Frank Fenner

Can smallpox return?

In spite of careful scrutiny of every rumour of suspected smallpox, no case has been recognized since the last outbreak in October 1977. A review of theoretical sources suggests that the possibility of infection is remote. However, one cannot absolutely exclude the unwitting storage of the variola virus in a deep-freeze cabinet, its deliberate secret storage with a view to using it as a biological weapon, or its theft from a laboratory stock. Yet even if an outbreak of smallpox were to arise, it could readily be controlled by surveillance and containment unless public health services had completely broken down.

When a global smallpox eradication programme was first proposed in 1958, endemic smallpox had been eliminated from all the countries of Europe and North America and from several others. There was therefore a prima-facie case that once the cycle of human-to-human transmission had been broken in all countries of the world, the disease would not recur. However, from the outset of the Intensified Smallpox Eradication Programme in 1967, the newly created Smallpox Eradication Unit of the World Health Organization was acutely conscious that there might be a reservoir of the virus in animals or elsewhere, especially in the areas of tropical Africa and Asia where the disease was highly endemic. Other possible sources of recurrence came to the attention of the Unit during the ensuing years.

Dr Fenner is Emeritus Professor in the John Curtin School of Medical Research, Australian National University, GPO Box 334, Canberra, ACT 2601, Australia. He was Chairman of the Global Commission for the Certification of Smallpox Eradication, 1978–80, and Chairman of the Committee on Orthopoxvirus Infections, 1981–85.

Certification of eradication

As from 1971, when the last case was reported in South America, and concurrently with the need to explore the possibility of an animal reservoir, the Unit was faced with the need to provide convincing evidence that smallpox had indeed been eliminated from countries, regions, continents and, finally, the world. Prior to 1958, elimination had been achieved and recognized only in countries with highly developed public health services which were alert to the continuing presence of the disease elsewhere in the world and to the danger of its importation. For the global campaign, however, it was necessary to demonstrate that smallpox had been eradicated from countries with poorly developed health services, and objective external assessments therefore had to be made as to the validity of claims to this effect made by national health authorities. A scheme for the certification of smallpox eradication was consequently established. Starting from a rather poorly executed effort in South America in 1973, the scheme was rapidly developed into a highly efficient system that

coped successfully with the difficult problems of certification in the countries of the Indian subcontinent and the Horn of Africa. In 1977, when global eradication appeared imminent, the Director-General of the World Health Organization convened a Consultation on Worldwide Certification of Smallpox Eradication. A scheme of progressive national and regional certification was devised and it was recommended that a Global Commission for the Certification of Smallpox Eradication should be established. The aim was to prepare a report that would convince the World Health Assembly that the disease had indeed been eradicated worldwide and that vaccination against it could be discontinued everywhere.

There is no animal reservoir of variola virus.

International commissions

The essential features of the certification system were that:

- certification should be undertaken only for very large countries or for several contiguous countries;
- certification should not be undertaken until a period of at least two years had elapsed since the occurrence of the last known case of the disease in the region concerned;
- intensive investigations should be undertaken by national health authorities during the two years before certification, with assistance and advice from the World Health Organization, so as to provide convincing evidence that there had been no cases since the designated last case or cases;
- certification should be undertaken by international commissions of independent experts.

Over the period 1973–79, 22 such commissions certified smallpox eradication in 62 countries; 76 experts from 48 countries served on them. On no occasion did they make an erroneous judgement—subsequent events showed that endemic smallpox had been eliminated from every country for which certification had been accorded.

Global Commission for the Certification of Smallpox Eradication

The Consultation and subsequently the Global Commission noted, however, that there were many other countries where the establishment of international commissions was not appropriate but where something more was required than merely an official government statement. These included countries such as China, Namibia, and South Africa with which WHO at that time had no formal relations, others where smallpox was thought to have been eliminated before the Intensified Smallpox Eradication Programme was established but where the health services were thought to be unreliable, and countries considered to be at special risk. Various methods were used to determine whether smallpox was still endemic in these countries, certification finally being accorded by the Global Commission on the basis of the evidence obtained. On 9 December 1979 the Global Commission formally adopted a 122-page final report, in which it was concluded that smallpox had been eradicated

International Rumour Register: suspected cases of smallpox reported to the World Health Organization, 1980–86

