The Remaining Stocks of Smallpox Virus Should Be Destroyed

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Smallpox (variola) was a human infectious disease that was endemic throughout much of the world for more than 2000 years (*1*). Case-fatality rates were frequently 20 to 40 percent in nonimmune populations, and over the centuries smallpox killed more people of all ages, classes, and races than any other infectious disease. In the late 18th century Jenner first showed that material from a cowpox lesion could protect against smallpox, and this finding led eventually to vaccination with vaccinia virus, resulting in eradication of the disease from the United States by 1950 (*1*).

The global eradication of smallpox formally began as a resolution of the Twentieth World Health Assembly in 1967, when more than 40 countries still had endemic smallpox, and ended successfully with the last natural case in Somalia in 1977 (*1, 2*). By that time vaccination of the general public had already been discontinued in parts of the world, and since 1985, all routine vaccination has ceased. In 1978, a photographer working at the University of Birmingham, United Kingdom, became infected with a strain of smallpox virus that was being studied in a supposedly secure laboratory some distance from the room in which she worked (*3*). Her death, together with the suicide of the head of the smallpox laboratory, sharply emphasized the dangers of continued laboratory investigation of viable smallpox virus during the post-eradication era.

In December 1979 the Global Commission for the Certification of Smallpox Eradication recommended that any remaining stocks of viable smallpox virus should be destroyed or transferred to one of four designated reference laboratories in the United States, United Kingdom, South Africa, and Russia. This idea was endorsed by the World Health Assembly in May 1980. However, by the end of 1983, all variola virus stocks in South Africa were destroyed and the stocks in the United Kingdom were transferred to the Centers for Disease Control (CDC), so that all smallpox virus was at the CDC in Atlanta or the Research Institute for Viral Preparations in Moscow. CDC maintains a repository of approximately 450 smallpox virus samples that originated worldwide, which includes collections from many different countries that were transferred from the U.S. Army, the American Type Culture Collection, the National Health Institute of Japan, the National Health Institute of the Netherlands, and the Microbiological Research Establishment of the United Kingdom. The Russian collection contains some 150 smallpox virus samples from Brazil, Botswana, the Congo, Ethiopia, India, Indonesia, Pakistan, Tanzania, and the former Soviet Union.

With the development of DNA restriction endonucleases and cloning techniques during the 1970s, different orthopoxviruses were found to have characteristic DNA restriction patterns that could be used to distinguish smallpox from other potential human infections, such as vaccinia, monkeypox, and cowpox (*4–6*). Appropriate DNA restriction fragments representing the smallpox virus genome were cloned in bacterial plasmids, providing further specific reference reagents for the resolution of any future diagnostic problem involving suspected smallpox infections (*7*). Since 1983 such clones have been kept in a few laboratories in the United Kingdom, United States, the former Soviet Union, and South Africa, but because the cloned DNAs potentially could be used to create a smallpox-like virus by recombination with vaccinia or monkeypox viruses, in 1990 the World Health Organization (WHO) requested registration of all clones of smallpox virus DNA and restricted their use and distribution (*7*).

Because the smallpox virus DNA clones obviated the need for infectious virus for reference purposes, the WHO Ad Hoc Committee on Orthopoxvirus Infections resolved in 1986 that the remaining virus stocks in Atlanta and Moscow should be destroyed if no serious objections were received from the international health community. In addition, the committee recommended that smallpox vaccination to protect military personnel against the disease should be terminated (*8*).

Although smallpox was officially declared to have been eradicated in 1980, vaccination continued until recently for certain military personnel in a few nations. The continued existence of smallpox virus stocks in Russia and the United States was thought to represent a potential military hazard from any terrorist group that succeeded in gaining access to the virus. Recent political uncertainty in several parts of the world, including the former Soviet Union and its satellite countries, has reemphasized this danger. Destruction of the remaining smallpox virus stocks would eliminate this potential weapon, consistent with the aims of the International Biological and Toxic Weapons Convention of 1972.

Of course we cannot guarantee that somewhere in the world there is not another potential source of smallpox virus. For example, the corpse of a person who died of smallpox and was preserved in the Arctic permafrost, or a vial unknowingly retained in a laboratory, might still contain infectious virus. It is also possible that vials containing smallpox virus have been deliberately retained out of a misplaced suspicion of the motives of the U.S. and Russian governments. As long as work continues with infectious virus in Atlanta and Moscow, this may be seen to legitimize the holding of such stocks, and even continued work on smallpox, especially in the eyes of countries that may be engaged in the development of biological weapons. Destruction of the official WHO stocks would send the clearest possible signal to all countries that any work with live smallpox virus will from now on be regarded as criminal activity punishable by national and international authorities, and that the mere possession of such virus is illegal.

