Chapter 10

VIRAL HEMORRHAGIC FEVERS

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INTRODUCTION

The United States' involvement in Operations Desert Storm and Desert Shield (1990–1991) emphasizes the need for our armed forces to be ready for worldwide deployment at a moment's notice. This requirement often arouses much trepidation in military medical personnel who suddenly find themselves in a hostile environment that demands expertise in areas of medicine that are little known to most practicing physicians. Unlike trauma and surgical support of war wounds, which changes little from region to region, the general medical officer will need to know the infectious and parasitic diseases endemic in the region of conflict. Few of these diseases will be more challenging and potentially more lethal than the hemorrhagic fever viruses.

Hemorrhagic fever viruses are a diverse group of infections in which a hemorrhagic diathesis can result in significant morbidity and mortality. Most hemorrhagic fevers are zoonoses, with transmission to humans occurring through mosquito or tick vectors or through aerosol from infected rodent hosts (Table 10-1). Twelve distinct viral groups are associated with hemorrhagic fevers in humans and are found in both temperate and tropical habitats.[1] These viruses belong to four families: Flaviviridae, Bunyaviridae, Arenaviridae, and Filoviridae.

The viral hemorrhagic fevers within each family generally have similar epidemiological traits; however, the viruses are individually diverse and can be grouped by other shared characteristics. For example, the African viral hemorrhagic fevers occur mostly in southern Africa and consist of Rift Valley fever, Marburg virus disease, and Crimean-Congo hemorrhagic fever.[2] Ebola hemorrhagic fever is not included with the African viral hemorrhagic fevers because it has not been isolated in southern Africa. Significant outbreaks of hemorrhagic disease with person-to-person transmission have been associated with Lassa, Marburg, Ebola, and Crimean-Congo viral disease.[3] This chapter will address the hemorrhagic fevers by viral family.

HEMORRHAGIC FEVERS CAUSED BY FLAVIVIRIDAE

Flaviviruses are transmitted by mosquitoes or ticks. They can infect a multitude of vertebrate hosts and cause primarily encephalitis and hemorrhagic fevers.[4] Hemorrhagic fevers caused by Flaviviridae include dengue hemorrhagic fever, yellow fever, Kyasanur Forest disease, and Omsk hemorrhagic fever.

Dengue Hemorrhagic Fever

Epidemic illnesses that clinically resemble dengue have been reported in tropical and subtropical areas of the world since the 17th century.[5] In 1635, a disease was described in the West Indies that may have been dengue. Numerous outbreaks during the 18th and 19th centuries were described in Java, Egypt, India, Spain, Caribbean Islands, Americas, Indochina, and Southeast Asia.[6] In 1906, Bancroft[7] suggested that transmission to man may be through mosquito vectors. This hypothesis was conclusively shown by Cleland et al[7] in 1916 and 1919 in *Aedes aegypti*. Other vectors include *A albopictus* and *Culex fatigans*.[8] Dengue, endemic to some areas in the Pacific during World War II, was known to be a major threat to nonindigenous troops.[7] In 1944, for example, 24,079 cases were reported among U.S. troops in New Guinea and 20,000 cases were reported among military personnel on Saipan.[5] Transportation of men and supplies throughout the Pacific resulted in outbreaks in Japan, Hawaii, Australia, and many other Pacific islands. During the Vietnam conflict, dengue was reported in Burma, Cambodia, Vietnam, the Philippines, Indonesia, and India.[5]

Synonyms for dengue include dengue fever, break-bone fever, dandy fever, denguero, bouquet fever, giraffe fever, polka fever, 5-day fever, 7-day fever, hemorrhagic dengue (dengue hemorrhagic fever), and dengue shock syndrome (in the Philippines and Thailand).[6] Dengue hemorrhagic fever is actually a more severe form of dengue with hemorrhagic manifestations. The first reported outbreaks of dengue hemorrhagic fever were observed in the Philippines in 1953 and 1956.[1] The disease is strongly associated with urban environments and breeding of *A aegypti* vectors in domestic water containers. Dengue hemorrhagic fever has developed into a major pediatric disease in Southeast Asia and the Western Pacific, with over 600,000 hospital admissions and over 20,000 deaths in these regions over the past 20 years.[1] An outbreak in Cuba in 1981

TABLE 10-1

HEMORRHAGIC FEVER VIRUSES ASSOCIATED WITH HUMAN DISEASE

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*High viral antibody titers; viral isolation yet to be achieved

Adapted with permission from Samlaska CP. Arthropod-borne virus infections and virus hemorrhagic fevers. In: Demis, DJ, ed. *Clinical Dermatology*. New York, NY: JB Lippincott; 1991: Unit 14-22; 6.

resulted in over 340,000 cases and 156 deaths, the first outbreak in the Americas of the disease in its hemorrhagic form. Recent epidemics have occurred in China in 1978, 1980, and 1986, with hemorrhagic disease involving both children and adults.[8] All four serotypes are associated with disease; however, they are not cross-protective. Some authors[9] believe that subsequent infection with a heterologous dengue virus results in a much greater risk of developing life-threatening dengue hemorrhagic fever. Humans are considered to be the main reservoir for the virus.

Signs and Symptoms

Classic dengue begins abruptly after an incubation period of 5 to 6 days. Fever may be of the "saddleback" type, in which remission of all symptoms occurs after 2 to 3 days, followed by a second phase of mild fever and less severe symptoms lasting 1 to 2 days. The single-phase type is more commonly observed in epidemics, with fevers lasting for 3 to 8 days, accompanied by dizziness, headache, back pain, arthralgias, weakness, and eye pain. Flushing of the face and conjunctival injection are common features. An enanthem consisting of tiny glistening vesicles on the soft palate may be seen within 12 hours of onset. Dengue can occur with no obvious exanthem. More often, a morbilliform eruption begins on the third to fifth day on the inner surfaces of the upper arms, the lateral surface of the thorax, and in the lumbar area. The macular or scarlatiniform rash spreads to the face, neck, shoulders, and thorax (Figure 10-1). Pruritus can occur if the hands and feet are involved. In some cases, a petechial eruption is noted on the dorsa of the feet, legs, hands, and wrists. Cervical lymphadenopathy is frequently observed. Bradycardia may occur late in the illness and persist through convalescence. Recovery often requires 1 to 2 weeks and almost invariably is dominated by neurasthenia, mental depression, insomnia, and anorexia.

Hemorrhagic manifestations of dengue are seen predominantly in children. The symptoms are variable and include petechiae, purpura, oozing from venipuncture and injection sites, gingival bleeding, epistaxis, hemoptysis, hematemesis, melena, hematochezia, hematuria, uterine bleeding, and intracranial hemorrhage.[8] Shock can occur after several days of symptoms and is characterized by clinical and laboratory signs of hypovolemia. Hemorrhagic manifestations have been reported with all four serotypes.

