1 Viruses

1.1 Herpesviridae

Nonhuman primates are primary hosts to quite a number of herpesviruses (Kalter et al., 1980). Some nonhuman primate species are also highly susceptible to herpesviruses of human origin with at least the theoretical possibility of reinfection occurring in susceptible people.

Only one of the simian herpesviruses is known to induce a true zoonotic infection:

1.1.1 Herpesvirus simiae (B Virus)

Virus

H. simiae is a α-herpesvirus related to *H. hominis*. Its mature virions vary in size from 100 to 180 nm in diameter (Ressig and Melnick, 1954). Like other herpesviruses it is relatively temperature-labile, being inactivated at 36 °C within 9 days, or by heating to 56° within 30 min (Hull and Nash, 1960; Fleckenstein, 1979). It is also inactivated by extraction with ether and other liquid solvents (Fleckenstein, 1979).

H. simiae shows sequentially decreasing cross reactions with *H. hominis*, SA 8, and *H. suis* in neutralization, immunofluorescence-, Ouchterlony-, plaque-reduction and CF tests as well as in enzyme immunoassays (Brack, 1977; Eichberg et al., 1980; Hutt et al., 1981). Due to the dominance of *H. simiae*, sera of monkey origin usually react equally well with both *H. simiae* and *H. hominis* antigens, whereas sera of *H. hominis*-infected human beings usually neutralize *H. simiae* only at titers significantly below those observed with the homologous *H. hominis*, (Sabin, 1934; Burnet et al., 1939; Melnick and Banker, 1954; Hull et al., 1962; Schneweis, 1962; Cabasso et al., 1967; Watson et al., 1967; Kalter and Heberling, 1971 a, b; Martin et al., 1972).

H. simiae is a naturally occurring virus of Asian macaques, and particularly of the rhesus monkey *(Macaca mulatta)*. It has been less commonly observed in cynomolgus monkeys *(M. fascicularis)* (Hull and Nash, 1960; Hartley, 1964; Gralla et al., 1966) and bonnet monkeys *(M. radiata)* (España, 1973). *H. simiae*-like viruses have been repeatedly isolated from African primate species such as patas monkeys *(Erythrocebus patas)*, guerezzas *(Colobus guerezza)* (Loomis et al., 1981),

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and African green monkeys *(Cercopithecus aethiops)* (Sumner-Smith, 1966). Their true nature still needs to be defined.

Epidemiology

H. simiae, like many other herpesviruses, usually causes only transient, minor discomfort in its homologous host species (Macaques), thus it is easily overlooked. Rhesus monkeys usually are already infected in their natural habitat (Shah and Southwick, 1965; Pryor et al., 1970; Boulter and Grant, 1977). In one study in India approximately 73% of all adults expressed anti-herpesvirus antibodies (Orcutt et al., 1976). Transmission by bites or infected saliva has been regarded as the principal route of transmission between animals (Hackett, 1977), but recent investigations suggest that venereal transmission is the most important route (Tribe, 1982; Zwartouw and Boulter, 1984), although the virus does not seem to cross the placental barrier (Hackett, 1977). Consequently, neonates are free of B virus, and therefore any antibodies present up to 3 months of age are of maternal origin (Zwartouw et al., 1984). Spontaneous aerogenous infections are of a lesser importance, but do occur (Valerio, 1971; España, 1973) being similar to the experimental aerogenous infection of rabbits (Chapell, 1960; Benda and Polomik, 1969; Benda et al., 1969). Immature animals may act as a host to the virus without producing antibodies until they reach adulthood, the social and physiological stresses of which then trigger both virus shedding and antibody formation (Tribe, 1980). The virus has been isolated from healthy, seropositive rhesus monkeys soon after arrival (Boulter, 1975; Boulter and Grant, 1977) and up to 6 months after primary infection (Vizoso, 1975c). Transportation stress can reactivate the latent infection with increased virus shedding after arrival at the animal's destination (Hull and Nash, 1960; McCarthy, 1969; Tauraso, 1973). In monkey colonies kept in gang-cages or in semi-free conditions *H. simiae* infections may persist in the latent stage for generations (Zwartouw et al., 1984). In contrast colony-born monkeys raised in single cages usually are devoid of *H. simiae* in later generations (DiGiacomo and Shah, 1972).

Human infections usually result from either monkey bites or scratches; or from aerogenous infections, or from laboratory infections via broken glassware (Hummeler et al., 1959; Hull, 1973).

Clinical Symptoms

a) Nonhuman primates: The infection in monkeys usually runs a silent course, ie., without any recognizable signs in most cases. Occasionally transient lingual, oral or labial vesicles or ulcers develop, especially following transportation of the animals (Keeble et al., 1958; Keeble, 1960; Hartley, 1964; 1966; 1968; Cole et al., 1968; Hunt and Melendez, 1969; Hull, 1969; 1973). The lesions in the skin and mucous membranes of monkeys usually heal within 8–14 days without scarformation (but with virus excretion lasting for a longer period). In some of the very rare cases of fatal disease in monkeys a generalized necrosis of the skin, mucous membranes and the brain occurred (McClure et al., 1973; Daniel et al., 1975). Respiratory infections were also seen, accompanied by respiratory distress (España, 1973).

b) Man: 3 to 4 days following an infected monkey bite (scratches etc.), the bite wound becomes hyperemic, painful and vesiculated. This is followed by regional lymphadenopathy and a relatively minor increase in body temperature. Subsequently neurological symptoms develop, e.g. muscular pain, vomitus, intestinal spasm, nuchal stiffness, difficulty in swallowing, photophobia, hyperesthesia, paresthesia, loss of reflexes, urinary retention, ascending paralysis and finally death from respiratory paralysis (Sabin and Wright, 1934; Sabin, 1949; Willcox, 1958; Hummeler et al., 1959; Love and Jungherr, 1962; Mattingly, 1966; Sumner-Smith, 1966; Fierer et al., 1973; Hull, 1973). In aerogenous infections cough, sore throat and respiratory disease prevail (Hull, 1973). Out of 20 to 25 persons with clinical *H. simiae*-disease only five have survived (Wolf, 1974; Tribe, 1980); three of which with severe, permanent neurologic sequelae (Davidson and Hummeler, 1960), and two with disabling, but less severe neurologic disorders (Roth and Purcell, 1977; Breen et al., 1958; Bryan et al., 1975). In the fatal cases death usually occurred between the fifth day and four weeks after onset of the clinical disease.

Pathology

a) Nonhuman primates: Early lesions of lingual and oral stratified epithelia consisted in acanthosis, ballooning degeneration of the prickle cells and Malpighian cells, accompanied by giant cell - and intranuclear inclusion body formation. The resulting epithelial crevices are filled by serous or leukocytic exudates. The ensuing necrosis and ulceration may extend into the underlaying muscular tissues. Occasionally similar lesions can be observed within the esophageal tissues or the gastric pars cardiaca (Cole et al., 1968; Keeble, 1960; Valerio, 1971). In the generalized infections seen in fatal cases, necrosis of the upper digestive tract was prominent (Daniel et al., 1975) and which, in one animal, was combined with focal necrosis of the basal ganglia and surrounding white matter (Daniel et al., 1975).

In respiratory infections focal haemorrhagic pneumonia has been observed (España, 1973).

Occasionally focal glial nodule encephalitis (occurring predominantly in the *medulla oblongata* and *pons*) has been described (Melnick and Banker, 1954; Keeble et al., 1958; Keeble, 1960; Gralla et al., 1966).

b) Man: The main pathological lesions are those of a transverse necrotizing myelitis, ganglioneuritis of spinal ganglia and a necrotizing haemorrhagic encephalitis, which less commonly affects the pons, hippocampus, basal ganglia and cortical areas. [In contrast, the lesions of human *H. hominis* encephalitis are usually asymmetrical, being distributed predominantly throughout the frontobasal and temporomedial cerebral cortex (Spaar, 1976)]. Glial nodules are commonly observed, whereas inclusion bodies are rarely seen in either neurons or glial cells (Sabin and Wright, 1934; Sabin, 1949; Pierce et al., 1958; Thomas and Henschel, 1960; Davidson and Hummeler, 1960; Krücke, 1961; Hull, 1973). In the respiratory form, a haemorrhagic pneumonia with focal necrosis has been described (Hull, 1973).

Virus Isolation

H. simiae can be easily multiplied in rhesus monkey kidney cells (Krech and Lewis, 1954), VERO-, primary marmoset kidney, OMK, OMC, BS-C-1, LLCMK4-cells (Daniel et al., 1975), LLCMK2-cells (Hull et al., 1972), Hela-cells (Hummeler et al., 1959), HEK-, HEL-, WHE-, and primary rabbit kidney cells (Daniels et al., 1975). The typical herpesvirus-type CPE occurs 1 to 3 days after inoculation. Likewise, *H. simiae* can be cultivated on the CAM of chicken embryos (Krech and Lewis, 1954; Siegert, 1961).

Plaque formation can be observed in agar-overlayed VERO-cells within 21 days, progressing to round areas of 1.5 to 3 mm diameter at 5 days after inoculation (Daniel et al., 1975).

If the material has to be stored before inoculation onto cell cultures, storage in glycerin is recommended before freezing (Thomas and Henschel, 1960).

Experimental Animals

The experimental animals of choice are rabbits, which succumb to the typical local lesions, myeloencephalitis and finally death within 7 to 21 days after s.c. or i.m. inoculation; or within 3 to 8 days after intracerebral or corneal infection (Sabin and Hurst, 1935; Siegert, 1961).

Treatment

Animals with obvious clinical lesions or otherwise demonstrated virus shedding should be treated only for experimental purposes, otherwise they should be destroyed.

In man the prevention of monkey bites etc. is the most important part of any protection. Animal handlers and laboratory workers should always wear appropriate gloves, and aerosol formation should be avoided. *All* bite wounds from monkeys are *always* to be desinfected with an iodine solution. The animal in question should be observed for at least 2 weeks (Baker et al., 1982). The applications of γ-globulins or of formalin vaccines are of doubtful value. Topical treatment or i.v. injection of Acyclovir (Acycloguanisine-Burroughs Welcome Co.) has been recently recommended (Boulter et al., 1980; Juel-Jensen, 1982; Balfour, 1984). For i.v. treatment, dosages of between 10 mg/kg for 8 hrs over a 14 day period (Baker et al., 1982) and 200 mg/kg/day for a 10 day period have been recommended.

1.1.2 H. hominis

Spontaneous *H. hominis* infections have been documented in chimpanzees - *Pan troglodytes*; bonobos - *Pan paniscus* (McClure et al., 1980); gorillas - *Gorilla gorilla gorilla* (Heldstab et al., 1981); gibbons - *Hylobates lar* (Smith et al., 1969; Emmons and Lennette, 1970; Ramsey et al., 1982); owl monkeys - *Aotus trivirgatus* (Melendez et al., 1969; McClure and Keeling, 1971; McClure, 1974; Wolf, 1974); tamarins - *Saguinus spp.* (Hull, 1973) and tree shrews - *Tupaia glis* (McClure et al., 1972; McClure, 1974). So far no retransmission to man has occurred, but the possibility has to be kept in mind.

Epidemiology
The route of transmission in spontaneous infections of nonhuman primates is unknown. Contact with persons suffering from either acute or recurrent oral or genital herpes seems probable.

Clinical Disease (Nonhuman Primates Only)
In gorillas, gibbons and owl monkeys, localized cutaneous or oral vesicles or ulcerations prevail, whereas in tree shrews and sometimes in owl monkeys a generalized disease occurs. Also marmosets have been shown to be experimentally susceptible to *H. hominis.* They develop a systemic disease analogous to the disease in owl monkeys (Brack et al., 1972; Felsburg et al., 1973; Hunt et al., 1978). Type 2-infection of chimpanzees and bonobos were characterized by pustulovesicular lesions, which were noticed on the midshaft of the penis or inner labia, the gingiva and the tongue (McClure et al., 1980). *H. hominis* infection of nonhuman primates commonly leads to conjunctivitis. In gibbons, owl monkeys and tree shrews, fatal encephalitis is a frequent cause of death.

Pathology (Nonhuman Primates Only)
The cutaneous, oral and genital vesicles and ulcers are due to acantholysis, paraceratosis, coagulation necrosis and polykarocytosis of the squamous epithelia. Intranuclear inclusion bodies are present particularly in the periphery of the vesicles and ulcers (Melendez et al., 1969; McClure and Keeling, 1971; Hunt and Melendez, 1972). The generalized disease of tree shrews and owl monkeys is accompanied by focal necrosis and haemorrhages in all organs, usually with intranuclear inclusion body formation.

Meningoencephalitis in nonhuman primates due to *H. hominis* is characterized by lymphocytic perivascular cuffing, CNS-necrosis, and focal gliosis located in the cerebral cortex, perivascular white matter and pontine areas (Smith et al., 1969; Ramsey et al., 1982).

1.1.3 Varicella-Zoster Virus

On several occasions a chicken pox-like disease has been observed in chimpanzees, gorillas, and orang utans with a varicella-zoster virus of presumably human origin either being isolated or that its specific antibodies could be demonstrated (Heuschele, 1960; Klein et al., 1971; McClure and Keeling, 1971; White et al., 1972; Marennikova et al., 1973/74). The question remains, whether or not these were caused either by a true human virus or by a simian subtype, especially since at on at least one occasion chimpanzees suffering from the disease did not develop anti-varicella-zoster antibodies (Gold, 1966). So far, no retransmission to human beings has occurred, but this is theoretically possible, if the virus in question is one of human origin.

Clinical Disease (Nonhuman Primates Only)
Affected apes suffer apparently from pruritus, apathy, benign generalized pustular-vesicular rash (with the exception of palms and soles!), conjunctivitis and

slightly elevated temperature. Recovery occurs within 14 days (Klein et al., 1971; Marennikova et al., 1973/74).

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1.2 Poxviruses

Poxviruses have only a limited host specificity. Most simian poxviruses are transferable to man, and vice versa ie. human molluscum contagiosum virus causes spontaneous infections in nonhuman primates. The question of whether spontaneous infection of monkeys and apes by the smallpox viruses occurs as suggested by some earlier reports (Gispen, 1949, 1975; Raghavan and Khan, 1968) remains unsettled. Certainly, monkeys are susceptible to the variola virus by all routes of infection, which causes a usually mild disease of two weeks duration (Hahon, 1961). The poxviruses infecting nonhuman primates under non-experimental conditions are summarized in Table 1.

Table 1. Zoonotic poxviruses in simian primates

Genus: Orthopoxvirus (Vaccinia-Variola group):
Monkeypox-virus
(White-pox viruses)
Genus not allocated: Molluscum contagiosum-group:
Yaba-virus
Tanapox (Yaba-like-, OrTeCa-)virus
Molluscum contagiosum virus

Table 2. Nonhuman Primate Species Spontaneously Affected by Monkeypox

Old World Species	New World Species
Pan troglodytes	Saimiri sciureus
Gorilla gorilla	Callithrix jacchus
Pongo pygmaeus	Saguinus oedipus
Hylobates lar	
Presbytis entellus	
Macaca fascicularis	
Macaca mulatta	
Cercopithecus hamlyni	
Cercopithecus aethiops	

1.2.1 Monkeypoxvirus

Monkeypox is a pox-disease of nonhuman primates similar to Variola in man (Cho and Wenner, 1973). Old- and New World monkeys and anthropoid apes can be affected (Gough et al., 1982), as summarized in Table 2. Monkeypoxvirus was also isolated from a wild squirrel *(Funisciurus anerythrus)* in Zaire (Khodakevich et al., 1986).

The first known outbreak was reported at the Statens Seruminstitut, Copenhagen/Denmark (von Magnus et al., 1959). Since then, 9 additional outbreaks in captive primates have occurred, with the last one being in Paris (Arita and Henderson, 1976).

Virus

Monkeypox is a rectangular virus of typical poxvirus structure and of 200 to 250 nm size (Prier and Sauer, 1960; Cho and Wenner, 1973). It is resistant to ether and relatively resistant to cold (Cho and Wenner, 1973). The typical monkeypox virus, isolated from disease outbreaks, grows well within 48 to 72 hs on the chicken CAM, in rhesus monkey kidney cells, rabbit kidney cells and patas monkey cells. It forms large plaques in VERO cells even without agarose-overlay (Prier et al., 1960; Rouhandeh et al., 1967; Marennikova et al., 1972). The CPE in the cell cultures is characterized by a rounding of the affected cells, with subsequent granulation, condensation, vacuolation, degeneration (Rondle and Sayeed, 1972) and formation of cytoplasmic inclusion bodies.

Table 3. Comparison of Monkeypox-, Variola- and Vacciniavirus-Properties

Characteristics	Variola	Vaccinia	Monkeypox
Lesions on the CAM (48 h)	small	large	small
Rabbit Skin Passage	–	+	+
Lesions in Rabbit Skin	non haemorrhagic	non haemorrhagic	haemorrhagic
Keratitis in Rabbits	+	–	+
Pathogenicity in Juvenile Mice	–	fatal	fatal
Plaque Formation in Chicken Embryo Cultures	–	+	+

The monkeypox virus produces haemagglutinating antigen in chicken CAM in higher titers than variola virus, but lower than either vaccinia- or cowpoxviruuses (Rondle and Sayeed, 1972).

Some of the characteristics of monkeypox virus, variola virus and vaccinia virus according to Arita and Henderson (1968), Cho et al. (1972), Gispen and Brand-Saathof (1972) are summarized in Table 3.

The lesions on the chicken CAM are characteristic of this virus. Typical monkeypox virus produces minute (0,5 mm diameter) and non-haemorrhagic primary pocks after 48 hs. After 96 hs secondary pocks with typical central haemorrhages develop (Rondle and Sayeed, 1972). Even more typical are the lesions in the rabbit skin. Monkeypox virus can be experimentally transmitted to rabbits by the intradermal route, with the rabbits developing haemorrhagic necrosis at the injection site.

A puzzling finding is the existence of certain monkeypox virus-strains with different *in vivo* and *in vitro* characteristics.

Several "monkeypox" virus strains isolated from monkey kidney cultures in the absence of pox like disease, did not produce any haemorrhagic lesions on the CAM or in rabbit skin; they were thus named "white" poxviruses. Additionally the original monkeypox viruses sometimes contain variable portions of the more prominent and larger white mutants besides the classical haemorrhagic strains (Gispen and Brand-Saathof, 1972, 1974). "White" poxvirus strains are virtually indistinguishable from variola virus using laboratory methods, but wild white mutants differ from variola virus by the initiation of focal necrobioses with central cytolysis in coverslip cultures of RK 13 cells (Gispen and Brand-Saathof, 1972). DNA mappings of variola and monkeypox viruses have indicated that spontaneous production of "whitepox" from monkeypox virus was genetically impossible and that the "whitepox" viruses recovered from monkeypox virus stocks had an exogenous origin (Esposito et al., 1985). Dumbell and Kapsenberg (1982) considered that the Bilthoven-strains of "whitepox"viruses were due to laboratory contaminations by Variola strains, handled at the same time in that laboratory.

The plaques formed by monkeypox virus in chicken embryo fibroblast cultures are smaller than those produced by vaccinia-, and rabbit pox viruses. Such plaques are not induced by variola mayor nor alastrim viruses (Mika and Pirsch, 1960; McConnell et al., 1964b).

In experimental infections of *M.fascicularis*, specific CF-antibodies were demonstrable approximately 1 week p.i., and the titres of which declined with

Table 4. Antigen Contents of Several Poxviridae

	Vaccinia-Ag	Variola-Ag	Monkeypox-Ag
Variola	–	+	–
White pox	–	+	–
Monkeypox	–	–	+
White mutants MP	–	–	+
Vaccinia	+	+	–
Rabbitpox	+	+	–
Buffalopox	+	+	–
Camelpox	+	+	–

regression of the lesions. CFI-antibodies appeared approximately 12 weeks p.i. (Hall et al., 1973). The cross-specificity of the monkeypox virus antibodies depends on the methods used. Rondle and Sayeed (1972) distinguished monkeypox- from vaccinia- and cowpoxvirus but not from the variola virus by HI and neutralization tests. CF tests are less specific than Ouchterlony tests using absorbed sera (Esposito et al., 1977). In Immunoprecipitation using double diffusion in agar gel, three specific antigens were found in members of the poxvirus group (Gispen and Brand-Saathof, 1974; Gispen, 1975); these are summarized in Table 4.

Epidemiology

Monkeypox is endemic in the African tropical rain forests, particularly in the Congo, Zaire, West- and Centralafrica (Breman et al., 1980; Mutombo et al., 1983). Anti-monkeypox-antibodies have been demonstrated in sera of wild living *Cercopithecus ascanius, C. nigroviridis, C. petaurista* and *Colobus badius* (Breman et al., 1980; Arita et al., 1985). The virus has repeatedly caused human infections in those areas. The first isolation of human monkeypox was from a suspected Smallpox case in Bakansuku/Zaire (Marennikova et al., 1972), and similarly most of the later human infections were usually initially suspected as being Smallpox (Ladnyi et al., 1972; Lourie et al., 1972; Arita and Henderson, 1976). Until 1984 altogether 165 cases of human monkeypox virus infections have been reported in West and Central Africa, usually in people living in small villages in the tropical rain forests (Mutombo et al., 1983; Jezek et al., 1983; Anon, 1984; Arita et al., 1985). A substantial increase in incidence was observed after 1982 (Arita et al., 1985), two years after discontinuation of smallpox vaccination in 1980. Seasonal influences were observed in northern Zaire with a peak of human monkeypox being recorded during July and August, the period of highest rainfall (Arita et al., 1985).

Person to person transmission has occurred, but only nonvaccinated persons were infected (Henderson and Arita, 1973), with spread among vaccinated contacts being rarely observed (Gispen, 1975). Among family contacts the secondary attack rate was 10% (Jezek et al., 1983). Although most African cases have involved black patients also white people can be affected.

Aerogenous transmission is considered to be the main route of transmission between nonhuman primates (Cho and Wenner, 1973) and probably also to other species like man or as in one case anteaters *(Myrmecophaga tridactyla)* (Peters,

1966). Other routes of transmission, such as biting or contact are also considered possible (Ladnyi et al., 1972; Mutombo et al., 1983).

Geographical Distribution

Human monkeypox have been reported from Zaire (148 cases), Sierra Leone (1 case), Nigeria (3 cases), Liberia (4 cases), Ivory Coast (2 cases), Cameroon (2 cases) and Central African Republic (16 cases) (Anon, 1984; Khodakevich et al., 1985).

