Mouse Hepatitis Virus Infection, Liver, Mouse

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Synonyms. Hepatoencephalitis virus, murine hepatitis virus infection, mouse coronavirus infection

Gross Appearance

Gross lesions can occur in liver, intestine, and lymphoreticular organs. Intestinal lesions are described in detail elsewhere. Affected livers have random, small, pale or hemorrhagic foci to multiple confluent foci with depression of the capsular surface. The liver may be diffusely pale and covered with fibrinous peritoneal exudate. Infant mice can be runted, jaundiced, or may manifest neurologic signs, including tremor, incoordination, or convulsions (Piazza 1969). During the acute phase of infection, involution of lymph nodes, spleen, and thymus can occur. Recovered mice develop mild splenomegaly or lymphadenomegaly, particularly in cervical nodes. Athymic nude mice can become progressively cachectic (wasting disease). Their livers are contracted with rough, nodular surfaces (Ward et al. 1977), and splenomegaly can be pronounced (Ishida et al. 1978).

Microscopic Features

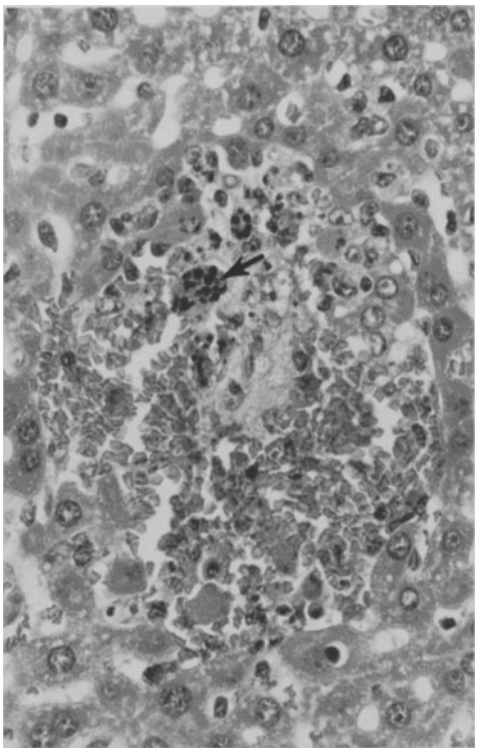
Depending on virus and host factors, foci of necrosis, leukocytic infiltration, and syncytium formation may be encountered in several organs. Acute focal hepatocellular necrosis is accompanied by hemorrhage and mild mixed leukocyte infiltration. Lesions in susceptible mice are more severe and often coalesce, with parenchymal collapse. Nuclei of degenerating cells often have characteristic dense, marginated chromatin, or chromatin is condensed in multiple dense bodies (Fig. 148). Syncytia arising from hepatocytes or other cells can be present (Fig. 149; Barthold 1985, 1986a; Barthold and Smith 1984; Jones and Cohen 1962; Piazza 1969). In athymic nude mice, parenchymal collapse, fibrosis, and syncytium formation are pronounced (Fujiwara et al. 1977; Ishida et al. 1978; Tamura et al. 1977; Ward et al. 1977). They often have marked myelopoiesis in portal regions (Fig. 150) and spleen (Ishida et al. 1978). Hepatocellular mitotic activity is elevated in infected nude mice or immunocompetent mice recovering from mouse hepatitis virus infection (Fig. 151; Barthold 1985, 1986a; Carthew 1981; Jones and Cohen 1962). Discrete nodular foci of macrophage or leukocyte accumulations (microgranulomas) are often present in the liver of recovering mice (Fig. 152).