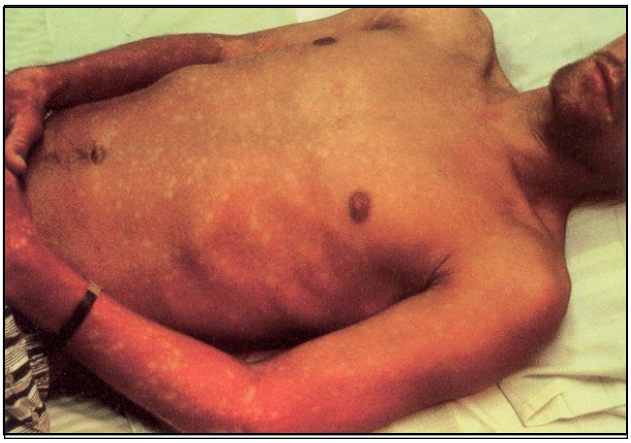

Fig. 10-1. Scarlatiniform eruption of dengue fever. Note the "white islands within a sea of red," a classic description for the cutaneous findings of dengue fever. Photograph: Courtesy of Thomas P. Monath, M.D.; formerly, Walter Reed Army Institute of Research, Washington, D.C.

Laboratory Findings and Treatment

Laboratory features of dengue include leukocytosis, atypical lymphocytes, and thrombocytopenia.[10] Dengue virus inhibits marrow proliferation early in the course of disease but not in later stages. Although laboratory evidence of disseminated intravascular coagulation can be detected in severe cases of dengue hemorrhagic fever, morphologic evidence is usually found only in adolescents and adults.[10] Coagulation defects include prolongations of the partial thromboplastin time, prothrombin time, and thrombin time, as well as decreased factors II, V, VII, VIII, IX, and X. Disseminated intravascular coagulation is not central to the pathogenesis of dengue hemorrhagic fever, because treatment with heparin has not proved successful.

Treatment of dengue hemorrhagic fever is supportive. Live attenuated vaccines are currently being developed. The need for vaccination against all four known serotypes of dengue virus is dependent on the relative risk of developing hemorrhagic disease during subsequent infections with a different serotype.[9]

Yellow Fever

Military medicine has provided significant contributions to science and the understanding of human disease. One of the most significant of these contributions came from U.S. Army Major Walter Reed and his studies on yellow fever in the late 1800s. In 1878, Charles Finlay was the first to suggest that

yellow fever was spread by mosquito bites, particularly *A aegypti*, instead of alkaline earth.[11] Many physicians were skeptical, and due to the lack of well-planned experimental medicine as well as incorrect assumptions, Finlay was unable to prove the association over 20 years of work. Through well-controlled experiments, Walter Reed was able to show that

- the mosquito could pick up the "poison" from an infected victim during the first 2 to 3 days of illness,
- the mosquito had to live for at least 12 days before the disease could be transmitted to man,
- blood taken from an infected person could produce infection in normal subjects if injected into their bloodstream, and
- the offending agent was not bacterial because filtered blood failed to stop infection of injected normal subjects.

Initiation of mosquito control measures in Havana subsequently resulted in a marked reduction in the disease. For his meticulous studies and implementation of informed consent, Walter Reed is known as the founder of modern and ethical clinical experimentation.[11]

Although a safe and effective vaccine against yellow fever has been available for 50 years, the disease continues to occur in Africa and South America.[12] In the Americas, the disease remains confined to the Amazon, Orinoco, Catatumbo, Atrato, and Magdalena river basins.[13] The virus is sustained in *Aedes* mosquito vectors, monkeys, and marmosets. The Pan American Health Organization received reports of 2,255 cases of sylvatic yellow fever between 1965 and 1983. In Africa, yellow fever occurs sporadically in forested areas and in large outbreaks, usually in savanna regions; 2,840 cases of yellow fever were reported in Africa between 1965 and 1983. Several large epidemics have occurred in West Africa, Nigeria (1969, 1970, 1986), Gambia (1978–1979), and Burkina Faso (1983).[12] The true incidence of the disease is grossly underestimated, based on postmortem collections of liver samples in Brazil.[6,13]

Signs and Symptoms

Yellow fever shares many of the clinical manifestations observed in other hemorrhagic fevers; however, in yellow fever, severe hepatic involvement is characteristic. Three clinical phases are found in patients with yellow fever: (1) infection, (2) remission, and (3) intoxication. Infection begins abruptly with fever, headache, generalized malaise and weakness, lumbosacral pain, nausea, and vomiting. During the 3 days of symptoms, the virus can easily be isolated from blood. Bradycardia, called Faget's sign when accompanied by fever, can be a significant physical finding. Remission may last as long as 24 hours, followed by intoxication, which can progress to death 7 to 10 days after presentation. Features of intoxication include jaundice and scleral icterus (Figure 10-2), as well as albuminuria, oliguria, cardiovascular instability, and hemorrhagic manifestations. Neurological features include delirium, stupor, convulsions, and coma. The case-fatality rate for severe yellow fever is 50%.[13]

Laboratory Findings and Treatment

Laboratory findings for yellow fever are diverse and complex, reflecting fulminant hepatitis, dis-

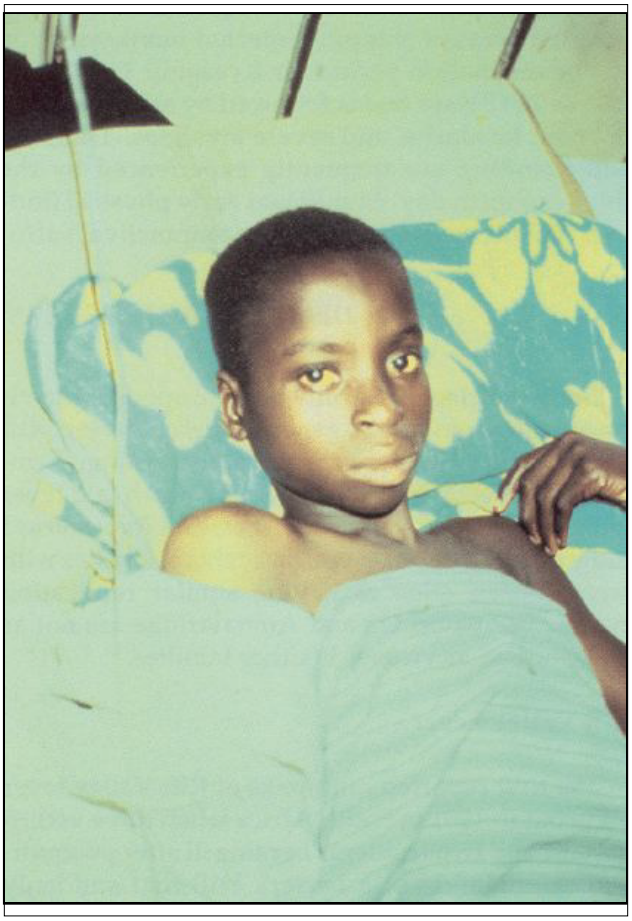

Fig. 10-2. Jaundice and scleral icterus in a patient with yellow fever. Photograph: Courtesy of Thomas P. Monath, M.D.; formerly, Walter Reed Army Institute of Research, Washington, D.C.

seminated intravascular coagulation, and renal failure. Death is usually due to refractory hypoglycemia and metabolic acidosis, although fulminant infections resulting in death within 2 to 3 days of onset have been reported. The diagnosis can be confirmed by use of an immunoglobulin (Ig) M-capture enzyme-linked immunosorbent assay (ELISA) or complement-fixation test.[12] The differential diagnosis of yellow fever includes other forms of hemorrhagic fever, malignant malaria, leptospirosis, and viral hepatitis. Treatment is supportive and may require intensive care.

