Why the Smallpox Virus Stocks Should Not Be Destroyed

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Unlimited by climate and ever present, smallpox virus (also known as varida virus) was one of the most devastating scourges of humanity. In 18th-century Europe it regularly killed 200,000 to 600,000 people every year, with case mortalities ranging from 10 to 30%; in nonimmune populations such as the Amerindians of Mexico and Peru in the 16th century and of North America in the 18th century, case mortalities often exceeded 50 percent. Fortunately, the fact that smallpox virus has only one host, humans, made eradication of the disease possible. In 1967, when the number of smallpox cases worldwide approached 10 million, the World Health Organization (WHO) initiated a smallpox eradication campaign that was based on vaccination of large populations and on rigorous follow-up and treatment of case contacts. This campaign was spectacularly successful; the last case of smallpox occurred in October 1977 and in October 1979 the world was declared free of smallpox (*1*).

Almost immediately thereafter the possibility of destroying all existing stocks of smallpox virus began to be discussed. In 1981 WHO recommended that this be done with the exception of the stocks in the Centers for Disease Control (CDC) in Atlanta and the Institute for Viral Preparations in Moscow. To clear the way for the subsequent destruction of these stocks (*2*), work was initiated in these two laboratories, under P4 safety/isolation conditions, to clone and sequence the genomes of selected smallpox virus isolates (variola major strains Bangladesh 1975 and India 1967 and variola minor strain Garcia 1966) (*3*). At least two smallpox virus strains have now been sequenced completely; their sequences have been discussed extensively at several meetings and are about to be published.

The WHO recommendation to destroy all smallpox virus stocks in Atlanta and Moscow was not widely discussed in the scientific community. However, it was debated this summer in a workshop held during the IXth International Congress of Virology in Glasgow, Scotland. The main arguments for destruction are (i) to prevent the accidental release of the virus from its two isolation facilities; (ii) to prevent terrorists from acquiring the virus as an agent of biological warfare; and (iii) to eliminate this, the most devastating of all human pathogens. Elimination of the virus is, according to this line of reasoning, acceptable because its genome has been cloned into plasmids and has been sequenced. However, the arguments are not persuasive. The danger of accidental smallpox virus release from the two isolation laboratories is surely minimal. Although three smallpox deaths resulted from accidental laboratory infections in the 1970s (*4*), these tragedies occurred because simple but essential administrative precautions were ignored, which could not occur in P4 isolation facilities. As for the use of smallpox virus as a military or terrorist weapon, this is also a most unlikely scenario because smallpox virus can be readily controlled by public health measures including rigorous case contact evaluations and vaccination. In addition, many far more readily accessible and effective potential biological weapons exist. It is naïve to imagine that the destruction of smallpox virus would contribute substantially to reducing the terrorist armamentarium.

The third argument relates to the emotional, sociological, and political desirability of eliminating this frightening scourge of humanity. However, the destruction of smallpox virus in its two established locations provides only an illusory increment of safety because at least three additional potential sources of smallpox virus still exist. First, there are the cadavers of smallpox patients preserved in permafrost. Such cadavers, which could easily become exposed, have been shown to contain smallpox virus antigens and are being tested for the presence of infectious smallpox virus (*5*). Second, it is possible that smallpox virus–containing specimens collected during the smallpox eradication campaign still exist, unrecognized and unidentified, in laboratories in various parts of the world. Third, monkeypox virus causes a disease in humans that resembles smallpox (*6*). The two viruses are similar but monkeypox virus has a much wider host range; its primary natural hosts are monkeys and squirrels. The major difference between monkeypox virus and smallpox virus is that monkeypox virus is transmitted poorly in humans; there is no recorded case of more than four successive horizontal human-to-human transmissions. Four hundred and four cases of human monkeypox virus infections (of which 33 were fatal) were recorded during the period 1970 to 1986, mostly in Zaire.

With the recent example of the emergence of human immunodeficiency virus (HIV) as a human pathogen vividly before us, there is ample room for concern that monkeypox virus could evolve into a threat. Even more to the point, the recent publication of the genomic sequences of at least two smallpox virus strains and the existence of plasmids containing all segments of the smallpox virus genome have made it possible to insert specific smallpox virus genes into the monkeypox virus genome by homologous recombination. There is the distinct possibility that replacement of a single monkeypox virus gene with the corresponding smallpox virus gene could result in a virus with all the virulence characteristics for humans of smallpox virus itself.

In summary, the destruction of the smallpox virus isolates in the high-security laboratories in Atlanta and Moscow does not remove the threat of smallpox from the world.

