The last case of endemic smallpox in the world occurred in October 1977 and the last case of smallpox (a laboratory-associated case) in August 1978. In spite of careful scrutiny of all rumours of suspected smallpox, no case has been recognised since then.

A review of all the sources from which infection could occur again suggests that any such possibility is remote, but it is absolutely impossible to exclude the unwitting storage of variola virus in a deep-freeze cabinet, theft from a known laboratory stock, or its deliberate secret storage for possible use as a weapon of biological warfare. However, even if an outbreak of smallpox were to arise from any such source, it could be readily controlled by surveillance and containment, unless public health services had completely broken down.

When the 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 countries in other continents. 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 the newly-created Smallpox Eradication Unit in WHO was acutely aware that there might be an animal or other reservoir of the virus, especially in the highly endemic areas of tropical Africa and Asia.

Concurrently with the need to explore the possibility of an animal reservoir, from 1971, when the last case was reported in South America, the Smallpox Eradication Unit had to show convincing evidence that smallpox had indeed been eliminated from countries, including those with poorly developed health services, from regions, from continents and finally from the world.

So it started a scheme for the certification of smallpox eradication which 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. Subsequently a Global Commission for the Certification of Smallpox Eradication was established, whose ultimate aim was to convince the World Health Assembly that smallpox had indeed been eradicated worldwide, so that vaccination against the disease could be discontinued everywhere.

On 9 December 1979 the Global Commission formally adopted a 122-page Final Report, which concluded that smallpox had been eradicated worldwide, and included a number of recommendations for the post-smallpox eradication era. This report and its conclusions and recommendations were adopted by the World Health Assembly on 8 May 1980. Over seven years have elapsed since that declaration, ten years since the last case of endemic smallpox (variola minor) occurred in Somalia, and 12 years since the last case of endemic variola major occurred in Bangladesh.

Is there any evidence that smallpox has recurred after its supposed elimination from a country? To investigate this, an International Rumour Register was maintained at WHO Headquarters in Geneva, and both WHO and national staff undertook to make an accurate diagnosis of every suspect case or rumour, supported by the diagnostic expertise of the WHO Collaborating Centres in Moscow, USSR, and Atlanta, USA. Since 1980, 131 rumours have been investigated, excluding cases of monkeypox in western and central Africa. None was smallpox. The commonest clinical conditions that were confused with smallpox in the post-eradication era (as indeed when smallpox was endemic) were chickenpox and measles.

However, two laboratory-associated cases occurred in Birmingham, England, in 1978. On 27 August of that year, the British health authorities reported that a medical photographer in the University of Birmingham was suffering from variola major. Since she worked in rooms immediately above a
laboratory in which WHO-sponsored research with variola major virus was being carried out, it was clear that the infection was laboratory-associated, although the exact route of infection was never determined. The woman unfortunately died—the last ever victim of a disease that used to kill millions. The only secondary case was a very mild attack in the photographer’s mother. This incident alerted medical authorities throughout the world to the potential dangers of infection from laboratories in which variola virus was being used.

Many laboratories used to carry stocks of variola virus as an aid for diagnosis. In response to enquiries by WHO in 1975, no fewer than 75 laboratories confirmed that they then held stocks of the virus, but following a recommendation that only WHO Collaborating Centres for Poxvirus Research should hold the virus, this number was reduced to 18 by July 1977. The Birmingham outbreak led to a further reduction to seven laboratories at the end of 1979, and by 1983 only the WHO Collaborating Centres for Smallpox Diagnosis in Atlanta and Moscow held stocks of the virus. Both of these are high security laboratories and they are regularly inspected by WHO experts in microbiological safety. In spite of the very small risk of escape from such laboratories, a WHO committee that met in March 1986 suggested that WHO should recommend that these stocks should also be destroyed. This suggestion was based on the fact that cloned preparations of variola virus DNA are now available, which are safe to handle in open laboratories and could be used in any emergency for comparative studies of the nature of an orthopoxvirus.

Smallpox due to variolation—using material from a victim’s scabs to confer “immunity” on others—caused outbreaks in China in the early 1960s, 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 an outbreak of smallpox, using material from an early case. With the elimination of the endemic disease in 1976 the likelihood of continuing variolation disappeared. In Afghanistan and China there were many professional variolators and they used stored material which they regularly replenished with fresh scabs, since they found it unreliable for more than a year. But outbreaks ceased once the activities of the variolators stopped.

Five other possible sources for a return of smallpox can be envis-
aged: 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.