Kyasanur Forest Disease

Kyasanur Forest disease was first reported in 1957 as a fatal epizootic disease in monkeys in the Shimoga District, Karnataka State, India.[14] Although the virus has been isolated from ticks, major outbreaks of the disease are usually related to exposure to infected regions as a consequence of clearing forested areas or shipping infected monkeys.[15]

The incubation period for Kyasanur Forest disease is 3 to 8 days and is followed by an acute onset of fever, headache, and severe myalgias. Diarrhea and vomiting are frequently experienced by the third or fourth day. Significant early physical findings include severe prostration, conjunctival suffusion, photophobia, cervical and axillary adenopathy, and, rarely, splenomegaly or hepatosplenomegaly. Papulovesicular lesions involving the soft palate are seen in most patients. Bronchiolar involvement can result in blood-tinged sputum and evidence of pneumonia. Although hemorrhagic manifestations were commonly observed in initial patients, hemorrhagic involvement in more recent cases is rarely observed. This difference has been attributed to a large number of individuals with secondary diseases, such as tuberculosis and heavy helminthic infections,[15] in earlier series. In addition, although neurological manifestations were initially thought to be rare, more recently documented infections show clear evidence of neurological involvement. The mortality rate is 5% to 10%. An ELISA has been developed for Kyasanur Forest disease virus.[16] Treatment is supportive.

Omsk Hemorrhagic Fever

Omsk hemorrhagic fever was first reported to infect muskrat trappers and skinners in the Asian portions of the Soviet Union during the 1940s and 1950s.[1] Aerosol transmission and ticks have been implicated in its spread. The virus has virtually disappeared and little is known about its current reservoir status.

HEMORRHAGIC FEVERS CAUSED BY BUNYAVIRIDAE

Bunyaviridae is a family of arthropod-borne viruses composed of five genera: *Phlebovirus* (eg, Rift Valley fever), *Nairovirus* (eg, Crimean-Congo hemorrhagic fever), *Hantavirus* (eg, hemorrhagic fever with renal syndrome), *Uukuvirus*, and *Bunyavirus*.[4] Bunyaviruses share several basic characteristics with arenaviruses, such as having similar replication cycles. Bunyaviridae and Arenaviridae are not as well studied as viruses in other families.[17]

Rift Valley Fever

The first reported outbreaks of Rift Valley fever occurred in 1951 in South Africa when three veterinarians and two residents became ill after postmortem examination of a berserk bull that suddenly died. The virus has subsequently been isolated from cattle, sheep, and antelope. Epidemics are associated with these animal reservoirs and mosquito vectors, most commonly *Aedes caballus* and *Culex theileri*. Rift Valley fever virus can be maintained by mosquitoes alone through transovarial transmission.[1] Numerous cases have been associated with handling carcasses, meat, and internal organs of infected animals.[1,18] Recent epidemics include the 1987 outbreak in Mauritania and the 1977 outbreak in Egypt.[18] Currently, three antigenic strains of Rift Valley fever virus have been identified.

Signs and Symptoms

The initial clinical manifestation of Rift Valley fever is a biphasic fever, the first bout lasting 4 days. After 1 or 2 days of normal temperatures, the second fever spike occurs, lasting 2 to 4 days. The most common complication of Rift Valley fever (10% of patients) is retinitis characterized by macular cotton-wool exudates, which can permanently impair vision if bilateral involvement is present. Hemorrhagic features occur toward the end of the first week of illness, manifested by epistaxis, hematemesis, and/or melena. Massive gastrointestinal hemorrhage due to acute hepatic necrosis is often

fatal. Additional clinical features include jaundice, encephalitis, and disseminated intravascular coagulation. Rift Valley fever virus has been associated with spontaneous abortions in ewes and may be associated with human abortions and congenital malformations.[19]

Laboratory Findings and Treatment

The laboratory features of Rift Valley fever are similar to those found in other hemorrhagic fevers and depend on the severity of disease. Although an IgM-capture ELISA is available for Rift Valley fever virus, the assay has a low sensitivity, reported at 26%.[20] Inoculation of sera into *Aedes pseudoscutellaris* cells is the most sensitive method of confirming the disease. Inoculation intracerebrally into suckling mice and detection of type IgM gamma globulins can also be used.

Interferon[21] and ribavirin (2 g intravenous [IV] loading dose, followed by 1 g every 6 h for 4 d, then 0.5 g every 8 h for an additional 6 d)[22] have been shown in animal models to be effective therapeutic agents. A live attenuated vaccine is available; however, it should be used with caution in women of childbearing age due to the reported association with microcephaly and hydrops amnii.[19]

Crimean-Congo Hemorrhagic Fever

The first reported cases of Crimean-Congo hemorrhagic fever occurred in 1944 on the Crimean peninsula.[3] It has become a prominent pathogen in Europe, Asia, and Africa.[23] The tick vectors are species of *Hyalomma*. Natural reservoirs are currently unknown.

Signs and Symptoms

The incubation period of Crimean-Congo hemorrhagic fever is 2 to 7 days.[2] Clinical features include an abrupt onset with violent headaches, lumbosacral muscle spasms, dizziness, sore eyes, photophobia, fever, rigors, chills, leg pains, nausea, vomiting, sore throat, abdominal pain, and diarrhea. Patients often have injected and flushed conjunctiva or chemosis. Half the patients will have hepatomegaly. A petechial eruption is common.[3] In severe cases, a hemorrhagic diathesis develops by the third to fifth day, manifested by petechiae, purpura (Figure 10-3), epistaxis, hemoptysis, hematemesis, melena, and hematuria. The disease can progress to hepatorenal failure, resulting in jaundice, mental obtundation, stupor and eventual coma, and death. The mortality rate is reported to range from 15% to 70%.[3]

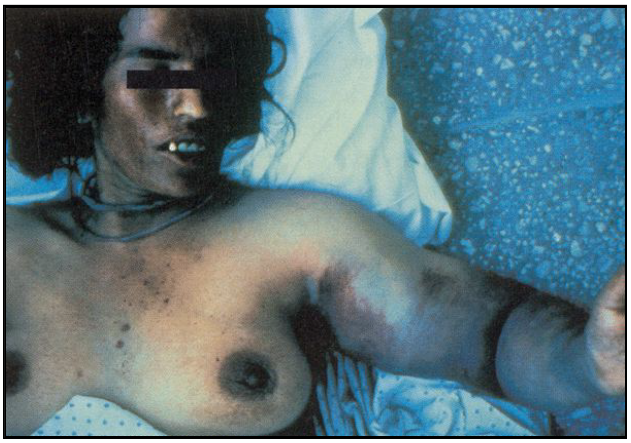

Fig. 10-3. Crimean-Congo hemorrhagic fever with purpura involving the axillae and arms. Photograph: Courtesy of David I. H. Simpson, Department of Microbiology and Immunobiology, The Queen's University of Belfast.

