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Monkeypox and its relevance to smallpox eradication[1]

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During the past 3 years, 13 patients in scattered smallpox-free areas of Africa have experienced illnesses clinically similar to smallpox. In no instance was there spread of infection from man to man. The responsible virus has been identified as monkeypox, a virus closely related to but distinct from smallpox virus and previously isolated only from outbreaks in captive monkeys. For smallpox, epidemiological data, as well as other observations, indicate that there is no reservoir other than man. The occurrence of sporadic although not apparently communicable smallpox-like illnesses caused by monkeypox makes this and related poxviruses of considerable research interest.

An important consideration in deciding upon a programme for global smallpox eradication has been the apparent absence of a natural reservoir of the virus apart from man. As there are no long-term human carriers of the virus, the interruption of man-to-man transmission of smallpox should result in eradication of the disease itself. However, since the probability of success for the global eradication programme is contingent upon the assumption that there is no animal reservoir for the virus, WHO research activities in smallpox since the inception of the programme have emphasized studies to elucidate this question with greater certainty.

Very few outbreaks of pox-like illness of any sort have been reported among free-living primates, and it is doubtful whether any of them were caused by either monkeypox or smallpox virus. Naturally occurring pox infections in non-human primates have been recorded in France (1767, 1842), Panama (1841), Trinidad (1848), Brazil (1922), and India (1936). However, none of these outbreaks were investigated by virological techniques and in the light of subsequent observations it is reasonable to suppose that most, if not all, of the outbreaks were caused by viruses other than those of the poxvirus group. The only episode in which smallpox virus was recovered from primates with a pox-like infection was reported from Indonesia in 1949. Two orangutans in a zoo were simultaneously afflicted at the time of a smallpox epidemic in the area. The disease did not spread. Considering the extent and prevalence of smallpox in areas of Asia, Africa, and America where non-human primates are numerous, the paucity of available reports suggests that smallpox is not readily transmitted to primates or at least does not spread easily.

Monkeypox

Closely related to but biologically distinct from variola virus is monkeypox virus. Monkeypox as a specific entity in the group of poxvirus diseases was first described in 1959, and between then and 1969, 10 outbreaks of monkeypox were recorded in animals in captivity. Virus was isolated in 6 of the outbreaks and all strains appear to have similar characteristics when tested by various laboratory methods. The causative agent is considered to be one of the variola-

[1] Further details of the studies mentioned in this article, and lists of the relevant references, will be found in *Bull. Wld Hlth Org.*, 1968, 39, 377–383; 1972, 46, 569–539.

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vaccinia group of viruses in the poxvirus complex by virtue of the physical appearance of the organism (rectangular, with a " diameter " of 200–250 μ), the formation of cytoplasmic inclusion bodies, and its serological relationship with viruses of the variola-vaccinia complex.

The virus shares some properties with variola virus and some with vaccinia virus. On chorioallantoic membrane the virus forms small whitish lesions similar to but not identical with those produced by variola virus. It resembles vaccinia virus in that it can be passed serially in rabbit skin; it is fatal when injected intracerebrally into 3-week-old mice; and it induces plaque formation in monolayer tissue cell cultures. However, the monkeypox virus differs from both variola and vaccinia viruses in causing haemorrhagic, necrotic lesions in rabbit skin. No differences are observed among these 3 viruses in the gel diffusion test.

When monkeys are infected with monkeypox virus the cutaneous disease usually appears as a single crop of lesions consisting of multiple, discrete, blanched, shot-like papules varying in diameter from less than 1 mm to approximately 4 mm. These lesions may appear over the entire trunk and tail, and are particularly abundant on the palms of the hands and the soles of the feet. The contents of the papules become thick and pus-like. The papules frequently become umbilicated and are later covered with reddish-brown crusts that fall off in 7–10 days, leaving a small scar. Circular, discrete, ulcerated oral lesions sometimes occur.

Outbreaks of monkeypox

In 1967 WHO made inquiries of 27 major biological institutions in 10 countries that handle large numbers of monkeys, to ascertain how frequently outbreaks of monkeypox were being observed and whether any human infections had been noted. In 1970, inquiries were again directed to these as well as to 24 additional institutions located in a total of 25 countries. It was found that 10 episodes had been observed in the preceding decade, in Denmark, France, Netherlands (2), and the USA (6). No pox-like illness, however, had been noted among the monkey handlers during these outbreaks. In 6 of the outbreaks monkeypox virus was isolated, but in the remaining 4 the diagnosis was made on clinical grounds. Considering that over 130 000 monkeys are imported annually into the USA alone, the number of outbreaks is surprisingly small.

