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Haemorrhagic fever with renal syndrome: Memorandum from a WHO Meeting*

Haemorrhagic fever with renal syndrome (HFRS) is a public health problem throughout most of the European and Asian land mass. Although predominantly associated with rural areas, it is now being recognized as an urban problem in some countries, and also presents a particular hazard to laboratory staff who use rodents for biomedical research. In wild rodents (rats, mice and voles) the infection is asymptomatic. Human infection with the HFRS agent(s) is sporadic, but under special circumstances epidemics occur; the infection may be completely silent, or associated with mild or severe disease. Severe cases are usually seen in the Far East. The epidemiological features of the disease vary from country to country and depend upon a variety of factors, the elucidation of which requires a multidisciplinary approach. The recently discovered Hantaan virus is the etiologic agent of HFRS in Asia. It is now possible to detect Hantaan virus antigen by immunofluorescence using either infected mouse lung or infected human cells as substrate. Prevention measures to date have concentrated on rodent control; the role played by the ectoparasites of rodents, if any, has still to be elucidated. Antigens have been detected in rodents captured in HFRS-endemic areas in China, Finland, Japan, Sweden, and the Soviet Union. None of these have been cultured as yet, but preliminary results with the Puumala agent detected in Finland indicate a relationship with the Hantaan virus. Sera collected from Scandinavian patients react to a high titre with both Puumala and Hantaan agents, whereas sera collected from patients in East Asia have much higher titres against the homologous antigen. Surveillance is very important and further research on the virus is needed, especially to identify the virus in the West and to determine strain differences.

HISTORICAL BACKGROUND

Between 1951 and 1954, more than 3000 United Nations troops stationed in the demilitarized zone in the Korean peninsula developed a rare disease that had not previously been recognized by western physicians. The illness, which was characterized by fever, headache, pain in the back and abdomen, a flushed face and various haemorrhagic manifestations, became known as Korean haemorrhagic fever. The mortality rate was considerable, 5-10% of those affected dying of shock and renal failure. Since that time, the disease has gradually moved southwards so that it is now widespread among both military and civilian populations in rural and urban areas.

Although not described in the Korean peninsula before 1951, it seems probable that the disease is an ancient one and occurs widely. In 1932 a disease with similar clinical features was described in the Amur river valley of Russia and at the same time cases were reported among Japanese troops in Manchuria. The disease was given a variety of names by Japanese and Russian workers and extensively investigated. Infectivity studies in human volunteers showed that the disease could be transmitted by inoculation of the blood or urine of patients who were acutely ill; however, despite intensive efforts, the etiological agent was not detected. In the last two decades, cases with similar clinical, epidemiological, and pathological features have been recognized in a wider area of the Soviet Union ranging from Murmansk Oblast in the north to the Urals in the west and extending into Hungary, Czechoslovakia, Yugoslavia and Bulgaria in the south-west.

A disease resembling HFRS has been known to exist in Heilongjiang province in north-east China since 1934-35 when doctors of the Japanese occupation forces reported cases among troops and the local people. Although there were no further reports until 1955, the disease is now recognized to be widespread and to involve both rural and urban areas. In 1980, over 30 000 cases were reported from 23 provinces or autonomous regions with a case fatality rate of 6.4%.

* This Memorandum originated from a meeting of the Working Group on Haemorrhagic Fever with Renal Syndrome, organized by the WHO Regional Office for the Western Pacific and held in Tokyo, Japan, on 22-24 February 1982. The names of participants are given on page 275. Requests for reprints should be addressed to the WHO Regional Office for the Western Pacific, P.O. Box 2932, 12115 Manila, Philippines; or the WHO Regional Office for Europe, Scherfigsvej 8, DK-2100 Copenhagen Ø, Denmark; or Chief, Virus Diseases, World Health Organization, 1211 Geneva 27, Switzerland. A French translation of this article will appear in a later issue of the *Bulletin*.

