11. ORTHOPOX VIRAL DISEASES

The eradication of smallpox or variola major *gave numerous poxviruses the chance, at least indirectly, to come into light as agents of vesiculo-pustular eruptions or of minor or animal pox disease. The last one is no longer a curiosity of purely academic interest for human medicine. When the vaccinations which protected effectively against most of these viral infections, were stopped, a restrictive and regulatory mechanism was undermined. As a result, new problems are gradually emerging.*

The most worrying of these new developments is certainly the current spread of monkeypox and white pox. If other viruses can appear which are virologically and biochemically indistinguishable from classic smallpox, this raises the fearsome possibility of the virus having some place for an animal reservoir as yet unknown. The results of very active, intensive studies in this area have provided clues which are reassuring but not conclusive.

Moreover, a growing number of new poxviruses isolated from rodents are under study in connection with the highly pathogenic Class 4 viruses (Lassa, Marburg, Ebola, Hanta and Filoviruses). They show that such investigations may produce some surprises when attention is turned to new species of animals.

The recent discovery of the role of squirrels in maintaining monkeypox virus in the wild is a warning sign. Meticulous vigilance must be maintained, and extended to other reservoirs and possibly to other vectors.

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HISTORICAL BACKGROUND

1. Smallpox worldwide and in Africa

Smallpox was for a long time one of the deadliest endemo-epidemic diseases of man. Its occurrence more than a thousand years before Christ in China and in the Indus Valley can be taken as a certainty. This is based on the writings of the Tcheou Dynasty, in which it is mentioned under the name of *tai-tou*, and on the worshipping of various Hindu divinities such as Shitola Māta goddess of smallpox, shown riding a donkey and spreading smallpox with a basket of grain on her head, or the Kakurāni, vedic word in the sacred language of the Brahmins.

While smallpox has sometimes been confused with chickenpox and measles, its symptoms and contagiousness are so clear that the disease could not have escaped the eyes of Sumerians, Egyptians, Hebrews, Greeks, and Romans.

The Mediterranean Basin was free of smallpox until the sixth century AD. Rigöli-Merei (Dixon, 1966) and others, who claim they were able to identify the traces of smallpox on the face of Ramses V and the skins of Egyptian mummies are hard to believe. Neither the *Corpus Hippocraticum*, nor the writings of Rome, nor the Bible or any other Semitic documents mention any sporadic or epidemic diseases that could be identified as smallpox.

When one considers the effects that migrations, invasions, and natural disasters may have had on the spread of disease through the ages, it is illogical to restrict oneself to the major historical periods and usual paths of military expeditions or expanding trade. While such advances were indeed spectacular, they did not preclude the various means of the spread of disease linked to the countless low-amplitude movements that are the rule in all countries. Smallpox definitely followed such a pattern of spread from one place to another, interspersed with epidemic outbreaks.

The occurrence of smallpox in Europe starting in the sixth century is established by the testimony of *Saint Gregory of Tours* (*"lues valetudinaria"*, 578 AD) and *Marius of Avenches* (570 AD). To attribute the introduction of smallpox to the arrival of the Saracen armies alone is a somewhat simplistic approach, although these invaders undoubtedly helped. Smallpox had crept unobserved into the Middle and Near East as well as the Caucasus. The endemic foci in the Holy Land and the Cis-Caucasus definitely constituted additional sources of smallpox from which, through the Crusaders, the disease came to Europe.

Smallpox's extension in Europe lasted for three centuries, from the seventeenth through the nineteenth centuries. The scourge was characterized by the fact that, unlike bubonic plague and cholera, it spared no one. The illustrious victims of this disease include Elizabeth I of England; Mary, the wife of William of Orange; and Louis XV, who died of smallpox on May the 10th, 1774.

The New World was infected by African slaves brought in by the conquistadors during the sixteenth century. Mexico was infected in 1519-1520 by an apparently healthy young black slave owned by the Spaniard Narvaez. The disease appeared in Brazil in 1560 and in Peru in 1570. This introduction by African slaves proves that smallpox was already well established in West Africa by this time.

It necessarily entered Africa by a number of routes. One can logically surmise that West Africa was contaminated by the Moors, for links with the Maghreb were numerous, especially overland towards the Niger River with its vast empires of Ghana, Mali, Manding, and Songhay and towards Segou (Bambara Kingdom).

In the northeast, Ethiopia was occupied by the Egyptians of the eleventh Dynasty, and trade continued there for centuries. Ethiopian territory at the time largely exceeded the country's modern boundaries. Its trade links spread southward to the level of Zanzibar. In the centre, the boats of the Nile went as far as the cataracts in the Kingdom of Kush and its capital, Meroë, which supplied wood, ivory, tropical animals, and leopard skins. The caravan routes to the west linked up with Chad and with Niger.