Pathogenesis

The initial multiplication of the monkeypox virus occurs in local cellular components, most probably in either fixed or wandering connective tissue cells (Cho and Wenner, 1973). The different steps in the pathogenesis of monkeypox virus infections are summarized in Fig. 1.

In experimentally infected *M. fascicularis* a constant viremia appeared between the 3rd and the 14th day p.i. (Cho and Wenner, 1973).

Clinical Symptoms

a) Nonhuman primates: Differences exist in the susceptibility of the different host species. Anthropoid apes are usually more severely affected than monkeys, while cynomolgus monkeys suffer more than rhesus monkeys (Wenner et al., 1968).

After an incubation period of usually 3 to 4 days a sharp temperature rise heralds the onset of disease. The animals become anxious, with older ones occasionally becoming aggressive. Anorexia follows on the following day, with behavioral abnormalities such as sucking on the fingers or lips also becoming apparent.

As to the development of the pocks, two types of lesions can be distinguished:

1. Acute, marked facial edemas, with ulceration in mucous membranes and papule formation being visible, generalized lymphadenopathy, respiratory distress and death from asphyxia. Fatal cases usually belong into this group. Anthropoid apes are especially prone to such severe infection.
2. More commonly the infection occurs as a benign cutaneous eruption. 7 to 8 days after experimental infection itching and vesicular exanthema become obvious. Occasional coughing and mucopurulent nasal discharge indicate the presence of early lesions in the respiratory tract, which are mostly associated with the primary infection and virus multiplication. On the next day the first typical pocks appear as papules of 1 to 4 mm diameter, which then develop into pustules containing thick, purulent material. The vesicles become umbilicated and covered by crusts. After desquamation of the scabs or crusts within 7 to 10 days small scars remain (Prier and Sauer, 1960). The most common sites of pock formation in the monkeys are the buttocks, hands, and feet, but also the mucous membranes of the tongue, oral cavity, pharynx, larynx and trachea are commonly involved (Sauer et al., 1960); as well as the spleen, tonsils, lymph nodes, testes and ovaries (Wenner et al., 1969).

b) Man: In human monkeypox an incubation period of 7 to 21 days is assumed (Arita et al., 1985). The disease starts with a fever lasting for 2 to 4 days, which is followed by the eruption of pocks of approximately 5 mm diameter. All pocks

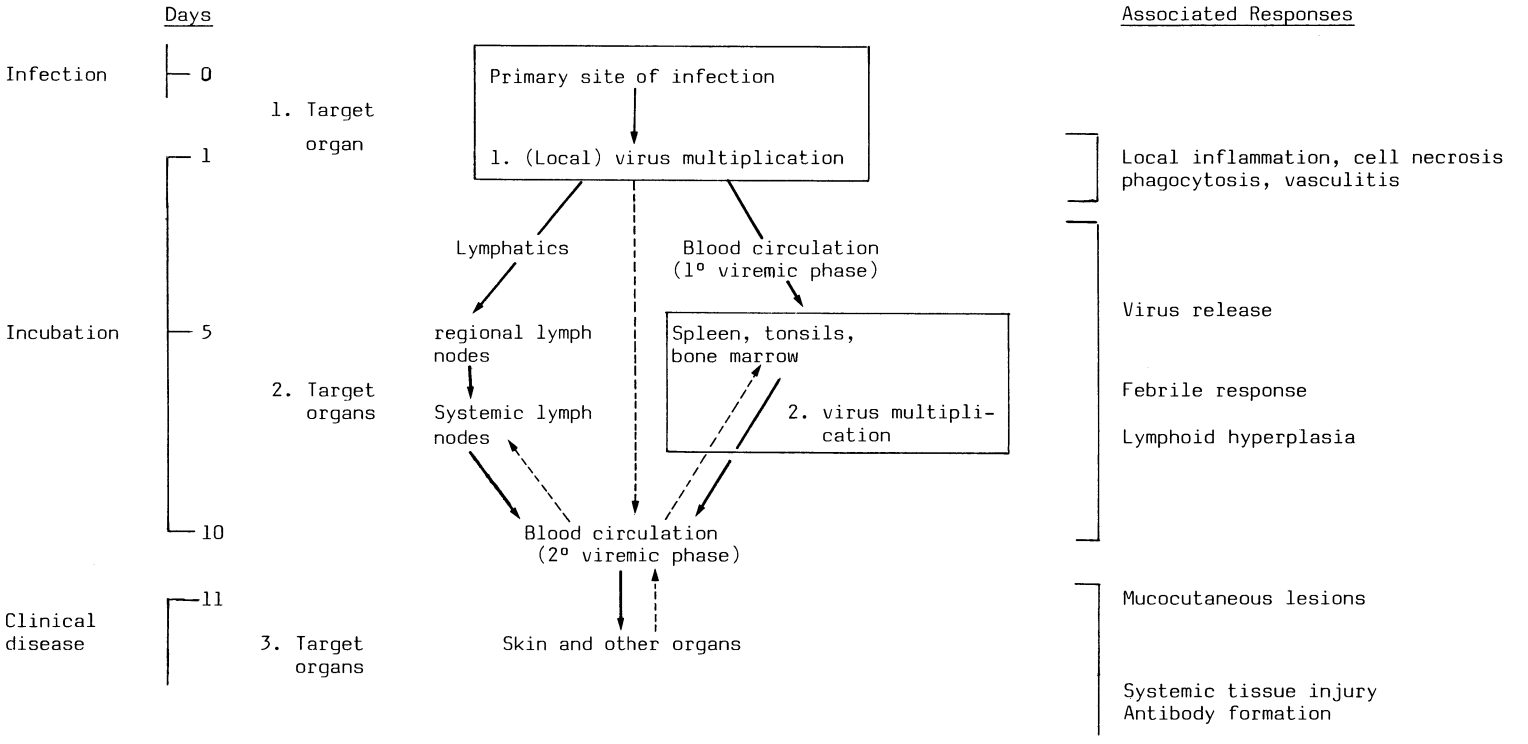

Fig. 1. Model for the pathogenesis of monkeypox. Model is based on data derived from MPV from cynomolgus monkeys infected intramuscularly

develop simultaneously from the papular stage through vesicles, umbilication and desquamation, and look very similar to smallpox lesions (Fig. 2). After shedding of the pocks small scars with initial hypopigmentation and later hyperpigmentation remain.

In minor cases the lesions are limited to the extremities, whereas in more serious infections generalization all over the entire body can be seen. One of the secondary landmarks of human monkeypox which differentiates human monkeypox from smallpox is the pronounced lymphadenopathy, expecially in the neck and inguinal regions, which either develops simultaneously with the fever or follows a day later (Jezek et al., 1983).

Human monkeypox can be fatal, with its fatality rate in man having been reported as being 14% (Jezek et al., 1983). So far 8 patients have died, all were children between 7 months and 7 years of age, and all were not vaccinated against Smallpox (Mutombo et al., 1983).

Pathology

a) Nonhuman primates: A reddened papule covered by a small crust appears 4 days p.i. at the injection site in experimental infection of monkeys. The histo-

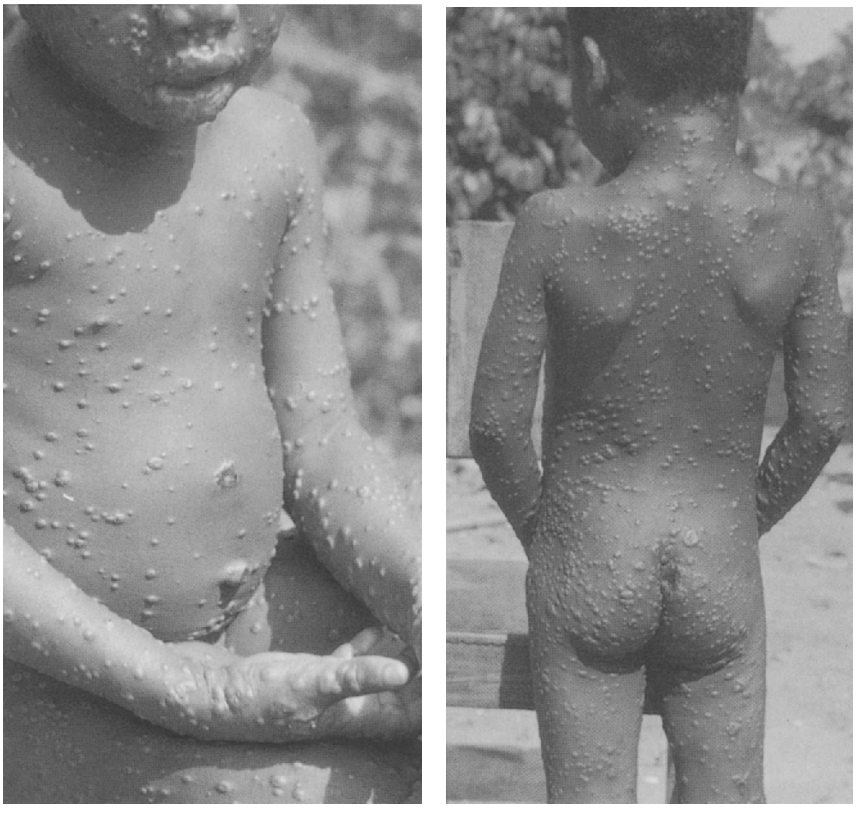

Fig. 2. Monkeypox in an infant (Jezek, 1983)

pathological characteristics of these papules consist of acanthosis, often accompanied by the formation of broad and elongated rete ridges, all of which result in a localized epidermal thickening. Guarnieri bodies have been seen within the cytoplasm of granular cells, and in a few cases intranuclear inclusion bodies were also observed (Sauer et al., 1960). The papule then develops into a typical pock lesion, covered by a central crust and surrounded by peripheral hyperaemia. The cells disintegrate and are separated by serous exudates, which result in small, multifocal liquid-filled cavities within the granular layer (Fig. 3) (Wenner et al., 1969). The cellular damages may extend down into the corium, but usually spare the basal germinal layer.

Extension into deeper tissues quite often leads to hyalinization and heavy inflammation of the skeletal muscles (Wenner et al., 1968). The lesions extend in a peripheral direction, becoming flattened and umbilicated, and due to the emigration of granulocytes the exudate becomes purulent. The final involution of the pocks is accompanied by enlargement of the crusts, decreasing hyperaemia and resolution of the edema. Reepithelization begins from the pustular borders as well as from the hair follicles. Some days later the overlaying crusts are shed. During generalization the exanthema passes through the same steps, but over a much shorter period of time - usually within 4 days.

b) Man: The monkeypox-lesions in a two year old boy who died after 5 days illness, consisted of a disseminated rash indistinguishable from smallpox, with similar lesions being present in the boy's mouth. Marked lymphadenitis was noted on the right side of the neck. A post-mortem skin biopsy of a papule revealed acanthosis with enormous elongation of the rete ridges, but no paracer-atosis. The rete ridges and dermal papillae in the center of the papule were nec-

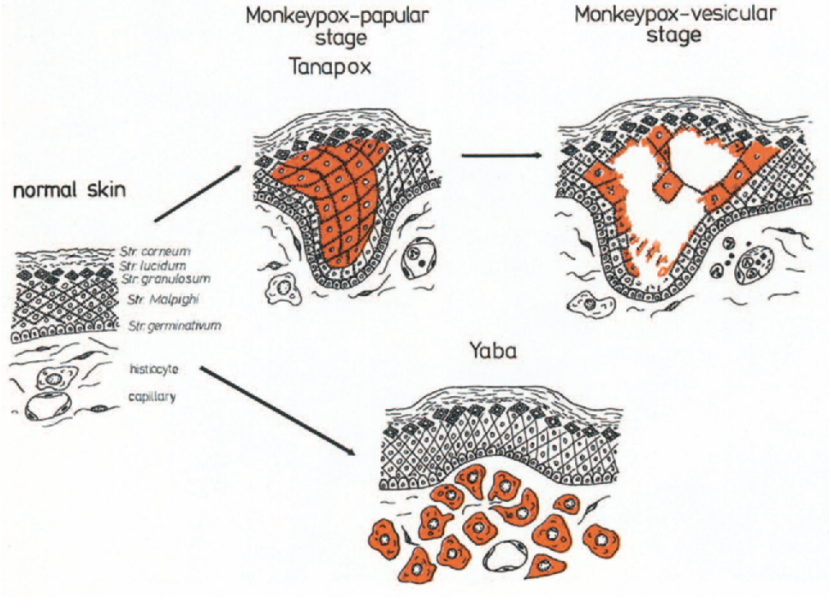

Fig. 3. Morphogenesis of simian pox lesions

rotic. The stratum spinosum above the central necrotic area was edematous. The formation of minute vesicles and the presence of multinucleated giant cells also occurred in the stratum spinosum. Guarnieri type inclusion bodies were present in lining cells of the tortuous sweat gland ducts (Stagles et al., 1985).

Treatment

The prevention of secondary infections by using antibiotics is the most important step in both man and nonhuman primates.

Endangered persons and animals can be protected by variola-vaccination, as it is effective against monkeypox as well (McConnell et al., 1964; Peters and Verlinde, 1966).

Methisazone (1-methyl-isatin-3-thiosemicarbazone) which has been used in smallpox-prophylaxis, failed to protect monkeys against experimental monkeypox infections (Peters, 1966; Cho and Wenner, 1973).

1.2.2 YABA-Virus

In 1957 a series of subcutaneous "tumorlike" growths caused by a poxvirus belonging to the molluscum contagiosum group were noticed as occurring in 20 out of 35 rhesus monkeys over a period of 5 months at the West African Council for Medical Research, Yaba/Nigeria (Bearcroft and Jamieson, 1958). Additional cases have been observed in captive-born rhesus monkeys in England (Spencer, 1985); in baboons (Niven et al., 1961; Bruestle et al., 1981; Walker et al., 1985); and in *Macaca fascicularis* and *M. speciosa* (Ambrus et al., 1969). The infection could not be transmitted to *Erythrocebus patas*, *Cercopithecus mona*, *Cercocebus torquatus*, *Cercocebus fuliginosus*, *Cebus fatuellus*, *Saimiri sciureus*, mice , dogs, guinea pigs, rabbits, hamsters or rats (Ambrus et al., 1963; Grace and Mirand, 1963; Ambrus and Sandström, 1966).

Virus

The virus grows in primary vervet kidney cells, VERO-, LLCMK2, MA10 and BSC-1-cells and in the CAM of 10–11 day old chicken embryos (Sandström et al., 1966; Yohn et al., 1964, 1966). The resulting CPE consists of nucleolar hypertrophy at 24 h and cytoplasmic inclusion body formation at 4 days, which stain brilliantly with FITC-labelled anti-Yabavirus-antiserum. Another type of CPE is expressed by the formation of microtumors on the chicken CAM or BSC-1 cells after inoculation with low virus titers (Yohn et al., 1964; Sandström et al., 1966).

The virus can be demonstrated by immunofluorescence using anti-Yaba-antiserum derived from monkeys in the convalescent stage in the cytoplasm of tissue culture cells and in the tumor tissues, but not in the nuclei or nucleoli (DeHaven and John, 1966; Levinthal and Shein, 1964; Taylor et al., 1968). No immunological cross reactions with Vaccinia, Monkeypox or Orf-virus have been observed (Behbani et al., 1968).

Epidemiology

The natural route of transmission is unknown, although arthropod vectors have been suggested (Hunt and Jones, 1973). In one outbreak, transmission occurred through an infected tattoo needle (Casey et al., 1967).

Experimental subcutaneous or intravenous inoculation of tumor tissue filtrates or virus suspension into rhesus monkeys, baboons or African green monkeys resulted in an analogous "tumorlike" formation within 3 to 4 weeks (Niven et al., 1961; Sproul et al., 1962, 1963). After subcutaneous inoculation only subcutaneous nodules developed in the initial infection, but after i.v. inoculation or with increasing passages, metastases developed in the lung and heart or along the lymphatics (Feltz, 1961; Grace and Mirand, 1963).

Human infection has resulted from accidental puncture by a contaminated needle (Grace and Mirand, 1963, 1965).

Clinical Diseases

Nonhuman primates: The initial clinical sign is the rapid development of small, slightly reddened papules, which, after several passages, grow larger (up to several cm in diameter) and appear as subcutaneous nodules or masses. They appear particularly at the hairless parts of the dorsovolar and dorsoplantar surfaces of the extremities and on the face, but they never spread on to the trunk (Bearcroft and Jamieson, 1958; Ambrus et al., 1969; Spencer, 1985; Walker et al., 1985).

6 weeks later the nodules spontaneously regress and because of this they should be called pseudotumors rather than true neoplasms.

CF-fixing antibodies develop shortly after the occurrence of the pseudotumors, but true protective immunity does not develop as the pseudotumors can reappear several times in the same animal.

Man: 5–7 days p.i. slowly growing nodules up to 2 cm in diameter developed in volunteers. In spontaneous cases these pseudotumors were observed particularly on the hands and feet, with an associated regional lymphadenopathy and fever. The pseudotumors disappeared spontaneously within a few weeks.

Pathology

The subcutaneous (and otherwise located) pseudotumors are essentially of histiocytomatous structures with large, pleomorphic cells growing beneath the cutaneous squamous cells (Fig. 3). These cells are characterized by large nucleoli, hyperchromasia of the nuclear walls, and during proliferation, numerous mitotic figures in the enlarged, and often burst nuclei. Occasionally large numbers of eosinophils can be seen during proliferation. In some tumor cells irregular, eosinophilic cytoplasmic inclusion bodies can be demonstrated (Andrews et al., 1959; Niven et al., 1961; Sproul et al., 1963). Intracytoplasmic oval or brick-shaped virus particles can also be demonstrated using the electron microscope (Spencer, 1985). There is no collagen fiber production in Yaba-pseudotumors in contrast to the rabbit- and deer fibromas caused by poxviruses (Behbehani et al., 1968).

Regression of the pseudotumors is usually associated with multinucleated giant cell formation.

1.2.3 Tanapox-(Yaba-Like-, OrTeCa-, Benign Epidermal Monkeypox-, BEMP-)Virus

Pseudotumors which grossly resembled early pox-lesions or pseudotumors induced by Yaba virus were found simultaneously 1967 in three monkey colonies in Oregon, Texas and California and 1970 in another colony in Maryland (McNulty, 1972). Monkey species involved were *Macaca mulatta, M. nemestrina, M. fuscata* and *Cynopithecus niger* (Hall and McNulty, 1967; Crandell et al., 1969). All animals of the 1967 outbreaks were obtained from the same dealer (McNulty, 1972). These tumors were caused by a poxvirus, whose biological properties differed markedly from those of the Yaba-virus.

Cebids and callitrichids were not affected (Hall and McNulty, 1967). Experimental infections could not be initiated in either squirrel monkeys *(Saimiri sciureus),* lorises, galagos, sheep, swine, chicks, mice, hamster or New Zealand white rabbits (Crandell et al., 1969); whereas in German checker rabbits, a proliferative, non-necrotizing epidermal lesion was produced (Crandell et al., 1969).

Another poxvirus, serologically closely related to Tanapoxvirus has been recently isolated from a spontaneous outbreak in *Callithrix jacchus* (Gough et al., 1982).

Virus: Tanapoxvirus can be propagated in HuAm-cells, AgMK, E-BSC, R-BSC and CV-1 cells with the CPE appearing 18 days p.i. including the formation of small plaques up to 1 mm in diameter. The cytoplasmic inclusion bodies in the infected tissue cultures are smaller than those produced by Yaba-virus (Nicholas, 1970a). Tanapoxvirus does not induce any CPE in either rabbit kidney cells, chicken embryo- or HeLa cells, and it also does not initiate pock-formation on the chicken CAM (Nicholas and McNulty, 1968).

Tanapox- and Yaba-virus cross react in CF-, CFI- and neutralization tests (Nicholas, 1970b; Hall et al., 1973).

Human tanapox-Virus infection was first observed 1957 and 1962 in Kenyan children (España et al., 1971; Jezek et al., 1985). From 1978 to 1981 more than 163 cases of human Tanapox infection were discovered in Zaire (Arita and Gromyko, 1982) with the majority of tanapox cases observed in Lisala and in nearby villages located along or near the Zaire river (Jezek et al., 1985). Independent of these natural outbreaks transmission from infected monkeys to their animal handlers occurred (McNulty et al., 1968).

Clinical Disease

Nonhuman primates: After a 4–5 day incubation period small, reddened papules appeared on the face, chest, anus and perineum of infected animals. They developed into circular, flat, firm elevations up to 10 mm in diameter within 14 days, becoming umbilicated and covered by small central crusts. The surrounding erythema is only of a minor degree. The papules begin to exfoliate by the 10th day, but they never develop into either a vesicular or pustular form (Hall and McNulty, 1967; McNulty et al., 1968; Kupper et al., 1970; McNulty, 1972). Healing with scar formation takes 3 to 4 weeks.

Man: In general, the clinical course of human tanapox has two stages. In the majority of cases the illness started with pre-eruptive symptoms, the most common

being fever of 38 to 39 °C, which usually lasts for 2 to 4 days. The short febrile illness is sometimes accompanied by severe headache, backache, and prostration.

The eruptive stage often started with an itching sensation at the site of development of the skin lesions and with the appearance of a circular spot. This macule is slightly elevated at the centre but lacks the central abrasion usually observed in insect bites. The macule subsequently changes to a dark, slightly raised papule with a rough surface and a readily palpable underlying induration. As the focal skin lesions developed, the fever and general symptoms abated. The papule continued to grow into an elevated lesion of pock-like appearance with little or no liquid but a considerable amount of necrotic tissue. By the end of the first week the skin lesion was usually more than 10 mm in diameter with a large erythematous areola of several centimeters diameter surrounded by swollen edematous skin. This acute stage was commonly associated with local lymphangitis and regional lymphadenitis.

The skin lesions may develop into larger nodules but more frequently brake down as a result of trauma or necrosis. The so formed ulcers were round, shallow excavations with a lightly raised perimeter and a base of soft necrotic tissue, they spread peripherally as well as into the corium. The ulcers remained about the same size for several days, the acute inflammatory reaction then diminished, the ulcer's perimeter flattened and their floor now contained granulation tissue. Re-epithelization started from the periphery and the regional lymphadenopathy diminished (Jezek et al., 1985).

In African patients the lesions were located on the front or on lower parts of the body not usually covered by clothes (Jezek et al., 1985).

Accidentally infected animal handlers developed solitary lesions along the scratched parts of their hands and also their anus (McNulty, 1972).

