hypothesis has risen in part merely because of the ubiquity of bats when sought in affected areas and the frustration of researchers in identifying a source of virus.

PATHOLOGY AND PATHOGENESIS In humans and in animal models, Ebola and Marburg viruses replicate well in virtually all cell types, including endothelial cells, macrophages, and parenchymal cells of multiple organs. The earliest involvement is that of the mononuclear phagocyte system, and this is responsible for initiation of the disease process. Viral replication is associated with cellular necrosis both in vivo and in vitro. Significant findings at the light-microscopic level include liver necrosis with Councilman bodies (intracellular inclusions that correlate with extensive collections of viral nucleocapsids), interstitial pneumonitis, cerebral glial nodules, and small infarcts. Antigen and virions are abundant in fibroblasts, interstitium, and (to a lesser extent) the appendages of the subcutaneous tissues in fatal cases; escape through small breaks in the skin or possibly through sweat glands may occur and, if so, may be correlated with the established epidemiologic risk of close contact with patients and the touching of the deceased. Inflammatory cells are not prominent, even in necrotic areas.

In addition to sustaining direct damage from viral infection, patients infected with Ebola virus (Zaire subtype) have high circulating levels of proinflammatory cytokines, which presumably contribute to the severity of the illness. In fact, the virus interacts intimately with the cellular cytokine system. It is resistant to the antiviral effects of interferon α, although this mediator is amply induced. Viral infection of endothelial cells selectively inhibits the expression of MHC class I molecules and blocks the induction of several genes by the interferons. In addition, glycoprotein expression inhibits αV integrin expression, an effect that has been shown in vitro to lead to detachment and subsequent death of endothelial cells.

Acute infection is associated with high levels of circulating virus and viral antigen. Clinical improvement takes place when viral titers decrease concomitantly with the onset of a virus-specific immune response, as detected by enzyme-linked immunosorbent assay (ELISA) or fluorescent antibody test. In fatal cases, there is usually little evidence of an antibody response and there is extensive depletion of spleen and lymph nodes. Recovery is apparently mediated by the cellular immune response: convalescent-phase plasma has little in vitro virus-neutralizing capacity and is not protective in passive transfer experiments in monkey and guinea pig models.

CLINICAL MANIFESTATIONS After an incubation period of ~7 to 10 days (range, 3 to 16 days), the patient abruptly develops fever, severe headache, malaise, myalgia, nausea, and vomiting. Continued fever is joined by diarrhea (often severe), chest pain (accompanied by cough), prostration, and depressed mentation. In light-skinned patients (and less often in dark-skinned individuals), a maculopapular rash appears around day 5 to 7 and is followed by desquamation. Bleeding may begin about this time and is apparent from any mucosal site and into the skin. In some epidemics, fewer than half of patients have had overt bleeding, and this manifestation has been absent even in some fatal cases. Additional findings include edema of the face, neck, and/or scrotum; hepatomegaly; flushing; conjunctival injection; and pharyngitis. Around 10 to 12 days after the onset of disease, the sustained fever may break, with improvement and eventual recovery of the patient. Recrudescence of fever may be associated with secondary bacterial infections or possibly with localized virus persistence. Late hepatitis, uveitis, and orchitis have been reported, with isolation of virus from semen or detection of polymerase chain reaction (PCR) products in vaginal secretions for several weeks.

LABORATORY FINDINGS Leukopenia is common early on; neutrophilia has its onset later. Platelet counts fall below (sometimes much below) 50,000/μL. Laboratory evidence of disseminated intravascular coagulation may be found, but its clinical significance and the need for therapy are controversial. Serum levels of alanine and aspartate aminotransferases (particularly the latter) rise progressively, and jaundice develops in some cases. The serum amylase level may be elevated, and this elevation may be associated with abdominal pain suggesting pancreatitis. Proteinuria is usual; decreased kidney function is proportional to shock.