From the outstet, the East Coast and its hinterland maintained close links with Arabia, and the Indian Ocean islands and ports. The points of contact and exchanges with endemic areas were plentiful and varied, and contamination inevitable. Local conditions kept the cases within close confines, with outbreaks generally localized along the caravan routes.

While in the Red Sea and the Indian Ocean sea traders played a role in contaminating the African East Coast, the Portuguese, Dutch, English, and French seafarers also helped. The most accurate historical event is, in 1713, the introduction of smallpox from India at the Cape. An epidemic decimated the Hottentots in 1775, this time with Ceylon as the starting point. The South African population was contaminated through contact with clothes and bedding of smallpox victims who died during the voyage. This resulted in the death of 163 Europeans and more than one thousand natives.

Smallpox was also imported from Europe in 1767. It was at the end of the eighteenth century that *Edward Jenner* started to inoculate vaccinia of cowpox to protect the people against smallpox. The accounts of the first explorers on the African continent, such as Livingstone, Cameron, and Thomas Parke, noted regularly the occurrence of smallpox, insisting on its devastating effects.

The smallpox virus remained active in Africa and elsewhere, although depending on a wide variety of human and natural conditions. It was confronted under more with hosts, who had acquired various degrees of resistance through variolation (voluntary inoculation) and vaccination with cowpox vaccinia. It is therefore not at all surprising that strains of a very different virulence were identified. These were the high-mortality Asian strain, the low-mortality Brazilian strain, and the East African strain which was of intermediate virulence. The induction, as a result of vaccination, of a clinically altered form of smallpox called *varioloid* or *hornpox* was the subject of current but useless controversy.

On the other hand, the existence of *variola minor* is a fact that cannot be ignored. The presence of this mild form of smallpox was reported in 1694 at Barbados, among a shipment of slaves from Guinea. This fact was confirmed in 1752 at the same place and the disease was described a century later in Jamaica, under the name of *varioloid varicella.*

From 1896 onwards, the occurrence of a very mild form of smallpox, often mistaken for chickenpox, was reported among the black population of the United States. It was given a number of imaginative names, such as Cuban itch, elephant itch, and Puerto Rico scratches. This form of smallpox spread from state to state, causing occasional outbreaks of *variola major.* Beginning in 1911, considerable attention was paid to this form of smallpox in Brazil. Beaurepaire-Araguao called it para-variola; but the name "alastrim" or *variola minor*, predominated; the term comes from the Portuguese *alastar*, meaning to spread.

Cases of *variola minor* were imported into Great Britain from the West Indies as early as 1910-1920, but did not reappear after 1935. Switzerland has also known a small epidemic of this type in 1921, with 596 cases and seven deaths.

Such mild forms had been seen in South Africa among the Kaffirs since 1882. The cases, described as epidemic pemphigus, were especially prevalent at Kimberley. Cases were also reported in Graaf-Reinet in 1895. This form of *variola minor* continued to attract attention under the name *amaas*, of uncertain etymology, possibly from the Swahili term *amasi* (milk), or from the Dutch name *mazelen* confused with measles. Already in 1904 *De Korte* believed that it was a disease distinct from smallpox, in line with the opinion of the Bantu people, who made a distinction between "the disease that disfigures" and "her little brother".

In Zaire, *variola minor* gradually gave way to *variola major*, although the trend was interrupted here and there by lethal smallpox outbreaks. The relationship between the two forms of the disease was never really elucidated. What is certain is the severity of the scourge, as is underlined by the explorers and first expatriates. *Michaux* stated that in 1889-1897 "the terrible smallpox of the Congo rarely spares its victims" (Dixon 1962).

Although the first statistics did not appear until Rodhain's 1908 report, the authorities of the Congo Free State had taken energetic preventive measures starting in 1888. These measures resulted in the high priority given to setting up the Vaccine Institute at Boma, the capital of the State. Dr. *E. De Marbaix* was chosen to run this institute. The decision was made as soon as it became clear that vaccines imported from Europe were ineffective. When it was further ascertained that vaccine produced at Mateba quickly lost its activity during its transport to the Upper Congo, the government decided to create branches at different places: Eala, Nouvelle-Anvers (Makanza), Stanleyville (Kisangani), Bambili, Kasongo, Uvira, and Cabinda. Since 1903 Eala supplied vaccine to the Equator health district, to expeditions in the Uele region, in the Lado enclave, and in the Ubangi region. Kisangani supplied the camp at Lokandu and Tshopo. After being transferred to La Romée, where it was easier to obtain heifers, the vaccine production post was finally moved back to Kisangani. On 3,000 vaccinations a 60 to 90% success rate was yielded.