In Japan, the disease was first recognized in 1960 when an outbreak occurred in a limited area of Osaka city adjacent to the railway station. The disease, which continued to occur for approximately 10 years with 119 cases, was generally mild and only 2 patients died. Recently the infection has been reported in people living near certain ports and in scattered rural areas. HFRS has also been detected among laboratory staff working in animal rooms that house rodents.

In eastern Europe a major outbreak of HFRS occurred in Yugoslavia (Bosnia-Herzegovina) in 1967, during which 114 patients became ill and 3 died. In Norway, Sweden and Finland, a similar but milder form of HFRS has been recognized since 1934 and is known locally as nephropathia epidemica. In 1942 the disease caused a major outbreak among German and Finnish troops stationed in eastern Finland. Since that time, it has been responsible for more than 1000 cases, mainly in Finland. In Scandinavia, haemorrhagic manifestations are uncommon and the mortality is less than 1%.

Thus HFRS is a major public health problem throughout large parts of the European and Asian land mass. Cases are sporadic, but under special circumstances epidemics occur. Although predominantly associated with rural areas, it is now recognized as an urban problem in some countries and a particular hazard to laboratory staff using rodents for biomedical research.

CLINICAL FEATURES

Infection with the HFRS agent(s) may be completely silent or associated with mild or severe disease. The severe form is common in eastern Asia while the majority of Scandinavian cases are mild. Most of the available information on the severe form of the disease comes from studies carried out on troops stationed in the Korean peninsula during the 1950s.

Severe form

The clinical features are quite characteristic and the disease is usually correctly diagnosed in areas where it is endemic. The features of the mild form, however, are quite non-specific and the disease may be overlooked or misdiagnosed.

The incubation period of HFRS is variable, ranging from 1 to 5 weeks with a mode of 2–3 weeks. The patient usually presents with fever, headache, muscular pains, haemorrhagic features and proteinuria. About 20% of patients develop shock, serious haemorrhagic manifestations and renal failure. The disease has been arbitrarily divided into five phases: febrile, hypotensive, oliguric, diuretic and convalescent.

Febrile phase. The onset is usually abrupt and consists of chills, fever, lethargy and weakness. Severe frontal and retro-orbital headache and abdominal and lumbar pains are frequent features. The pain may be sufficiently severe for the patient to be operated on for a suspected acute abdomen. There is a characteristic facial flush, injection of the conjunctiva and widespread appearance of petechiae. Proteinuria appears after 3–5 days and is accompanied by a decrease in platelet count and a progressive leukocytosis. After about 5 days of illness, hypotension or shock may occur.

Hypotensive phase. Most of the symptoms and signs of the febrile phase remain although the patient's headache frequently subsides. Apprehension and restlessness may appear and later confusion, delirium and coma. About a third of the deaths occur at this stage. Massive proteinuria persists, the haematocrit rises, and the urine specific gravity drops to 1.010. Ecchymoses, haemoptysis, haematuria, haematemesis and melaena may occur at this stage as the platelet count continues to fall.

Oliguric phase. Over the next 3 or 4 days, oliguria becomes a prominent feature of the disease; blood nitrogen retention increases rapidly and various electrolyte abnormalities may develop. Hypervolaemia may occur and cause death as a result of cerebral or pulmonary complications.

Diuretic phase. This phase may last for several weeks and is associated with a rapid improvement in renal function. Some patients fluctuate between shock and hypertension with pulmonary oedema, and a severe electrolyte imbalance may occur. About one third of the deaths occur in this stage, associated with shock and pulmonary complications.

Convalescent phase. During this phase, which may last from 3 weeks to 3 months, recovery is completed. While the mortality of untreated cases may be in excess of 15%, with modern medical treatment (including dialysis) it is usually less than 5%.

Survivors, with the exception of those who have had haemorrhages into the central nervous system, usually make a complete recovery. Long-term sequelae are rare.

Mild form

A similar but mild form of HFRS occurs in Scandinavia; the haemorrhagic features are scanty and the mortality is less than 0.5%. The disease has an acute onset with fever, headache, nausea and vomiting. Occasionally the predominant symptom may suggest hepatitis, carditis or meningoencephalitis. After 3–6

days, backache and abdominal pain become important features and the patient develops proteinuria and oliguria. There is usually microscopic haematuria and moderate thrombocytopenia. The oliguria persists for a few days and is followed by polyuria as the patient's condition improves rapidly. The illness usually lasts for about 3 weeks and sequelae are uncommon.