DIAGNOSIS Most patients acutely ill as a result of infection with Ebola or Marburg viruses have high concentrations of virus in blood. Antigen-detection ELISA is a sensitive, robust diagnostic modality. Virus isolation and reverse-transcriptase PCR are also effective and provide additional sensitivity in some cases. Patients who are recovering develop IgM and IgG antibodies that are best detected by ELISA but are also reactive in the less specific fluorescent antibody test. Skin biopsies are an extremely useful adjunct in postmortem diagnosis of Ebola (and, to a lesser extent, Marburg) virus infections because of the presence of large amounts of viral antigen, the relative safety of obtaining the sample, and the freedom from cold-chain requirements for formalin-fixed tissues.

Rx TREATMENT

No virus-specific therapy is available, and, given the extensive viral involvement in fatal cases, supportive treatment may not be as useful as was once hoped. However, recent studies in rhesus monkeys have shown improved survival among animals treated with an inhibitor of factor VIIa/tissue factor. Vigorous treatment of shock should take into account the likelihood of vascular leak in the pulmonary and systemic circulation and of myocardial functional compromise. The membrane fusion mechanism of Ebola resembles that of retroviruses, and the identification of "fusogenic" sequences suggests that inhibitors of cell entry may be developed. Despite the poor neutralizing capacity of polyclonal convalescent-phase sera, phage display of immunoglobulin mRNA from convalescent bone marrow has produced monoclonal antibodies that have in vitro neutralizing capacity and mediate protection in guinea pig—but, unfortunately, not in monkey—models.

PREVENTION No vaccine or antiviral drug is currently available, but barrier nursing precautions in African hospitals can greatly decrease the spread of the virus beyond the index case and thus prevent epidemics of filoviruses and other agents as well. An adenovirus-vectored Ebola glycoprotein gene has proved protective in nonhuman primates and is undergoing phase 1 trials in humans.

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181 EBOLA AND MARBURG VIRUSES

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DEFINITION Both Marburg virus and Ebola virus cause an acute febrile illness associated with high mortality. This illness is characterized by multisystem involvement that begins with the abrupt onset of headache, myalgias, and fever and proceeds to prostration, rash, and shock and often to bleeding manifestations. Epidemics usually begin with a single case acquired from an unknown reservoir in nature and spread mainly through close contact with sick persons or their body fluids, either in the home or at the hospital.

ETIOLOGY The family Filoviridae comprises two antigenically and genetically distinct viruses: Marburg virus and Ebola virus. Ebola virus has four readily distinguishable subtypes named for their original sites of recognition (Zaire, Sudan, Cote d'Ivoire, and Reston). Except for Ebola virus subtype Reston, all the Filoviridae are African viruses that cause severe and often fatal disease in humans. The Reston virus, which has been exported from the Philippines on several occasions, has caused fatal infections in monkeys but only subclinical infections in humans. Different isolates of the four Ebola subtypes made over time and space exhibit remarkable sequence conservation, indicating marked genetic stability in their selective niche. Typical filovirus particles contain a single linear, negative-sense, single-stranded RNA arranged in a helical nucleocapsid. The virions are 790 to 970 nm in length; they may also appear in elongated, contorted forms. The lipid envelope confers sensitivity to lipid solvents and common detergents. The viruses are largely destroyed by heat (60°C, 30 min) and by acidity but may persist for weeks in blood at room temperature. The surface glycoprotein self-associates to form the virion surface spikes, which presumably mediate attachment to cells and fusion. The glycoprotein's high sugar content may contribute to its low capacity to elicit neutralizing antibodies. A smaller form of the glycoprotein, bearing many of its antigenic determinants, is produced by in vitro–infected cells and is found in the circulation in human disease; it has been speculated that this circulating soluble protein may suppress the immune response to the virion surface protein or block antiviral effector mechanisms. Both Marburg virus and Ebola virus are biosafety level 4 pathogens because of their high associated mortality rate and aerosol infectivity.

