

Update Le point

Articles in the *Update* series give a concise, authoritative, and up-to-date survey of the present position in the selected fields, and, over a period of years, will cover many different aspects of the biomedical sciences and public health. Most of the articles will be written, by invitation, by acknowledged experts on the subject.

Les articles de la rubrique *Le point* fournissent un bilan concis et fiable de la situation actuelle dans le domaine considéré. Des experts couvriront ainsi successivement de nombreux aspects des sciences biomédicales et de la santé publique. La plupart de ces articles auront donc été rédigés sur demande par les spécialistes les plus autorisés.

Bulletin of the World Health Organization, 56 (6): 819-832 (1978)

Viral haemorrhagic fevers of man*

D. I. H. SIMPSON¹

This article reviews the current state of knowledge on the viral haemorrhagic fevers that infect man, namely smallpox, chikungunya fever, dengue fever, Rift Valley fever, yellow fever, Crimean haemorrhagic fever, Kyasanur Forest disease, Omsk haemorrhagic fever, Argentinian haemorrhagic fever (Junin virus), Bolivian haemorrhagic fever (Machupo virus), Lassa fever, haemorrhagic fever with renal syndrome, and Marburg and Ebola virus diseases.

Haemorrhagic fevers of viral origin are by no means a newly recognized phenomenon. Smallpox and yellow fever have been known for centuries and, in the past, were easily the commonest viral diseases with haemorrhagic manifestations, causing untold numbers of cases and many thousands of deaths. Many of the other viruses responsible for haemorrhagic fevers have come to light only in the last 30 years. Although frequently labelled as "new" viruses, it is much more probable that they have existed in nature for years as "silent" enzootic foci into which man has accidentally intruded and become infected. Their routes of transmission vary considerably: by person-to-person contact in the case of smallpox; from the bites of mosquitos in the case of yellow fever or ticks with Kyasanur Forest disease; and by contact with rodents and their excreta as in arenavirus infections. The means of spread of some other infections has not yet been elucidated. Casals et al.^a drew up a classification of the viruses responsible for haemorrhagic fevers on the basis of their route of transmission, and a modification of this is shown in Table 1. Although this classification takes into account the usual routes of transmission, some infections of man have occurred by other means, either through contact with sick animals (e.g., Rift Valley fever) or sick patients (e.g., Lassa fever and Marburg disease). Lassa, Marburg, and Ebola viruses are particularly notable in that, once they have been transmitted to man through contact with their reservoir host, they are capable of adapting to man-to-man transmission. It is therefore theoretically possible for such infections to be carried by infected persons from their country of origin to countries where the natural host does not exist.

* A French version of this article will appear in a future issue of the *Bulletin*.

¹ Senior Lecturer, Department of Medical Microbiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England.

^a CASALS, J. ET AL. *Journal of infectious diseases*, 122: 437-453 (1970).

Table 1. Viral haemorrhagic fevers of man classified by route of transmission

Means of transmission	Disease
Man-to-man	Smallpox
Mosquito-borne	Chikungunya fever Dengue fever Rift Valley fever Yellow fever
Tick-borne	Crimean haemorrhagic fever/Congo/Hazara complex Kyasanur Forest disease Omsk haemorrhagic fever
Zoonotic	Argentinian haemorrhagic fever (Junin virus) Bolivian haemorrhagic fever (Machupo virus) Lassa fever Haemorrhagic fever with renal syndrome
Unknown	Marburg virus Ebola virus

In the absence of virological diagnostic facilities, a firm diagnosis based on clinical observations is extremely difficult to make, particularly when isolated cases occur. In epidemic situations, a clinical diagnosis may be made easier when several patients exhibit similar symptoms. The source of infection may also be recognized, which can often be helpful in arriving at a diagnosis. In their early stages, many virus infections have very similar symptoms, often appearing as nonspecific "influenza-like" illnesses with fever, headache, and generalized joint and muscle pains. In tropical areas, diagnosis is difficult because the signs can be confused not only with those of other virus infections but with protozoal and bacterial infections such as malaria and typhoid fever. In these circumstances, the trial use of antimalarial drugs and antibiotics is often justified. If Lassa, Marburg, or Ebola fever is suspected, the patient should be isolated without delay and barrier nursing instituted immediately. These three viruses have caused severe and frequently fatal outbreaks in hospitals and have been particularly severe among hospital staff, so stringent precautions are fully justified. Virological confirmation of the diagnosis should be sought without delay.

This review will attempt to summarize the principal features of the diseases produced by the viruses listed in Table 1. As smallpox seems to have been completely eradicated, it will be mentioned only briefly.

SMALLPOX (VARIOLA)

Smallpox has been known since ancient times and has caused huge epidemics on a worldwide scale with enormous numbers of deaths. Fortunately, the disease appears to have been totally eliminated from the world as a result of the World Health Organization's highly successful eradication programme.