Pathology

Nonhuman primates: The lesions of monkey tanapox closely resemble those of monkeypox arrested at the papular stage (Fig. 3). Histologically a thickened, pale epidermis in the affected areas of the skin is seen, which is characterized by a proliferation (acanthosis) and ballooning degeneration or necrosis of the prickle cells, extending down below the hairshafts and sweatglands. The nuclei of the proliferating epithelial cells may be vacuolated. Eosinophilic inclusion bodies appear mainly in the cytoplasm, but are sometimes also seen in the enlarged nuclei (Hall and McNulty, 1967; McNulty et al., 1968). The dermis can be infiltrated by varying amounts of inflammatory cells depending upon the degree of secondary bacterial infection. The covering crusts are composed of keratin, leukocytes, dead non-keratinized epidermal cells and cellular debris.

Man: Acanthosis with elongation of the rete ridges and vacuolization of epidermal cells of all layers has been described (McNulty et al., 1968). Inclusion bodies were not identified, but many nuclei showed hyperchromatosis along the nuclear membranes. Early lesions extended only into the upper corium, whereas in the late stages the lower dermis was also involved.

Immunity

Infected animals have been proven to be immune to challenge for 2 years (McNulty, 1972). Vaccination using Vacciniavirus did not produce any productive immunity (Hall and McNulty, 1967).

1.2.4 Molluscum Contagiosum

Molluscum contagiosum, a chronic skin disease of low infectivity in man, has been diagnosed in a few chimpanzees (Douglas et al., 1967; Schmidt and Butler, 1967). Small nodules appeared in the periorbital or inguinal regions of the infected animals. Typical "molluscum contagiosum bodies" could be demonstrated in the tissues, but attempts to isolate the virus were unsuccessful.

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1.3 RNA-Viruses

1.3.1 Arboviruses

Arboviruses of zoonotic properties involving nonhuman primates belong to several serogroups - Table 5

1.3.2 Chikungunya-Virus

Chikungunya virus derived its name from the main clinical symptoms in man. Chikungunya in Swahili means "painfully bent, stiff joints". It is sometimes referred to as "denguelike" because of the clinical similarities of the two arbovirus infections (McIntosh and Gear, 1981).

Table 5. Zoonotic arboviruses of nonhuman primates

Family	Genus	Species
Togaviridae	Alphavirus	Chikungunya-virus Mayaro-virus (Getah-virus) Bebaru-virus)
	Flavivirus	Yellow fever-virus Kyasanur Forest disease-virus Dengue-viruses 1-4 (Zika-virus)
Reoviridae	Orbivirus	Orungo-virus
Bunyaviridae	Bunyavirus	Oropouche-virus

The disease probably goes back as far as the 18th century, when in 1779 in Cairo, Alexandria and in Batavia (Jakarta) outbreaks of a disease were described, which closely resemble those of Chikungunya-virus infection. Other outbreaks have probably occurred in the Americas as far north as Philadelphia (Halstead, 1981), but retrospectively dengue-outbreaks can not be completely disregarded. The first ascertained outbreak of Chikungunya was observed 1952 in the Newala province of southern Tanzania (Robinson, 1955; Lumsden, 1955; Ross, 1956). Subsequent further isolations have been made in South Africa, Senegal, Uganda, Zaire, Congo, Angola, Nigeria and Zimbabwe (Gear and Read, 1957; McIntosh et al., 1963; McIntosh and Gear, 1975; Robin, 1981). In Senegal 55% of the human population showed antibodies against the virus (Robin, 1981). Human epidemics in Africa have been reported in southern Transvaal in 1957 (Gear and Reid, 1957; Gear, 1975); in Zimbabwe in 1964 (McIntosh et al., 1964); in Senegal in 1966 (Robin, 1981); in the Entebbe-area of Uganda in 1968 (Kirya and Okia, 1977); in Nigeria in 1969 and 1974 (Robin, 1981); and in Angola in 1970 ( ). Other epidemics were observed in India, Thailand, Cambodia, Vietnam, and Burma (Myers et al., 1964; Carey et al., 1969; Halstead, 1966). Anti Chik-antibodies were demonstrated also in a large of the human population of Indonesia, the frequency increasing with age (Kanamitsu et al., 1979).

In Africa *Papio ursinus*, *Cercopithecus ascanius*, *C. aethiops* and occasionally *Galago senegalensis* have been shown to harbor the virus with the development of high titered viremias (McIntosh, 1970; McIntosh et al., 1977; Kaschula et al., 1978; Robin, 1981). They are thus most probably the reservoir hosts, but isolations have also been made from a number of non-primates. The reservoir hosts in Asian countries are unknown, *M. mulatta* may be suspected because of the only mild disease associated with high titered viremias after experimental infection.

Chikungunya-antibodies have also been found in Africa born, less than 2yr old gorillas, chimpanzees and an orangutan (Harrison et al., 1967).

Virus: Chikungunya virions are spherical, approximately 42 nm in diameter with a hexagonal inner core of 25 to 30 nm diameter. It produces CPE in primary hamster kidney cells, BHK-21-, BSC-1-, VERO-, Fl-, HeLa- and rhesus monkey kidney cell lines. It replicates also in continuous *Aedes*-spp. cell lines.
Virus isolation can also be made via intracerebral inoculation of suspicious materials into 1 to 2 day old suckling mice, where it produces an acute encephalitis, and if fresh isolates are used, a haemorrhagic enteritis (Halstead, 1981).

Serology: Antisera prepared to Chikungunya-virus cross-react in CF- and neutralization tests with O'nyong nyong-, Mayaro- and Semliki Forest viruses; whereas vice versa only weak cross reactions occur (Halstead, 1981).

Epidemiology: As in yellow fever, two transmission cycles can be distinguished in Chikungunya-fever. One is monkey - mosquito - monkey, maintained with extension to forest living people via canopy-dwelling mosquitoes descending to the ground level. The other one depends on interhuman transmission by *Aedes aegypti* (Robin, 1981).

Main vectors besides *A. aegypti* are the forest dwelling *A. africanus*, *A. luteocephalus*, *A. furcifer*, *A. opok*, *A. dalzieli*, and occasionally *Culex pipiens fatigans* or *Mansonia fuscopenatta* (Halstead, 1981; Robin, 1981).

Clinical Disease

Man: After an incubation period of 3 to 12 days (in 2 accidental laboratory infections 22 and 80 hrs respectively), sudden fever with no prodromal symptoms develops. Other symptoms include headache, lymphadenopathy, joint pain, severe asthenia and anorexia, nausea and vomiting. 2 to 3 days later an irritating maculopapular or scarlatiniform rash develops over the trunk and limbs, whilst simultaneously the fever declines. The rush disappears after a few days, but the joint pain usually declines much more slowly, and, in approximately 50% of the patients apyrexial joint pain recurs intermittingly during the subsequent period, which may last up to 6 months.

In Asian patients mild haemorrhagic signs have been observed ie. petechiae, purpura and epistaxis (McIntosh and Gear, 1975).

Nonhuman primates: Information on clinical symptoms in monkeys depends on experimental infection. Rhesus monkeys develop a benign, transient, febrile illness, whilst vervet monkeys and baboons remain asymptomatic despite viremia (Robin, 1981).

Pathology

Man: The rare fatal human Chikungunya virus-infections are not well reported. The symptoms resemble those of a shock syndrome.

Nonhuman primates: No morphological lesions are reported.

Treatment

Antipyretics should be given to control the fever, but salicylates are to be avoided. Analgetics or mild sedatives may be sometimes be required to control pain for extended periods of time. Excessive losses of fluids and electrolytes due to vomiting should be treated accordingly to prevent severe dehydration.

1.3.3 Mayaro-Fever

The virus was isolated in Mayaro-county/Trinidad in 1954 (Anderson et al., 1957). 2 outbreaks of the disease in man were recognized in the Amazonian region of Brazil and one in the Bolivian rain forest (Causey and Maroya, 1957; Schaeffer et al., 1959; LeDuc et al., 1981; Pinheiro et al., 1981). Other virus isolations were made in Surinam, Panama and Colombia (Groot et al., 1961; Galindo et al., 1966; Metselaar, 1966). Serological evidences have also indicated the occurrence of human infections in Peru and Costa Rica (Downs and Anderson, 1958).

The Mayaro virus life cycle involves mammals, birds, and arthropods. Marmosets *(Callithrix argentata)* and cebids *(Alouatta belzebul, A. villosa)* have been implicated as natural reservoirs because of the high prevalence of antibodies in these primates and the occasional isolations of the virus (Anderson et al., 1957; Woodall, 1967; Hoch et al., 1981; Seymour et al., 1983).

Virus: The morphological characteristics of Mayaro-virus are essentially similar to those of other alphaviridae. It replicates and produces CPE in BHK-21, VERO, and HeLa-cell-lines; primary rhesus monkey kidney cells and in chicken- or mouse embryo fibroblasts (Pinheiro, 1981).

Mayaro virus and Semliki forest virus cross react to some degree in HI- and CF-tests, but still can be distinguished from one another (Casals and Whitman, 1957).

Epidemiology

Mayaro virus infections are widespread among forest living populations in certain neotropical areas (Pinheiro, 1981). The virus infects mammals (esp. nonhuman primates); caprimulgiform and columbiform birds and arthropods in their natural habitat.

Arthropod vectors of Mayaro virus are mosquitoes (*Haemagogus janthinomys*, *Haemagogus* sp., occasionally *Coquillettidia venezuelensis*, *Sabathes* sp., *Culex* sp., *Mansonia* sp., *Psorophora* sp., *Gigantolaelaps* sp., *Limatus flavisetosus* and *Wyeomyia aporonema*). Most of the available evidences point to a monkey - Haemagogus - monkey cycle (Groot et al., 1961; Berge, 1975; Hoch et al., 1981; Pinheiro, 1981).

Clinical Symptoms

Man: Mayaro fever is generally an acute, transient, benign, nonfatal, febrile illness accompanied by headache, epigastric pain, backache, arthralgia, generalized pain, chills, nausea and photophobia. A maculopapular or micropapular rash appears on the 5th day of illness, particularly on the trunk and the extremities, and lasts for about 3 days. Occasionally light jaundice or inguinal lymphadenopathy can also be observed (Pinheiro, 1981).

Nonhuman primates: No disease has been reported so far.

1.3.4 Getah-Virus

Antibodies to Getah virus without any disease are widespread throughout the Malaysian human population. Also neutralizing antibodies have been reported in wild macaques and *Presbytis* spp. in West Malaysia. Although the natural transmission cycle is unknown, the virus has been isolated from *Culex gelidus*, *C. tritaeniorrhynchus*, *Anopheles amictus*, and *Aedes vexans* in Malaysia, Australia and Japan. Even though these mosquitoes feed mainly on domestic animals and fowl, a jungle cycle can not be excluded based on the serological findings (Marchette, 1981).

1.3.5 Bebaru Virus

Antibodies to Bebaru Virus, known only in Malaysia, have been found in approximately 1/3 of the human sera sampled. The principal hosts are unknown, with the role of monkeys being vague. The virus has been isolated from *Culex* spp. and *Aedes butleri* (Chamberlain, 1980).

1.3.6 Kyasanur Forest Disease (KFD)

In 1956 large numbers of bonnet monkeys *(Macaca radiata)* and langurs *(Presbytis entellus)* were found dead in the Kyasanur Forest in the Shimoga-district, Mysore-State/India. At the same time a disease with 10% mortality was observed in human beings approximately one week after working in the forest (Work and Trapido, 1957; Fiennes, 1967; Rajagopalan and Anderson, 1971; Goverdhan et al., 1974). The etiological agent proved to be a flavivirus closely related serologically to Omsk haemorrhagic fever-, louping ill- and Powassan viruses (Seymour and Yuill, 1981).

Virus

The virus grows well in HeLa cells, human embryonic intestine, chicken embryos and other cell lines. Suckling mice and hamsters can easily be infected intracerebrally (Felsenfeld, 1972; Goverdhan et al., 1974).

The virus, although neutralized by anti Russian-Spring-Summer encephalitis-antisera does not show such cross reactions in Agar gel diffusion tests (Felsenfeld, 1972).

Epidemiology

Since KFD infections are highly fatal in the nonhuman primates monkeys are probably not only heterologous hosts to the virus, but may act as amplifyers, thus helping in the spread of the disease. The virus has also been isolated from forest rats *(Rattus rattus wroughtoni* and *R. blanfordi)*; shrews *(Suncus murinus)* (Boshell-M et al., 1968; Boshell-M and Rajagopalan, 1968; Rajagopalan et al., 1969), and four times from insectivorous bats *(Rhinolophus rouxi)* (Rajagopalan et al., 1969). Antibodies were demonstrated in the above mentioned species and in palm squirrels *(Funambulus tristriatus)*, gerbils *(Tatera indica hardwickei)* and forest mice *(Mus budooga)* (Berge, 1975 - cit. from Seymour and Yuill, 1981), indicating the probability of a rodent reservoir of the virus.

The KFD-virus is transmitted by several ixodid ticks, with *Haemaphysalis spinigera* and *H. turturis* being the principal hosts (Boshell-M et al., 1968; Trapido et al., 1964›). KFD-virus has also been occasionally isolated from *Ixodes petauristae*, and also from bat ticks (*Ornithodorus* spp.) collected during an epidemic (Seymour and Yuill, 1981).

The virus is transovarially transmitted in the three-host *Haemaphysalis* spp.. It also passes through all larval and nymphal stages in Ornithodorus (Bhat and Goverdhan, 1973; Shope, 1980).

Even though the virus appears also in the milk of experimentally infected monkeys 2 to 8 days p.i., it is not readily transmitted to nursing offspring (Shah, 1965).

The disease exhibits distinct seasonality in monkeys - most fatalities are observed during the post-monsoon dry season of the first half of the year, with peak incidents in February and March (Work et al., 1959; Goverdhan et al., 1974). This peak in monkey mortality corresponds well with the period of highest concentration of *Haemaphysalis* nymphs on the forest floor and their maximum activ-

ity (Rajagopalan et al., 1968; Rajagopalan and Anderson, 1971; Sreenivasan et al., 1983).

Kyasanur Forest disease has spread since its first discovery into the neighbouring southwestern and southeastern Shimoga and to North-Kanara districts (Shope, 1980). Outside India it has occurred in laboratory personel (Tauraso, 1973). Antibodies have also been demonstrated in recently imported rhesus monkeys (Meister, 1971).

Clinical Symptoms

Nonhuman primates: After experimental infection a biphasic illness ensues with viremia up to 14 days p.i. Erythrophagocytosis, erythro-, leuko- and thrombocytopenia occur 4 to 7 days p.i., followed by an encephalitic phase and finally, 24 hs prior to death, a shock-like fall of the blood pressure, bradycardia, epistaxis, diarrhea (Webb and Chatterjea, 1962; Webb, 1969) and elevated SGOT- and SGPT-values (Banerjee, 1978).

Man: In human cases myalgia, headache, nuchal rigidity, vomitus and tremor were observed and the patients had elevated SGOT- and SGPT-levels (Banerjee, 1978). In fatal cases profuse epistaxis and gastro-intestinal haemorrhage preceeded the final outcome.

Pathology

Nonhuman primates: In langurs and bonnet monkeys which died during epizootics, anal haemorrhage, pallor of the adrenal cortex, focal liver necrosis with cytoplasmic inclusion bodies were described (Iyer et al., 1960). Haemorrhages were seen in lungs, kidneys, brain and adrenals. In the brain a nonpurulent encephalitis marked by focal microgliosis and perivascular cuffing after 15 days of illness was reported (Webb and Burston, 1966).

Man: In three fatal human cases the pathology was similar to those described in monkeys (Iyer et al., 1959).

Treatment

Vaccination of endangered human beings using inactivated anti-Russian-spring-summer encephalitis vaccine was unsuccessful (Shah et al., 1962).

1.3.7 Yellow Fever

Yellow fever, one of the most devastating tropical and subtropical diseases of man has a long and interesting history. The virus probably originated in West Africa as a primary mosquito-parasite, but only after its introduction into the New World did it reach its full dimensions as a cause of dreadful epidemics in man and nonhuman primates.

Virus

Yellow fever virus is the prototype flavivirus. It is an enveloped, spherical virus of 38 nm virionic diameter, and contains a single-stranded RNA genome.

Yellow fever virus is sensitive to lipid solvents, chemical desinfectants, acids and heat (Bergold and Weibel, 1962; Robin and Beran, 1981).

YFV can be isolated from the blood at the beginning of the disease by inoculation into suckling mice or mosquito cell lines (Berge, 1975, - cit. from Seymour and Yuill, 1981; Varma et al., 1976).

For serological investigations CF-tests are recommended (Monath et al., 1980), but all serotests have to be evaluated with caution, since marked cross reactions with the other flaviviruses, especially Zika-viruses occur (Kalter and Heberling, 1971; Henderson et al., 1970).

Epidemiology

Africa: The yellow fever ecology in *Africa* follows two patterns:

a) Sylvatic cycle: Yellow fever virus is basically a commensal of West-African forest or bush living *Aedes* spp. (*A. africanus*, *A. vittalus*, *A. neoafricanus*, *A. furcifer-taylori*, *A. luteocephalus*- Felsenfeld, 1972; Monath, 1980, 1982). These transmit the infection during blood meals to monkeys living in the canopy (*Colobus badius*, *Cercopithecus aethiops*, *C. ascanius schmidti*, *Erythrocebus patas* - Simpson et al., 1965; Kirya and Okia, 1977; Monath et al., 1980), or as in the case of bush-dwelling mosquito species also to primate species living on the ground. The wild hosts of yellow fever virus in addition to those mentioned above are diana monkeys, mona monkeys, chimpanzees (*Pan* spp.), mangabeys (*Cercocebus* spp.), baboons (*Papio* spp.), bush babies (*Galago* spp.), and possibly hedgehogs (*Erinaceus* spp.) (Robin and Beran, 1981). Old World monkeys show only minor, transient symptoms after infection with yellow fever virus, and the ensuing viremia is of only short duration due to elimination of the virus by antibody-development (Woodall, 1968; Woodall et al., 1968; Kirya and Okia, 1977). After a yellow fever epizootic near Entebbe approximately 40% of the free living cercopithecids examined had anti-yellow fever virus antibodies (Kirya and Okia, 1977).

b) Urban cycle: Viremic monkeys - mostly *Cercopithecus* spp. roaming fields and plantations are also bitten by the peridomestic mosquito species *Aedes simpsoni* and *A. aegypti* living in villages, plantations etc. (Gear, 1977; Cordellier and Akoliba, 1981). *A. aegypti* breeding sites may be water cisterns as shown in certain villages in Ivory Coast (Lhuillier et al., 1985). Once these house-dwelling mosquitoes are infected they can subsequently transmit the infection to the villagers, and, as they are carried by the wind over large distances, can spread yellow fever epizootics rapidly. In *A. aegypti* the yellow fever virus is passed transovarially through the mosquito-generations (Beatty et al., 1980; Anon, 1982), which accounts for the survival of the virus during the dry season in emergence zones. The risk of an urban infection is much greater than that of acquiring the infection via the sylvatic cycle (Cordellier and Akoliba, 1985).

America: A. aegypti, after being shipped across the Atlantic ocean (Tribe, 1977) particularly during the period of slave-trading adapted quickly to the habitats of the Western hemisphere. In pre-Columbian times the Americas were probably free of yellow fever, at least no hints are given to any epizootic in the very detailed recording system of the pre-Columbian American cultures or in reports by the earliest Spanish or Portuguese conquerers. Once infected *A. aegypti* were intro-

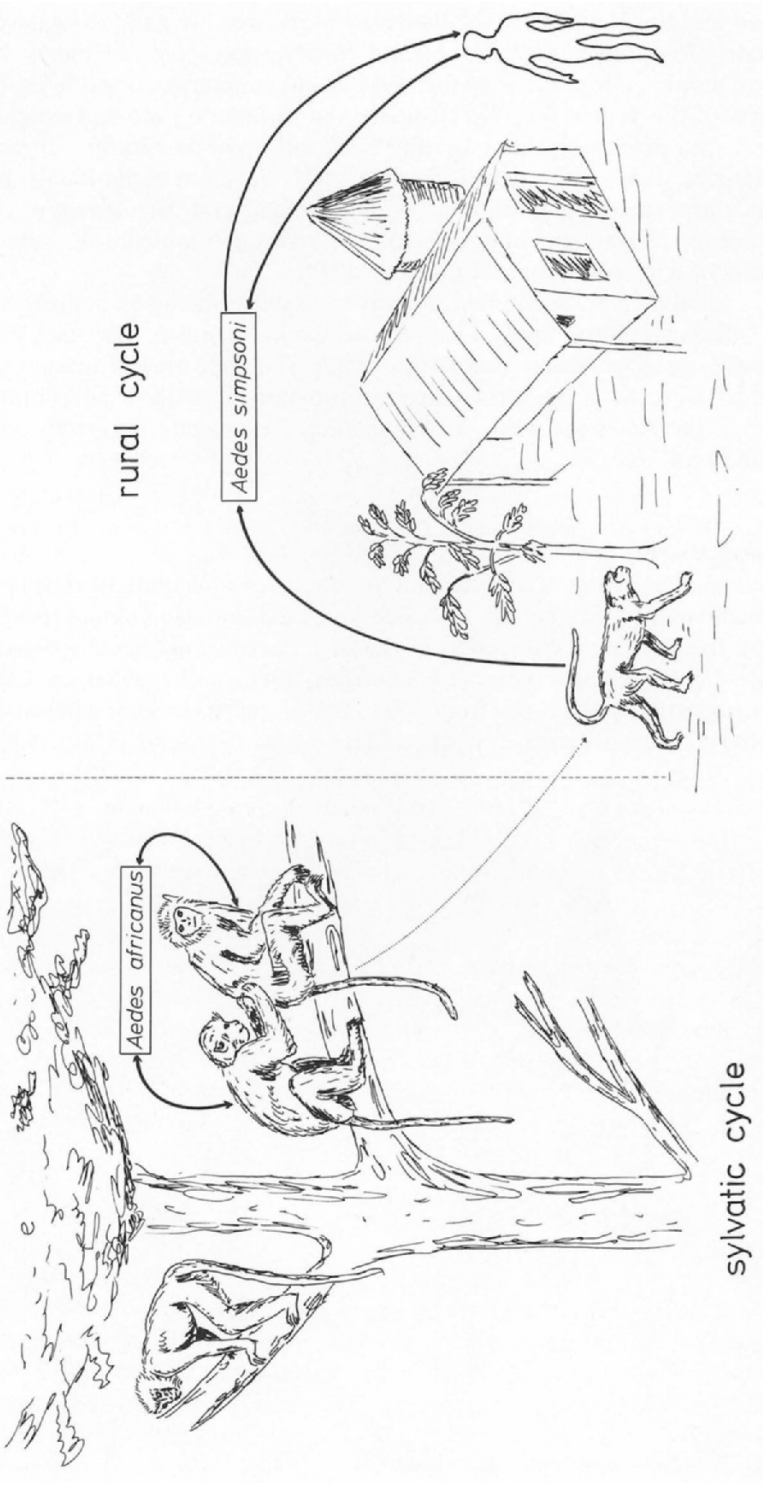

Fig. 4. Epidemiology of yellow fever in Africa

duced into the New World they adapted to the tree life and also passed the virus to native forest dwelling *Sabethes*- and *Haemagogus*-species (Fiennes, 1967). New World monkeys, in contrast to their Old World counterparts, are defenseless to the effects of the yellow fever virus, hence the devastating monkey epizootics associated with extremely high mortality rates still occur in neotropical monkeys (de Rodaniche, 1953; Kalter and Heberling, 1971; Seymour et al., 1983). *Alouatta* are particularly susceptible, followed by *A. trivirgatus* and *Saguinus* spp. *Ateles* spp., *Saimiri* spp., *Cebus* spp. and *Callicebus* may also develop clinical disease, but it is usually of a lesser severity (Hunt et al., 1978).