WHO Region	Number of reports								Results of investigation			
	1980	1981	1982	1983	1984	1985	1986	Total	Chicken-pox	Measles	Skin disease	Errors[a]
Africa	9	11	5	5	6	5	6	47	18	7	8	14
Americas	3	6	0	4	5	0	1	19	11	1	3	4
South-East Asia	12	4	3	8	8	5	2	42	17	7	2	16
Europe	1	2	0	0	0	0	0	3	3	0	0	0
Eastern Mediterranean	4	3	2	1	2	0	0	12	2	1	2	7
Western Pacific	2	4	0	1	0	0	1	8	3	3	1	1
Total	31	30	10	19	21	10	10	131	54	19	16	42

[a] In statistical reports or by news media.

worldwide. A number of recommendations for the future were included. This report and its conclusions and recommendations were adopted by the World Health Assembly on 8 May 1980. Ten years have now elapsed since the last case of endemic smallpox (variola minor) was reported, in Somalia, and it is 12 years since the last case of endemic variola major occurred in Bangladesh.

Has smallpox recurred?

Before considering the theoretical sources from which smallpox might recur, it is pertinent to examine the record and to see whether there is any evidence that smallpox has recurred in any country after its elimination was certified.

International Rumour Register

The Global Commission recommended that an international rumour register be established, and that the World Health Organization and national staff undertake investigations to assure accurate diagnosis of every suspect case or rumour.

Epidemiological studies conducted at the request of the Organization were supported by the diagnostic expertise of its collaborating centres in Moscow and Atlanta. Since 1980, 131 rumours have been investigated, excluding cases of monkeypox in western and central Africa (see table). None related to smallpox. The commonest clinical conditions that were confused with smallpox in the post-eradication era, as when smallpox was endemic, were chickenpox and measles.

Confirmed cases

Apart from rumours of smallpox cases occurring since global eradication, there have been two instances of smallpox in countries that had been free of the disease for years. These instances were not due to importations from countries where smallpox was endemic. Each occurred in a country in which an international commission had not been able (China) or required (UK) to operate. Although in each instance the spread of the disease was successfully contained, it is worth discussing the matter in some detail for it illustrates two kinds of source from which smallpox could recur.

Variolation-associated cases in China, 1963–65. Certification of smallpox eradication in the People's Republic of China presented peculiar difficulties for the Global Commission. The country did not become a member of the World Health Organization until 1972. In 1979 the Chinese health authorities gave the Organization a brief statement that smallpox had been eradicated from the country in 1960. In 1985, information was provided that smallpox had recurred many years previously in Shanxi Province and the Nei Monggol (Inner Mongolia) Autonomous Region, where endemic smallpox had been absent for 10 and 5 years respectively. Investigations conducted during the same year by a team of Chinese experts revealed that two separate outbreaks had occurred in Shanxi Province in 1963 and 1965, involving a total of 17 cases of generalized smallpox after variolation (i.e., the deliberate inoculation of pus from smallpox cases on to healthy persons) and 15 cases in contacts of variolated persons, and that three outbreaks had occurred in different locations in the Nei Monggol Autonomous Region in 1962, 1963 and 1964, with a total of 198 cases of generalized disease after variolation and 88 contact cases.

There is a need to maintain high security in the two laboratories still holding stocks of variola virus. Better still would be the destruction of the stocks.

The period 1959–62 was a time of great difficulties in much of China and vaccination was discontinued over most of the country, including the remote mountainous areas where the outbreaks occurred. Since it was believed by the local people that variolation or vaccination could eliminate poison in newborn infants and would prevent other diseases of childhood, as well as smallpox, they sought local or visiting variolators to inoculate their children. Investigations showed that a number of persons had practised variolation in the Shanxi outbreaks but that single itinerant variolators were responsible for the outbreaks in the Nei Monggol Autonomous Region. A variety of methods was used to store the virus-infected scabs, but the principal variolator in the Nei Monggol Autonomous Region, for example, had found that material was rarely potent for more than five months and had maintained fresh material for many years by periodic variolation of children, usually relatives, and storage of fresh scab material. In both regions the outbreaks ceased after the activity of variolators was prohibited, an action that coincided with the provision of free vaccination facilities.

Laboratory-associated outbreak in England, 1978. On 27 August 1978 the British health authorities reported that a medical photographer in the University of Birmingham was suffering and subsequently died from variola major. Since the disease was no longer epidemic and the photographer worked in rooms immediately above a laboratory in which research with the variola major virus was being carried out, it was clear that the infection was associated with the laboratory. The exact route of infection was never determined and the only secondary case was a very mild attack in the mother of the photographer. However, the case alerted medical authorities throughout the world to the potential dangers of infection from laboratories in which variola virus was being used.