Since the development of specific tests for HFRS, it has been possible to evaluate retrospectively diagnoses of the disease based on clinical criteria. In endemic areas it has been found that experienced clinicians were able to make a correct diagnosis in more than 95% of severe cases; however, the mild form of the disease caused considerable confusion and was frequently misdiagnosed. Serological surveys show that the infection is frequently subclinical since up to 4% of the population in endemic areas have specific antibody, frequently with no relevant clinical features.

There are still many gaps in our knowledge of the pathogenesis, clinical features, and management of HFRS. Further work is needed to determine the best treatment for severe cases and the value of hyperimmune globulin, antiviral agents, and interferon in the prevention or treatment of the disease. Little is known of the effect of HFRS on pregnancy, although severe cases of fetal death *in utero* and premature labour have been recorded.

There has been little in the way of long-term follow-up of mild cases to determine whether infection with HFRS predisposes to chronic renal disease or other sequelae. An essential prerequisite for much of this work is to find a suitable animal in which infection with the HFRS agent will produce a disease resembling human infection. No suitable animal is available at present, although characteristic renal pathology has been noted in squirrel monkeys infected with a strain of the Hantaan agent.

EPIDEMIOLOGY

HFRS is now recognized to be an asymptomatic infection of wild rodents (rats, mice and voles) in many parts of the Eurasian land mass; however, the finding of infection among urban and laboratory rats suggests that it may already have been transported throughout the world.

The epidemiological features of the disease vary from country to country and region to region and depend upon a variety of factors whose elucidation requires a multidisciplinary approach involving clinicians, epidemiologists, zoologists and laboratory workers.

Three epidemiological types are recognized, each with a separate reservoir host.

(*a*) *Rural type.* The majority of cases still occur in rural areas. In the Korean peninsula, although the disease occurs throughout the year, two seasonal peaks are recognized, a small one in June (late spring) and a longer one between September and October. Cases usually appear singly but clusters have been reported when groups of susceptible people are exposed to a contaminated focus. Person-to-person spread has not been documented. The reservoir host in these rural areas (and in much of China and the USSR) are mice of the *Apodemus* species. Seasonal peaks of the disease coincide with peak numbers and peak infection rates of *Apodemus* mice in the countryside. During these periods which coincide with the planting and harvesting seasons, the mice are reproductively active and come out of their burrows to copulate. Gravid mice deposit large quantities of infected excreta on the ground. Farmers working in the fields during these periods come in contact with the infected excreta, either by the inhalation of aerosols or by direct inoculation through cuts and scratches in the skin. The disease occurs predominantly in the 20–50-year age group and is more common among males, usually farmers or soldiers stationed in rural areas. Although there are nine species of field rodent in the endemic areas, only *Apodemus agrarius coreae* harbours the virus. Infected animals may excrete the virus in saliva, urine and faeces for periods of up to two years.

In the rural areas of China also, the disease has two seasonal peaks which appear to be related to the density of the rodent population, more than 90% of which is made up of *Apodemus agrarius* species. The size of the rodent population appears to be related to the area of rice cultivation. By contrast, in the Soviet Union, HFRS antigen has been detected in the lungs of 10 different species of rodent trapped in different geographical regions. The highest infection rates were observed in *Rattus norvegicus* (25%) and *Clethrionomys glareolus* (12.8%). Significant rates were also detected in a variety of *Apodemus* and *Microtus* species.

In Finland, the incidence of HFRS among the rural population is more than four times greater than in the urban population. The majority of cases occur in rural areas around Lake Finland, north of the 60th parallel.

The disease has a marked peak in the early winter with more than half of the infections occurring between November and January. More than 80% of patients are men, mostly between the age of 15 and 35 years. The natural host of the disease in Scandinavia appears to be the bank vole, *Clethrionomys glareolus*, and the incidence of HFRS correlates well with the prevalence of these rodents.