In todays Americas only the sylvatic cycle exists, being maintained by the canopy dwelling mosquitoes (*Aedes leucocelaenus*, *A. fulvus*, *Sabethes chloropterus*, *Haemagogus* spp. (Robin and Beran, 1981). The once present urban cycle ceased to exist with the *A. aegypti* eradication program in 1934. Man contracts yellow fever in the Americas when, at tree-cutting, the mosquitoes are forced down to ground-level.

Clinical Disease

Nonhuman primates: Experimental yellow fever infections of *Lemur fulvus* are clinically inapparent, but are associated with a 3 to 4 day viremia (Rodhain et al., 1985). In experimental infection of rhesus monkeys leukopenia (primarily granulocytes) ensued (Daberkow and Knüttgen, 1966) and the Serum LDH-activity increased rapidly 100 h p.i. from 200 to 300 U/ml to levels of 4000 to 5000 U/ml mostly due to an increase of the s-LDH-5-fraction (Scott et al., 1976). In fatal

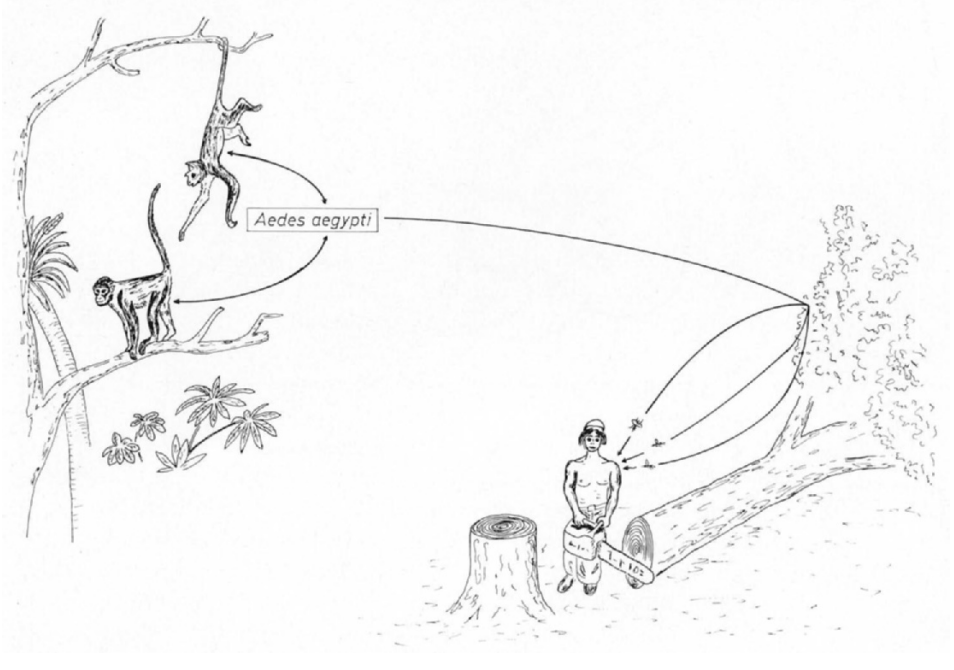

Fig. 5. Epidemiology of yellow fever neotropics

infections of nonhuman primates after a 60 h incubation period, fever and leukopenia are apparent, with death occurring at 100 h p.i.

Man: After a 3 to 10 day incubation period (Hunt et al., 1978) the disease begins with fever, headache, backache, muscle ache, nausea, epistaxis, and a lack of correlation between pulse (bradycardia) and body temperature (39–40 °C) (Faget's sign). After 2 to 3 days either recovery starts or a biphasic course of fever etc. may occur. In serious forms icterus develops at the same time. Haemorrhage and bloody vomitus are characteristics of the most serious, often fatal form of the disease (Robin and Beran, 1981). Renal failure due to lower nephron nephrosis is indicated by a significant albuminuria and anuria (Johnson, 1975).

Pathology

Nonhuman primates: At the necropsy of monkeys wich died from yellow fever, haemorrhagic diathesis and fatty liver degeneration or extensive hepatocellular necrosis were the most common lesions (Smetana, 1962). These are eventually accompanied by the occurrence of "Councilman bodies" (David-West and Smith, 1971). In experimentally infected rhesus monkeys lipids (mainly triglycerides) accumulate in the liver (Liu and Griffin, 1982).

Man: Icterus with haemorrhages in various organs are common. The gastric and intestinal contents may contain partially digested blood. The hepatic lesions are characterized by midzonal necrosis, trabecular disorganization, acidophilic degeneration and fatty metamorphosis of hepatocytes, and the formation of hyaline cytoplasmic masses, the so-called "Councilman bodies". In the kidneys haemoglobinuric lower nephron nephrosis is seen. The myocardium may show degenerative changes (Robin and Beran, 1981).

Treatment

No specific treatment is available, supportative treatment of the dehydration is indicated.

1.3.8 Dengueviruses

Currently four antigenically distinct serotypes of dengue virus, types 1 through 4, are known. Types 1 and 2 are prevalent in West Africa, 1 to 3 in South and Central America and types 1 to 4 in Asia (Shope, 1980). Dengue outbreaks have been described in the past in the latitudes of mild to tropical climates on all continents. The first isolations were accomplished in 1943/44 (Halstead, 1981) although outbreaks of disease resembling dengue fever have been described since the 18th century, particularly in tropical Asia and Australia.

Studies by Monath et al. (1974) indicated dengue virus-infections in both human beings and monkeys in the Nupeko Forest/Nigeria, which were later confirmed in serological studies (Fagbami et al., 1977). In the latter neutralizing antibodies against type 2 dengue virus were demonstrated in 74% of "monkey" sera from the gallery forest at Nupeko and in 38% of "monkey" sera from the lowland rainforest. Meister (1971) demonstrated anti-dengue-antibodies in 7% of rhesus monkeys during quarantine.

Virus

Dengue virions are spherical, approximately 50 nm in diameter and enveloped. The envelopes carry knob-like projections.

Dengue viruses grow in primary rhesus monkey kidney-, LLC-MK2-, BSC-1-, Vero- or other cell lines. Plaques are formed under agar- or methylcellulose-overlay. Explant techniques are more successful in recovery of dengue virus than others, most efficient is the co-cultivation of explants with LLC-MK2-cells (Marchette et al., 1972).

Epidemiology

Studies by Rudnick (cit. from Halstead, 1981) revealed a jungle cycle of dengue virus in Malaysia, involving forest dwelling monkeys and *Aedes niveus*, which feeds both on monkeys and man. Whether or not similar conditions exist in Africa and the tropical Americas is unknown.

In the more important urban cycle *A. aegypti* is the principal vector. The virus has also been recovered from naturally infected *A. albopictus* involved in outbreaks in the Pacific area.

Dengue viruses can be transmitted transovarially in the mosquitoes, but larvae are not infected by development in contaminated water.

Clinical Disease

Nonhuman primates: clinical symptoms in spontaneously infected monkeys are not known. After experimental infections of *Macaca* sp., *Cercopithecus* sp., *Cercocebus* sp. and *Papio* sp. an asymptomatic viremia 1 to 7 days p.i. results (Halstead, 1981).

Man: In human dengue virus-infections two types of disease can be distinguished:

One, "Dengue fever", is characterized by a biphasic fever 2 to 7 days p.i.. A sudden developing 39.5 to 41 °C fever is accompanied by frontal or retro-orbital headache. During the first two days of fever a transient, macular, generalized rash and myalgia or bone pain occur. From days 2 through to 6 of the fever, nausea and vomiting are frequent and a generalized lymphadenopathy, cutaneous hyperaesthesia, taste aberration and anorexia may develop. A second generalized maculopapular rash and fever follow 1 to 2 days after defervescence of the first symptoms, disappearing 1 to 5 days later and occasionally followed by desquamation of the epithelium. Epistaxis, petechiae and purpuric lesions are sometimes noticed.

The other form of dengue virus-infection is "Dengue haemorrhagic fever" or "Dengue-shock". This was first described in the Philippine Islands, occurring predominantly in children. An initial phase of sudden fever, malaise, vomiting, headache and cough is followed after 2 to 5 days by rapid deterioration and collapse. Petechiae on the forehead and extremities are frequent. The mortality ranges from 10 to 40%. In the surviving patients convalescence begins after a 24 to 36 hrs crisis.

Pathology

Nonhuman primates: No pathological lesions in dengue virus infected monkeys have been published.

Man: Minimal to moderate haemorrhages are usually found in several organs, and in most patients yellow to bloody effusions in the serous cavities are found. Disturbances in the normal haematopoiesis are indicated by arrested megakaryocytosis in the bone marrow with peripheral megakaryocytosis in the capillaries of the lungs, kidney, liver, and spleen. In the liver varying degrees of fatty metamorphosis to focal midzonal necrosis are seen, as well as sinusoidal non-nucleated cells with vacuolated acidophilic cytoplasm, resembling Councilman bodies.

1.3.9 Zika Virus

Zika virus was first isolated in 1947 from a sentinel rhesus in Zika forest/Uganda (Dick et al., 1952). Several isolations have been made from naturally infected human beings in Uganda, Nigeria, and Senegal, and from mosquitoes in the Central African Republic, Ivory Coast, and Malaysia (Boorman and Porterfield, 1956; Weinbren and Williams, 1958; Hadow et al., 1964; Simpson, 1964; Marchette et al., 1969).

Virus
Zika virions are of typical flavivirus-shape. They are spherical, enveloped, 18 to 45 mm in diameter, and contain single-stranded RNA. The virus is inactivated by ether, sodium deoxycholate and chloroform (Robin, 1981).

Epidemiology
The virus reservoir is unknown. West African monkeys might be included in the cycle as suggested by serological evidence (Chamberlain, 1980; Robin, 1981; McCrae and Kirya, 1982). It has been isolated from *Aedes aegypti*, *A. africanus*, *A. opok*, *A. luteocephalus*, *A. vivittatus*, *A. dalzieli*, *A. furcifer-taylori*-group, and *Anopheles gambiae*. The epidemiological pattern may be similar to that of yellow fever with *A. africanus* transmitting the virus among canopy living monkeys.

Clinical Symptoms
Nonhuman primates: No clinical symptoms have been reported in the sentinel monkeys.

Man: The few human illnesses, including one laboratory infection, were characterized as a benign febrile illness with malaise, headache, backache and possibly maculopapular rash (McIntosh et al., 1975).

1.3.10 Orungovirus

Orungovirus was first isolated in 1969 in Central Africa (Anon, 1969) and several epidemics have been reported in Nigeria (Fabiyi, 1981). The highest number of seropositive people were found in the Guinea savanna (Fabiyi, 1981). Orungovirus was also isolated during a yellow fever epidemic in the Gambia (Monath et al.,

1980 - cit. from Cordellier et al., 1982). Besides man, 24% of *Cercopithecus mona* and *aethiops* (and 50 % of sheep) in Nigeria were seropositive (Fabiyi, 1981) and the virus was also recovered from mosquitoes feeding on a *C. aethiops.*

Life cycle: Aedes dentatus, A. aegypti, A. gambiae, A. africanus, A. opok, Culex perfuscus and *Anopheles spp.* are regarded as vectors of Orungovirus (Fabiyi, 1981; Cordellier et al., 1982). Orungovirus, like other arboviruses, can be transmitted transovarially in the mosquito (Cordellier et al., 1982).

Clinical Symptoms

In nonhuman primates the disease is unknown.

Man: Orungo-fever is characterized by nausea, vomiting, myalgia, headache, conjunctivitis, leucopenia and fever lasting up to 7 days with fine papular rashes involving the face, chest, and abdomen (Fabiyi, 1981). Death is a possible sequela (Fabiyi et al., 1975).

1.3.11 Oropouche-Virus

Oropouche virus was first isolated from a febrile patient in Trinidad in 1955. It caused several epidemics in the Amazonian region of northern Brazil from 1967 to 1975 (Parkin, 1975; Pinheiro, 1981). The virus was isolated from a sloth *(Bradypus tridactylus)* in Brazil, while monkeys also seem to be involved in the epidemiology based on evidence from serological studies (Hubbert et al., 1975).

Virus

Oropouche virus is one of at least 16 simbuviruses of the bunyaviridae-family. Its enveloped virions are of 90–100 nm in diameter. The virus multiplies in primary chicken embryo-, Vero-, and BHK-21-cells. It also forms plaques in BHK-21-, MA III- and LLC-MK2 cell lines (Pinheiro, 1981). All the bunyaviridae cross react serologically to some extent, but they can be differentiated by CF-techniques. Oropouche virus contains a haemagglutinin.

Epidemiology

Serological studies have indicated that the Oropouche virus is maintained in monkeys, sloths, birds, and possibly other animals. In Trinidad many *Alouatta-* and *Cebus* spp. were seropositive and antibodies to the Oropouche virus were found in most monkeys and wild birds (particularly formicariidae) surveyed in the Amazon basin (Pinheiro, 1981).

The vectors in nature are still unknown, although the virus was isolated from *Coquilletidia venezuelensis, Aedes serratus, Culex quinquefasciatus* and *Culicoides paraensis* (Pinheiro, 1981).

Clinical Symptoms

Nonhuman primates: So far, no disease has been reported in spontaneously or experimentally infected monkeys.

Man: Oropouche fever is characterized by a fever of abrupt onset, with headache, myalgia, arthralgia, chills, dizziness, and photophobia. Nausea, vomiting,

diarrhea and epigastric pains may also sometimes be present. The illness usually lasts 2 to 7 days, recurrences do occur.

Pathology

No lesions have been reported in either man or nonhuman primates.

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1.4 Rhabdoviruses

1.4.1 Rabies-Virus

Today rabies is distributed worldwide, and is still extending its geographical boundaries. The infection, although primarily carried in carnivorous animals (mainly canids), is transmissible to other mammalian species including man, and consequently, has been reported in a number of recently imported nonhuman primates of different geographical and taxonomic origin (Schmitter, 1914; Boulger, 1966; Kaplan, 1966; Richardson, 1971a, b; Richardson and Humphrey, 1971; Fiennes, 1972; Miot and Sikes 1973; Röttcher and Sawchuk, 1978). At least one human fatality has been ascribed to bites from a rabid monkey (Prakash, 1970), and thousands of human rabies-vaccinations have been required after monkey bites (Richardson, 1971).

Virus

The virological characteristics of the rabies virus are generally well known, making a lengthy discussion within the context of the present chapter unnecessary. For references see Beran, 1981.

Epidemiology

The reservoir hosts of the rabies virus are primarily carnivorous animals - in Africa: mainly dogs, jackals, hyenas, *Viveridae*, and possibly also wild felids and foxes; in subtropical and tropical Asia: dogs, foxes, wolves, jackals and mongooses; in South- and Central America: vampire bats and dogs (Beran, 1981). Occasionally monkeys are also considered to be vectors (Ressang and Umboh, 1963; Fiennes, 1971; Beran, 1981).

The routes of spontaneous infection in freeliving monkeys and apes are largely unknown. The application of live vaccine has been suggested as being the source of infection in several monkeys affected by rabies (Richardson and Humphrey, 1971; Aaron et al., 1975). Man, usually keepers, can be infected by rabid animals via biting, licking or mucosal contamination.

Pathogenesis

Following percutaneous infection the rabies virus can be recovered from the site for a brief period; after approximately 24 hrs the virus starts replication apparently usually in the myocytes. The virus remains at the site for a variable and, in many cases, for extended periods of time. The primary route by which the virus reaches the CNS is via nerve pathways, the mechanism of which being incompletely understood (Beran, 1981).

After reaching the spinal or dorsal root ganglia, the rabies virus spreads rapidly throughout the CNS. From here it spreads via the peripheral nerves throughout the body, particularly to richly innervated tissues such as the salivary glands. The appearance of rabies virus in saliva usually preceeds the onset of clinical disease; the exact period depending on the animal species involved. In Arctic foxes, Vampire bats and birds, however, salivary shedding occurs for undetermined subclinical periods (Beran, 1981).

Only fragmentary information exists on the incubation period in nonhuman primates. In spontaneous infection of monkeys it has been calculated as lasting several weeks to months (Fiennes, 1972). Experimentally infected rhesus monkeys developed furious rabies in 15 to 35 days or, in other cases, the silent variety after a 105 day incubation period (Richardson, 1971).

Clinical Symptoms (Nonhuman Primates Only)

The silent form of the disease is reported to occur in naturally infected monkeys or apes (Abdussalam, 1966; Fiennes, 1971, 1972), although a naturally infected chimpanzee developed furious rabies (Anon, 1966 b). In comparison experimentally infected rhesus monkeys developed either furious or silent rabies (Richardson, 1971 a).

The most obvious clinical signs of silent monkey rabies are salivation, automutilation and paralysis or sudden death (Fiennes, 1972). Signs of aggression towards animal caretakers including biting, which may be due to furious rabies, are difficult to evaluate because they are also part of the natural behavior pattern of all monkeys and apes.

Pathology (Nonhuman Primates Only)

As in human rabies, little is seen macroscopically other than the lesions due to automutilation. The histopathological lesions are characterized by microglial foci, perivascular lymphocytic cuffing and neuronal degeneration. Negri bodies are usually found mainly in the "cornu ammonis" and in the neighbouring cortex (Richardson, 1971 a; Fiennes, 1972), but they were missing in one rabid chimpanzee (Miot and Sikes, 1973). Virus antigen can also be demonstrated in nonhuman primate brains by FA-techniques (Richardson, 1971 a).

Treatment

Nonhuman primates living in semi-free conditions or in outdoor corrals in endemic areas should be vaccinated using inactivated vaccines. Baer et al. (1979) recommended a combination of poly IC complexed to poly L-lysine and carboxymethylcellulose together with human diploid rabies vaccine.

Rabid nonhuman primates are to be destroyed. Bite lesions inflicted by apparently normal or sick nonhuman primates must always be treated properly, not only because of possible rabies but also because of other serious infections such as tetanus or *Herpesvirus simiae.*

1. If possible, as the first step the wounds should be bled.
2. Extensive flushing with water and soap further reduces the amount of infectious agents present.
3. Antiseptic treatment using 40–70% alcohol, iodine tincture, 0,1% quaternary ammonium compounds – in the latter all traces of soap have to be removed before using these compounds.
4. Identification and observation of the monkey in question for at least 3 weeks. Brains of such animals after death or sacrifice have to be especially examined (i.e. demonstration of Negri-bodies, FA-tests, infant mouse inoculation).
5. Vaccination programs in human beings after being bitten or licked by an animal proven to be rabid.

1.4.2 Marburg-Virus

In 1967 several laboratory workers in Marburg and Frankfurt/Germany, and in Belgrad/Yugoslavia, who were involved in handling tissues or blood of African green monkeys *(Cercopithecus aethiops)* that were recently imported via London from Uganda, suffered from a hitherto unknown infectious haemorrhagic disease. The infection also proved to be transmissible to human contacts (physicians, nurses, wives). This initial outbreak involved 31 people, 7 of which died in the course of the disease.

Owing to its initial place of appearance the virus was named "Marburg Virus" (it is sometimes also referred to as "Green Monkey" or "Vervet" - Virus). Its morphological characteristics are similar to those of other rhabdoviruses except for its distinctively larger size, which lead Kiley et al. (1982) to place it into a new family: Filoviridae.

The infection was not observed again until 1975, when two hitchhikers traveling through South Africa and Zimbabwe (formerly Rhodesia) for several months, contracted the infection (Gear et al., 1975; Conrad et al., 1978). Those two travelers did not have any known contact with monkeys. One patient died, and again, the infection was passed on to a contact person - an attending nurse.

The disease surfaced again in 1980 in Kenya (Johnson et al., 1981) and Zimbabwe/Rhodesia (Slenczka, 1981). Two patients were involved in each incidence; one man died. Whether or not nonhuman primates participate regularly in the infectious cycle remains an unsolved and sometimes controversial question. Experimentally infected nonhuman primates *(C. aethiops, Macaca mulatta, Saimiri sciureus)* all died within a few days (Haas et al., 1968; Simpson et al., 1968a, b; Simpson, 1969a, b; Maass et al., 1969). All sera collected from wildliving monkeys during or shortly after the 1967 outbreaks were free of anti-Marburg virus antibodies (Johnson et al., 1981), indicating that the monkeys were incidental hosts to the virus. On the other hand, shortly before the European outbreaks occurred, numerous sick vervet monkeys were found in the Greek River area of Uganda, and at the same time an acute haemorrhagic disease of unknown mortality rate was observed in the local people of the same district (Smith, 1982). Since, according to Smith (1982), the collecting and shipping practices at that time at the single Ugandan dealers' place were well below normal hygiene standards, the possibility of the transference of any infectious disease by subclinically infected monkeys can not be discounted.

Virus

The organism found in the cytoplasm and extracellular spaces of infected organisms and tissue cultures had been classified as a rhabdovirus, as its chemical composition and its morphological appearance is similar to those of rabies and vesicular stomatitis viruses and is morphologically indistinguishable from the Ebola-virus (Johnson et al., 1981). Whether or not the slight differences in size between rabies- and vesicular stomatitis virus on the one side and Marburg- and Ebola-virus on the other justify the latter being regrouped as Filoviridae, can not be decided within the scope of the present publication; for historical reasons they will still be regarded as rhabdoviruses.