In 1959 a disease of monkeys had been reported that closely resembled smallpox, and was caused by an orthopoxvirus. A group of expert virologists was called together in 1969, and met biennially thereafter, to discuss various technical problems relating to orthopoxviruses and to consider especially the disease 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. But the new "genetic engineering" technology has proved that variola virus could not be derived from monkeypox virus, and the conclusion among virologists is that there is no animal reservoir of variola virus—smallpox was a specifically human disease.

Variola virus is very resistant, and viable virus has been obtained from scabs kept in a European laboratory 13 years after they were collected, although it was unlikely to have had sufficient strength to infect humans. This belief is supported by interviews with variolators in Afghanistan, who reported that scabs which they had collected were seldom able to induce infection after one year, even when stored at moderately low temperatures. But could the virus survive in vials stored in a deep freeze in a laboratory, or in the corpse of a fatal case of smallpox that has been deep frozen in an Arctic region? Three instances of unwitting storage in a deep freeze cabinet of what was probably variola virus have come to the notice of WHO since 1979:—one in Tanzania, one in California and one in the United Kingdom. In all cases the ampoules were immediately autoclaved.

The excavation of the remains of persons who have died of smallpox, in towns in Europe, for example, is much more frequent than the likelihood of discovering a long-frozen corpse of a smallpox victim, but this carries a negligible risk of surviving viable virus, since most such remains consist only of bones. In 1986, poxvirus particles were indeed identified by electron microscopy in the skin lesions of a mummified child who died of smallpox in Italy in the sixteenth century. But careful testing showed that the poxvirus particles were not viable.

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 virolog-
ists suggested that monkeypox virus might have been “transformed” into variola virus. However, studies of the DNA of the accepted species of the genus Orthopoxvirus show that the differences between the DNA molecules of each species are too great for such a “transformation” to occur.

Some viruses, such as the herpes viruses, 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 immuno-suppression, either by chemotherapy or because of a malignant disease of the lymphoid system. No such occurrence has even been recognised, and this potential source can be excluded.

### Deliberate Release

In 1973 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. But the risk of 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 for production of vaccine to be rapidly reactivated 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 person or group contemplating the release of variola virus to assure themselves and their colleagues of protection against smallpox. 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.

Deliberate release or the threat of it by an individual or group, as an act of sabotage or terrorism, cannot be absolutely excluded, although the possibility is remote because access to the virus is so restricted. The existence of such a possibility underlines the need for maintaining “military” as well as microbiological security in the two laboratories still holding variola virus stocks or, better, the destruction of all such stocks.

---

### International Rumour Register

In compiling its International Rumour Register, WHO recognised that prompt reporting, investigation and diagnosis of all reports or rumours of suspected cases of smallpox are essential tools for maintaining the public confidence in the fact of eradication. Assistance in this investigation and the collection of specimens for laboratory testing has come from state and regional health departments, often staffed by veteran smallpox fighters.

The time required for national health authorities to investigate the suspected cases varied considerably, partly depending on the apparent seriousness of the rumours.

For example, a report from Kenya caused some public health concern because the patient, who died three days after developing a rash, had been a traditional healer, perhaps an ex-varioliator who had used material from smallpox patients to immunize others at a time when smallpox was still endemic in his area. Prompt investigation and collection of specimens by Kenyan health officials and rapid laboratory investigation proved within a week that he had chickenpox.

On the other hand, information provided at a meeting of an international organization required nine months of investigation to establish that rumours of smallpox in several countries of sub-Saharan Africa were false.

Rumours of smallpox, especially those generated by the media, could spread rapidly and cause international concern. Ironically, one “doctor-confirmed” rumour arose at an international health seminar in Ixtapa, Mexico, in 1985, where 250 delegates were warned to see their doctor upon returning home because a delegate had been diagnosed by a hospital doctor as having smallpox. The rumour circulated abroad before a diagnosis of chickenpox was confirmed by the WHO collaborating laboratory.

### Suspected cases of smallpox reported to WHO Headquarters, Geneva, 1980-1986

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>9</td>
<td>11</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>47</td>
<td>18</td>
<td>7</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Americas</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>19</td>
<td>11</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>12</td>
<td>4</td>
<td>3</td>
<td>8</td>
<td>5</td>
<td>2</td>
<td></td>
<td>42</td>
<td>17</td>
<td>7</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Europe</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>31</td>
<td>30</td>
<td>10</td>
<td>19</td>
<td>21</td>
<td>10</td>
<td>10</td>
<td>131</td>
<td>54</td>
<td>19</td>
<td>16</td>
<td>42</td>
</tr>
</tbody>
</table>

1 In statistical reports, or by the news media.