In 1936 *Bourguignon* published the results of production and vaccination trials with vaccine lymph cultivated on the chorio-allantoic membrane of chicken embryo carried out at the government's request. He concluded that the technique was feasible in Africa, giving results comparable to those of the classic vaccine in man and a yield of 250 doses per egg. This underlined the authorities' uninterrupted interest in the problem.

One question often raised concerned the apparent contradiction between continuous campaigns of Jennerian vaccination with revaccination, and regular outbreaks of minor smallpox epidemics. More than 12 million vaccinations and revaccinations were performed from 1950 through 1954, while an average of no fewer than 3,000 cases of smallpox was recorded

each year from 1950 through 1959. The most commonly cited causes of failure of the vaccination were provoqued by the vaccinated individuals themselves, either through exposure to the sun or by rubbing the site with lemon juice and other substances; others managed to escape vaccination by all kinds of means. Some were quite skilled at this game, for which others paid with their lives.

The immunogenic strength of the vaccine lymph was always checked upon the lymph's release for use, but was not controlled often enough during the campaigns themselves. The campaigns for smallpox eradication proved later that a heat-stable, lyophilized vaccine was necessary in the tropics and that the intradermal inoculation techniques used had to include safeguards against interference by the vaccinated subjects themselves, as stated above. The last criterion was met by the multiple puncture method using a bifurcated needle or the needleless Ped-O-Jet injector.

Hidden or open opposition to vaccination was followed by smallpox epidemics (*variola major*) in Kinshasa and Lower Congo in 1961-62. This attitude was completely opposed to the behaviour characterizing the native populations at the beginning of the century: these had observed themselves that smallpox epidemics disappeared almost completely in vaccinated populations. Such a complimentary appraisal cannot be expressed any better than by the surprising answer of Sultan Gilima, high chief of the Azande. This high chief was endowed with great common sense and was also a keen observer with a deeply humanistic attitude although he was illiterate. When asked what he considered were the white man's greatest contributions to the health of the Congolese population one evening during an endless conversation at Duru, he had replied without hesitation, smallpox vaccination and neo (=neo-salvarsan) for yaws.

The second point was understandable if one considers the miraculous effects that these injections had on yaws lesions, but the first assertion was quite unexpected. The explanation lay in the disappearance of the decimating smallpox epidemics that the Sultan and all those who had survived them would never forget. It was definitely the magnitude of this scourge that led the native tribes to try variolation.

2. Voluntary inoculation or variolation

From time immemorial it was known that lethal and benign cases of smallpox coexisted and that a person who had recovered from smallpox was safe from subsequent infection. These facts prompted attempts to protect healthy individuals with a minimum of harm, through voluntary inoculation with pustular fluid or crusts taken from patients with mild cases of smallpox. This strategy was justified when one compares the risks of death due to smallpox and variolation, which were respectively 1:7 and 1:500.

The practice had definitely not its origin at a specific place. The oldest accounts are found in ancient Chinese writings, as well as in the Veda and in Brahmin precepts. Variolation seems to have been practised by itinerant inoculators at fairs or markets, in Nepal, Pakistan, Afghanistan, and Iran. It gradually spread to the nearby territories of Kazakhstan, Caucasus, and the countries on the Black Sea, including Turkey.

From the early eighteenth century onwards this practice raised considerable interest and much controversy in Europe. *Lady Mary Wortley Montagu*, the wife of the British ambassador to Turkey, unquestionably played a starring role. Impressed by the protection that this practice conferred on the beautiful Circassian or Cherkess women, she had her three-year-old son inoculated in 1718, and persuaded the Princess of Wales to do likewise with her grandchildren. This was also the period when the Greek physician *Emmanuel Timoni(us)* informed the Royal Society of a means of inoculating smallpox by incision.

In France, variolation was the subject of an enthusiastic report by *La Condamine* (1754) in a dissertation presented to the Academy of Sciences. La Condamine saw it as a way to spare one-quarter of humanity from disfigurement. The Duke of Orleans had his children inoculated by *Tronchin*, a Swiss doctor, giving rise to the term tronchinisation. However, this did not prevent Parliament from banning, in 1763, the use of a practice that was considered "magical, deadly, and criminal, performed on dupes by murderous impostors". The results of this practice were undeniably uncertain and some accidents were inevitable. These controversies highlighted nevertheless the interest in induced resistance through the transmission of vaccine to man and finally the discovery of vaccination and the eradication of smallpox.