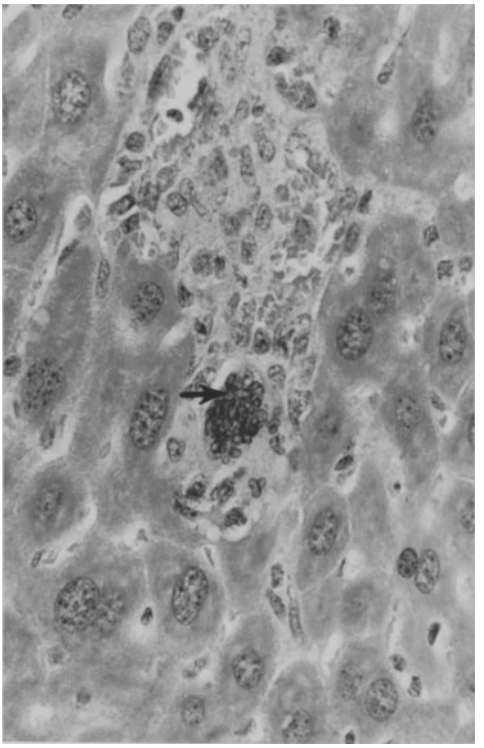
Two patterns of mouse hepatitis virus infection are seen: *respiratory* and *enteric*. The enteric pattern is described elsewhere. The respiratory pattern is most often associated with hepatitis. Mild necrosis of nasal epithelium, perivascular lymphocytic infiltration in the lung, and focal necrosis with syncytia in lymph nodes, spleen, brain, bone marrow, mesothelium, and other organs can also be present. In resistant adult hosts, lesions are restricted to upper respiratory mucosa, with minimal dissemination (Barthold 1985, 1986a; Barthold and Smith 1984, 1987). Athymic mice have endothelial syncytia in blood vessels of lung, heart base, brain, and other organs. Syncytia, necrosis, and marked myelopoiesis are frequent in bone marrow and spleen. Epithelial syncytia in the intestine are occasionally present (Barthold 1985, 1986a; Fujiwara et al. 1977; Ishida et al. 1978; Tamura et al. 1977; Ward et al. 1977), but most virus activity is in gut-associated lymphoid tissue and lamina propria (Barthold and Smith 1987).

Ultrastructure

Kupffer's cells and hepatocytes develop a number of nonspecific degenerative changes. Specific changes include dissociation of ribosomes from endoplasmic reticulum, aggregation of ribosomes, formation of discrete, compact arrays of electron-dense reticular structures (reticular inclusions), and virion formation. Virions bud into cytoplasmic cisternae and are usually dispersed in small numbers, but occasional compact aggregates can be found. Virions are pleomorphic with a corona of surface spikes and an average diameter of about 90 nm. These changes, including reticular inclusions, have been observed in a variety of infected cells in vitro (NCTC 1469 cells) and in vivo

T. C. Jones et al. (eds.), *Digestive System*





(oligodendroglia, astrocytes, Kupffer's cells, hepatocytes, and enterocytes) (Barthold et al. 1982; David-Ferreira and Manaker 1965; Lampert et al. 1973; Ruebner et al. 1967; Svoboda et al. 1962).

Differential Diagnosis

Necrotizing hepatitis and focal hepatitis mimic lesions induced by a number of other pathogens. Idiopathic focal hepatic necrosis can be encountered in normal mice in the absence of pathogens. Careful examination of liver lesions for multinucleate syncytia and examination of other organs, including nose, lung, and bowel helps to provide a definitive diagnosis. Antigen of the virus can be demonstrated in active lesions (Barthold and Smith 1984, 1987; Barthold et al. 1990; Brownstein and Barthold 1982), and seroconversion of recovered mice is confirmatory. Virus isolation is a difficult and insensitive means of diagnosis. Wasting disease in nude mice must be differentiated from other chronic infectious diseases, including those caused by polyoma virus, Sendai virus, pneumonia virus of mice, mouse adenovirus, and *Pneunocystis carinii*. Histologic findings are confirmatory.

Biologic Features

Natural History

Mouse hepatitis virus is represented by innumerable different strains that are generally highly contagious and spread by respiratory or orofecal routes. In utero transmission of the virus can be shown experimentally, but only under the somewhat artificial combination of highly virulent strain, susceptible host, and stage of pregnancy. These events are not likely to occur under natural conditions (Barthold et al. 1988). Respiratory strains vary widely in their virulence. Most of these virus strains are only mildly pathogenic,