Laboratory Findings and Treatment

Laboratory data reflect the degree of hepatorenal dysfunction and coagulopathy caused by the disease. Leukopenia, thrombocytopenia, and raised serum transaminases are usually present. Disseminated intravascular coagulation is an early and prominent feature of Crimean-Congo hemorrhagic fever. The diagnosis can be confirmed by injecting serum intracerebrally into day-old mice for virus isolation, ELISA (the most sensitive), indirect immunofluorescence tests, and complement-fixation tests.

Treatment is usually supportive. Ribavirin (2 g IV loading dose, followed by 1 g every 6 h for 4 d, then 0.5 g every 8 h for an additional 6 d) may have clinical utility.[22]

Hemorrhagic Fever with Renal Syndrome

Synonyms for hemorrhagic fever with renal syndrome include Korean hemorrhagic fever, Far Eastern hemorrhagic fever, epidemic hemorrhagic fever, hemorrhagic nephrosonephritis, Songo fever, epidemic nephritis, and neuropathia epidemica. Korean hemorrhagic fever was first appreciated in 1951 during the Korean conflict, when United Nations troops were afflicted with a hemorrhagic disorder previously unknown to Western medicine.[24,25] By 1954, more than 3,200 cases were confirmed,

with 480 deaths. The disease may have existed in Asia for at least 1,000 years, documented in a Chinese medical book written about AD 960. The pathophysiology of the disease was little known until 1976, when culturing of the prototype Hantaan virus resulted in the development of an immunofluorescent antibody assay for serologic diagnosis.[24] The subsequent 14 years have resulted in an explosion of medical knowledge on Hantaan virus diseases and their epidemiology. We now know that the Hantaan virus has a worldwide distribution and is frequently found in healthy wild rodents.[6]

Three serotypes of Hantaan virus are associated with hemorrhagic fever with renal syndrome and can cause disease ranging from mild to severe. Transmission to man occurs through the aerosol form of urine, feces, and saliva from infected rodents.

- Hantaan virus serotype is associated with the most severe forms of hemorrhagic fever with renal syndrome and occurs in Korea, China, and southeastern Siberia.[26] The rodent host is the field mouse *Apodemus agrarius*. In the Far East, two peaks of human disease occur in the spring and summer.
- The Seoul serotype is associated with a less severe form of hemorrhagic fever with renal syndrome and causes urban outbreaks due to infestation of rats: *Rattus rattus* and *R norvegicus*. Rat infestation has been documented worldwide, including in the United States.
- Puumala virus infections result in the mildest form of the disease, called nephropathia epidemica.[27] It is most frequently documented in Europe and the western part of the former USSR. The natural host is the bank vole, *Clethrionomys glareolus*. The peak incidence of disease is in the mid-to-late summer.

Additional serotypes are being identified. Prospect Hill virus was isolated from a meadow vole on Prospect Hill in Frederick, Maryland. Another serotype called Leakey virus has been isolated from domestic mice in West Virginia. Neither virus (Prospect Hill or Leakey) has yet been proven to be associated with human disease. It should be noted that a number of human infections have occurred in Korea and Japan among personnel working in medical center animal rooms.[24] The potential for transmission of the disease by importing infected animals to research centers further underscores the worldwide nature of this disease.

Signs and Symptoms

In the severe forms of hemorrhagic fever with renal syndrome, five distinct clinical phases exist: (1) febrile, (2) hypotensive, (3) oliguric, (4) diuretic, and (5) convalescent. The incubation period is 2 to 3 weeks but can range from 4 to 42 days.[28] The febrile phase begins abruptly and lasts 3 to 7 days. Additional clinical features include chills, malaise, weakness, myalgias, anorexia, dizziness, headache, and eyeball pain. A characteristic facial flushing extending to the neck and chest is frequently observed. Conjunctival hemorrhage (Figure 10-4) and fine petechiae distributed over the axillary folds, face, neck, soft palate (Figure 10-5), and anterior

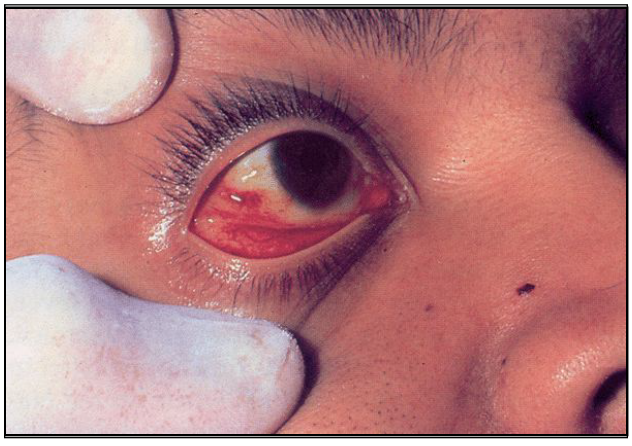

Fig. 10-4. Conjunctival hemorrhage in a patient with hemorrhagic fever with renal syndrome.

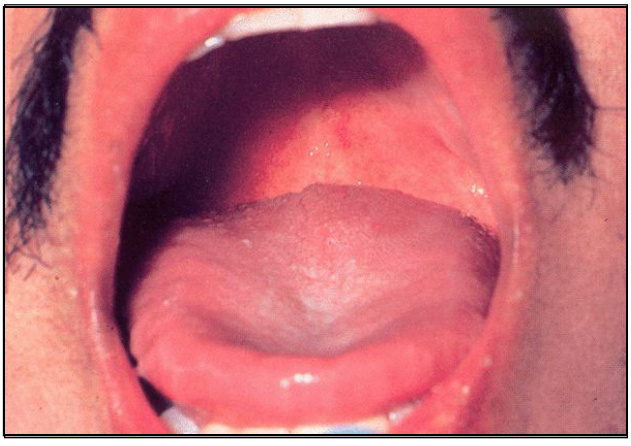

Fig. 10-5. Petechiae involving the palate in a patient with hemorrhagic fever with renal syndrome.