Because of the similarity between the epidemiology of HFRS in rural areas and certain rickettsial

diseases, a number of workers have suggested that the disease may be transmitted by mites, fleas, ticks or chiggers. Although this possibility has not been completely excluded, there are currently no hard data to support the concept that ectoparasites are important in the spread of HFRS from rodents to man.

(*b*) *Urban type.* In recent years, cases of HFRS have been recorded in urban areas of the Korean peninsula and China among individuals who have never been out of the city. The reservoir in these cases appears to be the household rats (*Rattus norvegicus*), which have presumably become infected by contact with rural rodents.

In Japan, outbreaks of disease have occurred around the railway station in Osaka and the port of Nagoya. The epidemiology of these outbreaks suggest that they may have been due to the importation of infected rodents from abroad.

(*c*) *Laboratory infections* have occurred among medical and other personnel involved in trapping and handling wild rodents and people using laboratory-bred rodents for biomedical research. Since 1975, 195 cases have been reported from 16 institutions in Japan and outbreaks have occurred in laboratories in Moscow, Helsinki and Seoul where certain strains of inbred rodents have been found to be chronically infected with the HFRS agent(s).

Because of the complexity of the ecology of HFRS and the different patterns encountered in different parts of the world, many questions remain unanswered. The reservoirs of infection in nature are incompletely understood and much remains to be learnt about the mode of transmission. Seroepidemiological surveys are essential to defining the natural history of the disease. Data already to hand indicate that infection is extremely widespread and the agent is present in a number of countries in which no clinical cases have been recognized.

DIAGNOSTIC TESTS

Detection of the etiological agent(s) and specific antibodies directed against them

In 1976 Lee & Lee (*1*) demonstrated an antigen in the lungs of certain wild *Apodemus agrarius coreae* captured in Korean rural areas where HFRS was endemic. Lung tissue from these mice reacted specifically in an immunofluorescent test with convalescent sera from patients who had recovered from the disease.

In 1978, Lee et al. (*2*) reported that this antigen reflected the presence of the etiological agent of HFRS and that infected lung tissue could be used as a substrate to detect antibody rises in the sera of patients recovering from the disease. Diagnostic increases in immunofluorescent antibody were detected in 113 out of 116 severe cases and 11 out of 34 milder cases with suspected HFRS.

The agent identified in the lungs of Korean mice has been designated the Hantaan virus after a river of the same name. The Hantaan virus can be isolated in *Apodemus* mice by inoculation of blood and serum collected from man during the early stage of infection. The mice show no signs of illness but specific antigen can be detected in their lungs by indirect immunofluorescence. Antigen appears about 10 days after inoculation and can subsequently be found in the kidney, liver, parotid glands and bladder. While peak virus shedding occurs about 3 weeks after inoculation, virus can be detected in the lungs for 6 months and occasionally for up to 2 years. Histological preparations of infected mouse tissue show no evidence of inflammation.

The Hantaan virus has not been isolated directly in cell culture; however, following multiple passages in *Apodemus agrarius*, it has proved possible to adapt one strain (76–118) to grow in a human cell line. After several passages in A-549 cells (originally derived from a patient with carcinoma of the lung), specific antigen can be detected in the cytoplasm by immunofluorescence. It is now possible to detect antibodies to the Hantaan virus using either infected mouse lung or infected A-549 cells as substrate. Specific fluorescence shows up as discrete pinpoint granules distributed through the cytoplasm of the cells.

Soviet workers have recently reported the development of enzyme-linked immunosorbent assays and a solid phase of radioimmunoassay which may be up to 16 times as sensitive as immunofluorescence for the detection of HFRS antigen. Antibody detected by these techniques appears to rise more slowly and peaks later than antibodies detected by immunofluorescence. These studies are of considerable importance as they are more suited to large-scale screening of sera than immunofluorescence, provide objective endpoints, and can be readily adopted to the detection of class-specific antibody.