Following an incubation period of about 12 days, patients with smallpox suddenly develop fever, headache, and pain in the limbs followed by vomiting and rapid prostration. There may be a prodromal rash, especially in the groin, axillae, and flanks. In mild cases

this rash is erythematous but severe cases develop petechial haemorrhages over much of the body. The initial symptoms last 4–6 days. A focal rash appears 3–4 days after the onset of illness, occurring first on the buccal and pharyngeal mucosae, face, forearms, and hands and spreading to the trunk and lower limbs. At first macular in type, the rash becomes papular and later vesicles appear followed by pustulation. In the most severe cases, toxæmia becomes steadily worse and haemorrhages occur in the skin accompanied by bleeding from the mouth, nose, vagina, and bowel; most of these patients die by the end of the first week of illness. Transmission occurs by contact with a patient suffering from the disease and can be acquired by the aerosol route.

Chickenpox (varicella) is frequently confused with smallpox in the early stages of infection.

CHIKUNGUNYA FEVER

Chikungunya virus was first isolated from mosquitos and patients during an epidemic in the Newala district of the United Republic of Tanzania in 1952–53. The name is derived from the local word for the main symptom, a “doubling-up” as a result of excruciating joint pains. Since then, chikungunya virus has frequently been isolated from man and mosquitos during epidemics in India and southeastern Asia as well as in eastern, western, central, and southern Africa. The largest epidemics in recent years have been in cities of the Indian subcontinent. It was estimated in 1965 that there were 300 000 cases in a population of nearly two million in Madras.

Following an infective mosquito bite there is an incubation period of 3–12 days followed by the sudden onset of fever and crippling joint pains, which may incapacitate the patient within a few minutes to a few hours of onset. The pain in the limbs and spine is so severe as to cause patients to double up and become immobile. Headache is usually mild, there is no retro-orbital or eye pain, and patients have anorexia and constipation. The disease has a biphasic course: following 1–6 days of fever, the temperature returns to normal for 1–3 days and then there is a second period of fever for a few days. In the second phase of illness, 80% of patients develop a maculopapular, pruritic rash on the trunk and extensor surfaces of the limbs. After 6–10 days, patients usually recover completely although, rarely, joint pains can persist. Leukopenia is the only unusual finding during examination of the blood.

In India and southeastern Asia, chikungunya virus has been implicated in outbreaks of haemorrhagic fever, often in association with dengue viruses. In 1965, 242 cases were reviewed during the Madras epidemic of chikungunya fever; although most patients had mild infections, 11% had haemorrhagic manifestations, none of which were severe. During an outbreak in Calcutta in 1963–64, chikungunya virus was isolated from 11 patients with haemorrhagic fever; nine had haematemesis and melaena, four had petechiae, and two died of shock. Paired sera from seven of these patients had rising antibody titres against chikungunya virus and two patients also had dengue virus type 2 antibodies. Chikungunya virus has repeatedly been isolated, as well as all four dengue virus serotypes, from patients during haemorrhagic fever outbreaks in Thailand and Singapore, but it has been suggested that if patients with “shock” were the only ones accepted as having true haemorrhagic fever then chikungunya fever would be excluded. No haemorrhagic complications associated with chikungunya virus infections have ever been reported from Africa.

Chikungunya virus is transmitted in Africa by *Aedes africanus* and *A. aegypti*, while *A. aegypti* transmits the disease in the urban centres of India and southeastern Asia. No vertebrate host other than man has been discovered, although there is evidence that monkeys may be a maintenance host in Africa.

DENGUE FEVER

The four dengue virus serotypes are endemic throughout the tropics, particularly in Asia, the Caribbean, and the Pacific. Some of the largest outbreaks in recent years have occurred in the Caribbean, most recently in Puerto Rico and Jamaica and other Caribbean islands. Dengue viruses are also active in West Africa and there have been numerous recent outbreaks in the Pacific islands. An extensive outbreak of dengue fever type 2 recently affected the Seychelles.

“ Classical ” dengue fever

The “ classical ” form of dengue fever usually affects adults and older children. Following an infective mosquito bite, there is an incubation period of 5–8 days followed by the sudden onset of fever, which often becomes biphasic, with severe headache, pain behind the eyes, backache, chilliness, and generalized pains in the muscles and joints. A maculopapular rash generally appears on the trunk between the third and fifth day of illness and spreads later to the face and extremities. Lymphadenopathy, anorexia, constipation, and altered taste sensation are common. Occasionally, petechiae are seen on the dorsal surfaces of the feet and on the legs, hands, axillae, and palate late in the illness. In young children, upper respiratory tract symptoms predominate and dengue fever is rarely suspected. The illness generally lasts for about 10 days, after which recovery is usually complete, although convalescence may be protracted. Laboratory findings reveal leukopenia, a mild thrombocytopenia, and slight lymphocytosis.

