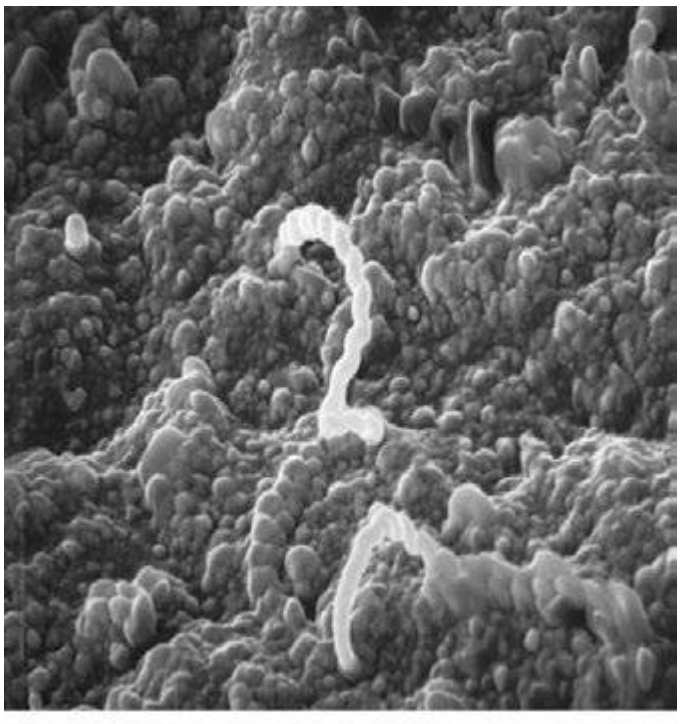

FIGURE 208-2 Transmission electron microscopic image of *Leptospira interrogans* invading equine conjunctival tissue. *(Image kindly provided by Dr. JE Nally, National Animal Disease Center, U.S. Department of Agriculture, Ames, IA. This image appears on the homepage of the European Leptospirosis Society website [http://eurolepto.ucd.ie/].)*

Reliable data on morbidity and mortality from leptospirosis have gradually started to appear. Current information on global human leptospirosis varies but indicates that approximately 1 million severe cases occur per year, with a mean case–fatality rate of nearly 10%.

As a zoonosis, leptospirosis affects almost all mammalian species and represents a significant veterinary burden. Rodents, especially rats, are the most important reservoir, although other wild mammals as well as domestic and farm animals may also harbor these microorganisms. Leptospires establish a symbiotic relationship with their host and can persist in the urogenital tract for years. Some serovars are generally associated with particular animals—e.g., Icterohaemorrhagiae and Copenhageni with rats, Grippotyphosa with voles, Hardjo with cattle, Canicola with dogs, and Pomona with pigs—but may occur in other animals as well.

Leptospirosis presents as both an endemic and an epidemic disease. Transmission of leptospires may follow direct contact with urine, blood, or tissue from an infected animal or, more commonly, exposure to environmental contamination. The dogma that human-to-human transmission is very rare is challenged by recent findings on household clustering, asymptomatic renal colonization, and prolonged excretion of leptospires. (Both of the latter features imply human infection sources that are not recognized.) Because leptospires can survive in a humid environment for many months, water is an important vehicle in their transmission. Epidemics of leptospirosis are not well understood. Outbreaks may result from exposure to flood waters contaminated by urine from infected animals, as has been reported from several countries. However, it is also true that outbreaks may occur without floods, and floods often occur without outbreaks.

The vast majority of infections with *Leptospira* cause no or only mild disease in humans. A small percentage of infections (~1%) lead to severe, potentially fatal complications. The proportion of leptospirosis cases that are mild is unknown because patients either do not seek or do not have access to medical care or because the nonspecific symptoms are interpreted as an influenza-like illness. Reported cases surely represent a significant underestimation of the total number. Certain occupational groups are at especially high risk, including veterinarians, agricultural workers, sewage workers, slaughterhouse employees, and workers in the fishing industry. Risk factors include direct or indirect contact with animals, including exposure to water and soil contaminated with animal urine. Leptospirosis has also been recognized in deteriorating inner cities and suburban areas where rat populations are expanding.