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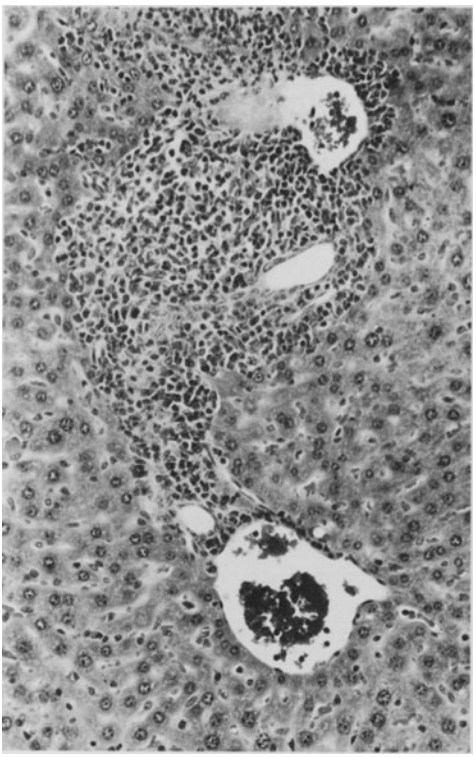
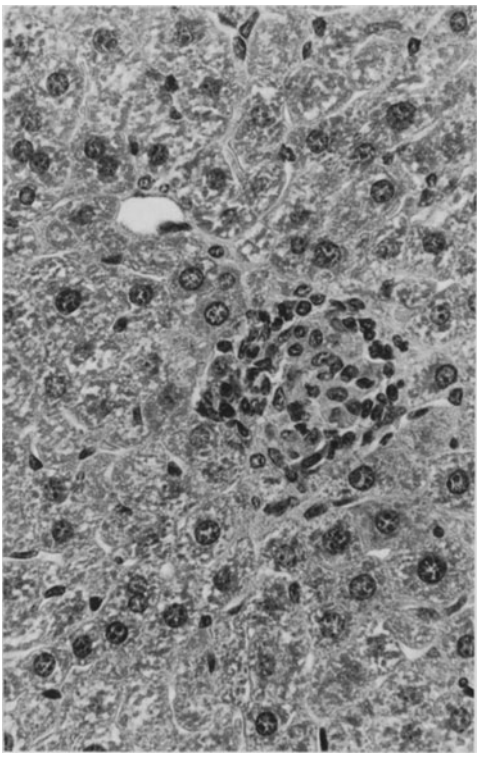
Fig. 148. (*above*) Mouse hepatitis virus infection, liver, mouse. Focal necrotizing hepatitis with hemorrhage. Note the large, degenerating cell with densely clumped chromatin (*arrow*), a frequent finding in these lesions. H&E, ×410

Fig. 149. (*below*) Liver, mouse. Focal hepatitis with a characteristic syncytium (*arrow*), probably of histiocytic origin. H&E, ×660





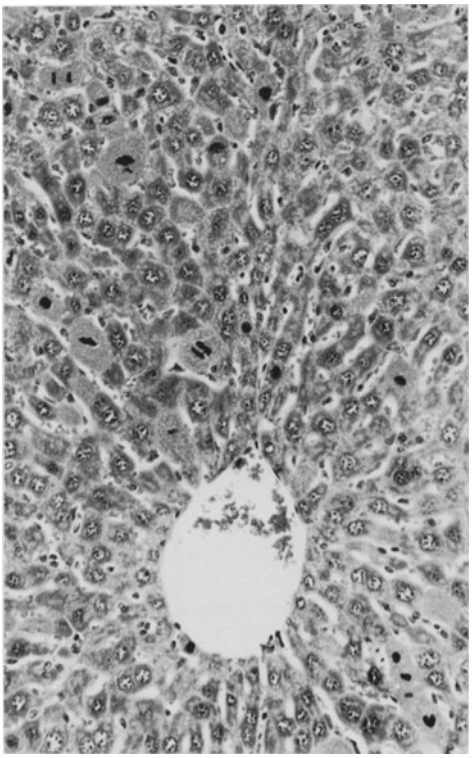


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Fig. 150. (*upper left*) Extramedullary myelopoiesis, liver, athymic nude mouse infected with mouse hepatitis virus. H&E, ×165