Surprisingly, the first mention of smallpox inoculation in Africa comes from Boston, Massachusetts in USA. It dates back to 1706, when the Puritan minister *Cotton Mather* had received a slave, whom he named Onesimus. The latter informed his master that he had been inoculated in Barbary. Mather became fascinated with this problem and discovered that the captains in the slave trade subjected the young slaves to this

practice. Having learned of Timoni's note, he drew Dr. *John Wood*'s attention to the similarities between the Turkish and African practices. During the Boston smallpox epidemic of 1721 he persuaded Dr. *Zabdiel Boylston* to inoculate 240 individuals, of whom all but five or six, survived after a mild smallpox infection. It was subsequently hypothesized that the deceased patients had probably been infected prior to inoculation.

From the outset, it can be inferred that variolation was a familiar practice on the West Coast of Africa and in the hinterland, where the slave raids were conducted. If one remembers, in addition, that the Persians had invaded and occupied the northern coast of East Africa before the Arabs and Portuguese took over, it is not surprising to learn that variolation was practised in Ethiopia, especially in Tigre and Shoa. A French doctor estimated in 1912 that 20% of the population there had been inoculated against smallpox and specified that the liquid from the pustules was mixed with honey and butter.

The East Coast and neighbouring islands were under Arab influence. The Sudan was in contact with Ethiopia, while the Equatoria Province served as a link with northern Zaire. The Arabs dominated the territories between the East Coast and the interior, roughly along a line between Bagamoyo and Ujiji with extensions towards Maniema and the Luluaba (Niangwe, Kasongo). This axis was crossed by numerous communication tracks for trading caravans.

The explorers of the southern lake region and the Zambezi River Basin mentioned variolation in their reports. Campbell (1822) mentions the practice among the Mashona, Livingstone among the Kwena. It was indeed astonishing to see that the variolation-practising Bantu who pushed south were not exterminated by the devastating epidemic. This epidemic, that struck the Hottentots, was introduced into the Cape region from the East Indies, as said before. Inoculation on the forehead, between the eyebrows was reported by Burton (1860) in East Africa, by Stuhlmann, a companion of Emin Pacha, among the Ganda tribes, and by a White Father in Mpala in 1885; it was also observed in 1929 by a medical auxiliary, Hollebeke, in Katanga, where it was performed by the healers of Sultan M'Siri.

It is known for sure that the white man did not listen to the black man, who quickly gave up trying to teach him about such matters. Likewise, most of the European doctors avoided healers, whose practices were always considered ineffective and often harmful.

Variolation was widely practised during epidemics. Old women, blacksmiths, and healers were the usual vaccinators. The techniques showed some similarities. The liquid used was collected from healing pustules from mild cases; the scabs, whether or not soaked in water for several days before use, were administered via the nasal route by the Chinese, who sometimes rubbed the inoculum over the person's body. In Sierra Leone old women collected the scabs and mixed them with oil and clay before applying the mixture with needles, thorns, or feathers. As contact with the blood was generally sought, the inoculators made shallow cuts, scarified, or scratched the subject's skin. The blacksmiths prepared the site of inoculation by cauterizing it with red-hot iron. The inoculation sites differed but included the arm, leg, and deltoid region. Imperato (1969) made an interesting study of this practice in Mali.

The widespread practice of variolation and the awareness of its efficacy definitely contributed to the population's willingness to participate in mass vaccination campaigns, making the eradication of smallpox possible.

3. Smallpox eradication

The eradication of smallpox is one of the glorious pages in the history of preventive medicine, all the more so because this campaign had to be conducted under sometimes extremely difficult field conditions.

The Central African countries, including Burundi, Rwanda, and Zaire, had the courage to join this programme as early as 1965. They were firmly determined to carry through the operation in close cooperation with the World Health Organization. Zaire in particular proved that it was capable of accomplishing a mission of great magnitude despite the occurrence of unrest, the miserable state of its roads, and the destruction of bridges by the rebels. This memorable campaign is one of the brightest jewels in the crown of Zaire's public health achievements.

An excellent paper by *R. Lekie* (1971), who was in charge of the project, relates how the campaign was conducted and how it was cleverly combined with the administration to all children under 15 years of age, of BCG supplied by UNICEF.

The group in charge of the National Smallpox Eradication Campaign coordinated, managed, and supervised all of the activities and implementation in four stages: planning, preparation which included recruitement, training of manpower with ensuring the complete range of supplies, pilot projects (Eastern Kasai, Ubangi), and finally extension of the campaign to the whole country as of March the eleventh, 1968.

The field operation itself was entrusted to four groups covering an area from mobile bases. Each group was composed of five autonomous vaccination units, one propaganda team, and an assessment team. An average of 95% coverage of the 25 million inhabitants of this huge territory (2,500,000 km^2), some of whom were scattered across such impenetrable areas as flooded rain forests, was achieved in 41 months, or five months ahead of forecasts, on July the 31th, 1971. This amounted to an average per team per day, of 1,200 smallpox vaccinations (left shoulder, and close to 100% take rate) and 600 BCG vaccinations (left forearm) with a range from 500 to 10,000 vaccinations per team per day.