Dengue haemorrhagic fever

In the past two decades, the incidence of epidemics of a severe disease syndrome caused by dengue viruses has increased throughout southeastern Asia, India, and the western Pacific. It occurs most frequently in young children aged between 2 and 13 years; it is associated with numerous haemorrhagic manifestations and is quite often fatal. Since its recognition in the Philippines in 1953, dengue haemorrhagic fever has occurred in Burma, Democratic Kampuchea, eastern India, Indonesia, Malaysia, Singapore, Thailand, Viet Nam, and several western Pacific islands. Over 500 cases a year are admitted to hospital in the Philippines. In the Bangkok-Thonburi area in Thailand, 10 000 persons with the disease were hospitalized in the period 1958–63 and all but 25 of these were less than 14 years of age; 694 of these children died—an indication of the severity of the disease. Epidemics continue to occur annually in Thailand, the highest number of cases in a single year being 8288 in 1973 with 310 deaths. Only indigenous populations are involved in these epidemics, with neither ethnic origin nor socioeconomic conditions apparently having any effect on the incidence of the disease. Outbreaks of classical dengue are uncommon during haemorrhagic disease epidemics but immigrants from nonendemic areas often suffer from classical dengue while the haemorrhagic disease occurs in the indigenous population.

The haemorrhagic syndrome is almost entirely confined to indigenous children, often as young as 6 months of age. In the initial phase, the child may have fever, upper respiratory symptoms, headache, vomiting, and abdominal pain. Myalgia and arthralgia are uncommon. This minor illness, during which the child is often not confined to bed, lasts 2-4 days and many children recover without any further symptoms. In a proportion of children, the initial phase is followed by an abrupt collapse with hypotension, peripheral vascular congestion, petechiae, and sometimes a rash. There are different degrees of shock. The child is often restless and sweating and has cold, clammy extremities and a hot, feverish trunk. The fourth and fifth days are critical and purpura, ecchymoses, epistaxis, haematemesis, melaena, coma, convulsions, and severe shock indicate a poor prognosis. Should the patient survive this period, however, recovery is usually complete. Laboratory studies reveal thrombocytopenia, a prolonged bleeding time, an elevated prothrombin time, a raised haematocrit, hyperproteinaemia, and a positive tourniquet test. The liver is often enlarged, soft, and tender.

Several hypotheses have been proposed to explain why dengue viruses, which previously caused relatively mild illnesses, now cause devastating epidemics. The two principal suggestions are that either there is an unusual response to infection in the host or an increase in the virulence of the virus. Haemorrhagic manifestations are thought to be due to double infection with dengue viruses, with a critical interval, which may be of the order of 6 months, between the two infections. The first infection probably sensitizes the patient, while the second appears to produce an immunological catastrophe. In children aged less than 2 years, haemorrhagic fever with shock has resulted from primary dengue infection. It is thought that dengue haemorrhagic fever occurs only in areas where two or more dengue viruses are simultaneously or sequentially endemic, or that it may result from simultaneous infection with two different dengue serotypes. However, cases of fatal haemorrhagic fever on Niue Island in the Pacific have occurred as a result of primary dengue infection, with only one dengue serotype active. It is therefore possible that some dengue strains possess unusual potential to cause severe disease or that some people may be more susceptible to infection. In the Caribbean, *A. aegypti* populations are steadily increasing in parallel with an increase in dengue virus infections and it is interesting to speculate whether dengue haemorrhagic fever will appear there too.

Dengue viruses are transmitted only by certain *Aedes* species, particularly *A. aegypti*, *A. albopictus*, *A. polynesiensis*, and *A. scutellaris*. *A. aegypti* is by far the most important mosquito in urban areas and only through its control can dengue infections be reduced.

RIFT VALLEY FEVER

Until recently, this virus was generally regarded as a cause of severe disease in sheep and cattle in East and South Africa, causing heavy mortality in lambs and calves. Man has quite frequently been infected through handling sick animals or carcasses but the illness thus acquired, although often serious, rarely caused death. First isolated in 1930 in Kenya, the virus has caused several huge epizootics. One of the largest outbreaks was in South Africa in 1951 when some 100 000 sheep and cattle died and it was estimated that 20 000 humans were infected, although no deaths occurred.^a First reports of significant disease in

^a WEISS, K. E. *Bulletin of epizootic diseases of Africa*, 5: 431-458 (1957).

man, with several deaths, accompanied another large epizootic in South Africa in 1974–75. Most of the patients were farm workers and veterinary surgeons who acquired their infections while cutting open carcasses and handling tissues of animals that had died from the disease. More recently, Rift Valley fever virus has caused disastrous epizootics in the Sudan and Egypt. In the Egyptian outbreak in late 1977, it has been estimated that there may have been 20 000 human infections and at least 80–90 deaths. Many of the severely ill patients showed a marked tendency to haemorrhage.

