this year that the WHO effort to totally eradicate the disease began. At this time Cockburn (1967:161-164) enumerated a series of difficulties that could hinder the program's success. His warnings about poor case reporting and unreliable staff were to be realized in subsequent years. In 1967 reporting was so poor that some areas were reported as having more smallpox deaths than they had cases. Efficiency of reporting was as low as 1.3% in rural areas of Nigeria. Techniques were improved considerably and a search and containment procedure was initiated that proved to be more effective than mass vaccination(Henderson, 1976:30). Still, even with improvements in case reporting, setbacks

were to occur. In 1972 a WHO epidemiologist uncovered an epidemic in an Indian state that had been declared smallpox-free (Henderson, 1976:31).

Even with conscientious health workers, the problems in such a program are great. People may refuse to be vaccinated because of their beliefs about disease causation or fear of the individuals administering the shots. Smallpox cases may be hidden from health workers and quarantine requirements ignored. Vaccinations must be inspected about 6-8 days after the inoculation to insure that they have been successful. This is often difficult in isolated areas.

Nomadic tribes present a substantial problem in such an effort, especially when they cross national boundaries. During 1976 and 1977 Africa was the only place in the world reporting smallpox. Heavy rains, warfare, inadequate transportation and communication, and difficulty in locating nomadic groups were among the problems encountered by WHO workers in Somalia. It was estimated that under these conditions, transmission might continue for 4-6 months without being detected (MMWR, 10-28-77:353). Surveillance workers were recruited locally, and a reward was offered for uncovering a case of smallpox. Finally, on October 26, 1977, the last case of naturally transmitted smallpox in the world was reported in Somalia. Intensive surveillance continued in the surrounding areas for an extended period (MMWR, 10-27-78).

Even with the last reported case, eradication was not complete. It was not until May 8, 1980 that the WHO made the declaration of smallpox eradication official. There are several well-founded reasons for this conservatism. Among these are the fear that the disease will return because of infection arising in a laboratory that continues to hold the virus, that infection will arise spontaneously from an individual who comes in contact with old scabs from a smallpox victim (the virus can survive in dust under appropriate conditions for several years as reported by the World Health Organization, 1980:62), and that the disease might re-evolve from an animal reservoir. Only when control measures such as vaccination can be totally discontinued can a disease be considered eradicated. The WHO has called for an end to vaccination and asked all nations to eliminate vaccination requirements for crossing their borders. Still, vaccination continues among some military personnel and other groups. The practice can result in a severe and possibly fatal illness in unprotected individuals who are exposed to a newly vaccinated individual. An actual occurrence such as this was witnessed in January 1981 when six cases of vaccinia developed among the contacts of a recently vaccinated member of the Canadian military forces (MMWR, 9-18-81:453-455).

The fear that the virus will be introduced from laboratories is also well grounded in actual fact. Less than a year after the last case of naturally transmitted smallpox was recorded, a British photographer developed a severe case of smallpox. It was acquired while she was working in a laboratory where research was being done with the variola virus. In spite of the fact that she worked on the floor above where the virus was kept, she developed the disease and died from it on September 11, 1978 (MMWR, 9-15-78:346). In the attempt to locate all of

her contacts, it was discovered that one of them had traveled to North Dakota on August 18. Fortunately, the individual was located and found to be free of the disease (MMWR, 9-1-78:319).

A statement six years earlier by Burnet and White illustrates why such occurrences are deemed so dangerous.

> If a population has been freed from any disease still prevalent in a country with which it communicates, it is in a particularly dangerous position should control ever break down. In the absence of constant immunization by clinical and sub-clinical infections, a highly susceptible population will arise, and if the infection re-enters at a time when the measures that eliminated it have become ineffective, the resulting epidemic will be abnormally severe. (Burnet and White, 1972:171)

In the United States in 1978 the population was in a particularly vulnerable position for such an occurrence. Existing at the time was a large population of unvaccinated individuals from 0-7 years old, surrounded by an older, vaccinated population with waning immunity. The vaccinated individuals might exhibit the disease in a modified and atypical form (see above). They would be attended by many physicians who had never seen a case of smallpox. As it is, the early lesions of smallpox are very similar to chicken pox and the diseases are often mistaken for each other. These factors make prompt identification and control of an epidemic difficult. In addition, the unvaccinated children were in a position not unlike that of virgin populations since vaccination had been protecting the population for several generations, and their ancestors had not been selected for resistance to smallpox. To prevent occurrences such as this, the WHO has reduced the number of laboratories holding the virus from 76 in 1976 to 7 in 1980 (World Health Organization, 1980: 62). The goal is for only four laboratories to keep the virus.