EPIDEMIOLOGY Marburg virus was first identified in Germany in 1967, when infected African green monkeys (*Cercopithecus aethiops*) imported from Uganda transmitted the agent to vaccine-laboratory workers. Of the 25 human cases acquired from monkeys, 7 ended in death. The six secondary cases were associated with close contact or parenteral exposure. Secondary spread to the wife of one patient was documented, and virus was isolated from the husband's semen despite the presence of circulating antibodies. Subsequently, isolated cases of Marburg virus infection have been reported from eastern and southern Africa, with limited spread.

In 1999, repeated transmission of Marburg virus to workers in a gold mine in eastern Democratic Republic of Congo was documented. The secondary spread of the virus among patients' families was more extensive than previously noted, resembling that of Ebola virus and emphasizing the importance of hygiene and proper barrier nursing in the epidemiology of these viruses in Africa.

In 1976, epidemics of severe hemorrhagic fever (550 human cases) occurred simultaneously in Zaire and Sudan, and Ebola virus was found to be the etiologic agent. Later, it was shown that different subtypes of virus—associated with 90 and 50% mortality, respectively—caused the two epidemics. Both epidemics were associated with interhuman spread (particularly in the hospital setting) and the use of unsterilized needles and syringes, a common practice in developing-country hospitals. The epidemics dwindled as the clinics were closed and people in the endemic area increasingly shunned affected persons and avoided traditional burial practices.

The Zaire subtype of Ebola virus recurred in a major epidemic (317 cases, 88% mortality) in Democratic Republic of Congo in 1995 and in smaller epidemics in Gabon in 1994–1996. Mortality was high. Transmission to caregivers and others who had direct contact with body fluids was common, and poor hygiene in hospitals exacerbated spread. In the Congo epidemic, an index case was infected in Kikwit in January 1995. The epidemic smoldered until April, when intense nosocomial transmission forced closure of the hospitals; samples were finally sent to the laboratory for Ebola testing, which yielded positive results within a few hours. International assistance, with barrier nursing instruction and materials, was provided; nosocomial transmission ceased, hospitals reopened, and patients were segregated to prevent intrafamilial spread. The last case was reported in June 1995.

Separate emergences of Ebola virus (subtype Zaire) were detected in Gabon from 1994 through 2003, usually in association with deep forest exposure and subsequent familial and nosocomial transmission. Nonhuman primates sometimes exhibited die-offs, and Ebola infection was confirmed in at least some animals. In a 1996 episode, a physician exposed to Ebola-infected patients traveled to South Africa with a fever; a nurse who assisted in a cutdown on the physician developed Ebola hemorrhagic fever and died despite intensive care. The index patient was identified retrospectively on the basis of serum antibodies and virus isolation from semen. Thus, distant transport of Ebola virus is an established risk, but limited nosocomial spread occurs under proper hygienic conditions.

In 2000–2001, an indolent outbreak of the Sudan subtype claimed the lives of 224 (53%) of 425 patients with presumptive cases in Uganda.

The Reston subtype of Ebola virus was first seen in the United States in 1989, when it caused a fatal, highly transmissible disease among cynomolgus macaques imported from the Philippines and quarantined in Reston, VA, pending distribution to biomedical researchers. This and other appearances of the Reston virus have been traced to a single export facility in the Philippines, but no source in nature has been established.

Epidemiologic studies (including a specific search in the Kikwit epidemic) have failed to yield evidence for an important role of airborne particles in human disease. This lack of epidemiologic evidence is surprising and seems to conflict with the viruses' classification as biosafety level 4 pathogens based in part on their aerosol infectivity and with formal laboratory assessments showing a high degree of aerosol infectivity for monkeys. Sick humans apparently do not usually generate sufficient amounts of infectious aerosols to pose a significant hazard to those around them.

Available evidence points to a nonprimate reservoir for these viruses, but an intensive search has failed to elucidate what this reservoir might be. Speculation has centered on a possible role for bats, but that