Possible sources of a return of smallpox

The two examples given above illustrate two possible sources for a return of smallpox. Five others can be envisaged: an animal reservoir, viral persistence in the environment, transformation of another orthopoxvirus into variola virus, reactivation and excretion in a human subject, and deliberate release.

Laboratory stocks of variola virus

When smallpox was endemic in countries with virus laboratories, variola virus was considered one of the safer pathogens, since all personnel could be protected by vaccination. Many laboratories carried stocks of variola virus as an aid for diagnosis. In response to enquiries from the World Health Organization in 1975, involving 823 laboratories in 181 countries, 75 laboratories confirmed that they were holding stocks of the virus. Following a recommendation that only the Organization's collaborating centres for poxvirus research should hold the virus, the number was reduced to 18 by July 1977. The Birmingham outbreak led to a further reduction to seven laboratories by the end of 1979, and by 1983 only the collaborating centres in Atlanta and Moscow held stocks of the virus. These high-security laboratories are regularly inspected by the Organization's experts in microbiological safety. Both the experts and the laboratory staff must be vaccinated to protect themselves at work and the public outside. In spite of the very small risk of escape from such laboratories, a committee of the Organization suggested in March 1986 that WHO should recommend the destruction of these stocks. This suggestion was justified by the availability of cloned preparations of variola virus DNA, which are safe to handle in open laboratories and could be used in an emergency for comparative studies on the nature of an orthopoxvirus.

Variolators' materials

Outbreaks of smallpox caused by variolation occurred in China in the 1960s, as already described, and outbreaks associated with variolation were a problem in the eradication campaigns in Afghanistan and Ethiopia. In Ethiopia, variolation was practised only in the face of outbreaks, using material from early cases; with the elimination of the endemic disease in 1976 the likelihood of continuing variolation disappeared. In Afghanistan, however, the situation was similar to that in China, in that there were many professional variolators who used stored material which they regularly replenished with fresh scabs, since they found it unreliable for more than a few months. Throughout the period of the Intensified Smallpox Eradication Programme in Afghanistan, variolation was decreasing because of the increasing knowledge of vaccination. Leaders of surveillance teams made special efforts to contact village leaders and explain the adverse consequences of variolation, and the immediate provision of vaccination by surveillance teams in response to reports of cases of smallpox helped to reduce the activities of variolators. The last known case in Afghanistan occurred during 1973.

Any vial of virus with a suspicious label or no label which is found in a deep-freeze cabinet should be destroyed by autoclaving.

Animal reservoir?

The example of jungle yellow fever and its impact on the proposal to eradicate yellow fever was not lost on the Smallpox Eradication Unit, especially as a disease of monkeys caused by an orthopoxvirus and closely resembling smallpox had been reported in 1959. The absence of evidence of an animal reservoir in countries from which smallpox had been eliminated earlier gave no cause for complacency, since the situation in Asian and African countries was unknown. A group of expert virologists was therefore called together in 1969 and met biennially thereafter, to discuss various technical problems relating to orthopoxviruses and to give special attention to monkeypox and any evidence relating to an animal reservoir of variola virus. Their activities received a stimulus in 1970 when it was discovered that, in central and western Africa, monkeypox virus caused a sporadic smallpox-like disease in humans.

The remote possibility of biological warfare or terrorism now constitutes the only reason for maintaining vaccine reserves together with expertise for the diagnosis and control of smallpox.

The group faced a major problem when it was recognized in 1971 that a virus that had been recovered some years earlier from normal cynomolgus monkey kidney cells in the National Institute of Public Health at Bilthoven in the Netherlands was indistinguishable from the variola virus. Over the next few years, four similar isolates were made in the WHO Collaborating Centre in Moscow from the organs of a chimpanzee, a monkey, a rat and a squirrel, all shot near locations in Zaire where cases of human monkeypox had occurred. Subsequently the Moscow workers claimed to have obtained identical virus strains from their laboratory stock of monkeypox virus. The problem was not solved for several years, and then only by the use of the new technique of restriction endonuclease digestion of viral DNA.

The Bilthoven isolate proved to be identical with an isolate of variola virus from India that had been handled simultaneously in the same laboratory and was thus a contaminant. It was shown by restriction endonuclease analysis that variola virus could not be derived from monkeypox virus. The origin of the isolates obtained from animals shot in Zaire was never established; accumulating evidence, including the failure to isolate any virus from hundreds of samples from wild animals in Zaire, except that monkeypox virus was obtained on one occasion from a sick squirrel, has convinced virologists that these strains were also laboratory contaminants. The conclusion is that there is no animal reservoir of variola virus—smallpox was a specifically human disease.