Following an incubation period of 3–7 days, the disease begins abruptly with fever, malaise, chills, headache, pains in the muscles and joints, eye pain, and photophobia. Facial flush and conjunctival congestion are common features. In most cases this illness lasts only a few days and then clears up completely, although convalescence may be prolonged. However, in a small proportion of cases the illness is biphasic, with a recrudescence of symptoms accompanied by nausea and vomiting. In the most severe cases purpura, epistaxis, haematemesis, melaena, and profuse gastrointestinal bleeding have developed, accompanied by extensive necrosis of the parenchymal cells of the liver. Death has resulted in several cases. In South Africa, 30 patients developed central blindness associated with retinitis, and permanent damage resulted in a few cases; one patient developed encephalitis but recovered. Encephalitis and retinal damage have also been reported from Egypt.

Rift Valley fever virus is transmitted in South Africa by *Aedes caballus* and *Culex theileri*. In Egypt the vector appears to have been *Culex fatigans*, while in Uganda the virus has been isolated from *Eretmapodites* and *Mansonia* spp. The natural reservoir is still unknown, although it has been suggested that rodents may be involved in the natural maintenance cycle.

Effective attenuated and inactivated vaccines have been developed in South Africa for veterinary use and an inactivated vaccine grown in monkey kidney cell culture has shown some promise for use in man.

YELLOW FEVER

The first reported outbreak of yellow fever was in Barbados in 1647; since then innumerable appalling epidemics have occurred in the West Indies, Central and South America, and the southern United States of America throughout the seventeenth, eighteenth, and nineteenth centuries, as well as in seaports in more temperate regions of the Western Hemisphere. This virus is believed to have originated in Africa and to have been carried to the Americas by trading and slaving ships, which may also have introduced one of its important vectors, *Aedes aegypti*. Epidemics generally took place in urban conurbations, being transmitted from man to man by *A. aegypti*. The elimination of this vector almost completely eradicated yellow fever from towns but sporadic cases of the disease continued to occur in rural areas, particularly those bordering on forest. It was later discovered that yellow fever virus is maintained in a sylvan cycle involving monkeys and forest-dwelling mosquitos such as *Haemagogus* and *Sabethes* species in South America and *Aedes africanus* in Africa, where *A. simpsoni* provides the link between monkey and man.

Yellow fever is still the most important cause of viral haemorrhagic disease, being active in several South American and African countries. Two devastating epidemics have taken place in Africa in the last two decades. The larger of these was in Ethiopia between

1960 and 1962 when there were enormous numbers of cases and between 15 000 and 30 000 deaths. *A. simpsoni* was the mosquito host involved in the man-mosquito-man cycle. The other large epidemic occurred in Senegal in 1965, with several thousand cases and several hundred deaths; *Aedes aegypti* was the main mosquito vector. Sporadic cases continue to occur in rural areas in West Africa and South America.

The disease in man varies from an inapparent infection in native Africans to a fulminating disease terminating in death. After an incubation period of 3-6 days, the illness begins suddenly with fever, rigors, headache, and backache. The patient is intensely ill and restless with a flushed face, swollen lips, a bright red tongue, and congested conjunctivae; nausea and vomiting develop. A tendency to bleed may be seen early in the course of the disease. This stage of active congestion is followed quickly by one of stasis: the facial oedema and flushing are replaced by a dusky pallor, the gums become swollen and bleed easily, and there is a marked bleeding tendency with black vomit, melaena, and ecchymoses. The pulse rate is slow, despite high fever, and the blood pressure falls leading to albuminuria, oliguria, and anuria. Death, if it occurs, is usually within 6-7 days of onset and rarely occurs after 10 days of illness. The jaundice that gives the disease its name is generally apparent only in convalescing patients. Mortality may be quite low, often of the order of 5%. At postmortem, the organs seen to be particularly affected are the liver, spleen, kidneys, and heart. Typically, necrosis is apparent in the liver, involving cells in the mid-zone of the lobule; the cells around the central vein are normally spared. Hyaline necrosis is evident and typical Councilman bodies have been described.

A safe and very effective live, attenuated vaccine grown in chick embryo cells (17D) has been available for some years and provides longlasting immunity. This vaccine produces few, if any, complications, unlike the French neurotropic vaccine strain, which has produced postvaccination encephalitis in a small number of cases.