In an effort to identify areas where continuing transmission of monkeypox virus might be occurring naturally, arrangements were made through WHO for the collection of over 2 200 sera from 14 species of African and Asian monkeys. These were tested by WHO collaborating laboratories for the presence of poxvirus neutralizing antibody. In none were significant levels of antibody found. Since antibodies have been shown to persist in high titre for at least 70 months following monkeypox infection, it seemed likely that if any of these monkeys had experienced a monkeypox virus infection, antibody would have been detected. The observations suggest that among apes and monkeys, monkeypox in the natural environment either occurs as an occasional chance outbreak resulting from the transmission of virus from some other animal reservoir or is highly localized to a presently unrecognized geographical area.

A large-scale field investigation was undertaken in Liberia in an effort to identify an alternative animal reservoir for the virus. The area selected was one where human monkeypox infections had occurred (see below). Blood and tissue specimens were obtained from a large number of mammals of various species. Although poxvirus antibodies were detected in the blood of a number of animals of different species, no poxvirus isolates were obtained. Since it is not possible to differentiate antibodies induced by poxviruses of the variola-vaccinia-monkeypox group and antibodies induced by other more distantly related groups of poxviruses, no conclusions could be drawn from the study. The mystery of the reservoir of monkeypox virus remains.

Experimental pox disease in monkeys

Information as to the potential of monkeys to serve as hosts and as a possible reservoir of variola virus can be appraised experimentally and a number of studies on this subject have been and are being conducted. Monkeys, including *Macaca mulatta*, *M. sinicus*, *M. cynomolgus*, *M. nemestrinus*, and *Cercopithecus*, have been used for the past 70 years as experimental animals for studies of the variola-vaccinia group of pox diseases. Diverse methods of inoculation and different quantities of inoculum have been employed, so that it is difficult to draw definite conclusions about the relative susceptibility of different species to the natural aerosol route of infection.

In 1961, using the aerosol route (mass median diameter less than 5 μ), *M. irus* monkeys from the Philippines were infected with several viruses, including variola major and minor, vaccinia, and monkeypox. A mild dermal eruption was observed only in animals exposed to smallpox (variola major) and monkeypox viruses. Papules appeared on the ninth or

tenth day after exposure, limited to the face and hands and gradually resolving within 3–4 days. Several deaths occurred in animals 6–7 days after exposure to monkeypox virus. Neutralizing antibodies were found in surviving monkeys 10–11 days after exposure. In 1966 Indian *M. mulatta* exposed to variola virus by aerosol showed similar features. The incubation period was 5 days and the rash was centrifugal in distribution and appeared after an average of 7–8 days (range 6–11). Two deaths occurred in 109 monkeys infected with variola virus.

In 1969 *M. irus* monkeys from the Philippines were infected with variola virus and an effort was made to transmit variola infection serially from one monkey to the next by aerosol exposure. With each passage the number of cutaneous lesions became fewer in number and in 3 experiments monkeys in the third, third, and eighth passages of the virus respectively failed to become infected. Thus, while this species of monkey is obviously susceptible to variola virus and is able to transmit the virus by the aerosol route, the apparent rapid loss of pathogenicity of the virus on passage resulted in a spontaneous interruption of transmission of the infection. These experimental observations further support the belief that a simian reservoir of variola virus is unlikely.

Additional studies were undertaken to determine whether other species of monkeys might be more susceptible to variola infection than the Macacas so frequently used in experimental work. Three common New World species that normally live in close contact with man (*Ateles paniscus*, *Cebus apella*, and *Lagothrix lagothrica*) were found to be insusceptible to variola minor virus and to show little susceptibility to variola major. African green monkeys (*Cercopithecus aethiops*) were found to be susceptible to both variola major and minor but developed no cutaneous lesions following inoculation. It was again confirmed that *M. irus* is the monkey most susceptible to experimental variola virus infection.

Monkeypox in man

In August 1970 the first recognized case of human monkeypox occurred in Zaire, in an area where there had been a systematic vaccination programme and no cases had been recognized for over 2 years. During the next 10 months 6 cases of suspected smallpox were detected in Liberia, Nigeria, and Sierra Leone, where no cases had been observed for 18 months or more. Six other cases have since been reported, one in Ivory Coast (1971), and 5 in Zaire (1971, 1972) in widely separated areas. Most occurred in young children and 3 died during the course of the illness. None of the patients had previously been vaccinated. Nine of the 13 experienced apparently typical smallpox illnesses with the usual distribution of the rash: 4 patients each had fewer than 10 lesions, from which the scabs had already separated by the fifth day. All cases occurred in smallpox-free areas and no source of infection could be identified for any of the patients. Specimens from the patients were examined at the WHO Regional Reference Centres for Smallpox in Atlanta and Moscow and a virus closely related to if not identical with monkeypox virus was isolated from 7 patients; in the remaining 6 cases, epidemiological evidence suggested that the infecting agent was monkeypox. Both before and since that time, many isolates from suspected smallpox patients in African countries have been examined and found to be perfectly characteristic strains of variola virus.