Viral persistence in the environment

The variola virus is very resistant, and viable virus has been obtained from scabs kept in a European laboratory 13 years after they were collected. However, experiments with variolators' materials showed that the variola virus in them remained viable for no more than a few months, less under tropical conditions. But since the virus survives virtually indefinitely if deep-frozen, it is conceivable that it may still exist under

either of two circumstances: in vials stored in a deep freeze in a laboratory, unknown to present staff, or in the corpse of a fatal case of smallpox that has been deep-frozen in a cold region. Three instances of the unwitting storage in a deep-freeze cabinet of what was probably variola virus have come to the notice of the World Health Organization since 1979: one each in the United Republic of Tanzania, the United Kingdom, and the United States. In all cases the ampoules were immediately autoclaved. Indeed, any vial of virus with a suspicious label or no label at all which is found in a deep-freeze cabinet should be destroyed by autoclaving.

The excavation of the remains of persons who have died of smallpox, for example in European towns, is much more probable than the discovery of the long-frozen corpse of a smallpox victim. The risk of viable virus being present is negligible, since most such remains consist only of bones. In 1986, however, poxvirus particles were identified by electron microscopy in the skin lesions of a mummified child who died of smallpox in Italy in the sixteenth century. The important point to note is that careful testing showed that the poxvirus particles were not viable.

Transformation of another orthopoxvirus into variola virus

In the early days of virology it was believed that variola virus could be transformed into vaccinia virus by passage in cows, and more recently some Soviet virologists suggested that monkeypox virus might have been transformed into variola virus. However, studies on the DNA of the accepted species of the genus *Orthopoxvirus* show that the differences between their DNA molecules are too great for such transformation to occur.

Reactivation and release from a human subject

Some viruses, such as the herpesviruses, persist for life in infected persons and at intervals are reactivated and cause the subject to become infectious for others. Poxviruses, as a group, do not exhibit this type of behaviour. If such reactivation were to occur, it would be most likely in patients subject to immunosuppression, either by chemotherapy or because of a malignant disease of the lymphoid system. However, no such occurrence has ever been recognized.

Deliberate release

In 1972 many nations signed a convention outlawing the production and use of biological weapons. Unfortunately, this does not completely exclude the possibility that variola virus might be deliberately released as a means of warfare. However, the risk of any such act leading to the re-establishment of endemic smallpox should not be exaggerated. Smallpox spreads comparatively slowly by face-to-face contact. Unless the public health services had completely broken down, the existence of reserve stocks of vaccine and the capacity to resume vaccine production rapidly would ensure the containment of any outbreak that followed a deliberate release of variola virus. With the cessation of vaccination and vaccine production, it will become increasingly difficult for any persons or groups contemplating the release of variola virus to assure protection against smallpox for themselves and their colleagues. The resumption of vaccination against smallpox by a country could legitimately be interpreted as a sign that it might be considering the use of variola virus for aggressive purposes.

The deliberate release of the virus or the threat to release it for purposes of sabotage or terrorism cannot be absolutely excluded, although the possibility is remote because access to the virus is so restricted. A document made public in December 1984 describes experiments conducted secretly at a busy United States airport in 1964 and 1965 with aerosols containing *Bacillus subtilis* as a marker, to test the possibility that the variola virus might be released in this way and thus cause outbreaks of smallpox a few weeks later in the diverse places to which infected passengers travelled. The existence of this possibility means that there is a need to maintain high security in the two laboratories still holding stocks of variola virus. Better still would be the destruction of the stocks. It is a melancholy but realistic thought that the very remote possibility of biological warfare or terrorism now constitutes the only reason for maintaining vaccine reserves together with epidemiological and laboratory expertise for the diagnosis and control of smallpox. □

New hearts for old

The American Society of Law and Medicine, at its conference on health law and ethics in August, considered the marketing of the artificial heart. Professor George Annas, Professor of Law at Boston University, felt that the furore about the artificial heart had been fanned by the media, ably aided and abetted by cardiothoracic surgeons and physicians themselves.

Annas's premise is that there has been an extrinsic factor in the decision-making process about artificial hearts, and that is the magic of the symbol of the artificial heart as life itself. By inserting artificial hearts we are pushing away natural death; technology has affected the way we think about death. Annas maintains that technology has now taken on a life of its own. The artificial heart sustains life and therefore has become identified with life.

— From Kathleen King, Health law and ethics. *Medical journal of Australia*, **146**: 22-26 (1987).