CRIMEAN HAEMORRHAGIC FEVER

During the summers of 1944 and 1945 over 200 cases of a serious, acute, febrile illness accompanied by severe haemorrhagic manifestations occurred in the USSR in the steppe region of western Crimea. Many of the cases were among troops of the Soviet Union helping with the harvest. First called acute infectious toxicosis, the disease was later named Crimean haemorrhagic fever. Virus strains were isolated from blood samples of patients with acute disease and from the tick *Hyalomma marginatum marginatum*. It was later realised that a similar disease had been known for many years in other areas of the USSR, particularly the Central Asian republics, and the same syndrome has since been described in areas of the USSR bordering the Black and Caspian Seas and in Bulgaria and Yugoslavia.

The Crimean haemorrhagic fever virus strains were later shown to be antigenically and biologically closely related to Congo fever virus, first isolated in 1956 in what was then the Belgian Congo from the blood of a febrile child. Further investigations have shown the virus to be widespread in East and West Africa. Another virus, Hazara, isolated in Pakistan has also been shown to be related.

In the USSR, the disease is sharply seasonal, with peak incidence in June and July. Agricultural workers, especially those involved in animal husbandry, are most at risk. It is possible that domestic animals act as amplifying hosts during the epizootic season.

Following an infective tick bite, the incubation period is of the order of 7–12 days. The illness begins abruptly with fever, chills, malaise, irritability, headache, and severe pains in the limbs and loins followed by anorexia, nausea, vomiting, and abdominal pain. Fever is continuous but may be remittent and sometimes biphasic, resolving by crisis or lysis after 8 days. The face and neck are flushed and oedematous, the conjunctivae and pharynx are injected, and there is oedema of the soft palate. The mouth is dry and the breath has a foul odour. Patients are depressed and somnolent. In most cases a fine petechial rash begins on the trunk and then covers the entire body. The liver is enlarged in about 50% of cases but the respiratory system is unaffected. A haemorrhagic enanthema appears on the soft palate and uvula early in the illness and other bleeding manifestations, including haematemesis and melaena, appear on about the fourth or fifth day in over 75% of patients. Leukopenia and severe thrombocytopenia are common. Large purpuric areas caused by subcutaneous extravasation of blood occur at times. Bleeding occurs in descending order of frequency from the nose, gums, buccal mucosa, stomach, uterus, intestines, and lungs. Gastric and nasal haemorrhages often lead to death. Involvement of the central nervous system is seen in 10–25% of cases and usually indicates a poor prognosis; it includes neck rigidity, excitation, and coma. The mortality rate is often as high as 30–50%, usually due to shock, secondary blood loss, or intercurrent infection. This severe disease is in sharp contrast to the pattern of disease in Africa, where haemorrhagic phenomena and deaths are only rarely reported. A recent report^a described an unusual outbreak of haemorrhagic fever in Rawalpindi District, Pakistan where the index case, a farmer, was admitted to hospital with haematemesis and melaena. A laparotomy was performed following which four members of the operating team became ill and two of them died. A virus similar to Crimean haemorrhagic fever virus was isolated.

KYASANUR FOREST DISEASE

This disease is caused by a flavivirus which, like Omsk haemorrhagic fever virus, is antigenically related to the tick-borne encephalitis complex but only rarely causes disease involving the central nervous system. The virus was first isolated in Mysore State, India in 1957 and human infections, which still occur, are limited to villages surrounding Kyasanur Forest. The virus is now known to be widely distributed in India but human infections do not occur outside Mysore.

After an infectious tick bite, there is an incubation period of 3–7 days before the sudden onset of fever, frontal headache, severe myalgia, and prostration. This is quickly followed by nausea, vomiting, confusion, and restlessness. The conjunctivae are injected and the palate is suffused and often covered with maculopapular haemorrhagic spots. A generalized lymphadenopathy has been noted and many patients have bronchiolar involvement. The fever generally lasts 5–12 days and sometimes follows a biphasic course; a mild meningo-encephalitis occasionally occurs during the second phase. Epistaxis, haematemesis, haemoptysis, melaena, and bleeding gums are common and sometimes there may be uterine bleeding. Albuminuria, leukopenia, and thrombocytopenia are usual findings. A small

^a *Weekly epidemiological record*, 51: 301-308 (1976).

proportion of patients may die, usually 8–12 days after the onset of illness, developing coma or bronchopneumonia prior to death. The majority of patients, however, make an uneventful and complete recovery.

The virus is transmitted by *Haemaphysalis* ticks, especially *H. spinigera*, and is maintained in small mammals. In Mysore State, the silent enzootic situation was dramatically altered by man's need for more grazing land. Cattle were put to graze around the forest and provided the *Haemaphysalis* tick with a new and plentiful source of blood meals, which produced a population explosion among the ticks. The abundant ticks fed on other mammalian species such as monkeys, and these became infected with Kyasanur Forest disease virus and developed marked viraemia and an illness from which they died. It was noted in 1957 that human infection was preceded by illness and death in forest-dwelling *Langur* and *Macacus* monkeys, which acted as amplifiers of the virus.