By contrast, retaining the smallpox virus stocks in Atlanta and Moscow and studying in detail their molecular pathogenesis would be of enormous benefit to humanity. For this purpose the complete virus is required; mere knowledge of the smallpox virus genome sequence, and availability of smallpox genes cloned into plasmids, will not suffice. The reason is that we are only just beginning to understand how viruses cause disease at the biochemical and molecular level. Viral pathogenesis is an extremely complex process that involves not only the interaction of structural components of the virus with those of the host cell, but also, especially in the case of poxviruses in general and smallpox virus in particular, proteins that mimic or interfere with host immune and regulatory functions. Among such virus-encoded proteins identified thus far in poxviruses are the following: cytokines and lymphokines resembling epidermal growth factor and transforming growth factor (*7*); proteins similar to the receptors for interleukin-1β, interferon-γ, and tumor necrosis factor (*8*); cytokine and lymphokine response modifiers (*9*); proteins involved in the regulation of complement

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(*10*); and proteins that bind to interleukin-1 or have zinc finger motifs (*11*). All of these proteins are expressed in a precisely regulated temporal sequence in precisely regulated amounts. The combined effects of these proteins cannot be gauged merely by guessing at motifs in strange sequences that may or may not be operative, and if operative, may or may not be produced from cloned fragments at levels corresponding to the situation in vivo. Furthermore, clones representing individual or small groups of smallpox virus genes will not suffice because their coding regions would very likely be separated from the control elements that regulate their expression, such as enhancers and promoters, as well as genes that encode transcription factors and repressors for them.

The realization that poxvirus genomes encode all these hitherto undreamt of proteins that function to counteract host defense mechanisms is less than 10 years old (*12*). Should we now destroy this extraordinary paradigm of host-virus interactions before we have discovered which human defense mechanisms smallpox virus has evolved to evade? Lacking such knowledge we would certainly be in a poor position to cope with a poxvirus that may evolve to fill the biological niche once occupied by smallpox virus. To answer such questions, research with active smallpox virus, both in vitro and in vivo, is needed. Who is to say that knowledge of the mode of action of some smallpox virus–encoded factor or factors may not point the way to solving the problem of HIV pathogenesis?

The following additional observations are relevant in this regard. First, smallpox virus is uniquely adapted to the human organism. Its study should therefore provide information concerning viral mechanisms for evading the human immune system in particular and human defense mechanisms in general, that may be exploitable for drug development. Comparing the mechanisms that operate during smallpox virus infection with those that operate in infections with monkeypox virus and cowpox virus may also provide valuable insights. Further, both smallpox virus genomes that have been sequenced are derived from isolates that were passaged in eggs, a procedure that may select variants that lack genes found in natural smallpox virus isolates. It is essential that isolates that have not been passaged be sequenced, as well as additional isolates possessing differing degrees of virulence, so as to identify the nature and interplay of the gene products responsible for such differences.

Second, no animal model for infection by smallpox virus is available. However, techniques have recently been developed for studying viruses outside their normal host species. For example, poliovirus normally infects primates and humans. Transgenic mice have been generated that contain the poliovirus receptor and can be infected by poliovirus; thus, it has become possible to study this virus in mice. The future will almost certainly provide a broad range of opportunities for studying how smallpox virus causes disease in experimental animals.

Third, one of the most serious current threats to human health is posed by reemerging infectious agents—agents that were once thought to be controlled, but have reappeared, often in the form of variants. They are causing disease not only where they were once endemic, but also where they had never been encountered before. For all the reasons discussed above, smallpox virus is a prime candidate for becoming such a reemerging infectious agent. Clearly, intensified efforts to understand the mechanisms by which it causes disease, and how such mechanisms could be countered, are required.

In summary, we should be much more alarmed by the thought of smallpox virus being destroyed than by smallpox virus being studied responsibly and expertly in one or two laboratories. The intact smallpox virus is infinitely more valuable than knowledge of the sequence of its nearly 200,000 base pairs; in intact form it provides an unrivalled opportunity for broadening our base for understanding not only smallpox, but also other virus-caused diseases. There is no question that the cost involved in guaranteeing the safe preservation of smallpox virus is negligible compared with the cost that would be incurred if the opportunity for gaining insight into the mechanisms of viral pathogenesis that would result from studying it were lost irretrievably. For all these reasons it would be most inadvisable to abort research into the mechanisms of smallpox pathogenesis at this time. Rather, such research should be supported vigorously, and decisions concerning the destruction of smallpox virus should be deferred for at least 10 years.

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