Fig. 151. (*upper right*) Liver, mouse recovering from mouse hepatitis virus infection. Increased hepatocellular mitotic activity. H&E, ×165

Fig. 152. (*below*) Microgranuloma, liver, mouse recovering from mouse hepatitis virus infection. H&E, ×410

even in nude mice (Hirano et al. 1975), while some can be highly virulent in adult mice (Le Prevost et al. 1975). In naturally infected, uncompromised adult mice, the infection is usually subclinical. Clinical disease can be precipitated during active infection by a variety of stressful situations, particularly immunosuppression, alteration of macrophage function, and tumor transplantation (Barthold 1985, 1986a). The respiratory pattern is usually subclinical, unless in infant or immunocompromised mice, which manifest signs of encephalitis and hepatitis (Barthold 1985, 1986a; Barthold and Smith 1987). Athymic nude mice infected with this virus develop chronic wasting disease lasting up to several weeks (Hirano et al. 1975). The virus can be introduced in a population of laboratory mice by feral mice, subclinically infected mice, or infected biologic products. Transplantable tumors, particularly lymphoreticular and ascites tumors, commonly carry the virus, which can cause oncolysis or other abnormal host–tumor kinetics (Barthold 1985, 1986a).

Pathogenesis

The course of infection with mouse hepatitis virus is dependent on the strain of virus and host factors, which consist predominantly of genotype and lymphoreticular function (Barthold 1985, 1986a; Hirano et al. 1975, 1981; Le Prevost et al. 1975; Piazza 1969). Apparently, many viral strains exist, as mouse hepatitis virus is subject to a high rate of mutation and recombination, events which no doubt contribute to the survival of the virus in mouse populations. Hepatotropism and neurotropism are characteristic features in most strains when virus is inoculated intraperitoneally or intracerebrally (Piazza 1969). The role of these organs in natural disease is secondary and not essential for successful infection and transmission. Hepatitis, however, is a very common lesion in naturally infected mice. Strains of virus that cause respiratory infections seem to replicate in nasal or olfactory mucosa as a primary target and then disseminate to other internal organs if the host is susceptible (Barthold and Smith 1992). Strains of low virulence in resistant hosts cause asymptomatic infections limited to the nasal mucosa, but some extend directly into the brain through the olfactory tracts (Barthold et al. 1988). In susceptible hosts, vascular endothelial cells become infected, with hematogenous dissemination to multiple organs (Barthold and Smith 1992). Intestine can be infected, but involvement is mild with minimal lesions compared to enteric strains (Barthold 1985, 1986a; Barthold and Smith 1983, 1984, 1987). Fecal transmission seems to play only a minor role with respiratory strains of virus. Virus is recoverable and viral antigen is demonstrable in most organs for only about 1–3 weeks after inoculation, after which time infection is cleared (Barthold 1985, 1986a; Barthold and Smith 1983, 1987; Fujiwara et al. 1977; Tamura et al. 1977). Infection in immunocompetent mice is short term with no carrier state (Barthold and Smith 1990), but selected low-virulence, neurotropic strains can persist in the brain, causing chronic demyelination when inoculated intracerebrally (Stohlman and Weiner 1981). This does not seem to play a crucial role in the natural history of the infection.

Much of what is known about host resistance to mouse hepatitis virus has been derived from studies on strains of respiratory type. Host genotype is a significant factor in resistance and seems to be mediated through a number of mechanisms (Bang 1978; Hirano et al. 1975; Taguchi et al. 1976, 1979; Piazza 1969). Lymphoreticular function is also an important factor (Bang 1978; Dupuy et al. 1975; Levy-Leblond and Dupuy 1977; Taguchi et al. 1979; Tardieu et al. 1980). Neonatal mice have immature lymphoreticular function and are thus highly susceptible to infection, usually dying of hepatitis or encephalitis. Natural resistance develops at about 2 weeks of age, but significant differences in susceptibility continue to be present in adults, depending on genotype (Bang 1978; Barthold and Smith 1987; Hirano et al. 1975; Taguchi et al. 1979). Maternal antibody seems to play a protective role through this period of age-related susceptibility. Antibody to respiratory strains of the virus appears to be transferred primarily through colostrum, and not in utero, and continues to be absorbed through the bowel of infant mice until around 2 weeks of age. Maternally derived antibody seems to protect pups against different mouse hepatitis virus strains (Barthold et al. 1988). Mice that have recovered from active infection with one strain of mouse hepatitis virus resist reinfection with the homologous strain, but are fully susceptible to infection with another strain of the virus. Furthermore, recovered mice can be actively reinfected with the same strain of virus after several months. Thus immunity to mouse hepatitis virus is highly strain specific and not long-lasting, analogous to com-