A surveillance and support unit was set up immediately after the dismissing of the last group in August 1971. This unit proved to be highly efficient, especially with its discovery of human monkeypox.

Smallpox was diagnosed for the last time in October 1970 in Burundi and in Rwanda. In Zaire the last case occurred in August 1971. The eradication of this disease from these three countries was certified on June the 30th, 1977. This campaign, which helped to eradicate one of the most troublesome smallpox foci in the world, deserves the admiration of everyone.

MAJOR CHALLENGES

Preliminary remarks

The aphorism *Nature hates a vacuum*, while incorrect as such, is not totally devoid of truth. The disappearance of smallpox, characterized by strictly person-to-person transmission, raised speculation as to whether another poxvirus might not take its place. The abundance of poxviruses in nature, especially the orthopoxviruses, which do not have specific host relationships, has been cause for the utmost vigilance. Indeed, it is likely that some poxviruses may have played an unsuspected role in cases of *variola minor* (alastrim and other forms) or of modified smallpox in vaccinated subjects. The still crude virological techniques of the time made aetiological diagnosis of those viruses hardly feasible.

It is impossible to determine retrospectively the importance of orthopoxviruses in sporadic cases or small epidemics of *variola major* and *minor* occurring from time to time in vaccinated and revaccinated populations. It will be therefore impossible to know whether the virus isolated by *Van Breuseghem* (1942) during an alastrim epidemic in Stanleyville (Kisangani) and adapted to the rabbit and white mouse was a variant of the classic smallpox virus or another orthopoxvirus. No conclusions can be drawn from analysis of the results of the rudimentary virological tests that he could carry out. In addition, the determinant criterion for the diagnosis of *variola minor* was its low death rate, which could only be established on a series of cases. The small number of such cases left the door wide open for interpretation.

The commotion that this finding caused was, at that time quite understandable as, at one side smallpox was a diagnosis to avoid for a good health administration, and *variola minor*'s name replaced at the other side by the appellation *alastrim* was a simple epidemiological concept, although it called for as many vaccinations as real smallpox. This was the situation until in August 1970 a non-vaccinated child presented clinical signs of smallpox, but monkeypox could be isolated from the crusts.

1. Human monkeypox

Definition

Monkeypox is an eruptive fever indistinguishable from smallpox. Its incidence is highest among unvaccinated children, in whom it can be fatal. It occurs as isolated cases and the risk of interhuman contagion is nil or very slight.

1.1. *Historical background*

1.1.1. *The virus isolated from monkeys*

Monkeypox virus was isolated in 1958 by von Magnus and coworkers at Copenhagen from a group of *Macaca cynomolgus* monkeys presenting an eruptive disease 51 to 62 days after their arrival from Singapore. This epizootic was affecting 20 to 30% of the monkeys.

In 1959 an epidemic broke out in a colony of 2,000 monkeys at the Philadelphia firm MSD. Ten percent of the monkeys, mostly *Macaca philippinensis*, were infected but the death rate was under 0.5%.

In 1962, the disease made a new appearance in a group of cynomolgi that had been irradiated totally at Walter Reed Institute's breeding facilities.

The most serious incident occurred at the Rotterdam Zoo in 1964. A very wide variety of primates were affected: orangutans, chimpanzees, gibbons, macaques,

long-tailed monkeys, saimiris, and marmosets. Among the 23 sick monkeys, eleven died including six of the nine orangutans.

An investigation carried out in 26 major biological institutes in 1964 revealed four other epidemics; the latest reported of the total of ten (1969) occurred in Paris in a group of chimpanzees imported from Sierra Leone.

1.1.2. *Monkeypox in humans*

In August 1970 an unvaccinated nine-month-old infant arrived at Basuku with a fever and eruption compatible with a diagnosis of smallpox. Thanks to the intervention of the smallpox surveillance unit a virological examination of the crusts was ordered. The results pointed to monkeypox as the probable aetiological agent. This diagnosis was subsequently confirmed and followed by the same diagnosis in more than 150 sick infants in Zaire. Other cases were also discovered in the Central African Republic, in the Cameroon, Nigeria, Ivory Coast, Liberia, and Sierra Leone.

The discovery in 1970 of human cases in Africa raised many questions. One is whether they had existed earlier, undetected in the mass of smallpox cases, but able to emerge when smallpox was eradicated. Another is why no human cases had been detected in Asia.

1.2. *The pathogen*

Monkeypox virus is an orthopoxvirus, a member of the Poxviridae family.

Orthopoxviruses are large viruses (250-300 nm) producing inclusions, known as Guarnieri's bodies, in the cytoplasm of infected cells. They are resistant to physical conditions, and have nucleoprotein antigens in common to all six genera: the possible existence of genetic recombination.