The 13 cases of presumed monkeypox, 11 of which were in children, all occurred in small remote villages. Twelve of the 13 lived in or on the edge of dense tropical rain forests where monkeys abound and are often eaten. However, no illnesses have been observed in monkeys in any of the areas. In each instance, intensive searches were conducted in all neighbouring villages to identify other persons with recent pox infections but only these few cases have been found. Vaccination scar surveys were conducted among the household and village contacts of each of the patients. While most of the close contacts had previously been vaccinated or had scars from smallpox occurring some years before, almost 200 unvaccinated persons in close contact with patients were identified; none contracted the disease.

White poxviruses

One further puzzling finding has been the isolation from monkey kidneys of 3 strains of poxvirus that differ significantly from monkeypox and are difficult to distinguish from variola virus. Two strains were isolated from monkey kidney tissue cell culture and one from the kidney of an apparently healthy chimpanzee captured in the area where a human monkeypox case had occurred. The relationship of this virus to smallpox and monkeypox is, as yet, uncertain. A number of WHO collaborating laboratories and reference centres are now engaged in a variety of different lines of research to assess the situation. At the same time, smallpox surveillance teams are constantly searching for smallpox-like illnesses in man throughout areas of the world that are now non-endemic.

Conclusions

The observations so far made can be briefly summarized as follows:

1. Some species of non-human primates are susceptible on aerosol exposure to both variola and monkeypox viruses and may develop pox-like lesions on the skin. Studies to date suggest that while continuing transmission of monkeypox from animal to animal is possible, such transmission of variola virus is possible for only a few passages before it dies out.

2. Outbreaks of monkeypox in captive animals occur infrequently and naturally occurring outbreaks have not yet been detected. A natural reservoir of monkeypox has not been identified.

3. Monkeypox does occur in man, but rarely, producing a clinical picture resembling that of mild to severe smallpox; no case of man-to-man transmission has been recorded.

4. Three strains of a poxvirus, isolated from kidneys of apparently healthy monkeys, seem to resemble variola virus more closely than monkeypox virus. The significance of these isolates is at present obscure.

As to the possible existence of a simian reservoir of smallpox, it is significant that in countries with large simian populations, such as Malaysia and the Philippines, smallpox has been eliminated and has not recurred except when imported. While a definite answer to the question is not possible, the likelihood of the existence of an animal reservoir seems remote. Nevertheless, until this matter can be decided with absolute certainty, it is essential to continue ecological surveys on mammals (not only non-human primates) and to pursue further research on the biology and ecology of variola-like diseases in man. Thorough epidemiological, clinical, and laboratory investigations of all suspect smallpox cases occurring in areas where smallpox transmission is believed to have been or has been interrupted is of special importance.

Anticoagulant rodenticides

The advent of anticoagulant rodenticides in the early 1950s undoubtedly marked a turning point in rodent control. These substances have two main advantages in comparison with the acute poisons. First, when used in appropriate concentrations, anticoagulants do not produce symptoms in the rodent that cause it to stop feeding before a lethal dose has been ingested. This characteristic makes the complete eradication of discrete infestations possible, provided that baiting is efficient and continued over a long enough period. Second, birds are relatively resistant to anticoagulants, and although all mammals are affected they generally acquire a lethal dose only after feeding on the bait on more than one occasion; moreover, vitamin K_1 is a powerful antidote if it is administered in time. Thus accidental deaths involving anticoagulants are easier to prevent. Their main disadvantage is that bait must usually be laid down more often than in treatments with acute poisons, but this is only apparent if the latter are conducted without pre-baiting, in which case there would be an accompanying loss of effectiveness...

Although most of the anticoagulants on sale are generally effective, laboratory tests have shown that some are discernibly better than others for the control of certain species of rodent. In some instances this can be ascribed to an obvious physiological effect. It is well known, for example, that at the recommended dosages some anticoagulants affect the clotting factors in mammalian blood much more quickly than others. Similarly, the effect of one anticoagulant on the clotting factors may fall off more quickly than that of another. In some instances, variations in the effectiveness of different anticoagulants in the field may reflect differences of palatability, which may depend partly on the concentration of the poison...

The use of anticoagulants for the control of field rodents has not increased as quickly as might have been expected considering their success against commensal rodents. Several factors, including those that follow, may be responsible. (1) Their toxicity for some species of agricultural importance is generally lower, perhaps because vitamin K_1 is more available to these rodents. (2) The large areas of land that usually require to be baited encourage the use of acute poisons (without pre-baiting). (3) For practical purposes, a degree of control well short of 100 % is usually acceptable. (4) Difficulties are encountered in maintaining bait fresh for any length of time because of attack by bacteria, moulds, ants, cockroaches, land crabs, etc. Nevertheless, anticoagulants have been used with considerable success against field rodents in several countries.

From: Bentley, E. W. (1972) A review of anticoagulant rodenticides in current use. *Bull. Wld Hlth Org.*, 47, 275-280.