OMSK HAEMORRHAGIC FEVER

An epidemic of Omsk haemorrhagic fever occurred in Omsk and Novosibirsk Oblasts in Siberia between 1945 and 1948. The virus was transmitted by the tick *Dermacentor pictus* and by contact with infected muskrats (*Ondatra zibethica*). Most of the more recent cases of disease in man appear to have been acquired through direct contact with muskrats. Most infections originate in the northern forest–steppe–lake belt of western Siberia, which contains much wet grassland and swamp.

Following an incubation period of 3–7 days, the illness begins abruptly with fever (which often follows a biphasic course), headache, vomiting, and diarrhoea. An enanthema of the palate, sometimes haemorrhagic, generalized lymphadenopathy, and meningism are common findings. Epistaxis, haematemesis, melaena, and uterine bleeding may occur, accompanied by a marked leukopenia, thrombocytopenia, and albuminuria. The central nervous system is rarely involved. The case fatality rate is low (0.5–3%). Convalescence may be prolonged but there are no sequelae.

The precise epidemiology of Omsk haemorrhagic fever is still unknown. There exists a biological cycle of unknown complexity, which may involve rodents and ticks. Muskrats, which were introduced into the region some 60 years ago for hunting purposes, are somehow infected and are capable of transmitting the virus by direct contact.

JUNIN, LASSA, AND MACHUPO VIRUSES

All three of these viruses are members of the arenavirus taxon, a name derived from the inclusion-like dense particles seen by electron microscopy that give the virion an appearance of having been sprinkled with sand. The three viruses have rodents as their natural hosts and reservoirs in which they induce a persistent infection: the rodent suffers no ill effects and develops no immune response, although during its lifetime the animal continues to excrete virus, particularly in the urine. The rodents are presumably infected at birth.

Argentinian haemorrhagic fever (Junin virus)

Although Junin virus was first isolated in 1958, the disease has been known since 1943 and has caused annual outbreaks (with between 100 and 3500 cases) of severe haemorrhagic illness in the Buenos Aires, Cordoba, and Santa Fé provinces of Argentina. The mortality rate in individual outbreaks has ranged from 10% to 20%, although the overall mortality is generally 3–15%. The disease is sharply seasonal, coinciding with the maize harvest, when rodent populations reach their peak, and it affects mainly agricultural workers.

The main reservoir hosts are *Calomys laucha* and *C. musculinus*, although other rodent species may also be involved. The mode of transmission of Junin virus to man has not been conclusively established. The virus may be carried in the air from dust contaminated by rodent excreta or may enter via the oral route in foodstuffs similarly contaminated. Infection may also be acquired through skin abrasions. Direct transmission of the virus from man to man rarely, if ever, occurs.

After an incubation period of 7–16 days, the onset of illness is insidious with chills, malaise, headache, myalgia, retro-orbital pain, and nausea followed by fever, conjunctival injection and suffusion, an enanthema, exanthema, and oedema of the face, neck and upper thorax. Petechiae and lymphadenopathy are common. After a few days, the patient's condition becomes appreciably worse with the development of hypotension, oliguria, haemorrhages from the gums and nose, haematemesis, haematuria, and melaena. Oliguria may turn to anuria, and pronounced neurological manifestations may develop. Death may result from anaemic coma or hypovolaemic shock caused by plasma leakage. Most patients recover when the fever falls by lysis and is followed by a pronounced diuresis and rapid improvement. Subclinical infections are rare.

Bolivian haemorrhagic fever (Machupo virus)

Machupo virus causes a very similar infection in rural areas of Bolivia, where sporadic outbreaks occur in the Beni region. The most notable epidemic affected 700 people in San Joaquin township and had an 18% mortality rate. Transmission from man to man is unusual, but a small outbreak took place in 1971 well outside the endemic zone. The index case, infected in Beni, carried the infection to Cochabamba and caused five secondary cases and four deaths by direct transmission.

The rodent reservoir of Machupo virus is *Calomys callosus*; over 50% of this species caught during the San Joaquin epidemic were infected. The illness in man is very similar to that caused by Junin virus and mortality varies from 5% to 30%. Clinically inapparent infection is very rare.

Lassa fever

Lassa fever is perhaps the most publicized of all the viral haemorrhagic fevers with a case fatality of 36–67% among hospitalized patients. Twenty-one medical workers are known to have been infected, ten of whom died. Lassa, once it has been successfully transmitted from its natural reservoir host to man, is capable of adaptation to man-to-man transmission. Thus, it is theoretically possible for such an infection to be introduced from its country of origin to countries where the natural host does not exist and still be capable