A distinction is made between two groups:
- the first, of avipox-, capripox-, leporipox-, parapox-, and entomopoxviruses, is characterized by very specific host relationships;
- the second group of other orthopoxviruses does not present such a host specificity. This last genus includes the variola, vaccinia, ectromelia, rabbitpox, and monkeypox viruses.

Monkeypox virus is virulent and pathogenic in laboratory animals. In monkeys it produces generalized lesions. Intradermal inoculation to the rabbit produces extensive haemorrhagic and necrotic lesions. Intracerebral inoculation kills suckling mice.

When inoculated to embryonated chicken eggs it produces small pustules with necrosis and haemorrhagic centres on the chorio-allantoic membrane (CAM). It forms large plaques on monkey kidney cell cultures, with cytopathogenic effect visible after 24 hours. It produces large plaques on Vero cells, making it possible to distinguish it from variola virus. It also has a cytopathogenic effect on other cells.

Monkeypox virus is much more virulent in chick embryos and suckling mice than the variola virus.

1.3. *Epidemiology*

1.3.1. *Sources of contamination*

As the virus was discovered in monkeys, it was logical that attention should be turned to monkeys as the first likely source of contamination. In 1972 the virus was isolated from the kidney of an apparently healthy chimpanzee and from a laboratory-raised cynomolgus in the Netherlands.

The investigations of wild primates captured in areas where cases of human monkeypox had been diagnosed turned up in unrelated pieces of information. No viruses were isolated from these monkeys. Indirect haemagglutination tests (IH) yielded a large number of positive reactions but at very low titres that ruled out any specificity; Immunofluorescence (IF) yielded positive reactions for *Cercopithecus petaurista* and *Colobus badius*; radioimmunoabsorption assays (RIAA) yielded seven positive sera belonging to *Cercopithecus ascanius* and *Allenopithecus nigroviridis*.

A possible role in the transmission of the disease could thus be attributed to four species of monkeys which are traditionally eaten by man. However, these monkeys live in small bands on their own territories and avoid contact with other bands; the number of monkeys in each band is however too small for them to be reservoirs for the disease.

The investigations were then extended to a larger number of species. They included 317 specimens collected in Liberia, 63 in Nigeria, and 1,272 in Equator (Zaire). No such virus was isolated in the approximately 1,500 animals examined, representing 98 species.

Serological examinations carried out in the WHO collaborating centres (CDC, Atlanta, Georgia, and the Moscow Virology Research Institute, USSR) yielded negative sera for all 324 land rodents examined. Among the 34 primates belonging to five examined species, two sera tested positive. These were an already mentioned *Cercopithecus ascanius* and a *Cercopithecus pongonius*. These findings gave strength to the suspicion that *Cercopithecus* might be involved in the virus transmission.

However in December 1985 the most important findings were supplied by the isolation of a monkeypox virus from a sick squirrel, *Funisciurus anerythrus*, captured on the outskirts of Bodjoki, a village in Yambuku sector (Zaire). This discovery spurred new investigations in the sector, especially around the villages of Bodjoki and Bombanga II, where a case of human monkeypox had been diagnosed earlier that month. Only rodents, squirrels, and bats are left in this area of residual forest interspersed with cultivated fields. The primates have reverted to the forest galleries. The examination of 351 squirrels, among them 20.4% of the *Funisciurus anerythrus* and 16.2% of the *Heliosciurus*, showed that they carried antibodies. It can thus tentatively be concluded that the tree-dwelling squirrels constitute a virus reservoir that is in contact with both tree-living monkeys and man (who eats both squirrels and monkeys).

The presence of other orthopoxviruses remains open.

1.3.2. *Transmission*

Epidemiological observations rule out the possibility of arthropod-borne transmission, which is the route of infection for swine variola (via *Haematopinus suis* or the pig louse). The disease crops up in small villages located one hundred yards or so from the edge of the forest. Monkeypox disease appears as an accidental infection emanating from a poorly known animal disease.

To date the suspected animals include four monkey species (among which the chimpanzee), squirrels, and a few other species, such as the pangolin or scaly anteater. These villagers eat monkeys, the flesh of which is highly prized. The skins have a variety of uses.

However, examination of contacts with the carcasses of suspect animals during the two weeks preceding the onset of the varioloid rash gave no useful information. A case was reported to have developed 12 days after a chimpanzee bite in Kivu (Mutombo et al., 1983) and a second case of biten infant after kidnapping by a chimpanzee.

An assertion by Pygmies in the Central African Republic should be accepted with caution, to say the least. They attributed the outbreak of five cases of human monkeypox to the consumption of meat from monkeys and antelope on which cutaneous pustules had been noticed. However, there are no known cases among hunters or those who cut up and prepare skins of hunted game.