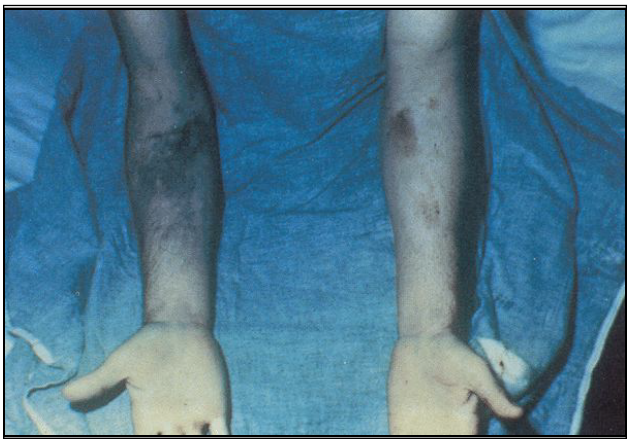

Fig. 10-6. Purpura in a patient with hemorrhagic fever with renal syndrome.

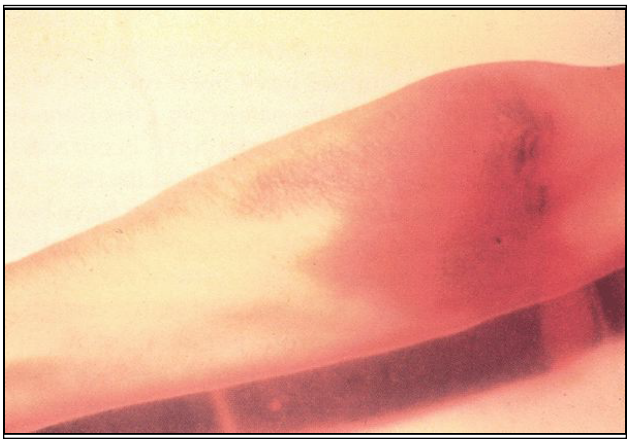

Fig. 10-7. Purpura involving the elbow in a patient with hemorrhagic fever with renal syndrome.

chest wall are frequently observed toward the end of this phase, as is purpura (Figures 10-6 and 10-7).

The hypotensive phase begins abruptly and can last for several hours to 2 days. Clinical manifestations include depressed sensorium, confusion, tachycardia, narrowed pulse pressure, hypotension, and cardiac arrest.[24] In severe disease, shock results in death in one third of the cases. In moderate disease, recovery usually occurs within 1 to 3 days.

The oliguric phase lasts from 3 to 7 days, and up to 60% of patients develop hypervolemia and hypertension. Symptoms and clinical features at this time include nausea, vomiting, epistaxis, conjunctival hemorrhage, cerebral hemorrhage, gastrointestinal hemorrhage, central nervous system symptoms (severe cases), and pulmonary edema (severe cases). Approximately 50% of the fatalities occur during the oliguric phase of the disease.

The onset of the diuretic phase is a good prognostic sign; however, recovery can be delayed because of marked dehydration, electrolyte imbalance, or secondary infections. The diuretic phase lasts for days to weeks.

Frequently, 2 to 3 months are required for the convalescent phase. This period is noted for a progressive increase in glomerular filtration rate resulting in up to 70% return of renal function within 6 months after the onset of disease. Vertical transmission from mother to child resulting in spontaneous abortion has been reported.[28]

Laboratory Findings and Treatment

Laboratory abnormalities reflect the degree of renal dysfunction at each stage of the disease; thrombocytopenia, anemia, azotemia, proteinuria, hematuria, hyperkalemia, and rising creatinine are typically observed toward the end of the hypotensive phase and through most of the oliguric phase. Many types of tests are available for serologic confirmation. The most sensitive and easy to perform is the ELISA; however, it can not distinguish between the Hantaan and Seoul variants.[28] Plaque-reduction neutralization tests are more specific for the serotypes. The differential diagnosis includes other forms of hemorrhagic disease, leptospirosis, scrub typhus, viral hepatitis, hemorrhagic glomerulonephritis, influenza, and many other disorders that can cause thrombocytopenia and acute renal failure.[28] Treatment is supportive, although ribavirin (2 g IV loading dose, then 1 g every 6 h for 4 d, followed by 0.5 g every 8 h for 6 d) may have clinical utility.[22]

HEMORRHAGIC FEVERS CAUSED BY ARENAVIRIDAE

The Arenaviridae family includes several viruses that cause often fatal hemorrhagic fevers (eg, Lassa, Argentine, and Bolivian hemorrhagic fevers).[4] Arenaviruses frequently use rodents as a reservoir.[29]

Lassa Fever

Due to the extremely contagious nature of the virus, Lassa fever has a propensity for infecting medical personnel. The first reported cases occurred in

northern Nigeria in 1969, when two of three nurses afflicted with the disease died.[3] Since then, numerous laboratory personnel have been infected with the Lassa virus. Naturally occurring infections resulting in nosocomial outbreaks have occurred in Nigeria, Sierra Leone, Guinea, and Liberia.[30] At least 10 instances of imported Lassa fever have been reported; however, none of these episodes has resulted in human disease.[3] The natural reservoir is the rodent *Mastomys natalensis*, and transmission to man is by aerosol.[22] Person-to-person transmission is important in nosocomial infections. In areas where the virus is endemic, Lassa fever occurs in higher frequency during the dry season.

Signs and Symptoms

The clinical spectrum of disease in Lassa fever is variable, with 9% to 26% of infections resulting in illness. The incubation period is between 1 and 3 weeks. Onset is frequently insidious, with fever, sore throat, weakness, and malaise followed by low back pain, headache, and a nonproductive cough. Additional variable features include retrosternal or epigastric pain, vomiting, diarrhea, and abdominal discomfort. Physical findings include fever, exudative pharyngitis, conjunctival injection, and, rarely, jaundice, petechiae, and cutaneous eruptions. Pulmonary manifestations can be significant, resulting in rales, pleural and pericardial friction rubs, and adult respiratory distress syndrome.[3] In the most severe form of the disease, patients can exhibit facial and neck edema, conjunctival hemorrhages, mucosal bleeding, melena, hematochezia, hematuria, vaginal bleeding, hematemesis, central cyanosis, encephalopathy, shock, and death. Women infected during pregnancy have the highest mortality rate, 16%.[30] A high incidence of fetal wastage also exists, particularly if the infection occurs during the third trimester.[3] Recovery usually begins a week after onset and about 20% of individuals will develop sensorineural deafness. The overall case-fatality rate is 1% to 2%.[3]

Laboratory Findings and Treatment

Laboratory abnormalities in Lassa fever are often nonspecific and include proteinuria, transient thrombocytopenia, and elevated transaminases, with aspartate aminotransferase values exceeding those of alanine aminotransferase. Although an IgM-capture ELISA is available for the detection of the disease, the indirect fluorescent antibody technique is the diagnostic test of choice. The differential diagnosis includes other forms of hemorrhagic fever, typhoid fever, gastroenteritis, pneumonia, pyelonephritis, postpartum sepsis, septic abortion, encephalitis, meningitis, and hepatitis. Treatment is supportive, although ribavirin (2 g IV loading dose, then 1 g every 6 h for 4 d, followed by 0.5 g every 8 h for 6 d) has been shown to be effective treatment in animal studies if administered before the seventh day of illness.[22]