Recently Brummer-Korvenkontio et al. (*3*) reported the presence of a similar antigen, the Puumala agent, in the lungs of bank voles, *Clethrionomys glareolus*, which had been trapped in an endemic area of north-east Finland, and developed an immunofluorescent test for detecting antibody in patients with the disease. Despite extensive attempts, it has not yet proved possible to isolate human strains of the Scandinavian agent in voles or in cell culture.

In the past two years, groups in China, Japan, and the Soviet Union have also reported the detection of specific antigens in the lungs of rodents captured in areas in which HFRS is endemic. Attempts to adapt the agent(s) to tissue culture have been complicated by

the frequent occurrence of adventitious agents in the inocula. Subsequently it has been found that the lungs of many captured rodents are infected with reoviruses. These viruses grow readily in all cell cultures producing a cytopathic effect which can be confused with the growth of the HFRS agent(s). These findings indicate the need for careful testing of inocula prior to attempts to isolate the HFRS agent(s) and the need for a standard reference for the detection of unwanted rodent agents.

Properties of the Hantaan agent

The Hantaan agent has not been adequately characterized because it has not proved possible to grow it in high titre. The infectivity of the virus for *Apodemus* mice is stable at pH 7–9 but lost at pH 5. While the virus is relatively stable at 4 °C and −20 °C and can be stored at −60 °C for 5 years at least, it is inactivated rapidly at 37 °C.

Relationship between the Hantaan and Puumala agents

When acute and convalescent sera from Scandinavian and east Asian patients with HFRS were tested against the Hantaan strain isolated in *Apodemus agrarius* and the Puumala strain detected in *Clethrionomys glareolus*, a one-way cross was observed. Sera collected from Scandinavian patients react to a high titre with both antigens, whereas sera collected from patients in east Asia have much higher titres against the homologous (*Apodemus*) antigen.

Danger of working with these agents

The performance of diagnostic tests for the detection of infection with the Hantaan and Puumala agents requires access to infected rodents, fixed tissues from infected animals, or infected cell cultures. Caution is required in handling materials infected with HFRS agents because of the risk of laboratory infections and the possible escape of the agents into the surrounding community.

Specimens from potentially infected humans should be handled with great care, preferably with facilities that provide a high degree of operator protection. Studies with infected animals (during trapping, bleeding, autopsies and inoculation) and involving passage of strains in tissue culture have proved to be very dangerous and require maximum precautions to protect laboratory personnel. Laboratory rodents that are used for biomedical research should be housed in quarters free from contact with wild rodents, and breeding colonies should regularly be tested for absence of infection with HFRS. When a colony is found to be infected, it should be replaced with noninfected animals and the quarters thoroughly disinfected.

When a new breeding stock is introduced into an animal house or imported from overseas, care should be taken to ensure that these animals are free from infection.

PREVENTION AND CONTROL

Preventive measures to date have used two different approaches: attempts to reduce the chances of being bitten by ectoparasites and rodent control. In the Republic of Korea, for some years all soldiers' uniforms were regularly soaked in benzyl benzoate; however, this was shown to have no influence on the frequency of the disease and has been abandoned. Rodent control measures have been practised in China for several years and appear to have a marked effect on the incidence of the disease. This method of control is, however, expensive and difficult to maintain over a long period of time because it is impossible to eradicate the reservoir of the virus from nature. Control of the disease will have to be practised at local and regional level. Basically, control depends upon reducing contacts between man and rodent excreta; however, with the adaptation of strains to cell culture it should prove possible to develop a vaccine that could be given to high-risk groups.

Surveillance

With regard to improving surveillance of the disease, because of limitations in the supply of reagents and the fact that few laboratories in the areas concerned have the facilities to work with the HFRS agents safely, it is not practicable to propose an expanded surveillance programme at present. Laboratories in the Republic of Korea and the USA have undertaken to assist with seroepidemiological studies aimed at defining the prevalence of HFRS in different countries and detecting the presence of the agent in wild rodent and laboratory stocks. Assistance is also needed for the exchange of information between laboratories engaged in studies of HFRS and in the training of staff.