Although somewhat variable, the basic architecture of Marburg-virions consists of elongated, cylindrical particles with a diameter of 70 to 80 nm diameter and lengths up to 3000 nm. Some virions are coiled up as circle-, spiral, hook- or six-shaped forms, whilst virions originating from tissue cultures and animal tissues other than blood tend to appear as bulbous forms of 220 to 750 nm diameter (Siegert et al., 1967; Zlotnik et al., 1968; Kissling et al., 1968, 1970; Simpson, 1970; Peters et al., 1971). The complex internal structures of the virions as revealed by contrast media, consist of a dark central nucleocapsid of approximately 20 nm diameter with a pitch of 78 Å; a surrounding tubular structure of approximately 50 nm diameter with cross striation of 45 Å periodicity; an intermediate layer, and finally an approximately 100 Å thick envelope studded with spikes of about 70 A size, and arranged in roughly 100 Å distance from one another (Siegert et al., 1967; Almeida et al., 1971).

The virus is heat inactivated at 56 °C in 60 min and by gamma radiation. It is sensitive to lipid solvents, glutaraldehyde, detergents and phenol (Kiley et al., 1982; Mitchell and McCormick, 1984). It replicates in GMK-AH1-, Vero-, LLC-MK2-, BHK2-, and other cell lines, usually without producing CPE. Only in embryonic human lung fibroblasts (Slenczka, 1969; Hofmann und Kunz, 1971) or in primary vervet kidney cells (Haas et al., 1968) can a distinctive CPE be observed as a spindling and separation of the cells.

For serological studies the demonstration of the CF antibodies which persist for approximately 2 years is most useful, although this can be sometimes of a limited specificity depending on the antigen used. Neutralization tests are technically difficult and often unsatisfactory (Henderson et al., 1971; Siegert and Slenczka, 1971). The most specific test is probably the fluorescent antibody test (Bonin, 1969). Marburg-virus does not cross-react with any of the several arboviruses tested (Casals, 1971) nor with the other rhabdoviruses including the Ebola-virus (Slenczka, 1981).

Epidemiology

Although the initial 1967 outbreaks in Germany and Yugoslavia could be doubtlessly traced back to a shipment of vervet monkeys received from the Entebbe area / Lake Victoria of Uganda, this does not necessarily imply that these monkeys are the reservoir hosts of the virus. It seems more likely, that these monkeys were incidental hosts to the virus after acquiring the infection shortly before or during the shipment to their European points of destination. They might have picked up the agent from other sources in Uganda or, as suggested by Hennessen (1969), during a stopover at London airport. Experimentally infected vervet monkeys (as well as rhesus- and squirrel monkeys) uniformly succumbed to the disease within 7 to 10 days, indicating their role as heterologous hosts.

Seroepidemiological surveys of monkeys have in the past sometimes been misleading due to technical problems. Sera taken from vervet monkeys in Uganda after the initial outbreak were positive according to CF-tests using crude guinea pig liver antigen (Henderson et al., 1971), but this was later proven to be a nonspecific response (Johnson et al., 1982). Johnson et al. (1982) using more specific immunofluorescence methods after the 1980 Kenyan outbreak found 4/136 *C. aethiops* and 1/184 *Papio cynocephalus* of Kenyan origin to possess anti-Mar-

burg virus-antibodies at titers of 1:64 to 1:128. All antibody-positive monkeys remained healthy, again questioning the specificity of the test. In Gabon no anti-Marburg virus-antibodies were found in either human or monkey sera (Ivanoff et al., 1982), whereas 1/499 human sera in the southeastern part of the Republic of Central Africa gave positive reactions in indirect fluorescence tests (Saluzzo et al., 1981).

The transmission of the Marburg virus to man in the initial cases depended on direct contact with the blood or tissues of the infected animals. In the 1975 outbreak in Zimbabwe, arthropod transmission from an unknown reservoir host has been considered, because the patient had been stung by an unidentified arthropod 6 days before clinical onset of the disease (Conrad et al., 1978). This assumption is supported by the successful propagation of Marburg virus in *Aedes aegypti* (but not in *Anopheles maculipennis* and *Ixodes ricinus* (Hofmann et al., 1969)).

In man - man transmission inadvertent percutaneous infection via small cutaneous wounds or accidental inoculation (contaminated needles or necropsy instruments) seem to be the most important route, although in one case sexual transmission 12 weeks after clinical recovery of the initial male patient is believed to have taken place (Slenczka, 1981). The agent is excreted in the urine (Siegert et al., 1968), and aerogenous infection is also considered to be possible (Simpson, 1969b).

Clinical Disease

Nonhuman primates: In experimentally infected vervet-, rhesus- and squirrel monkeys a febrile illness resulted regardless of dosage and the route of infection. The average incubation period ranged from 2 to 6 (up to 10) days, the resulting illness in all three species was almost identical and always fatal.

During the early febrile stage no overt signs other than occasional anorexia and slight weight loss were observed. The haematocrit values were diminished by 5-6% during the first 3 days (Simpson et al., 1968b). One to two days before death and only in the rhesus monkeys, a petechial skin rash appeared - principally on the flexor surfaces of the arms and thighs; on the chest, face and neck. The rash, however, was not noticed by Maas et al. (1969). At this stage, the animals did not eat or drink, sat huddled in their cages; seemed to be apathetic and did not respond to provocation (Slenczka, 1981). Immediately before death a sudden drop in body temperature occurred (Simpson, 1969 b, 1970). The animals became dyspnoic and, in some cases, suffered from diarrhea. In some individuals blood oozed from the rectum or vagina and blood samples often failed to clot. The lymphocyte numbers were reduced by as much as 90%, and the thrombocytes decreased by 50 to 80% (Slenczka, 1981).

In the survivors the rash disappeared around the 12th day, followed by desquamation at days 14 to 16 (Andrijich, 1981).

Laboratory findings are leukopenia, thrombocytopenia, elevated activated partial thromboplastin time, decreased prothrombin index, hypokalaemia, hypoproteinaemia, raised serum-urea and creatinine levels; elevated SGOT and SGPT activities (Stille and Böhle, 1971; Andrijich, 1981).

Pathology

Nonhuman primates: The specific lesions are haemorrhages in the great parenchymas of lungs, liver, and spleen; with hepato- and splenomegaly and fatty metamorphosis of hepatocytes. Histopathologically, focal necrosis could be demonstrated in virtually all organs, particularly in the liver and the reticuloendothelial system (Slenczka, 1981). In hepatocytes basophilic, Feulgen-positive inclusion bodies were described. Inflammatory responses were limited to early lesions. In the spleen and lymph nodes follicular necrosis and perifollicular haemorrhages were most noticeable. The splenic red pulp revealed a marked reduction in cell numbers. In the lungs edema and interstitial pneumonia prevailed, whilst the renal lesions consisted of glomerular microthrombosis and tubular damage (Slenczka, 1981).

Guinea pig: In the guinea pig essentially similar lesions as those described in monkeys occur, with the severity and extension of the liver damage increasing with passage number. 3 days p.i. disseminated acidophilic single cellular necrosis of the hepatocytes appeared, which further developed into regional necroses of different sizes during the next few days (Bechtelsheimer et al., 1970).

A variable glial nodule encephalitis with occasional perivascular infiltration and polioencephalitis occurs, affecting particularly the brain stem (Slenczka, 1981).

Man: At necropsy, signs of severe haemorrhagic disease in the skin, mucous membranes and large parenchymas predominate. The gut is filled with blood from diffuse haemorrhages without any ulcers or erosion. These hemorrhages in the Marburg-virus disease are probably due to intravascular coagulation (Gagal et al., 1970). Histopathologically, again focal necroses in almost all organs except the bones and skeletal muscles are a constant feature (Gedigk et al., 1971). The necrosis is most pronounced in liver, lymphatic organs and gonads with only a minimal inflammatory response occurring. Peculiar basophilic bodies of 1 to 4 &m appeared in the necrotic foci in the liver; signs of mitotic regeneration were marked (Bechtelsheimer et al., 1970, 1972). All patients which died from the infection showed glial nodule type panencephalitis with only discrete perivascular lymphocytic cuffing and haemorrhagic lesions varying from petechial meningeal haemorrhages to massive cerebral haemorrhages (Jacob, 1971; Slenczka, 1981).

Treatment

There is no treatment for Marburg-virus infected animals; they have to be destroyed.

In man convalescent serum can be administered, accompanied by symptomatic and supportive treatment.

Shock is to be treated accordingly. Vitamin K, platelet infusions, fibrinogen and epsilonaminocaproic acid should be given to counteract the bleeding.

Oliguric patients are given mannitol, anuric patients are to be placed on a dialysis program.

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1.5 Picornaviruses

1.5.1 Encephalomyocarditis - Viruses (EMC-Virus)

The EMC-viruses constitute a group of several antigenically related viruses of the genus *Enterovirus*, which share as a major feature the ability to induce myocarditis. The most commonly reported ones are the encephalomyocarditis-, Columbia -SK-, M. M. -, and Mengo-Viruses. They have been recovered worldwide from a variety of animals including man. Swine are the most commonly and seriously affected species.

EMC-viruses have also been isolated from nonhuman primates, e. g. in 1945 from a chimpanzee in Florida (Helwig and Schmidt, 1945); a rhesus monkey in Uganda (Dick et al., 1948; Dick, 1949); another chimpanzee in 1948 (Schmidt, 1948); a baboon and a "monkey" in Florida (Kissling et al., 1956); a baboon and two chimpanzees at the Tarpon Spring/Florida-Zoo (Gainer, 1967); two adult rhesus monkeys (Dshikidze et al., 1974) and a *Hapalemur griseus* in Madagascar (Coulanges et al., 1976).

Virus

The isometric EMC-virions have a diameter of approximately 30 nm. They are ether resistant, acid stable and withstand freezing temperatures down to −70° C. They are inactivated by 60 °C for 30 min. EMC-viruses pass through Berkefeld- and Seitz-filters or gradocol membranes with 30 nm pore size. They replicate in embryonating hens'eggs and produce CPE in embryonic and other cell cultures of chicken, mouse, monkey, hamster, swine and cattle origin (Murnane, 1981). Plaques of different sizes are formed after agar-overlay, depending on the individual virus strains. The virus is pathogenic in newborn and adult mice, young guinea pigs and newborn rabbits (Dshikidze et al., 1974).

Epidemiology

Rats, other wild rodents, and swine are suspected to be the reservoir hosts of EMC-viruses (Gainer, 1974; Murnane, 1981) with the pig being the most suscepti-

ble animal species of all. Infected rats excrete the virus in their feces. EMC-virus has also been recovered from swamp water in endemic areas. Pigs excrete the virus only for a short period of time after infection.

The infection of susceptible animals or man is probably acquired through food or water contaminated by infectious animal droppings or by consumption of viscera or meat of EMC infected animals. Although so far no monkey - man transmission of EMC-virus has been known, one has to be aware of the possibility at least, particularly if working with animals imported from the wild.

Clinical Disease

Nonhuman primates: In all EMC-virus infections of nonhuman primates the infected animals were either found dead or moribund, with the development of paralysis shortly before death (Helwig and Schmidt, 1945; Kissling et al., 1956; Roca-Garcia and Sanmartin-Barberi, 1957; Gainer, 1967; Coulanges et al., 1976). Experimentally infected *C. aethiops* showed sluggishness, anorexia, pale and edematous skin, tachycardia and, in the final stages, convulsions. ECG-changes were characterized by an increased PR interval and RS-T segment shifts, but these were not always present (Dshikidze et al., 1976).

Man: The best description is probably that of an accidental laboratory Mengo virus infection. The worker suffered from intermittent delirium, headache, nuchal rigidity, emesis and fever over a 4 day period. He developed a transient nerve deafness, but otherwise recovered uneventfully. In other human EMC-patients sudden fever of 2 to 3 days duration, severe headaches, pharyngitis and nuchal rigidity were reported, with a few patients being comatose on admission to the hospital. All patients recovered promptly with no residual complications (Murnane, 1981).

Pathology

Nonhuman primates: Interstitial myocarditis, often with massive myocardial necrosis, pulmonary edema and minor encephalitis have been reported in dead monkeys and apes (Gainer, 1967; Dshikidze et al., 1976; Murnane, 1981). In a *Hapalemur griseus* cerebral haemorrhages were the most conspicious features (Coulanges et al., 1978).

Man: So far no fatal infections have been reported in man, and thus the lesions in man induced by EMC-viruses are unknown.

1.5.2 Polioviruses

Human poliomyelitis used to be a worldwide threat as a crippling disease before vaccine-development. All three human polio-virus-strains are experimentally transmissible to macaques and apes. Spontaneous infections have occurred particularly in the pre-vaccine era in chimpanzees (Lindau, 1960; Douglas et al., 1970); gorillas (Froeschle and Allmond, 1965; Guilloud et al., 1969), and orangutans (Froeschle and Allmond, 1965; Guilloud et al., 1969). Recently an outbreak caused by type 1 was described in 3 captive *Colobus abyssinicus kikuyuensis* at the Institute of Primate Resarch in Kenya (Suleman et al., 1984).

Although no poliovirus transmission from nonhuman primates to man has been proven so far, the possibility at least exists theoretically.

Virus

The virions have a diameter of 20 to 30 nm; an icosahedral symmetry and lack an envelope. They are stable at pH 3 and are ether resistant, but are inactivated by temperatures of 50 to 60° in 30 min.. Synthesis of the virions occurs primarily in the cytoplasm of intestinal cells (Beran, 1981). Human poliovirus-strains are differentiated into 3 serotypes (Types 1-3) and so are the identical polioviruses isolated from nonhuman primates.

The polioviruses replicate best of all in HEK cells or in primary rhesus monkey cells and to a lesser extent in WI-38 cells (Melnick, 1976).

Specific identification of the serotype depends mostly on serum neutralization tests, although HI-CF-, Immunofluorescence-, or precipitation-tests may also be useful.

Epidemiology

All enteroviruses are excreted via the feces, with transmission occurring either via infected sewage or water. Direct fecal - oral transmission is also possible and has to be avoided especially when handling animals. Chimpanzees, e.g. can be symptomless carriers (Fiennes, 1967).

Clinical Symptoms

Nonhuman primates: Poliovirus-infections of nonhuman primates, as in man, do not necessarily induce clinical illness. The symptoms observed so far consisted of anorexia, weakness, paresis, hemiplegia or paraplegia. The disease may end fatally, as observed in a colobus monkey (Suleman et al., 1984).

Man: Human poliovirus-infections can remain subclinical, in other cases paralytic disease with fever, headache, gastrointestinal disease, nuchal rigidity and flaccid paralysis may develop. This latter may be life threatening if it extends to the respiratory muscles.

Pathology

Nonhuman primates: The poliomyelitic lesions of nonhuman primates are identical to those of human beings (Godglück, 1960). They consist of a nonpurulent myelo-encephalitis with extensive loss of ganglial cells and an associated glial-cell proliferation particularly in the spinal cord, *formatio reticularis*, cerebrallar nuclei, diencephalon and the cerebral cortex except for the temporal lobes, and the frontal- and occipital poles. The ultrastructural lesion in experimentally infected cynomolgus monkeys were characterized by membrane-bound vesicles in the cytoplasm of degenerating motoneurons. No virus particles were found (Hashimoto et al., 1984).

Man: The morphological lesions of human poliomyelitis are essentially similar to those of nonhuman primates, for a more detailed description see Ule, 1974.

1.5.3 Coxsackieviruses

Coxsackieviruses are differentiated from the polioviruses by their unique virulence in suckling mice. Human strains are readily transferable to a number of domestic animals, they have also been reported in wild animals, usually after human contact. Captive monkeys and apes have been found to be infected, occasionally even already upon arrival at the laboratory (Kalter and Heberling, 1971). Rhesus-, cynomolgus- and bonnet monkeys and chimpanzees have been successfully experimentally infected by serotypes A 2, 3, 4, 9, 12 and 16 and B 1, 3, 4, 5 and 6 (Kraft and Melnick, 1953; Melnick and Kaplan, 1953; Lou and Wenner, 1962; Schmidt et al., 1965; Tobe et al., 1967; Chandy et al., 1980). As virusexcretion has been demonstrated in naturally infected nonhuman primates, the possibility of re-transmission to man although so far not reported, has to be kept in mind; therefore the infection will be discussed briefly.

Virus

The morphological and cultural characteristics of coxsackieviruses are those of enteroviruses in general (for description see Kalter, 1982). Human coxsackieviruses are divided into serogroups A and B, and are subgrouped by numbers. Their serological typing depends primarily on neutralization and to a lesser extend on HI- and CF-tests. Most of the reported natural coxsackievirus infections of nonhuman primates have been identified by such serological evidence (Kalter and Heberling, 1971; Yamane, 1974), whilst in a few cases the agents have been actually recovered (Heberling, 1972; Kelly et al., 1978).

Clinical Disease

Nonhuman primates: Coxsackievirus infections of monkeys are symptomless in most cases (Heberling, 1972). Only in an infant chimpanzee, which died at 81 days of age due to a coxsackie B-5 infection (and upper respiratory infection by ß-hemolytic streptococci), were an associated myocarditis and interstitial pneumonia reported (Kelly et al., 1978).

Man: Although most human infections are probably subclinical, others, particularly if occurring in children, may be followed by a variety of syndromes. These range from symptomless fever to severe disease, including herpangina, meningoencephalitis, paralysis, exanthema, upper respiratory disease with or without pneumonia, pleurodynia, hepatitis, myo- and pericarditis (Gear and Measrock, 1973; Dery et al., 1974; Beran, 1981).

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1.6 Reoviridae

1.6.1 Orthoreoviruses

Reoviruses are a group of double-stranded RNA-viruses which occur in human beings, and, according to serological studies, in a number of animal species (Rosen, 1968).

The mammalian reoviruses are divided into serotypes 1, 2, and 3, natural infections have been reported in several species of nonhuman primates. Types 1 (= SV12) and 2 (= SV 59) were described in macaques (Hull et al., 1958) and chimpanzees (Sabin, 1959; Rogers et al., 1967; Soike et al., 1969); type 1 (= SA3) in African green monkeys (Malherbe et al., 1963) and type 3 in marmosets (Deinhardt et al., 1967). All three serotypes were described in gorillas, chimpanzees, orangutans, gibbons, baboons, geladas, African green monkeys, patas monkeys, rhesus monkeys, cynomolgus monkeys, bonnet monkeys, stumptailed macaques, Japanese macaques and langurs (Bhatt et al., 1966; Kalter and Heberling, 1971). Type 3 has been shown to be the most common type in nonhuman primates (Kalter and Heberling, 1971). Experimental infections of nonhuman primates are easily achieved. Interspecies transmission from man to animals and vice versa are known to occur (Thein and Scheid, 1981). Human infections generally occur early in childhood (Scharpe and Fields, 1985), certain reoviruses such as the rotaviruses are major pathogens.

Virus

The reoviruses possess segmented double stranded RNA. They are isometric, nonenveloped, and 50 to 130 nm in diameter (Atoynatan and Hsiung, 1964; Soike et al., 1967). They have a double capsid shell with the outer, indistinct, capsid layer consisting of 92 capsomeres, and the inner capsid being of icosahedral symmetry and of 45 nm in diameter.

Simian reoviruses grow well on primary monkey kidney cells (Heberling, 1972). Like other reoviruses they are assembled in the cytoplasm, forming large perinuclear cytoplasmic inclusion bodies (Easterbrook and Rozee, 1971) Mammalian reoviruses are distinguished into types 1, 2 and 3. They all haemagglutinate human type 0 erythrocytes, with types 1 and 2 also haemagglutinating squirrel monkey erythrocytes and type 3 less extensively cattle erythrocytes. The simian reoviruses SV 12 (Hull et al., 1956) and SA 3 (Malherbe and Harwin, 1957) are serologically identical to type 1, whilst SV 59 (Hull et al., 1958) corresponds to type 2 (Kalter, 1982).

Reoviruses are resistant to ether and acid treatment. They are quite stable at −20 °C or lower.

Epidemiology

Judging from serological studies (Kalter and Heberling, 1971) reovirus infections are common in both wild and captive monkeys. Most reovirus infections are inapparent or cause only mild symptoms in man or animals and consequently go frequently unrecognized. The viruses are excreted via the respiratory or intestinal tract and are horizontally transmitted.

Pathogenesis

Reoviruses are thought to enter the host primarily via the M-cells of the gastrointestinal tract. They then multiply in the lymphoid tissues of the Peyer's patches (type 1) and within 4 to 6 days spread to more distant organs in increasing concentrations. Another port of entry is the respiratory system, with multiplation of the viruses occurring in the peribronchial lymphoid tissues.

Reoviruses produce a lytic infection *in vivo*, but can also produce persistent cellular infections *in vitro*. In the lytic infection the host cell's metabolism and cytoskeletal organization are altered, whereas in the persistent infections the virus and the host cells adapt to each other, with the host cell being able to support viral replication without lysis (Sharpe and Fields, 1985).

Both type 1 and type 3 reoviruses can infect the CNS of experimentally infected newborn mice, with type 1 initiating a nonlethal infection of primarily ependymal cells with hydrocephalus as a possible result. Type 3 infects the neuronal tissues thus causing an acute and fatal encephalitis (Sharpe and Fields, 1985).

Clinical Symptoms

Nonhuman primates: Natural infections with type 1 have been reported in *Macaca mulatta*, *M. fascicularis* (Hull et al., 1956, 1958; Hull and Minner, 1957; Hull, 1968) and *Cercopithecus aethiops* (Malherbe and Harwin, 1957); those with type 2 in *M. mulatta* (Hull et al., 1958) and chimpanzees (Sabin, 1959); whilst type 3 has been isolated solely from marmosets (Deinhardt et al., 1967) and type 5 strains from fecal specimens of newly imported chimpanzees (Soike et al., 1969).

In the only outbreak associated with clinical disease, respiratory symptoms ranging from rhinitis to interstitial pneumonia predominated (Sabin, 1959).

In experimental type 2 infections of chimpanzees an upper respiratory tract illness was produced (Sabin, 1959).

Man: Most human infections are asymptomatic, but sometimes the viruses can be isolated in a variety of diseases.