Recreational exposure and domestic-animal contact are prominent sources of leptospirosis. Recreational freshwater activities, such as canoeing, windsurfing, swimming, and waterskiing, place persons at risk for infection. Several outbreaks have followed sporting events. For example, an outbreak took place in 1998 among athletes after a triathlon in Springfield, Illinois. Ingestion of one or more swallows of lake water during the swimming leg of the triathlon was a prominent risk factor for illness. Heavy rains that preceded the triathlon, with consequent agricultural runoff, are likely to have increased the level of leptospiral contamination in the lake water. In another outbreak, 42% of participants contracted leptospirosis during the 2000 Eco-Challenge-Sabah multisport endurance race in Malaysian Borneo. Swimming in the Segama River was shown to be an independent risk factor.

In addition, leptospirosis is a traveler's disease. Large proportions of patients acquire the infection while traveling in tropical countries, usually during adventurous activities such as whitewater rafting, jungle trekking, and caving. Transmission via laboratory accidents has been reported but is rare. New data indicate that leptospirosis may develop after unanticipated immersion in contaminated water (e.g., in an automobile accident) more frequently than has generally been thought and can also result from an animal bite.

PATHOGENESIS

Transmission occurs through cuts, abraded skin, or mucous membranes, especially the conjunctival and oral mucosa. After entry, the organisms proliferate, cross tissue barriers, and disseminate hematogenously to all organs (*leptospiremic phase*). During this initial incubation period, leptospires can be isolated from the bloodstream **(Fig. 208-3)**. The organisms are able to survive in the nonimmune host: they evade complement-mediated killing by binding factor H, a strong inhibitor of the complement system, on their surface. Moreover, pathogenic leptospires resist ingestion and killing by neutrophils, monocytes, and macrophages. During the immune phase, the appearance of antibodies coincides with the disappearance of leptospires from the blood. However, the bacteria persist in various organs, including liver, lung, kidney, heart, and brain. Autopsy findings illustrate the involvement of multiple organ systems in severe disease. Renal pathology shows both acute tubular damage and interstitial nephritis. Acute tubular lesions progress in time to interstitial edema and acute tubular necrosis. Severe nephritis is observed in patients who survive long enough to develop it and seems to be a secondary response to acute epithelial damage. The reported deregulation of the expression of several transporters along the nephron, including the proximal sodium-hydrogen exchanger 3 (NHE3), aquaporins 1 and 2 (AQP1 and AQP2), Na^+-K^+ ATPase, and the Na-K-2Cl cotransporter NKCC2, contributes to tubular potassium wasting, hypokalemia, and polyuria. Histopathology of the liver shows focal necrosis, foci of inflammation, and plugging of bile canaliculi. Widespread hepatocellular necrosis is not found. Petechiae and hemorrhages are observed in the heart, lungs **(Fig. 208-4)**, kidneys (and adrenals), pancreas, liver, gastrointestinal tract (including retroperitoneal fat, mesentery, and omentum), muscles, prostate, testis, and brain (subarachnoid bleeding). Several studies show an association between hemorrhage and thrombocytopenia. Although the underlying mechanisms of thrombocytopenia have not been elucidated, it seems likely that platelet consumption plays an important role. A consumptive coagulopathy may occur, with elevated markers of coagulation activation (thrombin–antithrombin complexes, prothrombin fragments 1 and 2, D-dimer), diminished anticoagulant markers (antithrombin, protein C), and deregulated fibrinolytic activity. Overt disseminated intravascular coagulation (DIC) has been documented in patients from Thailand and Indonesia. Elevated plasma levels of soluble E-selectin and