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Smallpox: Setting the Research Agenda

Donna E. Shalala

On 24 May 1999, the World Health Organization (WHO) adopted a resolution calling for a delay in destruction of the two known stocks of smallpox (variola) virus. Only 3 years earlier, WHO had called for the destruction of these stocks by 30 June 1999. This significant change in international position was based on sound security, public health, and scientific considerations, especially the threat of bioterrorism.

International attention was only starting to focus on many of these considerations in 1980, when WHO declared that smallpox, one of the most feared infectious diseases in history, had been eradicated. With the disease eliminated, WHO asked all laboratories to destroy their variola samples or deposit them at either the Centers for Disease Control and Prevention (CDC) in Atlanta or at a laboratory in Russia. Today, these facilities hold the only declared stocks.

"[A] terrorist incident involving smallpox could have devastating consequences..."

In anticipation of WHO's 1999 debate on the destruction of the variola stock, the Clinton administration carefully examined relevant security and public health issues. The Institute of Medicine (IOM) was asked to prepare an *Assessment of Future Scientific Needs for Live Variola Virus*, which concluded that "The most compelling need for long-term retention of live variola virus would be for the development of antiviral agents or novel vaccines to protect against a reemergence of smallpox due to accidental or intentional release of variola virus."

This information was considered by the United States and other countries particularly in the context of the growing threat of bioterrorism. An obscure threat just a few years ago, bioterrorism has recently emerged as one of the thorniest problems of the post–Cold War era. Most experts agree that a terrorist incident involving smallpox could have devastating consequences, and we cannot be certain that when the two declared variola stocks are destroyed, we will have actually eliminated all of the virus in existence.

Given these considerations, WHO decided not to destroy the declared virus stocks now, so that they could be used to develop the drugs and vaccines that might be necessary to combat a smallpox outbreak. The delay in destroying the variola virus provides a window of opportunity to conduct final research on this virus.

Currently there is no effective antiviral agent that could be used to treat infected individuals or to prevent variola, and the current vaccine is in short supply and cannot be used in immunocompromised individuals. The IOM report identifies areas in which research on variola could add to our knowledge of the genetic structure, immunology, and pathogenesis of the virus. Already, the genomic sequences of several strains of variola virus have been determined, and further understanding of its natural variation would provide a firm foundation for research on antiviral compounds and vaccines and for the development of additional DNA-based diagnostics. Additional portions of variola genomes could be cloned into bacterial plasmids to provide reference material to resolve new diagnostic questions and to allow for future studies of variola virus genes and proteins.

Research must be planned with an understanding of the inherent costs and the competition for scarce high-containment (biosafety level 4) laboratory space. However, a focused, open, and transparent international research effort with limited use of live variola will enhance our capacity to combat an intentional release of variola virus anywhere in the world. Research efforts must be targeted to the development of meaningful surrogate model systems for preliminary evaluation of candidate antiviral drugs and vaccines.

Finally, as with all public health issues, prevention measures must accompany the research agenda. That is why, under President Clinton's Initiative on Biological and Chemical Weapons Preparedness, preparations are already underway to strengthen our defenses against bioterrorism. Prevention and research may hasten the day when we can safely destroy the remaining stocks of variola virus and close the book on a deadly chapter in human history.

The author is Secretary of the U.S. Department of Health and Human Services in Washington, DC.