In an address to the World Health Assembly in May 1990, the then Secretary for Health and Human Services, Dr. Louis Sullivan, stated that technological advances now made it possible to sequence the entire smallpox virus genome within 3 years (*7*). He went on to say that after the completion of this project, the United States would destroy all remaining smallpox virus stocks held at the CDC. He invited the Soviet Union to consider the same course of action. In December 1990 the WHO Ad Hoc Committee on Or-

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thopoxvirus Infections endorsed proposals from the United States and the Soviet Union to sequence the smallpox virus genome, and unanimously agreed that all remaining smallpox virus stocks should be destroyed by 31 December 1993, provided that sufficient sequence information is available, and serious scientific objections have not been raised (*7*).

Since 1991, molecular biologists in the United States and in Russia have completely sequenced the genomes of two strains of variola major virus (Bangladesh 1975 and India 1967), and by the end of 1993 a third sequence is likely to be available, from a variola minor virus strain (Garcia 1966). (Variola minor strains, associated with case-fatality rates of less than 1 percent, are mild varieties of smallpox.) The complete nucleotide sequence of variola virus DNA (*9*, *10*) provides a valuable archival record. Although there is close sequence similarity to vaccinia virus DNA (*11*) over most of the central core region, the terminal regions display divergent sequences that probably encode proteins involved in the restricted human host range and virulence that distinguish smallpox from vaccinia (*10*). In the unlikely event that a smallpox-like virus were ever to reemerge in the future, the nucleotide sequence information now available could be used in confirming its identity. Adequate stocks of vaccinia virus (smallpox vaccine) will always be maintained at CDC to prevent transmission of a possible smallpox infection should such an event occur at any time in the future.

Destruction of the remaining stocks of smallpox virus would represent the first deliberate elimination of a biological species from this planet. Whether humanity has the right to exterminate a "living" species is controversial, and since 1991, when the proposal to destroy smallpox virus was brought to the attention of American microbiologists (*7*), strongly held views have been expressed both for and against the proposal. However, after debating this issue, the American Type Culture Collection through its Board of Directors, the American Society for Microbiology through its Council, and the International Union of Microbiological Societies through its Executive Board have all agreed that the remaining stocks of variola virus should be destroyed by 31 December 1993.

During an open debate held on 11 August 1993 at the IXth International Congress of Virology in Glasgow, Scotland, a number of other arguments were raised against virus destruction. It was suggested that publication of the complete nucleotide sequence might allow a future scientist to recreate virulent smallpox virus, and therefore that destruction of existing virus stocks is pointless. This argument is not compelling. Even though smallpox virus DNA (186,102 base pairs) might be synthesized in the future on the basis of the published sequence, the DNA would not be infectious. Co-infection of cells with smallpox DNA together with a related poxvirus, such as vaccinia virus, might yield a virulent virus, but how would this be assessed? Humans are the only natural hosts of smallpox virus. It would never be morally defensible to confirm the infectivity and virulence of a newly created smallpox recombinant virus by deliberate human infection.

A second proposal in favor of retaining the virus was that further research on smallpox virus with new or as yet undeveloped techniques might shed light on mechanisms of smallpox pathogenesis and yield information of benefit to mankind. But where would these experiments be carried out? There are now millions of unvaccinated persons worldwide who might suffer terrible consequences if the virulent virus were to escape from the laboratory as happened in Birmingham in 1978 (*3*). CDC has a biosafety level 4, maximum containment laboratory that has recently been used to grow smallpox virus for DNA sequencing purposes, but an equivalent facility does not exist in Moscow. The CDC laboratory is now fully engaged with work on new, highly dangerous viral pathogens such as Lassa virus, Ebola virus, and the new hantavirus pulmonary syndrome, for which no vaccines exist (*12*). If indeed further studies on poxvirus pathogenesis are needed, they should be carried out with a good animal model, such as ectromelia virus (mouse pox) or the Utrecht strain of rabbitpox in mice. There is no justification for retaining smallpox virus to study the pathogenesis of generalized poxvirus infections; the activity of particular genes that are peculiar to smallpox virus can be studied by use of cloned smallpox virus DNA, although the use of such clones and plasmids is now regulated by WHO (6), and should continue to be so regulated. Recombinant plasmids that contain smallpox virus DNA sequences are registered with WHO and may only be provided to requesting scientists after informing WHO and on the strict understanding that they must not be distributed to third parties or used in laboratories handling other orthopoxviruses.

Other infectious pathogens will be globally eradicated in the future. Immediate targets of WHO campaigns are dracunculiasis (guinea-worm disease) by 1995 (*13*) and poliomyelitis by 2000 (*14*). The guinea-worm is a parasite that cannot be stored frozen and would require infection of human subject volunteers if it were to be preserved. Yet we know little concerning the pathogenesis of dracunculiasis. In less than 10 years it is likely that all neurovirulent poliovirus stocks will be held in a few secure institutions, such as CDC. Should we continue to work on such infectious agents when so many new and reemerging infectious diseases make demands on our limited resources? We think not. And when viewed against the regrettable but wholesale extinction of species that results from human interventions in natural ecosystems, concern about the preservation of smallpox virus seems misplaced.

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