Argentine Hemorrhagic Fever

Argentine hemorrhagic fever is caused by the Junin virus, a single-stranded RNA virus.[31] The disease is endemic in agricultural and cattle-raising areas of Argentina, with the first reported outbreaks occurring in 1955 in Bragado city. Annual epidemics occur between January and August.[1] The primary reservoir hosts are the rodents *Calomys laucha* and *C musculinus*. Transmission to man occurs through aerosols from urine or feces. Junin virus can also infect through contact with abraded skin.[31]

Signs and Symptoms

The clinical manifestations of Argentine hemorrhagic fever range from subclinical to severe. After an 8- to 12-day incubation, an abrupt onset of fevers, asthenia, dizziness, retroocular and muscular

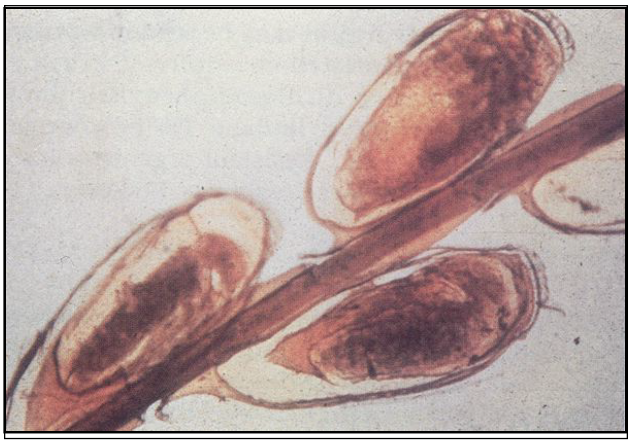

Fig. 10-8. Maculopapular eruption in a patient with Argentine hemorrhagic fever. Photograph: Courtesy of David I. H. Simpson, Department of Microbiology and Immunobiology, The Queen's University of Belfast.

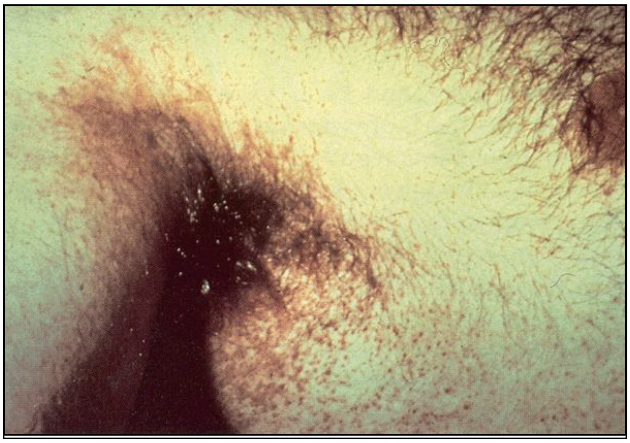

Fig. 10-9. Petechiae in a patient with Argentine hemorrhagic fever. Photograph: Courtesy of David I. H. Simpson, Department of Microbiology and Immunobiology, The Queen's University of Belfast.

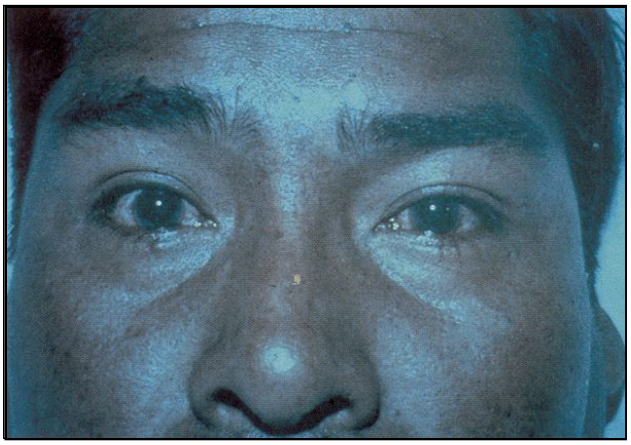

Fig. 10-10. Conjunctival hemorrhage in a patient with Argentine hemorrhagic fever. Photograph: Courtesy of David I. H. Simpson, Department of Microbiology and Immunobiology, The Queen's University of Belfast.

pain, lymphadenopathy, maculopapular eruptions, and cutaneous as well as pharyngeal petechiae takes place (Figures 10-8 and 10-9). Hemorrhagic manifestations are variable, resulting in conjunctival hemorrhage (Figure 10-10), hemorrhagic gingivitis, epistaxis, hematuria, metrorrhagia, and gastrointestinal bleeding.[32] In severe cases, bradycardia, hypotension, and shock can be observed. Neurological manifestations frequently occur, resulting in tremor (including of the tongue), areflexia, hyporeflexia, muscular hypotonia, ataxia, extrapyramidal signs, mental depression, and coma.[32] The acute phase of the illness lasts for 10 days. Approximately 10% to 16% of those infected die from their disease, usually as a result of severe central nervous system involvement.[31]

Laboratory Findings and Treatment

Laboratory abnormalities of Argentine hemorrhagic fever include leukopenia, thrombocytopenia, and bone marrow suppression early in the disease. Blood coagulation studies are variable; however, no evidence of disseminated intravascular coagulation has been found.[32] Renal involvement results in albuminuria, hyalin and granular casts, and Milani cells. Recent studies have demonstrated that the ELISA is more specific than indirect immunofluorescence tests.[33]

Treatment is supportive, although infusion of antibody-rich convalescent plasma is reported to decrease the mortality rate to 1% to 2%.[31] Animal studies suggest that ribavirin (2 g IV loading dose, then 1 g every 6 h for 4 d, followed by 0.5 g every 8 h for 6 d) may be useful in treating Argentine hemorrhagic fever.[34]

Bolivian Hemorrhagic Fever

In 1959, cases resembling Argentine hemorrhagic fever were reported in Bolivia. The causative agent was determined to be the Machupo virus, and the natural reservoir the rodent host *Calomys callosus*.[1] Machupo virus is transmitted to man by aerosolized rodent excreta, although person-to-person transmission has been reported. The virus is restricted to Bolivia, and rodent-control measures have greatly reduced the incidence of human disease.

The illness, known as Bolivian hemorrhagic fever, begins with 1 or 2 days of prodromal symptoms that consist of malaise, fatigue, headaches, and myalgias.[35] The febrile phase lasts 7 to 10 days and is characterized by severe headaches, excruciating back pain, and diffuse joint and muscle aches. A cutaneous hyperesthesia similar to a sunburn can be observed. Additional clinical features include upper-body flushing, conjunctivitis, cardiovascular lability, periorbital edema, gastrointestinal bleeding, encephalopathy, and proteinuria. Platelet counts are frequently depressed. Treatment is usually supportive. Clinically, little has been written about Bolivian hemorrhagic fever since the early 1970s.