Of the 76 human patients with monkeypox who admitted that they had contacts with animals, 49 (64.5%) cited monkeys, nine (11.8%) squirrels, seven (9.2%) rodents, eight (11.8%) cited antelope and two (2.7%) birds. The last two are doubtful sources of contamination. Interhuman transmission explained 34 of the 155 cases recorded in 1985, of whom 27 were secondary cases and the remaining seven were tertiary cases.

1.4. *Geographical distribution*

All of the cases of human monkeypox occurred in the vast tropical rain forest of Central and West Africa. The largest focus is in Zaire and spans over the Upper Equator, South Ubangui, Sankuru, Kwango and the Kwilu Districts of Bandundu). Foci have also been detected in the Central African Republic, Cameroon, Nigeria, the Ivory Coast, Liberia, and Sierra Leone.

1.5. *Clinical description*

The nature, distribution, and evolution of the pustules are identical to those of smallpox, except that the former are neither confluent nor haemorrhagic. The development of uni- or bilateral submandibular, axillary or inguinal lymphadenopathy, one to two days before the rash is a distinguishing factor seen in 90% of human monkeypox cases.

The disease is called mild when the patient has fewer than 25 pustules and does not seem to have any inconvenience by the infection; it is considered mild when there are 25 to 99 pustules and the patient is unable to go about his usual business; and it is called severe as soon as the number of pustules exceeds 100 and the patient is bed-ridden. Of the 131 recorded deaths, 17 (13%) were in this last category.

Diagnosis

The clinical aspect points to the diagnosis: two facts reinforce the suspicion that the victims are children under seven years of age and usually unvaccinated.

The specific diagnosis relies on the identification and/or isolation of the virus and the detection of circulating antigen or antibodies with a significant progressive rise in titre.

The material for laboratory analysis includes first the contents of the vesicles and pustules. These contents can be deposited on absorbent paper and then placed in a hermetically sealed haemolysis tube. Secondly the scrapings of the maculopapules or crusts can be examined and blood can be collected before the rash breaks out or in the final stage of the disease.

The virus may be identified by measuring and studying the morphology of the virus particles by

electron microscopy (EM); however, such equipment is available in only a few centres. The typical Guarnieri's bodies can be detected in smears from scrapings of the maculopapules or in the clear liquid of the vesicles; various staining techniques are used. These Guarneri bodies are at the most a complementary source of information.

2. Whitepox or white orthopoxvirosis

Between 1971 and 1978, four strains of whitepox were isolated from wild animals captured in Zaire. It is a virus that is biologically and biochemically indistinguishable from *variola* virus. These strains raised the feared possibility of the existence of an unknown animal reservoir. The first strain was isolated by *Marennikova* and coworkers (1972) from the kidney of a chimpanzee captured in a monkeypox area. The second was isolated from the kidneys of an apparently healthy monkey. The last two were isolated from rodents. All of the animals came from the Equator province.

Two suspect strains found in kidney cell cultures from apparently healthy cynomolgi, proved later to be due to laboratory contamination with *variola* virus (Gispen, Brand and Saathof, 1972-74). No other suspicious cases have been observed in endemic monkeypox areas and not a single whitepox strain has been isolated from man.

Whitepox virus was passed to *Cercopithecus aethiops* by intraperitoneal route. The animal developed a brief (four day) illness, which broke out on the second day in a vesicular rash that persisted for two weeks. Subsequent subcutaneous passage were performed successfully in three monkeys. It should perhaps be stressed that various poxviruses have been isolated in monkeys.

The importance of whitepox virus lies in its great resemblance to *variola* virus and the suspicion that it might be a spontaneous variant of monkeypox virus. While orthopoxviruses produce haemorrhagic vesicles on chorioallantoid membrane of embryonated chicken egg (CAM), whitepox presents as a white, non-haemorrhagic variant, producing vesicles like those produced by *variola* virus.

The key question is whether *variola* virus can be produced as a result of mutations from monkeypox or whitepox virus. This hypothesis is being studied in depth in various centres. One of these studies took as its starting point the molecular structure of the viral genome. The endonuclease-digested DNA was mapped by electrophoresis for comparison with other viral genomes. This study revealed that the DNA sequences of *variola* and monkeypox viruses are so distinct that the spontaneous production of whitepox virus from either one is genetically impossible. The whitepox viruses isolated from the typical monkeypox vesicles on CAM or from other sources must have an, as yet unknown, outside origin. This initial conclusion of the studies of *Esposito* and co-workers (1985) requires confirmation.

3. Tanapox

Definition

Tanapox is a febrile disease of short duration (three-four days) characterized by the appearance of one or two smallpox-like vesicles on the upper part of the body. It is caused by a virus with features distinct from those of the orthopoxviruses. It is probably transmitted by arthropods, and occurs in small epidemics.