Reovirus types 1, 2, and 3 have been recovered from patients with hepatitis and encephalitis, but their etiological relationship remains open to question (Thein and Schein, 1981). Types 2 and 3 cause febrile exanthema, diarrhea, and steatorrhea in children. In newborn babies reoviruses may cause congenital pneumonia, pneumopathy and diarrhea (Thein and Schein, 1981).

Pathology

Nonhuman primates: In natural reoviral infections in macaques interstitial pneumonia has been observed (Hull et al., 1956). Experimental infection resulted in hepatitis, meningitis and necrosis of the chorioid plexus (Hull et al., 1956, 1958; Thein and Scheid, 1981).

Man: Diffuse interstitial pneumonia with thickening of the alveolar septae and metaplasia of the pneumocytes, hyaline membranes and alveolar necrosis have been found in an infant infected with type 3 virus, and in a type 1 infection. In the latter focal myocardial degeneration, focal liver degeneration and centrilobular necrosis of hepatocytes were also observed (Thein and Scheid, 1981).

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1.7 Myxoviruses

1.7.1 Orthomyxoviruses - Influenza Viruses

Influenza viruses are of only limited host specificity, ie. porcine influenza viruses also cause disease in man and human influenza has been shown to infect a variety of avian species. Natural infections of nonhuman primates by human strains have been repeatedly reported - mostly by the demonstration of specific antibodies (Bhatt et al., 1966; Kalter et al., 1967, 1969; Nigi and Tanaka, 1973; O'Brien and Tauraso, 1973; Yamane, 1974; Romvary et al., 1976; Kalter and Heberling, 1978). They have also been sometimes associated with clinical disease (Johnsen et al., 1971; Romvary et al., 1976). Clinical symptoms and death resulted in some experimental infections of *M.mulatta* and *M.fascicularis* with type A influenza virus (Saslaw et al., 1946; Saslaw and Carlisle, 1965). Outbreaks of fatal respiratory disease related to human influenza epidemics without virological confirmation have been reported in *Pan sp.* and *Cebus apella* (Mouquet, 1926; Ratcliffe, 1942). These, however, could have been caused by other respiratory agents such as parainfluenza or respiratory syncytial virus.

Virus

Orthomyxoviruses are slightly stranded RNA viruses of 80 to 120 nm particle size, consisting of a nucleoprotein helix surrounded by a lipoprotein envelope. The envelope is studded with spike-like processes - the haemagglutinins. Orthomyxoviruses possess a mucinolytic enzyme (neuraminidase) capable of removing neuraminic acid side chains from mucoproteins.

They are sensitive to lipid solvents (ether) and heat above 37 °C. They are also destroyed by low pH, ultraviolet irradiation and formaldehyde.

All influenza viruses grow well in the allantois of embryonated chicken eggs and in a variety of tissue cultures, thereby producing polykaryotic giant cells. All myxoviruses react through their neuraminidases with the mucoproteins of erythrocytes, thus inducing haemagglutination (Hsiung and Swack, 1972). Influenza

viruses are serogrouped into A, B, or C-strains depending on their internal ribonucleoprotein and matrix protein (Dowdle and Coleman, 1974). A-viruses include human and animal influenza viruses, all of which are antigenically related (Easterday, 1981) B- and C-strains are restricted to man.

Epidemiology

Influenza viruses are aerogenically transmitted under nonexperimental circumstances. They can be excreted from naturally or experimentally infected nonhuman primates (Kalter et al., 1969; Johnsen et al., 1971). Hull et al. (1956) isolated Asian influenza virus from uninoculated monkey kidney cell cultures; infected animals might therefore be a source of human infection.

Clinical Symptoms

Nonhuman primates: Most incidental infections occur without any clinical symptoms, only gibbons have been reported to develop illness and sometimes death (Johnsen et al., 1971; Romvary et al., 1976). The animals became febrile with temperatures of up to 105 °F. They developed a serous to purulent rhinitis and suffered from coughing, anorexia, depression, weight loss and gastrointestinal disturbances. The disease lasted for 3 to 6 days, 2 naturally (and 2 experimentally) infected animals out of a total of 36 died after A2/Hong Kong/68-infection (Johnsen et al., 1971). One gibbon at the Budapest Zoo died of Victoria/75 induced respiratory disease (Romvary et al., 1976). Experimentally infected rhesus monkeys developed leukopenia at 3 to 7 days p.i. (Saslaw et al., 1946).

Man: Influenza is an acute respiratory disease of epidemic dimensions. The incubation period ranges from 1 to 3 days, followed by general malaise, chills, fever, headache, myalgias and respiratory disease shown usually as a light nonproductive cough.

Pathology

Nonhuman primates: The few fatally infected gibbons all died of acute pneumonia, which, in the naturally infected animals was of a purulent character, whereas in the experimental infections haemorrhagic-fibrinous bronchopneumonias prevailed. Some of the desquamated bronchiolar epithelium resembled multi-nucleated giant cells (Johnsen et al., 1971). PAS-positive plasma exudates or hyaline membranes were lacking in the lesions.

Man: The viral neuraminidase also destroys the mucoproteins of respiratory cellular walls, resulting in cellular death. Uncomplicated influenza is usually characterized by a focal fibrinous tracheitis. Peracute, fatal cases also show signs of circulatory collapse, with pulmonary haemorrhage and edema (Giese, 1974).

1.7.2 Paramyxoviridae

1.7.2.1 SV5 (Simian Haemadsorbing Virus - SHV)

SV5 has initially been recovered from spontaneously infected rhesus monkey kidney cell cultures by Hull et al. (1956). It has frequently been isolated from latently infected kidney cell cultures of Old World monkeys since 1960 (Emery and York, 1960; Chanock et al., 1961; Yoshida et al., 1965; Tribe, 1966; Rhim and Schell; Hsiung and Atoynatan, 1969). The isolation rate varied widely between 0 (Atoynatan and Hsiung, 1969) up to 70% (Emery and York, 1960) of the tissue cultures tested. SV5 is also classified as paramyxovirus 5.Other para-5-strains closely related to, or identical with, SV5 have been isolated from human sources and designed as SA-virus (Schultz and Habel, 1959); DA-virus (Hsiung, 1959; Hsiung et al., 1962; van Euler, 1963), clone-I-virus (Krim et al., 1961); WB (Liebhaber et al., 1965) or AT-7 (Behbehani et al., 1965). Anti-SV5-antibodies have been demonstrated in nonhuman primates and man as well (Hsiung et al., 1963; Aulisio et al., 1964; Kalter et al., 1967).

Virus

The morphological and cultured characteristics of paramyxoviruses are very similar to those of orthomyxoviruses. They are, however, slightly larger with 120 to 460 nm diameter (Choppin and Stoeckenius, 1964), and they do not replicate in chicken eggs. SV5 replicates in primary monkey kidney cells. The ensuing CPE in primary rhesus kidney cells is poor, but it is much more intensive in BHK-21-cells with the formation of large syncytia and intracytoplasmic inclusion bodies within 12 to 18 hrs (Holmes and Choppin, 1960). A highly sensitive method to recognize paramyxovirus infections is the ability of the paramyxovirus infected cells to haemadsorb erythrocytes (Hsiung, 1981). Other approved methods are neutralization tests and CP-tests (Atoynatan and Hsiung, 1969). Antigenic relationships among the different paramyxoviruses are very close, and the resulting cross reactions make serological diagnosis difficult (Hsiung, 1981).

Epidemiology

Despite the frequent isolation of SV5 from laboratory monkey tissues, sera taken either from monkeys in the field or on their arrival in captivity have only insignificant antibody-levels (Hsiung et al., 1962; Atoynatan and Hsiung, 1969; Nishikawa et al., 1974). Sera taken from indoor bred cynomolgus monkeys lacked anti-SV5-antibodies altogether (Sasagawa et al., 1981). During 30 to 90 days of quarantine the conversion rate to SV5 averaged 50% (Atoynatan and Hsiung, 1969; Nishikawa et al., 1974).

In the human populations tested, 50% of the samples taken at 2 to 5 yrs of age were seropositive with the frequency climbing to 80% at the age of 10 or greater (Hsiung et al., 1963; Kalter et al., 1967; Hsiung and Swack, 1972). For these reasons the status of SV5 as a monkey or human agent is unclear (Hsiung, 1981), as the infection of monkeys might occur during transit or soon after the first human contact (Hsiung and Swack, 1972).

The virus is easily spread by airborne transmission or by contact among monkeys (Larin et al., 1967). SV5 can also experimentally infect mice, hamsters, dogs and cats (Hsiung, 1981).

After infection of nonhuman primates at least, the development of circulating antibodies soon inhibits the propagation of the virus in cell cultures and possibly also limits the infectivity of the animals.

Clinical Symptoms

Nonhuman primates: The great majority of either natural or experimental SV5 infections of nonhuman primates are asymptomatic. Only very rarely were mild respiratory signs observed after experimental (intranasal) infections, or by the in-contact animals as a transient rhinorrhea and pharyngitis (Heath et al., 1966; Larin et al., 1967).

Man: So far, no clinical symptoms have been associated with the (serologically) described human infections.

Pathology

No lesions have been described in either nonhuman primates or man.

1.7.2.2 Parainfluenzavirus 3 (Haemadsorption Virus Type-1 (= HA 1)

The human parainfluenzavirus 3 is also able to infect and sometimes produce clinical illness in nonhuman primates (Churchill, 1963; Shah and Southwick, 1965; Kalter et al., 1967; Deinhardt et al., 1967; Nishikawa et al., 1974; Martin and Kaye, 1983; Jones et al., 1984). Although no retransmission to man has been reported, the theoretical possibility exists.

Virus

The morphological criteria of para-3-virus are similar to those of SV5. For cultivation rhesus monkey kidney cell monolayers are used, but the resulting CPE is indistinctive in most cases. Detection of viral growth is usually accomplished by haemadsorption with guinea-pig erythrocytes (Fulginiti and Stahl, 1974). Para-3-virus can be distinguished into human and bovine (shipping fever) strains. Those viruses isolated from outbreaks in nonhuman primates were related to the human variety (Churchill, 1963). In serotests antigenic cross-reactions have been reported with para-1, -2, and -5 and with the mumps-viruses (Hsiung and Swack, 1982).

Epidemiology

Similar to the situation in SV5 infections most imported monkeys are free of detectable antibodies upon arrival, but within a few weeks the frequencies and titers of antibodies start to climb (Atoynatan and Hsiung, 1969; Kalter and Heberling, 1971; Nishikawa et al., 1974), indicating the occurrence of infection either at or shortly after capture.

Clinical Symptoms

Nonhuman primates: Most PI-3 infections are asymptomatic, but outbreaks of clinical disease and even fatalities have been reported in *Erythrocebus patas* (Chur-

chill, 1963); "marmosets" (Deinhardt et al., 1967), *Hylobates lar* (Martin and Kaye, 1983) and chimpanzees (Jones et al., 1984). The symptoms observed ranged from mild upper respiratory disease, associated with a serous rhinorrhea, coughing, anorexia and lethargy (Martin and Kaye, 1983), to a rapidly fatal pneumonia (Churchill, 1963; Deinhardt et al., 1967). Experimentally infected *E. patas* showed increasing temperature 5 to 6 days p.i., followed by a slight nasal discharge in 2/4 animals 10 or 12 days p.i. (Churchill, 1963).

Man: Parainfluenza viruses belong to the most important viral pathogens for infants and children. They can affect the entire respiratory tract, initiating common colds, pharyngitis, laryngotracheobronchitis, bronchitis, bronchopneumonia or bronchiolitis. Occasionally infection of liver, central nervous system or salivary glands can occur (Fulginiti and Stahl, 1974).

Pathology

Nonhuman primates: The primary types of lesions were those of an acute bronchopneumonia, which, in less advanced cases affected the tips of the cardiac lobes most commonly, and in fatal cases extended throughout the entire lobes (Churchill, 1963; Deinhardt et al., 1967). Other lesions were pleurisy, pericarditis and peritonitis. Some of the advanced lesions were probably of bacterial origin, because respiratory pathogens, e.g. pneumococci, were invariably also isolated from such lungs.

1.7.2.3 Paramyxovirus-I (Sendaivirus-Type-D-Influenza)

Sendaivirus, which primarily infects rodents, is frequently isolated from infants with croup (Hsiung, 1981). The infectivity for nonhuman primates seems to be low, according to the failure to detect anti-para I-antibodies in most serological surveys (Kalter, 1967; Atoynatan and Hsiung, 1969; Nishikawa et al., 1974). In contrast to the serological studies, one outbreak of respiratory disease due to Sendaivirus has been reported in *Callithrix jacchus* (Flecknell et al., 1983).

Epidemiology

Like other myxoviruses, Sendaivirus is transmitted by dropletinfection. The way of introduction of the virus into the indoorkept marmoset-colony is unknown, but rodents should not have access to the animal-houses. There exists, however, the possibility of infection occurring via 6 young male marmosets brought into a colony 2 months prior to the outbreak of disease.

Clinical Symptoms

Nonhuman primates: In the afore mentioned outbreak animals of all ages were affected, with the most serious cases occurring in the young ones. The initial signs were inappetance, depression, tachypnoea and dyspnoea. Other symptoms were persistent sneezing, ocular and nasal discharge of a serous or purulent nature.

Man: Para I-virus outbreaks caused principally laryngotracheobronchitis (croup) in children between 4 months and 5 years of age (Glezen et al., 1976).

Pathology

Nonhuman primates: 2 infants died due to a purulent pneumonia of all lobes of the lungs, accompanied by extensive pulmonary oedema (Flecknell et al., 1983).

Man: In Sendaivirus infections of newborns the principal lesions are focal, haemorrhagic pneumonia with peribronchial or alveolar oedema and a remarkable thickening of the alveolar septae due to cellular infiltration. The bronchial epithelia, however, show only minor lesions (Siegert, 1967).

1.7.2.4 Pneumoviruses: Respiratory Syncytial Virus (RSV) Chimpanzee Coryza Agent

Respiratory syncytial virus was first isolated in 1955 from chimpanzees affected with coughing, sneezing and rhinorrhea (Morris et al., 1956). Subsequently the virus was demonstrated as a major cause of respiratory infection in man (Chanock and Finberg, 1957; Chanock et al., 1957). Respiratory viruses have also been isolated from cattle with acute respiratory disease (Philipps et al., 1981).

Virus

The virions contain single-stranded RNA. They are enveloped, spherical and have a size of approximately 90 to 130 nm. The surface is studded by regularly shaped projections, but the virions do not possess haemagglutinin or haemadsorption activity.

The virus grows well in tissue cultures of human, simian, bovine, porcine, and hamster origin (human strains best in man-derived cells and bovine strains best in cell cultures of bovine origin).

CPE appears 1 to 14 days p.i., and is characterized by the formation of syncytial giant cells (Morris et al., 1956; Chanock et al., 1957). RS-viruses are very labile, being inactivated by heating above 37 °C or reversely by freezing at −15 to −25 °C for several days, and by ether or low pH.

Epidemiology

RSV infections are worldwide distributed in animals and man. In nonhuman primates the virus has been isolated exclusively from chimpanzees (Morris et al., 1956; Dick and Dick, 1974), although antibodies against RSV have been found additionally in captive orangutans *(Pongo pygmaeus)*, gorillas *(Gorilla gorilla)*, gibbons *(Hylobates lar)*, cynomolgus *(Macaca fuscicularis)*, rhesus *(Macaca mulatta)*, vervet *(Cercopithecus aethiops)*, squirrel *(Saimiri sciureus)* and spider monkeys *(Cebus apella, Cebus albifrons)* (Kalter and Heberling, 1971; Richardson-Wyatt et al., 1981).

A high prevalence of RSV-infections has been shown to occur in domestic animals and man. Nonhuman primates are therefore most probably infected from man or domestic animals following capture. The virus is highly contagious, with asymptomatic or only mildly ill children being considered to be the reservoir, particularly during the winter season.

Transmission of the virus is via an aerogenous route either by direct contact or droplets.

Clinical Symptoms

Nonhuman primates: Coughing, sneezing and mucopurulent nasal discharge have been observed in chimpanzees (Morris et al., 1956). Experimentally infected *S. fuscicollis* failed to develop any clinical signs (Coates and Chanock, 1962).

Man: RSV- infections vary in severity from the asymptomatic to a fatal disease. Severe disease is more often seen in infants. The actual signs of RSV-infections are low grade fever, runny nose, cough and respiratory disease. In fatalities the disease rapidly progressed to respiratory failure, coma and death (Philipps et al., 1981).

Pathology

Nonhuman primates: No fatal infections have been observed so far.

Man: In infants which died of RSV-infections necrosis of bronchocytes and interstitial pneumonia were found. Cytoplasmic inclusion bodies have been seen in pulmonary parenchymal cells (Philipps et al., 1981).

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1.8 Pseudomyxoviruses

1.8.1 Measles Virus (Monkey Intra Nuclear Inclusion Agent = MINIA)

Measles virus quite commonly infects nonhuman primates of many species under natural conditions.

Affected species comprise *M. mulatta* (Habermann and Williams, 1957; Ruckle, 1956; Potkay et al., 1966; Hall et al., 1971; Renne et al., 1973; Remfry and Hovell, 1976; Remfry, 1976; Saha et al., 1979); *M. fascicularis* (Shishido, 1966; Yamanouchi et al., 1973); *M. radiata* (Saha et al., 1979), *Presbytis cristatus* (Montrey et al., 1980); *Colobus guereza* (Hime et al., 1975; Scott and Keymer, 1975; Hime, 1976); *Pan troglodytes* (MacArthur et al., 1979); *Callithrix jacchus, Saguinus oedipus, S. fuscicollis* (Levy and Mirkovic, 1971; Tribe, 1978); *Aotus trivirgatus* (O'Brien et al., 1981) and *Saimiri sciureus* (Kalter and Heberling, 1972; MacArthur et al., 1979).

Virus

The pseudomyxoviridae differ from the paramyxoviridae by their lack of neuraminidase. Within the pseudomyxoviridae the measles virus can be distinguished from other members by its ability to haemagglutinate primate erythrocytes, which is not prevented by receptor destroying enzymes (Swack, 1981). The human and simian measles virus strains - the monkey virus formerly designed as MINIA - are identical (Ruckle-Enders, 1962; Meyer et al., 1962).

Measles viruses are spherical to pleomorphic with 120 to 270 nm diameter, with occasionally filamentous forms occurring. The core consists of a single stranded RNA. The entire nucleocapsid is helically wound and the outer lipoprotein membrane contains numerous projections (Swack, 1981). It is heat-, acid-, ether- and radiation-labile.

In vitro isolation of measles virus is time consuming. The best results are obtained with primary human kidney cells. Primary cynomolgus monkey kidney cells and primary rhesus monkey kidney cells although supporting the replication of measles virus satisfactory, might be contaminated with either measles virus or foamy virus. Diploid cell lines of human origin, BS-C-I cells and VERO-cells are acceptable alternatives (Black, 1974). The CPE in measles virus infected tissue cultures is dominated by syncytial formation.

Antigenic relationships have been demonstrated between measles, canine distemper and rinderpest virus; whereas no cross reaction occurs between measles and foamy viruses (Ruckle, 1956).

Serological diagnosis depends on haemagglutination-inhibition-, CF-, haemolysis inhibition-, γ-M-antibody- or neutralization tests (Black, 1974).

Epidemiology

Nonhuman primates living in their natural habitat without human contacts are evidently free of measles virus infections (Meyer et al., 1962; Bhatt et al., 1966;

Shishido, 1966; Kalter et al., 1967; Kalter and Heberling, 1972). They obviously acquire the infection from man soon after capture. The measles infection rate in developing countries is quite high (Saha et al., 1979). 40% of children have been known to die in village epidemics in tropical areas (Remfry, 1976). The chance therefore of transmitting the infection to newly exposed and susceptible monkeys is accordingly high. As monkeys are highly susceptible to measles virus infections, a high percentage of urban rhesus monkeys are already infected and may iniatiate a monkey-monkey cycle in their urban habitat (Saha et al., 1979). Colony born cynomolgus monkeys, on the other hand, have been shown in one study to be free of anti-measles virus antibodies until the age of 3 months (Sasagawa et al., 1981), whereas in another series (Fujimoto et al., 1983) the newborn cynomolgus had appreciable HI-titers at birth which subsequently lowered linearly with a half-life period of 3,4 ± 0,4 weeks. This might simulate the human situation. Human maternal anti-measles-antibodies do cross the placenta, but are destroyed during the first week of life (MacArthur et al., 1979) and must, thereafter be actively produced.

Regardless of the immediate source of infection (man or monkey), once the infection is introduced into a monkey population it spreads very rapidly. In the survey by Meyer et al. (1962) none of 108 rhesus monkeys trapped in the jungles had measles antibodies, whereas all 108 monkeys expressed anti-measles virus antibody activity 8 weeks later. As a result, the infection rate of Old World monkeys transported to laboratories in the Northern hemisphere increases rapidly after capture or after arrival at the laboratory, and, consequently, most outbreaks of clinical monkey measles occur in recently imported animals (Ruckle, 1956; Potkay et al., 1966; Shishido, 1966; Valerio, 1971; Hime et al., 1975; Scott and Keymer, 1975; Remfry and Hovell, 1976).

As in man, the route of transmission to monkeys is probably by droplet infection from children or monkeys during their infectious period before appearance of the rash.

Clinical Symptoms

Nonhuman primates: In nonhuman primate, species or genus dependent differences in the course of the infection seem to exist. The disease in macaques is normally mild with clinical signs very often being missed entirely (Hall et al., 1971). In contrast, the disease in a marmoset colony resulted in 326 deaths (Levy and Mirkovic, 1971) and in colobines a fatality rate of up to 100% has occurred (Hime, 1975; Scott and Keymer, 1975).

In macaques the incubation period is from 6 to 10 days (Blake and Trask, 1921a, b; Taniguchi et al., 1954), and in colobus monkeys from 10 to 14 days (Hime et al., 1975). In both species the main symptoms of experimental infections were fever, leukopenia, conjunctivitis, and maculo-papular exanthema (Taniguchi et al., 1954). Respiratory signs such as dry coughs and nasal discharges (Scott and Keymer, 1975; Remfry 1976) are sometimes the leading symptoms. These are occasionally accompanied by conjunctivitis and a maculopapular rash, which particularly involves the ventral body and always spares the palms and soles (Potkay et al., 1966; Montrey et al., 1980).