HEMORRHAGIC FEVERS CAUSED BY FILOVIRIDAE

The morphologic structure of filoviruses is unique; they are the only mammalian viruses that are filamentous.[36] Ebola and Marburg viruses are the only members of this family and are among the most lethal of human viruses.[4]

Ebola Hemorrhagic Fever

Ebola virus is a single-stranded RNA virus named after a small river in northwestern Zaire. Ebola hemorrhagic fever, also known as Yambuku hemorrhagic fever, was first identified in 1976 when two epidemics occurred in southern Sudan and northwestern Zaire.[3,37] In 284 cases in the Sudan epidemic, the mortality rate was 53%. In the hospital-based Zaire epidemic, 88% of 318 infected patients died (Figure 10-11). Sporadic cases have been described in Sudan and Zaire, and Ebola virus may also be endemic in other parts of eastern and central Africa. The mode of transmission and natural reservoir hosts are unknown, although epidemiological studies suggest that spread of the disease occurred through casual contact or aerosol transmission.[3]

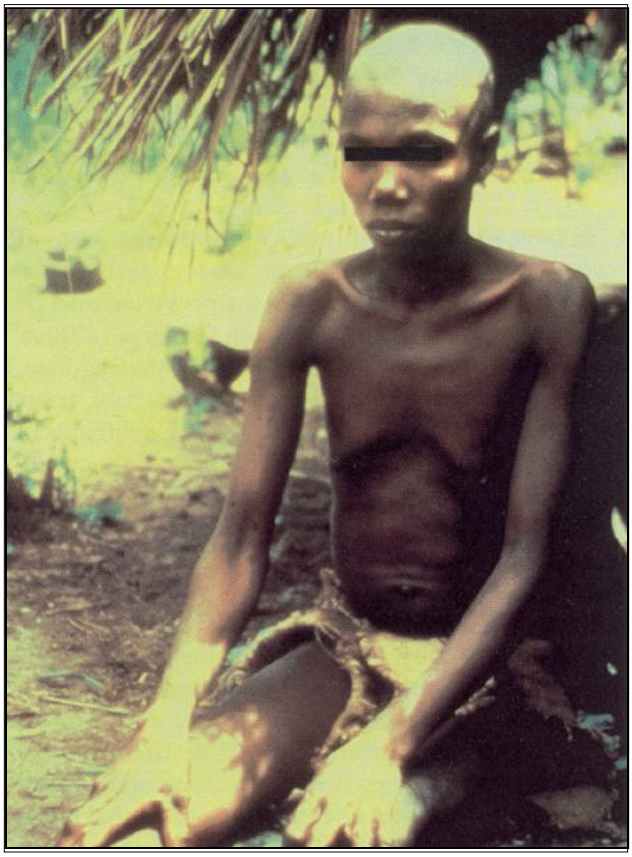

Fig. 10-11. Ebola infection in African patient 24 hours prior to death. Photograph: Courtesy of Thomas P. Monath, M.D.; formerly, Walter Reed Army Institute of Research, Washington, D.C.

In November 1989 at Hazleton Research Products in Reston, Virginia, 16 imported cynomolgus monkeys died from a hemorrhagic disorder.[38] Virological analysis resulted in the identification of a filovirus antigenically indistinct from Ebola virus. The monkeys had been imported from the Philippines, a previously unreported site for Ebola infections. This incident marked the first time a filovirus had been isolated from a nonhuman host not experimentally induced. Epidemiological analysis identified seven shipments of infected monkeys from the Philippines.[39] Four animal handlers were seropositive for the filovirus; however, none could identify an associated illness. Although cross-reactivity exists between this virus and Ebola, researchers at the Centers for Disease Control believe the virus is antigenically and genetically distinguishable from Ebola virus.[39] The lack of associated human disease suggests that this hypothesis is correct. Another possibility is that the virus is an attenuated form of Ebola; one might speculate on its possible use as a vaccine.

Signs and Symptoms

The incubation period of Ebola hemorrhagic fever ranges from 2 to 21 days. The onset of disease is abrupt, with symptoms resembling influenza, including fever, headache, malaise, myalgias, joint pains, sore throat, diarrhea, and abdominal pain. A fleeting morbilliform eruption often appears within the first week of illness, followed by desquamation (Figure 10-12). Additional physical findings include pharyngitis, conjunctivitis, jaundice, and edema (Figure 10-13). Hemorrhagic manifestations can develop after the third day of illness, manifested by petechiae, ecchymosis, conjunctival hemorrhage, gingival bleeding, oropharyngeal bleeding ulcerations, vaginal bleeding, bleeding from injection sites, hematemesis, and melena.[37]

Laboratory Findings and Treatment

Laboratory findings for Ebola virus include

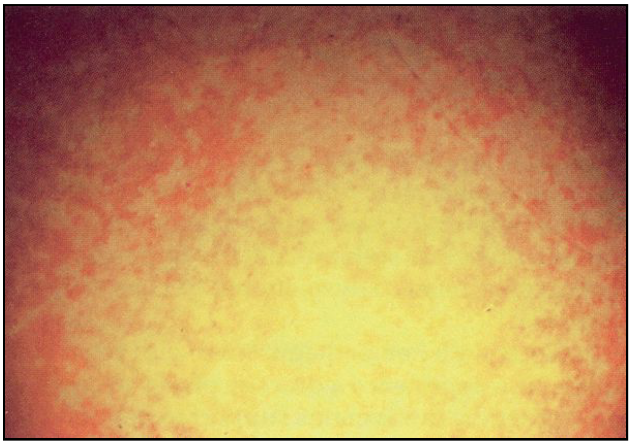

Fig. 10-12. Morbilliform eruption in a patient with Ebola hemorrhagic fever. Photograph: Courtesy of Thomas P. Monath, M.D.; formerly, Walter Reed Army Institute of Research, Washington, D.C.

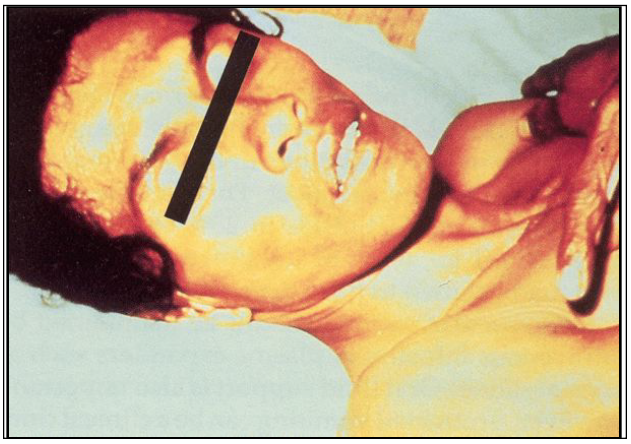

Fig. 10-13. Jaundice in a patient Ebola hemorrhagic fever. Photograph: Courtesy of Thomas P. Monath, M.D.; formerly, Walter Reed Army Institute of Research, Washington, D.C.

proteinuria and elevated transaminases, with aspartate aminotransferase values exceeding those of alanine aminotransferase.[3] The diagnosis is confirmed on identification of IgM or rising IgG antibodies by indirect immunofluorescence, Western blot analysis, or ELISA, or any combination of the three.