3.1. *Emergence*

In 1957 and in 1962, two small epidemics were observed among the Wapakomo, a population living in the periodically flooded Lower Tanga Valley (Kenya). A poxvirus with features differing from those of the orthopoxviruses was isolated in 1962 at Liverpool. The first one was confined to the pupils of Ngau Mission, but the second affected both sexes of all ages. What is more, it coincided with a Mansonia monkey population boom. *Jezek* claims to have seen tanapox on several occasions during monkeypox surveillance in the Equator province of Zaire (1985).

3.2. *The pathogen*

The virion is very similar to the orthopoxvirus virions except that it has an envelope visible under EM. It does not grow on CAM but is readily cultivated on human or monkey cell cultures. Only monkeys can be infected experimentally.

3.3. *Transmission and epidemiology*

In the hope of being able to identify the wild reservoir of this minor ailment, which was discovered by chance, investigators have screened for and found specific antibodies in various African monkeys. In addition, 20% of the Malaysian cynomolgi studied were positive for specific antibodies, whereas rhesus monkeys from India were negative.

3.3.1. *Sources of contamination*

A wild reservoir has been incriminated, in particular monkeys.

3.3.2. *Mode of spread*

Mansonia monkeys have played a role in the virus transmission in Kenya, but there are signs that inter-human transmission is possible.

3.4. *Geographical distribution*

Kenya and Zaire.

3.5. *The disease*

The incubation period is not known. The fever lasts only three to four days. The smallpox-like lesion begins as a papule on which a vesicle subsequently forms and umbilicates without ever changing into a pustule. The lesion occurs on the trunk, neck, face or arm, but never on the forearms, hands, legs or feet. It resembles the lesion of swine variola.

3.6. *Diagnosis*

This disease is fairly similar to modified smallpox as seen in vaccinated subjects.

It should be remarqued that molluscum contagiosum is a cosmopolitan viral skin infection first described in 1814 (*T. Bateman*) that also occurs in Central Africa. The causal virus cannot be cultivated.

It cannot be mistaken for a poxvirus infection.

4. Prospects for further study

A stochastic model predicts that epidemic outbreaks of human monkeypox would be limited even in the absence of vaccination.

It would however seem wise:

- to see whether vaccinating all children from birth to seven years of age in the well-identified areas where monkeypox is more prevalent, might be advisable;
- to continue the surveillance with a tenacity and efficacy which are worth the highest praise, to take advantage of as much outside technical assistance as possible (WHO collaborating centres in Atlanta and Moscow); this includes the possibility of carrying out other useful investigations that such surveillance offers;
- to see if a species of sheeppox really exists among forest antelopes;
- as epidemiological knowledge of monkeypox is very rudimentary, a longitudinal study of the disease should include serological study of age cohorts in the foci and careful history-taking from the patients as well as from their families.

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EXAMEN B

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After a brief history of the presence of smallpox in Africa the author collects all the available data about smallpox cases reported in most of the countries of Africa since 1925. He also gives information as to mortality due to smallpox. Detailed statistics are given for the Belgian Congo, such as distinction between smallpox and cowpox, the number of vaccinations and revaccinations and the breakdown of cases by province.

KHODAKEVICH L., SZCENIOWSKI M., NAMBU MA DISU, JEZEK Z., MARRENIKOVA S., NAKANO J. & MEIER F. (1987), Monkeypox virus in relation to the ecological features surrounding human settlements in Bumba zone, Zaire, – *Trop. Geogr. Med.*, 39, pp. 56-63.

The monkeypox virus was discovered in animals in 1958 and in man in 1971. The search for a reservoir revealed that rodents in man's immediate environment rather than wild animals and primates could be the carriers. The isolation of the virus from *Funisciurus anerythrus* (Thomas' tree squirrel) showed that this rodent is a prime candidate for transmission of the virus.

LEKIE R. (1971), La campagne d'éradication de la variole en République du Zaïre, – *Bull. Soc. Pathol. Exot.*, 64, pp. 761-775.

The author describes the strategy, organization and conduct of the smallpox eradication programme in the Republic of Zaire. The programme was combined with a BCG vaccination campaign for children under 15. Four vaccination groups, each of which was headed by a doctor and included an exploration team, three vaccination teams, and one assessment team covered the entire territory of the republic from March 1968 to July 1971. Each team vaccinated an average of 1,250 individuals daily to reach a grand total of 24 million smallpox vaccinations and 12 million BCG vaccinations at the end of the campaign. Despite the difficulties resulting from poor roads and transport, the mass vaccination campaign was effective, as it succeeded to arrest the disease's transmission.