of successful transmission. Hence the considerable worldwide public health concern. Lassa virus was first isolated from an American missionary nurse following the sequential infection of two other nurses in Nigeria; the virologist who made the isolation also became infected. A seasonal outbreak of Lassa fever with a high mortality rate of 53% among 23 patients admitted to hospital was reported from Jos, Nigeria in 1970. In March 1972, further cases of Lassa fever occurred among four patients and seven members of staff in a hospital in the Zorzor district of Liberia, and there were four deaths.^a The fourth major outbreak was not hospital-associated and took place between October 1972 and October 1974 in and around Panguma township, Sierra Leone. There were 64 cases, and most of the patients acquired their infection in the community. Several family outbreaks occurred. It was following this outbreak that investigators showed that the multimammate rat, *Mastomys natalensis*, is the possible reservoir host of Lassa virus. Lassa fever has continued to occur in West Africa, but usually as sporadic cases. Quite often medical personnel are those who manifest the disease, presumably being infected through contact with a febrile patient. Lassa virus infections appear to be much commoner than previously supposed and evidence for this has been supplied by Dr J. B. McCormick (personal communication) working in Sierra Leone. In an area endemic for Lassa virus he has found that almost 50% of patients with febrile illness have Lassa infection but very few develop severe clinical disease.

The mode of transmission of Lassa virus from rodent to man or from man to man is not yet known. Similarly, the pathogenesis of Lassa virus infection in its natural host is still not understood. It is, however, reasonable to suppose that Lassa virus, like some other members of the arenavirus group, induces a chronic carrier state in its natural host and a persistent infection develops leading to both horizontal and vertical transmission. Rodents such as *M. natalensis* may excrete the virus in urine and saliva and may thus contaminate food and water. It has been suggested that the low level of sanitation, the storage of grain and food within houses, and the ease with which rodents can infest mud-and-thatch houses increases contact between rodents and man. The means by which the virus is spread from person to person, however, is still not clear. Medical attendants or relatives providing direct personal care are most likely to contract the infection. Accidental inoculation with a sharp instrument or contact with blood has accounted for a few cases. Lassa virus has been isolated from the blood, pharynx, and urine of patients, so that airborne spread of the virus as well as mechanical transmission are likely to occur. Virus has been isolated from patients' urine during convalescence, indicating that the virus can persist after the acute illness has receded.

Lassa fever, like the illnesses caused by Junin and Machupo viruses, usually has a slow, insidious onset, and the nonspecific early symptoms make clinical diagnosis difficult. Later, severe prostration, pyrexia, pharyngitis, and tonsillitis with whitish exudative lesions and small vesicles and ulcerations, conjunctival injection, and occasionally a faint maculopapular rash become evident. In severe cases haemorrhages also occur. Although secondary cases are common, tertiary cases are rare.

HAEMORRHAGIC FEVER WITH RENAL SYNDROME

This disease (HFRS), also known as haemorrhagic nephrosonephritis and Korean haemorrhagic fever, has probably been known since 1913 in the far east of the USSR,

^a MONATH, T. P. *Tropical doctor*, 4: 155-161 (1973).

but the first recognition of the disease syndrome was in the Amur river region separating Manchuria and eastern Siberia. Hundreds of thousands of cases of HFRS continue to occur in the Upper and Middle Volga basins, Bashkiria, and the far east of the USSR, but never in Siberia. Cases have been recorded in Czechoslovakia, Yugoslavia, and Japan and in Korea in 1951, when United Nations troops were particularly affected; there are now between 100 and 800 cases treated in hospital every year in Korea, where the disease has remained endemic.

The incubation period of the disease is thought to be 2 weeks and illness then begins abruptly with fever, chills, prostration, headache, backache, and anorexia. The face is flushed, the conjunctivae and palate are injected, and patients have severe proteinuria. Petechiae appear early and hypotension and oliguria follow. Shock, haemorrhages, and acute renal failure may result, leading to death in about 5% of cases. In patients who recover, diuresis resumes on about the tenth day of illness and is followed by a fairly rapid recovery.

A viral etiology had been suspected for many years but, despite many claims to have isolated virus from patients, no conclusive evidence was forthcoming. The reservoir of infection appeared to be field mice (*Apodemus* spp.) and voles. Recently Lee & Lee,^a working in Korea, demonstrated an antigen in the lungs of a striped field mouse (*Apodemus agrarius*), which gave a fluorescent reaction with convalescent sera from patients who had suffered from the disease. Lee^b reported in 1977 that the etiological agent had been isolated from lung tissues of *A. agrarius* and from human acute phase sera by means of immunofluorescence. The agent was successfully propagated in *A. agrarius* but could not be grown in cell cultures or other laboratory animals. Antibodies to the agent were readily found in convalescent sera. Convalescent sera from patients in the USSR and Scandinavia have given a positive reaction when treated by immunofluorescence against this agent. Virus-like particles in crystalline array have been seen by electron microscopy in *A. agrarius* lung tissue.