Koplik's spots (small red spots often with a white center appearing in the buc-

cal mucous membranes ahead of the cutaneous rashes) are usually missed (Potkay et al., 1966), possibly because of technical reasons. Other clinical signs of measles in monkeys are facial edema (particularly as periorbital edema), erythema, progressive lethargy, anorexia and severe diarrhea (Levy and Mirkovic, 1971; Valerio, 1971; Hime et al., 1975; Scott and Keymer, 1975; Hime, 1976).

The non pruritic rashes are followed by a powdery to scaly desquamation of the exanthemas lasting several days (Potkay et al., 1966; Montrey et al., 1980). The scales may reach a diameter of up to 10 mm (seen in langurs), and the desquamation can continue sometimes for approximately 2 weeks after disappearance of the initial rashes.

Man: After a 12 to 14 day incubation period the early symptoms of chills, sneezing, conjunctivitis, cough, fever and characteristic Koplik's spots appear. 3 to 5 days later, during which time both fever and cough worsen, a maculopapular rash appears, beginning on the forehead and behind the ears. This rash spreads within the next few days over the face, neck, trunk and limbs, and once it is fully developed, the body temperature drops to normal levels (Black, 1974).

Pathology

Nonhuman primates: The predominating lesion in fatal cases is a proliferative, giant cellular, focal to extensive interstitial pneumonia (Valerio, 1971; Renne et al., 1973; Remfry, 1975). The alveolar walls are thickened by an infiltration of mononuclear cells or sometimes more fibrotic tissue (Levy and Mirkovic, 1971; Scott and Keymer, 1975). Similar cells emigrate into the alveolar spaces, which, on the other hand, remain virtually free of fibrin exudates (Scott and Keymer, 1975). Syncytial giant cells which appear in the alveolar or bronchiolar/bronchial epithelia are sometimes referred to as "Warthin-Finkeldey" cells (Scott and Keymer, 1975). This term, however, might be incorrect as by their definition, Warthin-Finkeldey cells are derived from lymphoid tissues. True Warthin-Finkeldey cells are found in monkeys, often in germinal centers of lymphfollicles (Nii et al. 1964; Tajima and Kudow, 1976). From their cellular origin the giant cells in lymphoid tissues can be distinguished into

a) lymphoid - the true Warthin-Finkeldey cells with somewhat irregular nuclei and often a common nuclear membrane,
b) reticular giant cells with a wide rim of cytoplasm with long cytoplasmic processes,
c) plasmacytic giant cells and
d) phagocytic giant cells (Nii et al., 1964).

The typical Warthin-Finkeldey giant cells rarely contain intranuclear or intracytoplasmic inclusions, whereas the syncytial giant cells in the bronchial/bronchiolar/alveolar epithelia in measles virus infections usually contain such intranuclear or cytoplasmic inclusion bodies.

Warthin-Finkeldey cells (and probably also other measles induced giant cells) have only a short life-span of 5 to 12 days subsequent to inoculation. The rapid necrosis is due to lethal cytopathic effects of the measles virus (Tajima and Kudow, 1976). Typical Warthin-Finkeldey cells appear also in the enlarged lymphnodes, spleen and lymphoid follicles of the intestinal wall (Levy and Mirkovic, 1971; Renne et al., 1973).

Epithelial syncytial cells similar to those appearing in the respiratory epithelia are also sometimes formed in the thyroid, intestinal epithelia, urinary bladder, renal pelvis, liver or even the brain (Hall et al., 1971).

The skin lesions (biopsies taken during the rash) are most pronounced in the epidermis and the hair follicles. They consist of acanthosis, hyperkeratosis and parakeratosis of the skin with necrosis of hair follicles. Syncytia of epithelial cells containing up to 20 nuclei were found in the epithelium and hair follicles (Hall et al., 1971).

Man: Human measles is characterized by formation of multinucleated Warthin-Finkeldey cells in the tonsils, lymphnodes, spleen, Peyer's patches, and lymphoid tissue of the appendix. They *do not* develop intranuclear or intracytoplasmic inclusion bodies.

In the lungs giant cellular macrocytic interstitial pneumonia is prevalent. Syncytia in the respiratory tract generally contain intranuclear and cytoplasmic inclusion bodies, the bronchial and bronchiolar epithelia show squamous metaplasia (Archibald et al., 1971).

The skin lesions are due to necrosis and vacuolization of the epidermal cells. They are also accompanied by dermal inflammation.

Subacute sclerosing panencephalitis and multiple necrosis have been linked to measles infections (Swack, 1981).

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1.9 Retroviruses

1.9.1 Spumavirinae = Foamy Viruses

Foamy viruses are probably among the most common latent viruses occurring in primary monkey kidney cell cultures. They have been of little concern as zoonotic agents in the past and their biological properties and potential still lie very much in the dark. Possibly they have to be reevaluated because simian foamy viruses have been isolated from human tumor materials (Achong et al., 1971; Young et al., 1973; Brown et al., 1978).

Foamy viruses are most often found in aged tissue cultures through their characteristic induction of multinucleated giant cells with large intracellular vacuoles. This characteristic appearance resembles the CPE induced by measles virus except for the absence of eosinophilic intranuclear inclusions in foamy virus infected cells (Hsiung and Swack, 1971). Foamy viruses are not restricted to primates, but have been isolated from cattle, cats and hamsters as well (Barahona et al., 1976).

Agents

Foamy viruses contain single-stranded RNA and an antigenically specific reverse transcriptase. The nucleocapsid has a diameter of 725 Å, surrounded by an envelope with 125 Å projections (Clarke and Attridge, 1968). The enveloped virions finally are of approximately 100 nm diameter (Kalter et al., 1980). Foamy viruses *in vitro* typically bud into intracisternal vesicles leading to dilation of the endoplasmic reticulum (Peries and Todaro, 1977).

Foamy viruses possess a RNA-dependent DNA-polymerase like the other retroviridae (Spiegelman et al., 1970; Parks et al., 1971).

So far, 12 simian foamy viruses (Table 6) can be distinguished by their biological properties, e.g. the ability to produce syncytia on primary rabbit kidney cells (Kalter et al., 1980). They are usually sensitive to chloroform and low pH (Johnston, 1971; Hooks and Gibbs, 1975) and they are inactivated by 60 °C for 30 min. The commonly known lack of haemagglutinin might not hold true since at least simian foamy virus I does exhibit haemagglutinin activity when guinea pig erythrocytes are used (Peries and Todaro, 1977).

Serological surveys depend on neutralization, immunofluorescence and CF-tests, but they are unreliable because foamy viruses are often isolated from seronegative animals (Hsiung and Swack, 1972). Circulating antibodies, on the other hand, do not inhibit the maintenance and growth of the foamy viruses *in vivo.*

Epidemiology

Most isolations of simian foamy viruses in nonhuman primates were achieved from primary kidney tissue cultures, particularly from aging ones. Others were isolated from lymphocytes or lymphoblastoid lines (Feldman et al., 1975; Barahona et al., 1976; Agrba et al., 1978; Rhodes-Feuilette et al., 1979; Neumann-Haefelin et al., 1983); brain (Hooks et al., 1972, 1973); throat swabs (Johnston, 1961; Swack et al., 1970) and in one case from ectopic endometrium (DiGiacomo et al., 1977).

Table 6. Simian Foamy Viruses

Virustype	Host species	References
1 = SAI	M. mulatta, M. fascicularis	Rustigan et al., 1955;
	M. cyclopis	Brown, 1957; Malherbe and Harwin, 1957; Johnston, 1961
	M. nemestrina, C. aethiops	Stiles et al., 1964; Swack et al., 1970; Digiacomo et al., 1977
2	M. cyclopis	Johnston, 1961
	M. mulatta	Hsiung et al., 1969
	P. hamadryas	Agrba et al., 1978
3	C. aethiops	Stiles et al., 1964
	M. mulatta	Stiles, 1968
4	S. sciureus	Johnston, 1971
5	S. sciureus	Johnston, 1971
	G. crassicaudatus	
6	P. troglodytes	Rogers et al., 1976
		Hooks et al., 1972
7	P. troglodytes	Rogers et al., 1967
		Hooks et al., 1972
8	Lagothrix sp.	Hooks et al., 1973
ULAFV	Cacajao rubicundus	Barahona et al., 1976
LK-3	C. aethiops	Neumann-Haefelin et al., 1983
FXV	C. jacchus	Marczynska et al., 1981
FB 10	P. cynocephalus	Rhodes-Feuilette et al., 1979

Foamy viruses are ubiquitous in wild and laboratory primates (Feldman et al., 1975; Kaschula et al., 1978), rhesus monkeys e.g. are heavily infected with type 1 (Stiles et al., 1964; Stiles, 1968). 50 out of 117 newly arrived, wild caught *M. fascicularis* were seropositive (Osterhaus and van Steenis, 1981).

Transmission of the foamy viruses within a primate population probably occurs via the respiratory route, and once the infection has become established in an animal, it appears to persist for a long time, probably for life (Swack and Hsiung, 1975). Additionally Agrba et al. (1978) and Kaschula et al. (1978) have presented evidence of an intrauterine transmission in a baboon.

Human infection may take the same route - another possible way is by contaminated vaccines. The frequency of human infection by simian foamy viruses is seemingly comparatively low. Johnston (1961) found no human infection with type 1 and 3 in Taiwan, Neumann-Haefelin (1983) reported two LK-3 infections in staff members working with infected monkeys. Brown et al. (1978) identified type 6 as the isolate from a human nasopharyngeal cancer.

Pathogenesis

Spumavirinae, like oncovirinae, possess a RNA-dependent DNA-polymerase (reverse transcriptase) which enables the virus to include a step into its life cycle in which the viral RNA is copied into the host cell DNA. This is the reverse of the direction in which cellular genetic information commonly flows and its potential still has to be evaluated. There are associations of foamy viruses with malignancies in both homologous and heterologous hosts, but the role of the virus still has to be clarified.

Clinical Symptoms

Nonhuman primates: So far, no clinical symptoms have been ascribed to simian foamy viruses in their homologous hosts, although they have been isolated from baboons suffering from haemoblastomas (Agrba et al., 1978) and the ectopic uterine tissue of a pigtailed macaque (DiGiacomo et al., 1971).

Man: The isolation of simian foamy virus from a nasopharyngeal cancer (Achong et al., 1971; Brown et al., 1978) or from a case of leukemia (Young et al., 1973) might have been incidental.

Table 7. Oncovirinae of Nonhuman Primates

Type	Host	Tissue	References
B-type			
-	Papio cynocephalus	prostate gland	Kalter et al., 1975
C-type			
SSV-1	Lagothrix lagotricha	fibrosarcoma	Theilen et al., 1971
GALV	Hylobates lar	malignant lymphoma	Gallo et al., 1978
GALV-1	Hylobates sp.	lymphosarcoma	Kawakami et al., 1972, 1976
GALV-SEATO		leukemia	
GBr-1			Hehlmann, 1976
GBr-3			
MAC-1	Macaca arctoides	continuous splenic cell line	Todaro et al., 1978a
MMC-1	Macaca mulatta	esophageal carcinoma	Rabin et al., 1979
	Macaca mulatta	placenta	Mayer et al., 1974
M 7	Papio cynocephalus	ovum, placenta, fetus	Kalter et al., 1973, 1975
M 28	Papio sp.		Todaro et al., 1976
BAB-8-K	Papio sp.		Todaro et al., 1976
PP-I-Lu	Papio papio		Todaro et al., 1976
BILN	Papio hamadryas	malignant lymphoma	Voevodin and Lapin, 1976
CPC-1	Colobus polykomos	kidney fibroblasts	Sherwin and Todaro, 1979
-	Pan troglodytes	placenta	Kalter et al., 1975
-	Saguinus fuscicollis	placenta	Kalter et al., 1975
-	Cebus sp.	urinary bladder	Kalter et al., 1974
OMC-1	Aotus trivirgatus	kidney cells	Todaro et al., 1978
TRV-1	Tupaia belangeri	placenta	Flügel et al., 1978
D-type			
Mason Pfizer Virus	Macaca mulatta	mammary carcinoma	Chopra and Mason, 1970
		lactating mammary gland	Ahmed et al., 1973
		placenta	Ahmed et al., 1974
SMRV	Saimiri sciureus	embryonic lung	Heberling et al., 1977; Colcher et al., 1977a
PO-1-La	Presbytis obscurus	lung cell cultures	Benveniste and Todaro, 1977; Todaro et al., 1978b
SAIDS	Macaca mulatta	blood (Simian AIDS)	Marx et al., 1984
SAIDS	Macaca cyclopis	lymphocytes (Simian AIDS)	Daniel et al., 1984

1.9.2 Oncoviruses

The significance of simian oncoviruses (Tab. 7) to man is still largely unknown. Sequences of simian oncovirus genoms have been demonstrated in human specimen and structural, genetic and serologic relationships between certain simian and human oncoviruses are known to exist.

Oncoviruses are capable of encoding their nucleotid sequences into the host cell genetic information (Fig. 6). Normal cells contain DNA sequences very similar to the viral *src*-gene. All retroviruses contain a sequence, called long term repeat (LTR) at the ends, and LTR causes cancer in birds when inserted near the cellular counterpart of the *myc* (Marx, 1984).

1.9.2.1 Baboon Endogenous Viruses (M7)

M7 is one of several C-type viruses related to feline RD114 which occurs in baboon placenta, fetal and prostatic tissues (Kalter et al., 1973, 1975a,c; Benveniste et al., 1974). M7-provirus was demonstrated in leukemic patients (Wong-Staal et al., 1976).

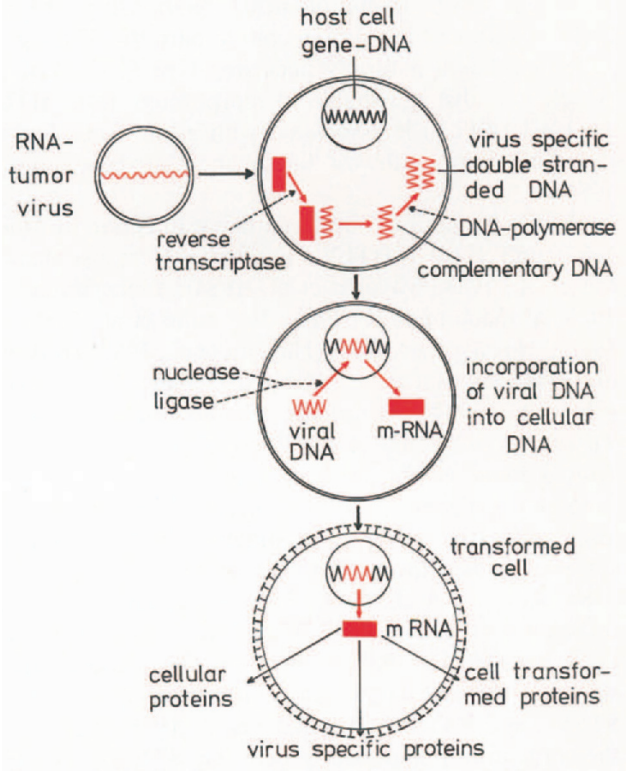

Fig. 6. Cellular sequences and consequences of RNA-tumor virus infections

1.9.2.2 SSV-1

SSV-1 is another C-type virus, which was initially isolated from a fibrosarcoma of a pet *Lagothrix lagotricha* (Theilen et al., 1971; Hunt and Jones, 1973). Its RNA can be hybridized with the RNA of human leukemic cells (Gallo et al., 1973; Sherr and Todaro, 1975), the nucleotide sequences of its transforming region *(v-sis)* show a 91% homology to those of the normal cellular locus *(c-sis)*, which includes one chain of human platelet-derived growth factor (Joseph et al., 1984). Peripheral leukocytes of a patient suffering from myelogenous leukemia produced a C-type virus (HL 23 V), which contained SSV-1 nucleotid sequences (Reitz et al., 1976). More than 50% of normal human sera have been shown to possess antibodies against SSV-1, "Simian Sarcoma Associated Virus" (SSAV) and the closely related "Gibbon Ape Leukemia Virus" (GALV)-group (Aoki et al., 1976; Kurth and Schmitt, 1977; Kurth et al., 1977; Kurth and Mikschy, 1978). A C-type virus derived from the HEL-12 strain of normal human embryonic lung fibroblasts is immunologically related to SSV-1 (and BaEv and RD114) (Prochownik and Kirsten, 1977).

1.9.2.3 STLV-1

The greatest impact on human health problems is possibly resulting from the close structural and immunological relationship between the human HTLV (HIV)-group and the simian counterpart, the STLV-group.

STLV-1 is a naturally occurring type C virus of certain nonhuman primates which is undistinguishable in morphology from HTLV-1 (Miyoshi et al., 1984). HTLV-1 (ATLV) is associated with adult T-cell leukemia of man with endemic distribution in southwest Japan, the Carribeans and Africa (s. Watanabe et al., 1986).

STLV-1 was first found as a latent infection in *Macaca fuscata* (Miyoshi et al., 1982), anti STLV-1/HTLV-1 antibodies were also demonstrated in *M. fuscata* (Ishida et al., 1983; Miyoshi et al., 1984); *Cercopithecus aethiops* (Hunsmann et al., 1983; Yamamoto et al., 1983; Tsujimoto et al., 1985), *C. pygerythrus* (Botha et al., 1985), *Macaca fascicularis* (Hayami et al., 1983; Hunsmann et al., 1983; Homma et al., 1984; Miyoshi et al., 1984), *M. cyclopis, M. mulatta* (Homma et al., 1984; Miyoshi et al., 1984), *M. radiata, M. speciosa, M. nemestrina* (Miyoshi et al., 1984), *Papio ursinus* (Botha et al., 1985), *Pan troglodytes* (Hunsmann et al., 1983) and *Gorilla gorilla gorilla* (Prowten et al., 1985).

STLV-1 strains of different origin all showed the genomic arrangement LTR - *gag* - *pol* - *env* - pX - LTR unique to the HTLV-family and nucleic acid hybridization indicated the high homology of each gene to that of HTLV-1 (Guo et al., 1984; Komuro et al., 1984). Sequence analysis of a *M. nemestrina* STLV-1 isolate revealed a 90% homology of the *env* - *pX* - LTR region with that of HTLV-1 (Watanabe et al., 1985 - cit. from Watanabe et al., 1986), the LTR nucleotid sequence showed an ever closer homology (95%) between the African subtype of STLV-1 and HTLV-1 (Watanabe et al., 1986). Nevertheless there are differences in the structural polypeptides between STLV-I and HTLV-1 (Yamamoto et al., 1984b).

Clinical and Pathological Features

The majority of STLV I-positive monkey sera were derived from apparently healthy donors. In several cases, however, these infections were associated with lymphoproliferative diseases or lymphomas (Homma et al., 1984; Fujimoto et al., 1985; Prowten et al., 1985).

HTLV-1, the human lymphotropic C-type retrovirus has been isolated from adult T-cell leukemia/lymphoma from various parts of the world, particularly in Japan, the Carribean and Africa (s. Hunsmann and Hinuma, 1984). HTLV-1 and its proviral DNA were also isolated from some homosexual AIDS and ELAS-patients (Gallo et al., 1983; Gelmann et al., 1983).

Experimental infections of cynomolgus monkeys with HTLV-1 resulted in the appearance of HTLV-1 specific antigens in peripheral lymphocytes and in the development of specific antibodies, but no animal developed any signs of leukemia (Yamamoto et al., 1984).

1.9.2.4 STLV III

STLV III is an exogenous type C retrovirus of nonhuman primates similar to HTLV III of man in its growth characteristics, T4 tropism, ultrastructural morphology and viral proteins (Kanki et al., 1985b).

STLV III strains were isolated from four macaques (STLV III $_{mac}$), three with immunodeficiency syndromes and one with transmitted lymphoma (Daniel et al., 1985; Kanki et al., 1985c) and from healthy wild caught *C. aethiops* - STLV III $_{Agm}$ (Kanki et al., 1985a). Anti STLV III antibodies were demonstrated in healthy *C. aethiops* (Kanki et al., 1985b). So far, no indications of STLV III infections were found in anthropoid apes, New World monkeys or prosimians (Hayami et al., 1985).

STLV III, like HTLV III, can be isolated preferentially from T4 lymphocytes rather than from T8 lymphocytes (Letvin et al., 1985), STLV III-infected cells revealed virus-specific proteins of 160, 120, 55 and 24 kilodaltons similar in size to the major *gag* and *env* proteins encoded by HTLV III (Kanki et al., 1985c).

Serological evidences and virus isolations suggest natural STLV III-like infections of man in Senegal (Barin et al., 1985; Kanki et al., 1986). The samples reacted strongly with all major viral antigens of STLV III $_{Agm}$, but showed only indistinct reactivity with the major viral antigens of HTLV III in special techniques (Kanki et al., 1986).

HTLV III is the first candidate as causative agent of AIDS in man (Gallo et al., 1983; Marx, 1984; Popovic et al., 1984). Other retroviruses incriminated in the etiology of human AIDS are HTLV-1 (Gallo et al., 1983) and LAV I and II / IDAV (Montagnier - cit. from Walgate, 1986), which are related to, but not identical with HTLV III (Weiss, 1984).

(The etiological agent of simian AIDS = SAIDS, although a retrovirus, is only distantly related to the HTLV-group since it is not a C-type but a D-type virus (Daniel et al., 1984; Marx et al., 1984; Desrosiers et al., 1985; Gardner, 1985)).

Clinical-Pathological Features

Although most STLV III infected animals appeared healthy, some of these infections were associated with definite disease.

One *M. mulatta* died with a lymphoma 26 months after being inoculated with materials from another spontaneous *M. mulatta* lymphoma. Inoculation of other macaques with lymphoma tissues resulted in death 47 to 511 days p.i., all from opportunistic infections such as candidiasis, cytomegalovirosis or cryptosporidiosis.

Two other *M. mulatta* of the same study died from a combination of candidiasis, cryptosporidiosis and a peculiar form of encephalitis characterized by macrophage infiltrates.

The fourth rhesus monkey developed diarrhea, facial rash, generalized lymphadenopathy, and splenomegaly (Daniel et al., 1985).

Experimentally STLV III $_{mac}$ infected rhesus monkeys developed a wasting syndrome, opportunistic infections, encephalitis and a drop in peripheral T 4 lymphocytes (Letvin et al., 1985).

1.9.2.5 Mason Pfizer Monkey Virus (MPMV)

Mason Pfizer monkey virus is the prototype of an exogenous simian tumor D-type oncovirus. MPMV was first isolated from a spontaneous mammary carcinoma of a rhesus monkey (Chopra and Mason, 1970) and subsequently also from normal, lactating mammary tissues or placenta of rhesus monkeys (Ahmed et al., 1973, 1974; Yaniv et al., 1974). Healthy rhesus monkeys from several primate centers harboured anti MPMV-antibodies (Fine et al., 1978).