mon respiratory coronavirus infections (colds) in humans (Barthold and Smith 1989a,b).

Infection of mice with other agents, such as K virus and retroviruses, can increase susceptibility to mouse hepatitis virus, presumably through effects on macrophages (Barthold 1985, 1986b). Recovery from the infection appears to be a function of cell-mediated immunity. Passive transfer of sensitized lymphocytes and macrophages, but not antibody, is protective (Levy-Leblond and Dupuy 1977; Tardieu et al. 1980). Athymic, T cell-deficient nude mice are unable to recover, succumbing to chronic progressive infection of multiple organs, particularly liver and brain (Fujiwara et al. 1977; Tamura et al. 1977). Other strains of mouse hepatitis virus cause enteric infections. They are more easily recognized because of their more severe clinical effects and more obvious intestinal lesions. Enterotropic strains infect primarily the intestinal mucosa and are less likely to disseminate widely to other organs (see p. 379 for further discussion of enterotropic infections).

Etiology

Mouse hepatitis virus is a coronavirus with many strains that possess complex antigenic interrelationships (Barthold 1985, 1986a; Piazza 1969), virulence, and organotropism (Barthold and Smith 1984, 1987; Hirano et al. 1981; Piazza 1969). The antigenic composition of a strain does not predict its virulence or organotropism (Barthold 1985, 1986a; Barthold and Smith 1984). Coronaviruses can be divided into four distinct antigenic groups, with antigenic homology within each group, but no common antigen among groups. Mouse hepatitis virus belongs to a group containing rat coronaviruses, human coronaviruses (OC43 group), bovine coronaviruses, and porcine hemagglutinating encephalomyelitis virus. Neonatal mice can be experimentally infected with all of these viruses by oronasal inoculation, but adult mice can only be infected with rat and mouse coronaviruses. Despite susceptibility to infection, mice transmit rat coronavirues inefficiently (Barthold et al. 1990).

Frequency

Mouse hepatitis virus is an extremely prevalent virus among laboratory mice throughout the world. Confusion exists over the true frequency of this infection for a number of reasons. Most infected mice do not manifest clinical disease and have limited lesions that are difficult to discern. In enzootically infected populations, disease is often transient, since mice recover rapidly or signs may be obscured by partial protection with maternal antibody. Evidence of past infection is usually confirmed by indirect immunofluorescence and enzyme-lifted immunosorbent sero-assays, which are most sensitive (Smith 1983; Smith and Winograd 1986).

Comparison with Other Species

There was considerable interest in mouse hepatitis virus when it was first discovered, since it provided a potential model of viral hepatitis in humans (Piazza 1969). However, close similarities turn out to be minimal. Focal necrotizing hepatitis is a nonspecific lesion and is seen as a feature of many infectious diseases in the mouse and other species. Mouse hepatitis virus, like coronaviruses of other species, has either respiratory or enteric primary tropism, depending on virus strain.

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Rat Parvovirus Infection, Liver

Robert O. Jacoby

Synonyms. Rat virus infection, Kilham rat virus infection, H-1 virus infection

Gross Appearance

Gross lesions normally occur only in rats infected as infants or fetuses. Mechanical or toxic injury may, however, facilitate virus-induced necrosis in adults (Margolis et al. 1968; Ruffolo et al. 1966). During acute infection, the liver may be soft and pale brown with rounded edges and contain gray–white foci (necrosis) or red foci (laked blood or hemorrhage). These lesions can be accompanied by ascites and icterus (Ruffolo et al. 1966; Coleman et al. 1983; Jacoby et al. 1987). Mild