Treatment is supportive and, as with all forms of severe viral hemorrhagic disease, may require intensive care. In the hospital setting, extreme care must be provided when handling any body secretions or blood products. The patient should be isolated and strict barrier-nursing techniques should be enforced. Recent evidence in animal models suggests that ribavirin (2 g IV loading dose, then 1 g every 6 h for 4 d, followed by 0.5 g every 8 h for 6 d) may have clinical utility in treating the disorder.[3]

Marburg Hemorrhagic Fever

Marburg is a single-stranded RNA virus that is morphologically similar to Ebola virus but is antigenically distinct. The virus is named after a small German town where the first cases were described, but the virus is found in nature in Zimbabwe, Kenya, and South Africa.[3] In Europe in 1967, 25 people became acutely ill after handling material from African green monkeys imported from Uganda. An Australian traveler died from Marburg hemorrhagic fever in 1975 after exposure in South Africa; two other patients survived. A third outbreak occurred in Kenya in 1980, resulting in one fatality and one survivor. Another isolated case occurred in South Africa in 1982. The most recent episode was reported in Kenya in 1987 and resulted in the death of a boy. The mode of primary transmission is unknown. Secondary spread of disease can occur through close contact with infected persons including sexual transmission.[3]

The incubation period of Marburg hemorrhagic fever ranges from 3 to 10 days. The clinical and laboratory features are indistinguishable from those of Ebola hemorrhagic fever (Figure 10-14). The diagnosis is confirmed by detecting IgG or IgM antibodies to Marburg hemorrhagic fever antigens by indirect immunofluorescence. Treatment is the same as for Ebola hemorrhagic fever.

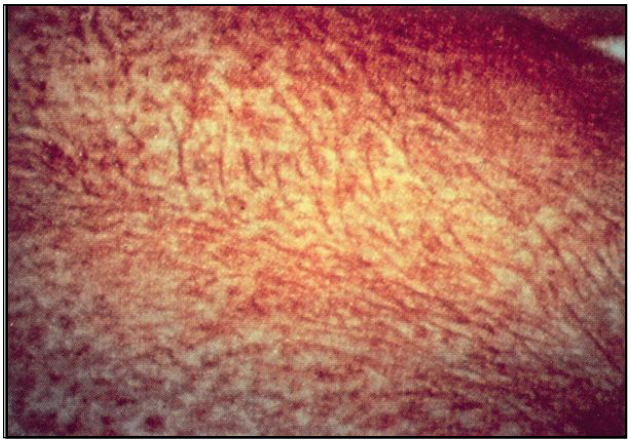

Fig. 10-14. Hemorrhagic diathesis observed in a patient with Marburg hemorrhagic fever. Photograph: Courtesy of David I. H. Simpson, Department of Microbiology and Immunobiology, The Queen's University of Belfast.

SUPPORTIVE TREATMENT

The severity of the various hemorrhagic fevers is quite variable. Many cases are initially categorized as fevers of unknown etiology until additional clinical findings become manifest. For example, during the Vietnam conflict, 3.4% to 28% of all patients hospitalized for fever of unknown etiology were eventually shown to have dengue.[5]

Intravascular volume should be maintained by intravenous infusion of plasma expanders such as normal saline. Oral fluid support is also important; however, protracted vomiting can be a clinical complication, necessitating even more aggressive intravenous support. Hemorrhagic manifestations and thrombocytopenia should be treated with platelet transfusions, intravenous plasma infusions, or both. If bleeding is severe and fractionated blood components are unavailable, whole blood should be transfused. Metabolic acidosis may require intravenous sodium bicarbonate, and a rising hemoglobin is treated with infusion of plasma. Acute renal failure should be treated with close monitoring of intravascular volume, close monitoring of intake and output with replacement of free water losses only (including insensible losses), and avoidance of volume expanders such as sodium-containing products. In severe cases, hemodialysis should be considered, if available.

Patients with hemorrhagic fever with renal syndrome also experience a diuretic phase, necessitating aggressive intravenous support to maintain intravascular volume. Antiviral therapy with ribavirin (2 g IV loading dose, then 1 g every 6 h for 4 d, followed by 0.5 g every 8 h for 6 d) may prove to be good adjunct therapy for supportive medical care in some viral hemorrhagic fevers. Adrenocortical steroids, antibiotics, and vasoactive agents have not been shown to alter the clinical course of disease.[5]

PREVENTION

The prevention of viral hemorrhagic fevers is based on two possible plans of action: (1) development of vaccines providing immunity and (2) control of the vectors or rodent hosts. Many vaccines are currently being developed; however, few are available. Control of mosquito vectors is an old concept spawned from Dr. Walter Reed's research on yellow fever. Because mosquitoes breed in open water, elimination of standing water sites around military installations helps to control regional disease. Use of insecticides such as malathion is effective, reducing vector populations in limited areas. Knowledge of vector feeding habits is also helpful; for example, the mosquito *A aegypti* prefers to feed indoors during daylight. Therefore, insect nets around beds are little protection against this vector, and windows should be screened securely.[5]

These measures are good for established regional areas; however, they cannot be implemented when the soldier is in the field. Most of the cases of dengue experienced during the Vietnam conflict were contracted by support troops who had contact with civilian populations.[5] The speed with which modern warfare is undertaken, exemplified by Operations Desert Storm and Desert Shield, also results in a much higher risk of contracting disease because of increased contact with civilians over large regions and the lack of preventive vector-control measures. These facts emphasize the need for development of effective vaccines that will essentially remove the potential for disease in high-risk areas.

SUMMARY

Hemorrhagic fever viruses are transmitted to humans by arthropods and through rodent excreta. The twelve viral groups producing hemorrhagic fever in humans are found in both temperate and tropical climates. Some of the hemorrhagic fever viruses are associated with large-scale epidemics. All of them can cause life-threatening hemorrhagic disease.

Although serologic tests such as ELISA are available, the diagnosis is dependent more on clinical presentation because of the acute nature of these diseases. Treatment is supportive in most patients and often requires intensive care. Ribavirin may have clinical utility in treating Rift Valley fever, Crimean-Congo hemorrhagic fever, hemorrhagic fever with renal syndrome, Lassa fever, and Argen-

tine, Ebola, and Marburg hemorrhagic fevers.

Prevention is based on development of vaccines or control of the arthropod and animal vectors. Because of the rapid mobility of modern warfare, the best possible preventive measure is vaccination; however, few vaccines are currently available. The medical officer in the field must be aware of the potential risk of these frequently fatal viral infections.

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