MARBURG AND EBOLA VIRUSES

Marburg virus disease is a severe, distinctive, haemorrhagic, febrile illness first described in 1967, when 31 cases of illness with seven deaths in the Federal Republic of Germany and Yugoslavia were traced to direct contact with blood, organs or tissue cell cultures from a batch of African green monkeys (*Cercopithecus aethiops*) that had been trapped in Uganda. Several secondary cases occurred in hospital personnel by contact with patients' blood. One further case occurred following apparent transmission of the virus by sexual intercourse 83 days after the initial illness, and virus was isolated from the semen. The case fatality rate was 29% for the primary cases but there were no deaths among the six secondary cases. The virus isolated from patients during the outbreak was quite distinct from any other known animal virus.

The first recognized outbreak of Marburg disease in Africa, and the first since the original 1967 outbreak, occurred in South Africa in February 1975. The first person to contract the disease was a young Australian man who had hitch-hiked through Southern

^a LEE, H. W. & LEE, P. W. *Korean journal of internal medicine*, 19: 371-383 (1976).

^b LEE, H. W. In: Pattyn, S. R., ed. *Ebola virus haemorrhagic fever*, Amsterdam, Elsevier/North Holland, 1978, pp. 341-343.

Rhodesia. He died in a Johannesburg hospital and shortly afterwards his female travelling companion and a nurse who had cared for him fell ill with the same disease; both women recovered. Virological studies showed that this outbreak was caused by Marburg virus. Again there was evidence of virus persistence in the body, when virus was cultured from fluid aspirated from the anterior chamber of the eye 80 days after the onset of illness.

Between August and November 1976, outbreaks of severe and frequently fatal viral haemorrhagic fever occurred in the equatorial provinces of the Sudan and Zaire, causing widespread international concern. In Nzara, Sudan, there were 70 cases, 33 of which ended fatally, and in Maridi, also in the Sudan, the epidemic caused 229 cases, 117 of which were fatal. Seventy-six of the 230 staff of Maridi hospital were infected and 41 died. In Zaire, the number of cases was 237, including 211 deaths.

The virus strains isolated from patients in both Zaire and the Sudan were found to be morphologically identical to Marburg virus but antigenically distinct. The name Ebola virus was given to the new strain.

The illnesses caused by Marburg and Ebola viruses are virtually indistinguishable. Both infections have an abrupt onset with severe frontal and temporal headache, followed by high fever and generalized pains, particularly in the back. The patients rapidly become prostrated and soon develop severe watery diarrhoea leading to rapid weight loss and dehydration. Diarrhoea, abdominal pain and cramping, nausea, and vomiting often persist for a week.^a In the Sudanese outbreak, knife-like chest and pleuritic pain was an early symptom and many patients complained of a very dry (rather than sore) throat, accompanied by cough. On white skins, a characteristic maculopapular rash appeared between days five and seven; this lasted 3–4 days and was followed by a fine desquamation. On black skins the rash, often described as being "like measles" was not so obvious and was often only recognized later with the appearance of skin desquamation. Conjunctivitis was a regular feature in all the outbreaks. An exanthema of the palate was reported from the Federal Republic of Germany but was not seen in South Africa. In the Sudan, pharyngitis was commonly noted and the throat was found to be dry and accompanied by fissuring and open sores on the tongue and lips. Patients were generally admitted to hospital on the fifth day of illness and their general appearance was described as "ghost-like", with drawn, anxious features, expressionless faces, deep-set eyes, a greyish pallor, and extreme lethargy.

A large number of patients in both the Marburg and Ebola outbreaks developed severe bleeding between days five and seven. The gastrointestinal tract and lungs were most frequently involved with haematemesis, melaena, and sometimes the passage of fresh blood in the stools. There was also bleeding from the nose, gums, and vagina, and subconjunctival haemorrhages were common. Petechiae and bleeding from needle puncture sites were very common. Death generally occurred between days 7 and 16, usually preceded by severe blood loss and shock.

Although monkeys are known to have introduced Marburg virus into the Federal Republic of Germany and Yugoslavia in 1967, primates are not believed to be natural reservoirs of the virus. Studies in the Lake Kyoga region of Uganda, where the vervet monkeys had been collected, revealed no evidence of an epizootic, nor was any illness detected among monkey trappers. Some workers have claimed to have demonstrated

^a SIMPSON, D. I. H. *Marburg and Ebola virus infections: a guide for their diagnosis, management, and control*. Geneva, World Health Organization, 1977 (Offset Publication No. 36).

naturally occurring antibodies to Marburg virus in some African primates, but this has not been generally accepted. Experimental laboratory infection of several primate species produced a uniformly fatal infection and caused an illness similar to that seen in man.

There is, as yet, no indication as to the source of infection in the African outbreaks. Ebola virus, once established in man, is capable of man-to-man transmission but close and prolonged contact, and particularly blood contact, with a sick patient is necessary for successful transmission to occur.