MPMV-related antigen was found in human breast cancer (Yeh et al., 1975) and in leukemic spleens (Kim, 1977), the RNA's of MPMV and of human breast cancers showed remarkable sequence homologies (Colcher et al., 1974).

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1.10 Hepatitis Viruses

Since the first report by Hillis (1961) of viral hepatitis in veterinarians exposed to newly imported chimpanzees, more than 200 cases of nonhuman primate derived human cases of viral hepatitis have been reported (Riopelle, 1963; Anon, 1964; 1974; Smetana, 1965; 1972; Mosley et al., 1967; Altman and Marzinsky, 1968; McInerney et al., 1968; Friedman et al., 1971a, b; Hinthorn and Price, 1971; McCollum et al., 1971; Dickerson et al., 1973; Pattison et al., 1975; Rill et al., 1975). Of 173 human cases 151 were associated with chimpanzees, 9 with woolly

monkeys, 5 with siamangs, 4 with gorillas, and 4 with celebes crested apes (Anon, 1973). As far as determined all simian primate derived human infections were caused by type A-hepatitis virus (Dickerson et al., 1972; Kovacs et al., 1974) evidence of chimpanzee-associated type B hepatitis in human beings is lacking (Pattison et al., 1975), although chimpanzees and cynomolgus monkeys are susceptible to type B-hepatitis virus under natural conditions as well (Maynard et al., 1971; Kornegay et al., 1985).

Viruses

At least 3 forms of viral hepatitis exist in man: A-, B-, and non A-, non B- (C) hepatitis (Krugman, 1978; Zuckermann and Howard, 1979).

A-hepatitis virus particles are roughly spherical, and nonenveloped. They have a diameter of 24 to 29 nm (Zuckermann and Howard, 1979). As they contain a single stranded RNA, they are classified within the family Picornaviridae, genus enteroviruses. The thermal stability of hepatitis A-virus (HAV) is greater than that of picornaviruses, *in vitro* replication is not blocked by guanidine, nor by other known inhibitors of poliovirus replication. HAV is antigenically distinct from other picornaviruses. The *in vitro* replication of HAV, although it is more difficult than that of other picornaviruses, is possible in marmoset liver explants, normal foetal rhesus monkey kidney cell lines or other primate cell cultures (Provost and Hillemann, 1975; Daemer et al., 1981; Binn et al., 1984). Unlike the typical picornaviruses HAV induces neither shutdown of host cell macromolecular synthesis nor a CPE but tends to induce a persistent infection (Lemon, 1985). The HAV antigen can be visualized in such cells by immunofluorescence which reveals a characteristic granular accumulation of antigen.

The hepatitis B-virus possesses a lipid envelope and the particle-size ranges around 42 nm. It contains DNA within its core similar to the Parvoviridae (Melnick, 1981) and an associated DNA polymerase. Antigenically hepatitis B core antigen (HbcAG) can be distinguished from hepatitis B-surface antigen (HBsAG). Another mark of hepatitis B virus infection is the e-antigen (HBeAG), indicating ongoing hepatic disease and a poor prognosis in man (Mayumi, 1978). As with hepatitis A-virus most attempts to cultivate hepatitis B-virus have been fruitless, only Ishida et al. (1978) achieved growth of hepatitis virus in human embryonic liver cells.

The term non-A, non-B hepatitis has been used for the classification of hepatitis of man that is not caused by the commonly recognized agents, namely hepatitis A or B-virus (Bradley, 1985). Two distinct agents are responsible for posttransfusion non-A, non-B hepatitis, both were also recovered from experimentally infected chimpanzees (Zuckermann and Howard, 1979; Bradley, 1985) with the $CHCl_3$ resistant non A:non B hepatitis virus probably visualized in liver biopsies of an experimentally infected chimpanzee as particles measuring 25 to 30 nm in diameter. The antigen was identified by double immunodiffusion assays (Zuckermann and Howard, 1979).

Epidemiology

Hepatitis viruses are infectious only to man and nonhuman primates, although they can be transmitted by other, especially water living animals.

Hepatitis A-virus is spread by the intestinal-oral route, including contaminated water (Grabow, 1976), shellfish or nonhuman primates. It has also been transmitted spontaneously between nonhuman primates such as chimpanzees (Smetana et al., 1970) or owl monkeys *(Aotus trivirgatus)* (Deluc et al., 1981). 33% of wild living cynomolgus monkeys (Burke and Heisey, 1984) and 25% of the chimpanzee population of the London Zoo and particularly all captive born chimpanzees of that zoo (and a hand reared orang-utan) had anti-HAV antibodies (Kessler et al., 1982). Similarly 36,6% of the chimpanzees, 38,2% of the baboons, 57,9% of the vervet monkeys, 40% of *Cebus albifrons,* and 50% of the common marmosets held at Southwest Foundation for Research and Education, San Antonio harboured anti-HAV antibodies (Eichberg and Kalter, 1980). Spontaneously acquired anti-HAV antibodies have also been demonstrated in *Cynopithecus niger, Ateles geoffroyi, Hylobates lar,* and *Mandrillus sphinx* (Smith et al., 1980).

Hepatitis A virus can experimentally be transmitted to chimpanzees, *S. mystax S. fuscicollis, S. oedipus,* and to lesser bushbabies *(Galago senegalensis moholi)* (Grabow, 1976), but does not cause overt clinical signs in tamarins (Deinhardt et al., 1967; Appleton, 1975 a, b; Lorenz et al., 1970; Hilleman et al., 1977; Karayiannis et al., 1986).

In hepatitis B-virus infections the basic reservoir is the chronic, asymptomatic carrier of HBsAG. The principal infectious body fluid is the blood plasma (Maynard, 1978). Accordingly hepatitis B was initially classified as transfusion hepatitis in the past, as it is transmitted by contaminated blood conserves, syringes, needles etc. However, evidence suggests the occurrence of other possible routes of transmission as well, since HBsAG has been found in a variety of body fluids - amniotic fluid, saliva, menstrual and vaginal discharges, seminal fluid, colostrum and breast milk, urine, bile, faeces, sweat etc. HBsAG has also been detected in captive gorillas (Linnemann et al., 1984), and approximately 50% of the chimpanzees when tested using passive haemagglutination and radio-immuno assays, and recently an outbreak of hepatitis B has been reported at the London Zoo (Zuckermann et al., 1978). Also up to 25% of wild caught chimpanzees had antibodies to hepatitis B-virus when tested several weeks or months after capture; also 10 of 26 chimpanzees in a holding compound in Africa possessed HBsAG (cit. from Kessler et al., 1982). Finally spontaneous hepatitis B was diagnosed in two *M. fascicularis* imported from Indonesia. The animals harboured anti HB_sAg-antibodies, respectively HB_sAg (Kornegay et al., 1985).

Hepatitis B-virus is experimentally transmissible to chimpanzees (Barker et al., 1973; 1975; Drucker et al., 1979; Sly et al., 1979). It is occasionally followed by chronic carrier stages also in the apes (Shoval et al., 1980; Thung et al., 1981).

Non A: Non B hepatitis so far has been diagnosed as a post transfusion hepatitis, the agent is also transmissable to chimpanzees (for references see Zuckermann and Howard, 1979).

Both types A and B hepatitis viruses are usually transmitted by the fecal-oral route or by infected environments from man to apes or monkeys and reverse, although exceptions have occurred in the past. 5 chimpanzee-man transmissions were related to bite or scratch lesions inflicted by the animals (Altman and Marzinsky, 1968). The initial infection of chimpanzees has been blamed upon their inoculation with pooled human blood in their country of origin (Hillis, 1961).

Transmission of hepatitis viruses between nonhuman primates is certainly helped by coprophagia. Infection of human beings from nonhuman primates is favoured by poor hygienic standards such as not wearing protective clothing, kissing the animals, negligence of personal hygiene etc. (Krushak, 1970; Friedmann et al., 1971b).

Clinical Symptoms

Nonhuman primates: Most spontaneous and experimental hepatitis virus infections of nonhuman primates are asymptomatic or nonspecific (Kessler et al., 1982). Clinical signs, if at all present, occur spontaneously particularly in newly arrived animals and often represent transportation stress rather than hepatitis virus infection. The symptoms range from mild respiratory infection to nonspecific gastrointestinal illness (McCollum et al., 1971; Dickerson et al., 1973; Friedmann et al., 1971a). Sometimes anorexia and persistant diarrhea have been reported (Dickerson et al., 1973; Rill et al., 1975). The most significant signs of virus hepatitis in chimpanzees were elevations of the serum liver enzymes and of bilirubin. SGOT values rose from normally 0 to 15 IU to 85 IU, bilirubin from 0.1 to 0.5 mg% to 2.0 mg% (Rill et al., 1975).

At least 2 fulminant spontaneous type A infections have been reported in chimpanzees (Smetana, 1965; Abe and Shikata, 1982). The animals came down with clinical disease a few weeks after arrival, and after 4, resp. 6 days of an illness characterized by fever, anorexia, vomiting, diarrhea and jaundice, they died.

In experimental HAV infections of chimpanzees both SGPT- and SGOT-levels became elevated 3 to 4 weeks after inoculation of the infective material. Whereas the changes of the SGPT-levels were of great significance, those of the SGOT-levels were not very reliable, since minor elevations occurred repeatedly without association to other disease parameters (Dienstag et al., 1975).

In the hepatitis A-virus infections of tamarins and galagos serum alanine-aminotransferase and isocitric dehydrogenase levels became elevated (Grabow, 1976; Purcell and Dienstag, 1978; Karayiannis et al., 1986).

Hepatitis B-virus infections of chimpanzees were evidenced by the demonstration of antigens/antibodies only. Experimentally type B-infected chimpanzees sometimes developed anorexia, lethargy and jaundice 27 weeks after inoculation of HBsAG positive plasma. The jaundice lasted for 10 days (Sly et al., 1979). During the illness the serum alanine aminotransferase-, aspartate aminotransferase-, alkaline phosphatase and bilirubin levels increased. Spontaneous hepatitis B infections of two *M. fascicularis* were associated with anorexia, lethargy and hepatomegaly (Kornegay et al., 1985).

Spontaneous non A:non B hepatitis virus infections so far have not been observed in nonhuman primates. Experimental transmission although inducing typical histological lesions, was not always followed by any clinical or biochemical abnormalities (see Zuckermann and Howard, 1979). Valenza and Muchmore (1985) recognized significant elevations of gamma glutamyl transferase in addition to aspartate aminotransferase and alanine transferase increase in experimentally infected chimpanzees.

Man: The clinical picture of viral hepatitis in man varies from inapparent infection to mild gastro-intestinal symptoms, to acute anicteric hepatitis, to acute

icteric illness and finally chronic liver disease. Extrahepatic lesions in hepatitis B include cases of arthritis, polyarteritis nodosa, glomerulonephritis, polymyalgia rheumatica or infantile papular acrodermatitis.

The incubation period, although occasionally overlapping, is 28–30 days in hepatitis A, and 40–180 days in hepatitis B (Zuckermann and Howard, 1979).

Pathology

Nonhuman primates: In the experimentally infected tamarins acute hepatitis with hepatocytic swelling and mononuclear infiltration developed near peak alanine aminotransferase levels (Karayiannis et al., 1986). The first signs of experimental type A viral hepatitis in chimpanzees occurred 3 weeks p.i. as focal accumulation of lymphocytes and macrophages at the periphery of the liver lobules with replacement of lost hepatocytes. The portal tracts were densely infiltrated by mononuclear cells, predominantly lymphocytes. Subsequently the necroses as well as the hepatocytic alterations developed further, occasionally progressing to the formation of acidophilic bodies. 6 weeks p.i. the portal inflammation was maximal, in places extending into the parenchyma, with an associated erosion of the limiting plate. Areas of focal necrosis occasionally connected inflamed portal tracts. The central lobular zone was always spared, septal or intralobular fibrosis was never observed.

6–8 weeks p.i. the lesions normally receded (Dienstag et al., 1975; 1976). In the chimpanzees which died of spontaneous hepatitis A, the macroscopial appearance of the liver was that of acute yellow atrophy. Histologically, massive hepatocyte necrosis with diffuse haemorrhages and mononuclear infiltration (Abe and Shikata, 1982) or "glandular transformation of liver cell cords" associated with varying inflammatory infiltrates (Smetana, 1965) prevailed. In hepatitis B inoculated chimpanzees, the morphologic lesions were far more variable. 12 weeks after exposure, histiocytes and lymphocytes accumulated focally throughout all parts of the lobule, especially in the centrolobular areas. Simultaneously, small areas of necrosis appeared and the sinusoidal lining cells were distinctively activated. One week later, focal necrosis and sinusoidal cell activation were more pronounced. Hepatocellular changes included sparse acidophilic bodies. The inflammatory infiltrates increased towards the climax between 15 and 22 weeks p.i. (Dienstag et al., 1976). Barker et al. (1973) described striking focal necrosis of single hepatocytes with hydropic changes in biopsies taken 25 weeks p.i.

Similar results were obtained in experimental hepatitis A infections of owl monkeys (Miller Keenan et al., 1984).

In liver biopsies taken from experimentally non A:Non B-infected chimpanzees the following lesions were described after an incubation period of 10 weeks: collections of mainly mononuclear inflammatory cells occurred in the portal tracts. Inflammatory infiltrates and focal intralobular necrosis was present. Kupffer cells were very prominent (Zuckermann and Howard, 1979).

The ultrastructural changes in experimentally non-A, non-B hepatitis infected chimpanzees were marked by peculiar convoluted membranes derived from the hepatocytic smooth endoplasmic reticulum (Bradley, 1985).

Man: The great variety of symptoms makes it difficult to describe the development of morphological lesions in the liver, but two features are constant in acute

viral hepatitis of both type A and B: Necrosis of hepatocytes and histiocytic periportal inflammation. The hepatocytes are swollen and show ballooning or "ground glass" appearance of their cytoplasm. Shrunken cells give rise to acidophilic bodies. The necrosis frequently tends to be zonal, being particularly extensively in the centrolobular areas (Zuckermann and Howard, 1979).

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1.11 Papovaviruses - SV 40

SV 40 produces a natural latent infection in the renal tissues of *M.mulatta, M.fuscata,* and *M.cyclopis,* less commonly of *M.fascicularis* (Sweet and Hilleman, 1960; Ashkenazi and Melnick, 1963; Yang et al., 1967; Shah and Nathanson, 1976). It is tumorogenic in newborn hamsters (Gerber and Kirschstein, 1962; Girardi et al., 1962; Gerber, 1963; Bonin et al., 1964; Unterharnscheidt et al., 1964; Allison et al., 1967) and transforms human cells *in vitro* (Koprowski et al., 1962; Shein and Enders, 1962; Chang and Sinskey, 1968; Steinberg and Defendi, 1979; Sack, 1981). The position of SV 40 as a true zoonotic agent is at best uncertain, since live SV 40 has been isolated from contaminated polio- and adenovirus-vaccines between 1954 and 1963, and consequently had been administered parenterally to a vast number of especially young people during that time (Gerber, 1967; Shah et al., 1972; Shah and Nathanson, 1976).

Virus

SV 40, like other papovaviruses, is small in size (45 nm), its capsid being of icosahedral symmetry. The virions contain doublestranded RNA and do not possess an envelope. They multiply in the nucleus (Kalter, 1972).

SV 40 growth is propagated in primary African green monkey kidney-, LLCMK2-, BSC-1 cells and other systems such as 3T3 cells of mouse origin or in human cells. SV 40 is capable of both lytic and non-lytic infection of the cell cultures depending on the cell system used (Sweet and Hilleman, 1960; Oxman,

1962; Ashkenazi and Melnick, 1962; Rabson and Kirschstein, 1962; Shein and Enders, 1962a, b; Black and Rowe, 1963a, b; Shein et al., 1963; Carp and Gilden, 1966). Monkey cells support productive or lytic infection, whilst mouse cells become transformed without production of virus. Human cells may become transformed and still produce the virus (Sack, 1981).

CPE appears, between days 7 and 29 p.i. in lytic infections of primary vervet monkey kidney cells, as a vacuolation of the cells - a marker which gave the virus its name as a vacuolating agent - followed by granulation, condensation and rounding of the cells (Ashkenazi and Melnick, 1962; Girardi et al., 1962; Meyer et al., 1962).

Some products in SV 40 infected cells appear to be the direct result of the expression of SV 40 genetic information (Oxman, 1967). One is the SV 40-T antigen detectable by FA-staining in the nuclei of SV 40 infected and SV 40 transformed cells. The antigen is never present in uninfected cells or in cells infected with other oncogenic viruses. It is synthesized before viral DNA-replication begins and has the characteristics of an early viral protein (Oxman, 1967).

SV 40 is relatively resistant to formalin, being inactivated in a biphasic curve. 99,9% of the virus is inactivated within the first 50 hrs (Gerber et al., 1961), but the residual SV 40 has been found alive even after 30 days (Hull, 1968).

Epidemiology

SV 40 is primarily a virus of Asian macaques. In the wild nearly all adult rhesus monkeys, but only a small proportion of juveniles possess anti-SV 40 antibodies (Meyer et al., 1962; Shah and Southwick, 1965). In captive situations SV 40 is not only readily transmitted to other macaque species but also to African monkeys, which are normally free of antibodies under natural conditions (Hsiung and Gaylord, 1961; Meyer et al., 1962; Hsiung et al., 1969; Kalter and Heberling, 1971).

SV 40 like other papovaviruses, appears to infect primarily the urinary tract in a latent form, and although the exact manner of transmission is unknown, urinary excretion seems to be most likely (Shah and Nathanson, 1976). Experimentally infected vervets developed viremia between the 2nd and 16th day p.i. The infection was further transmitted to noninfected control animals without induction of any visible changes (Meyer et al., 1962). Virus excretion via urine was maximal between 14 and 16 days p.i. and continued for up to 60 days (Fabiyi et al., 1967). Another way of virus excretion has been found via nasopharyngeal secreta during the viremic phase (Meyer et al., 1962).

Human exposure may result from close contact to infected monkeys. Shah (1966) found 14 of 161 human sera in Uttar Pradesh and 10 out of 37 animal handlers, all without vaccination record, to be seropositive. A much more common way of human infection has been the administration of SV 40 contaminated adeno- or poliovirus-vaccines to a great number of children and young adults particularly in the United States. The vaccines came first into general use in 1954 and were withdrawn in 1961, but could still have been used till 1963, the expiration date of the last lot manufactured in 1961 (Shah and Nathanson, 1976). Infected human beings, like macaques, may shed the virus with nasopharyngeal secreta (Morris et al., 1961).

Clinical Symptoms

Nonhuman primates: SV 40 infections of Cercopithecinae usually are thought to be asymptomatic (Ashkenazi and Melnick, 1962; Meyer et al., 1962). Fabiyi et al. (1968), however, reported increased urinary sediments including erythrocytes in experimentally infected vervet monkeys. Douglas-Sheffield et al. (1980) isolated SV 40 from a spontaneous fatal interstitial pneumonia and renal tubular necrosis in a possibly immune deficient young rhesus monkey. Gribble et al. (1975) found papova-like virions in 7 *M. mulatta* and 1 *M. speciosa* of the California Primate Research Center, suffering from spontaneous progressive leukoencephalopathy. Two of these viruses were tested further and proved to induce SV 40-T antigen and reacted in plaque reduction assays and restriction endonuclease digestion analysis like SV 40 (Holmberg et al., 1976).

Experimental intracranial inoculation of rhesus monkey fetuses induced hydrocephalus, generalized myoclonic seizures and severe incoordination which required anticonvulsants to control at 3 years of age (London et al., 1983).

Man: The major exposure of the population in the United States by SV 40 contaminated vaccines was not followed by any detectable immediate consequences, but Heinonen et al. (1973 - cit. from Shah and Nathanson, 1976) reported a higher incidence of malignancies, especially of neural tumors in children born to mothers who had received poliovirus vaccine during pregnancy.

SV 40 has repeatedly been seen in or isolated from patients suffering from progressive multifocal leukoencephalopathy (Penney et al., 1972 - cit. from Shah and Nathanson, 1976; Weiner et al., 1972; Peters et al., 1980; Hayashi et al., 1985) which is clinically apparent as ataxia, tremor, dysdiadochokinesia, and aproxia. It was also isolated from a malignant melanoma (Soriano et al., 1974). SV 40-T antigen has been demonstrated in meningeoma cells (Weiss et al., 1975 - cit. from Shah and Nathanson, 1976; Tabuchi et al., 1978; Zang and May, 1979).

Pathology

Nonhuman primates: The pathological lesions in the one reported fatal interstitial pneumonia consisted of hypertrophy and hyperplasia of pneumocytes, with interstitial infiltrates of primarily histiocytes. The renal tubular damage in this case involved the collecting tubules of the inner cortex and medulla with hypertrophy of the epithelial cells, some of which contained basophilic cytoplasmic and intranuclear inclusions. Necrotic or degenerating tubular epithelial cells, some with inclusions, were common. Additionally marked lymphoid depletion was observed in thymus, spleen, lymphnodes and bone marrow and was considered to be a sign of immune deficiency (Sheffield et al., 1980).

In the leukoencephalopathic monkey brains foci of demyelination on some with signs of confluence, were adjacent to blood vessels in the white matter of the brain and spinal cord. Increased microglia and large astrocytes were present throughout and adjacent to the foci of demyelination.

Basophilic and eosinophilic intranuclear inclusion bodies were present in the oligodendroglia and astrocytes. Inflammatory responses consisted of perivascular cuffing (lymphocytes, monocytes, and rarely plasma cells) (Gribble et al., 1975).

Man: In biopsy specimens taken from a patient with leukoencephalopathy and SV 40 infection, the leading lesions were demyelination with marked activity of

the macrophages and astrocytes; some of which contained small inclusion bodies. Marked chronic inflammatory reactions were present around blood vessels (Peters et al., 1980).

The malignant melanoma which originated from the skin of the back of a 73 year old patient had extensively metastasized to most internal organs (Soriano et al., 1974). The brain tumors were classified as meningeomas.

Hamsters: The experimental tumors of hamsters depended partially on the infected organs and thus were described as subcutaneous or muscular sarcomas (Bonin et al., 1964; Unterharnscheidt et al., 1964); or after intracerebral inoculation either as ependymomas (Gerber and Kirschstein, 1962) or fibrosarcomas (Girardi et al., 1962).

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