RECOMMENDATIONS

The Working Group made the following recommendations:

1. *Nomenclature*

Infections characterized by fever, haemorrhage and renal involvement, like those recognized in many

parts of the world, should be referred to as "haemorrhagic fever with renal syndrome (HFRS)".

2. *Epidemiology*

Further studies to clarify the natural history of the disease should be undertaken. In particular, further work is needed to determine:

— the importance of various species of rodents as reservoirs of infection in both rural and urban environments and to study the enzootic cycle of infection;
— the relative importance of aerosols, contact with rodent urine, and the role of ectoparasites in the transmission of the disease;
— the extent of infection among laboratory-bred animals;
— the factors influencing the severity of infection in man;
— whether transmission can occur from man to man; and if so, under what circumstances;
— the outcome of infections acquired during pregnancy;
— the duration of viraemia and excretion of virus in rodents and man.

3. *Clinical studies and treatment*

(*a*) Health workers should be alerted to the possible existence of HFRS in countries in which it has not been described and to the clinical features of the disease, especially in its mild form.
(*b*) Further studies to clarify the pathogenesis and pathophysiology of the disease in man should be undertaken.
(*c*) Attempts to improve the treatment of HFRS, particularly in areas of high mortality, should be encouraged. In addition, the role of specific immunoglobulin, antiviral agents, and interferon should be evaluated.

4. *Diagnostic tests*

(*a*) Reference and working reagents should be made available to competent laboratories.
(*b*) Live virus should only be manipulated in laboratories with appropriate levels of containment (special precautions are required for *in vitro* studies, and maximum precautions for animal experimentation).
(*c*) The development of additional diagnostic tests should be encouraged, in particular, systems that can be applied to the detection of antigen and antibody in large numbers of specimens, that can provide objective end-points, and that can be easily standardized.
(*d*) The development of assays for specific IgM with a view to establishing a diagnosis of recent infection by examining a single serum specimen should be encouraged.

5. *Use of rodents for biomedical research*

The Working Group expressed concern at the fact that some colonies of rodents used for biomedical research are infected with the agent of HFRS and recommends that this information should be actively disseminated.
In all facilities providing rodents for biomedical research, the animals should be housed in secure quarters free from contacts with wild rodents; laboratory workers should regularly check their colonies for evidence of infection and avoid introduction of new stocks unless they are known to be free of infection.
If laboratory rodents are found to be infected, new breeding stocks should be obtained and the rooms disinfected.

6. *Virology*

The following should be encouraged:

— attempts to isolate or adapt strains of the etiological agent(s) of HFRS from various parts of the world in cell culture and to develop cell culture systems in which infectivity assays can be performed;
— attempts to detect an animal model of clinical HFRS in man which will permit studies on pathogenesis and the evaluation of control measures, and enable comparison of the virulence of different strains to be performed;
— attempts to characterize biochemically the etiological agent(s) of HFRS and to compare strains by immunological techniques;
— attempts to develop strains in adequate titre which might be used for vaccine production.

7. *Prevention and control*

The following studies should be encouraged:

— determining whether rodent control measures can reduce the incidence of disease in the face of an epidemic;
— evaluating the use of specific immunoglobulin, antiviral agents, and interferon for the prevention and treatment of infection (such studies should initially be carried out on laboratory animals);
— investigating the possibility of developing a vaccine for the control of the disease.

8. *Exchange of information*

The exchange of information and of scientists between laboratories working on HFRS should be encouraged. Further regional or interregional meetings should be held periodically to review progress in the field.

9. *Reference centres*

The present Collaborating Centre for Research on Korean Haemorrhagic Fever in Korea University, Seoul, Republic of Korea, should act as the International Reference Centre for Haemorrhagic Fever with Renal Syndrome. The terms of reference of the Centre will be revised and will include:

— production and distribution of reference reagents;
— standardization of test methods;
— training of personnel and production of training manuals;
— maintenance of a repository of pedigreed virus strains;
— provision of reference services.

The above International Reference Centre should be given full support and links between it and other institutions working on HFRS should be fostered.

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