Smallpox is a viral disease unique to humans. To sustain itself, the virus must pass from person to person in a continuing chain of infection and is spread by inhalation of air droplets or aerosols. Twelve to 14 days after infection, the patient typically becomes febrile and has severe aching pains and prostration. Some 2 to 3 days later, a papular rash develops over the face and spreads to the extremities (Figure 1). The rash soon becomes vesicular and later, pustular (Figure 2). The patient remains febrile throughout the evolution of the rash and customarily experiences considerable pain as the pustules grow and expand. Gradually, scabs form, which eventually separate, leaving pitted scars. Death usually occurs during the second week.

The disease most commonly confused with smallpox is chickenpox, and during the first 2 to 3 days of rash, it may be all but impossible to distinguish between the two. However, all smallpox lesions develop at the same pace and, on any part of the body, appear identical. Chickenpox lesions are much more superficial and develop in crops. With chickenpox, scabs, vesicles, and pustules may be seen simultaneously on adjacent areas of skin. Moreover, the rash in chickenpox is more dense over the trunk (the reverse of smallpox), and chickenpox lesions are almost never found on the palms or soles.

In 5% to 10% of smallpox patients, more rapidly progressive, malignant disease develops, which is almost always fatal within 5 to 7 days. In such patients, the lesions are so densely confluent that the skin looks like crepe rubber;
some patients exhibit bleeding into the skin and intestinal tract. Such cases are difficult to diagnose, but they are exceedingly infectious.

Smallpox spreads most readily during the cool, dry winter months but can be transmitted in any climate and in any part of the world. The only weapons against the disease are vaccination and patient isolation. Vaccination before exposure or within 2 to 3 days after exposure affords almost complete protection against disease. Vaccination as late as 4 to 5 days after exposure may protect against death. Because smallpox can only be transmitted from the time of the earliest appearance of rash, early detection of cases and prompt vaccination of all contacts is critical.

**Smallpox Vaccination**

Smallpox vaccination is associated with some risk for adverse reactions; the two most serious are postvaccinal encephalitis and progressive vaccinia. Postvaccinal encephalitis occurs at a rate of 3 per million primary vaccinees; 40% of the cases are fatal, and some patients are left with permanent neurologic damage. Progressive vaccinia occurs among those who are immunosuppressed because of a congenital defect, malignancy, radiation therapy, or AIDS. The vaccinia virus simply continues to grow, and unless these patients are treated with vaccinia immune globulin, they may not recover. Pustular material from the vaccination site may also be transferred to other parts of the body, sometimes with serious results.

Routine vaccination is only recommended for laboratory staff who may be exposed to one of the orthopoxviruses. There are two reasons for this. First is the risk for complications. Second, U.S. national vaccine stocks are sufficient to immunize only 6 to 7 million persons. This amount is only marginally sufficient for emergency needs. Plans are now being made to expand this reserve. However, at least 36 months are required before large quantities can be produced.

The potential of smallpox as a biological weapon is most dramatically illustrated by two European smallpox outbreaks in the 1970s. The first occurred in Meschede, Germany, in 1970 (1). This outbreak illustrates that smallpox virus in an aerosol suspension can spread widely and infect at very low doses.

Another outbreak occurred in Yugoslavia in February 1972 (1). Despite routine vaccination in Yugoslavia, the first case in the 1972 outbreak resulted in 11 others; those 11, on average, each infected 13 more. Other outbreaks in Europe from 1958 on showed that such explosive spread was not unusual during the seasonal period of high transmission, i.e., December through April. One can only speculate on the probable rapidity of spread of the smallpox virus in a population where no one younger than 25 years of age has ever been vaccinated and older persons have little remaining residual immunity.

Where might the virus come from? At one time, it was believed that the smallpox virus was restricted to only two high-security laboratories, one at the Centers for Disease Control and Prevention in Atlanta, Georgia, and one at the Russian State Centre for Research on Virology and Biotechnology, Koltsovo, Novosibirsk Region. By resolution of the 1996 World Health Assembly (WHA), those stocks were slated to be destroyed at the end of June 1999. The desirability of such an action was reaffirmed by a World Health Organization Expert Committee in January 1999. On May 22, 1999, WHA, however, passed a resolution postponing destruction until 2002, by which time any promise of the variola virus stocks for public health research could be determined. Destruction of the virus would be at least one step to limit the risk for the reemergence of smallpox. However, despite widespread acceptance of the 1972 Bioweapons Convention Treaty, which called for all countries to destroy their stocks of bioweapons and to cease all research on offensive weapons, other laboratories in Russia and perhaps in other countries maintain the virus. Iraq and the Soviet Union were signatories to the convention, as was the United States. However, as reported by the former deputy director of the Russian Bioweapons Program, officials of the former Soviet Union took notice of the world’s decision in 1980 to cease smallpox vaccination, and in the atmosphere of the cold war, they embarked on an ambitious plan to produce smallpox virus in large quantities and use it as a weapon. At least two other laboratories in the former Soviet Union are now reported to maintain smallpox virus, and one may have the capacity to produce the virus in tons at least monthly. Moreover, Russian biologists, like physicists and chemists,
may have left Russia to sell their services to rogue governments.

Smallpox is rated among the most dangerous of all potential biological weapons, with far-reaching ramifications.

Dr. Henderson is a distinguished service professor at the Johns Hopkins University, holding an appointment in the Department of Epidemiology. Dr. Henderson directed the World Health Organization’s global smallpox eradication campaign (1966-1977) and helped initiate WHO’s global program of immunization in 1974. He also served as deputy assistant secretary and senior science advisor in the Department of Health and Human Services.

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