In 1967 Cockburn felt that the chance of smallpox re-evolving from an animal reservoir were slight (Cockburn, 1967:132). In 1967 Henderson discussed the possibility of monkeypox infections among humans. Such infections had already occurred but the general opinion at that time was that their ". . . capacity for spreading from one human being to another appears to be almost nil" (Henderson, 1976:33). Four years later, in 1980, a shift in position became evident. Between 1970 and 1979, 45 cases of monkeypox were recorded in West and Central Africa, with an overall death rate of 18%. According to the WHO report, it is likely that infections have occurred more frequently than reported, and that more cases would occur if the immunity level were lower (World Health Organization, 1980:61). During this time, it was established that human to human transmission of monkeypox had occurred several times, contrary to the general consensus in 1976. The new position is that monkeypox, while communicable between humans, does not have the potential for epidemic spread (World Health Organization, 1980:11). Not yet, at least. As disease evolves, so evolve the beliefs of the epidemiologist.

It is clear that vaccination imposes selection pressure on the pathogens that infect human beings. The worldwide eradication of smallpox and dramatic decline of other infectious diseases such as diptheria, pertussis, measles, rubella, mumps, and polio in developed countries illustrates this. The idea that vaccination might have other effects on the pathogens than those intended is not totally unknown.

> Immunization must not be a haphazard affair. It is manipulation of a living environment, and the biological balance therein is delicately poised.(Christie, 1974:1039)

The fact that human practices can effect the biological evolution of other species has been demonstrated in several instances. These practices are often associated with disease control. Insects that are resistant to DDT and other pesticides and bacteria that have developed resistance to various antibiotics are examples of this. Given that immunization constitutes a selective agent in a similar manner, what might the logical outcome of its large scale imposition be? Under natural conditions, most of the viral mutations that arise have to compete with the established form of the disease. When the established form is unable to succeed in making host to host transfers, new forms can become established. The forms that will be favored are those that can invade and multiply in spite of the immunological defenses the host produces in response to vaccination. Mutations that increase the invasive ability of a pathogen will be favored as well as those that alter the antigenic structure of the virus sufficiently for it to escape recognition by the host's antibodies.

It is difficult to determine whether or not this has happened with smallpox or any other disease. It is interesting to note that the previously accepted typology of smallpox into two forms - variola major and variola minor - was discovered to be too simplistic when virological observations during eradication showed that there was a wide spectrum of pathogenicity in the variola virus (World Health Organization, 1980:19). One might view this as a discovery due to increased sophistication in analysis, or as evidence of changes in the virus.

While the eradication program seems to have been successful in spite of the various problems encountered, it is important to study it carefully before these methods are applied to the eradication of measles or any of the other community viruses. At the present time in this country, measles is of very low frequency, and outbreaks can usually be traced to importations from endemic areas in other nations (MMWR, 10-30-81:535). Cases of the disease in individuals with documented vaccination or physician diagnosed cases have also been seen (MMWR, 9-8-81:456). Finally, the idea that measles is of a single antigenic type has recently been undermined by molecular studies (Birrer et al., 1981). Burnet and White (1972:143) state that eradication by immunization is possible when the disease is caused by a single antigenic type. When antigenic variants arise spontaneously, as they have been shown to do in the case of measles, control of the disease becomes increasingly problematic.

> We are now moving into a new world in which the old natural history of disease is being rapidly distorted, and we must be always alert to look beyond the immediate effect of some new procedure to see what the logical outcome of its large scale use will be. Antimicrobal drugs, like measures to prevent the spread of infection or immunization procedures, are potent weapons, but to the biologist they are merely new factors introduced into the environment within which the microorganisms of infection must struggle to survive. We must never underestimate the potentialities of our enemies. (Burnet and White, 1972:185)

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