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Mouse Hepatitis Virus Infection, Liver, Mouse

Stephen W. Barthold

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 on p. 317. 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 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 spelenomegaly 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 many 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. 114). Syncytia arising from hepatocytes or other cells can be present (Fig. 115) (Barthold 1985; Barthold and Smith 1984; Jones and Cohen 1962; Piazza 1969). In athymic nude mice, parenchymal collapse, fibrosis, and syncytium forma-

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tion 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. 116) and spleen (Ishida et al. 1978). Hepatocellular mitotic activity is elevated in nude mice or mice recovering from mouse hepatitis virus infection (Fig. 117) (Barthold 1985; 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. 118).

Two patterns of mouse hepatitis virus infection are seen: respiratory and enteric. The enteric pattern is described on p. 317. 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; Barthold and Smith 1984). Athymic mice have endothelial syncytia in blood vessels of lung, heart base, brain, and other organs. Syncytia, necrosis, and marked myelopoeisis are frequent in bone marrow and spleen. Epithelial syncytia in the intestine are occasionally present (Barthold 1985; Fujiwara et al. 1977; Ishida et al. 1978; Tamura et al. 1977; Ward et al. 1977).

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 (see p. 319). 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 (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

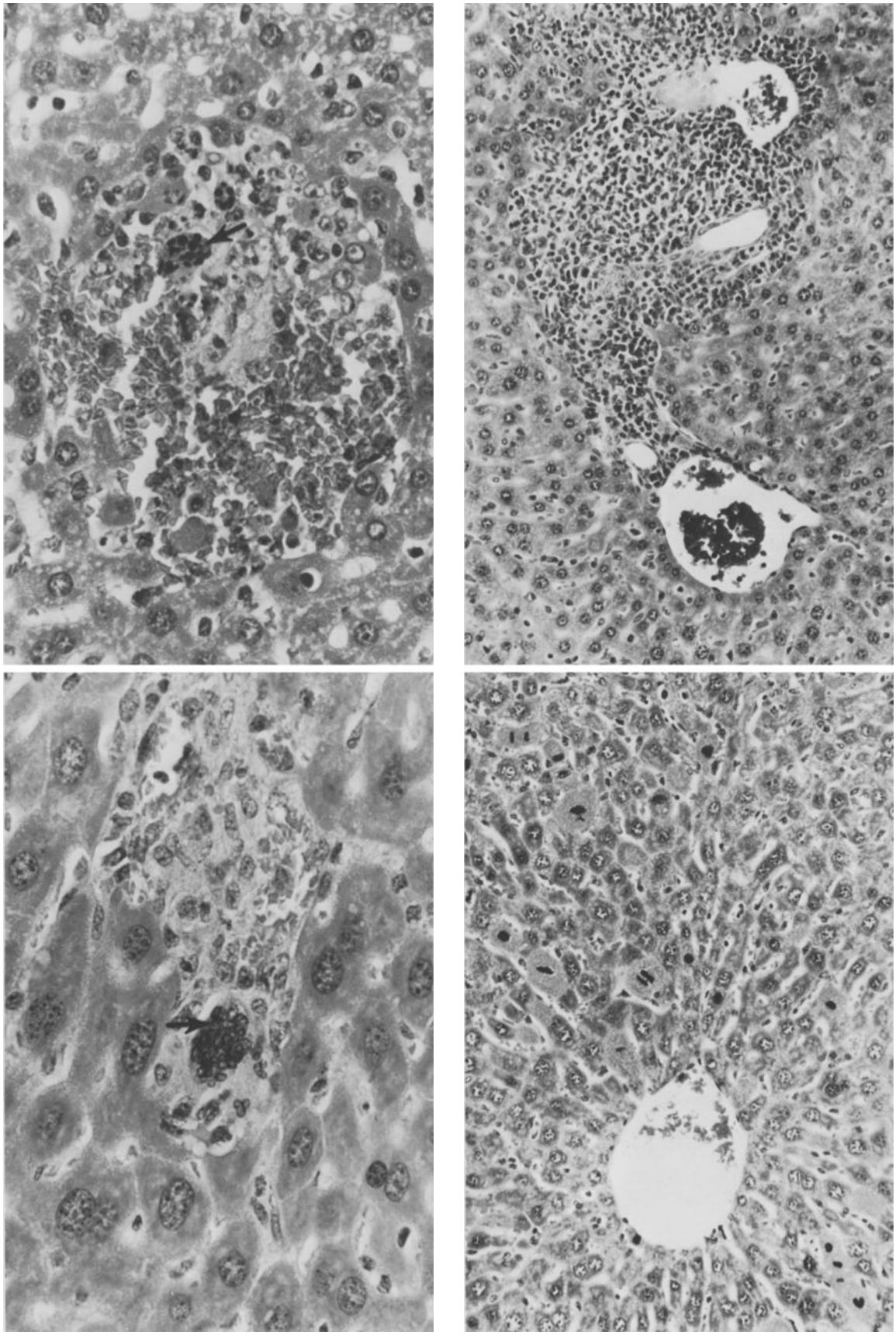
Necrotizing hepatitis and focal hepatitis mimic lesions induced by a number of other pathogens. Idiopathic focal hepatic necrosis can be encountered in normal mice in the absence of pathogens. Careful examination of liver lesions for multinucleate syncytia and examination of other organs, including nose, lung, and bowel for lesions, help provide a definitive diagnosis. Antigen of the virus can be demonstrated in active lesions (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, and mouse adenovirus. Histologic findings are confirmatory.

Biologic Features

Natural History. Mouse hepatitis virus is highly contagious and spreads by respiratory or orofecal routes. Respiratory strains vary widely in their virulence. Most strains are only mildly pathogenic, even in nude mice (Hirano et al. 1975), while others are 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). The respiratory pattern is usually subclinical, unless in infant or immunocompromised mice, which manifest signs of encephalitis and hepatitis (Barthold 1985). 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 to 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).

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; Hirano et al. 1975, 1981; Le Prevost et al.



1975; Piazza 1969). Apparently, many viral strains exist. Hepatotropism and neurotropism are characteristic features for 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.

Recent studies indicate that depending on viral strain, experimental or natural infections are mediated either through a respiratory or an enteric primary target (Barthold 1985; Barthold and Smith 1984). Strains of virus that cause respiratory infections seem to replicate in nasal or olfactory mucosa as a primary target, then disseminate to other internal organs if the host is susceptible. Strains of low virulence in resistant hosts cause asymptomatic infections limited to the nasal cavity, but some extend directly into the brain through the olfactory tracts. In susceptible hosts, vascular endothelial cells become infected, with hematogenous dissemination to multiple organs. Intestine can be infected, but involvement is mild with minimal lesions compared with enteric strains (Barthold 1985; Barthold and Smith 1983, 1984). 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 week after inoculation, after which time infection is cleared (Barthold 1985; Barthold and Smith 1983; Fujiwara et al. 1977; Tamura et al. 1977). Infection is short-term with no carrier state, but some neurotropic strains can persist in the brain, causing chronic demyelination (Stohlman and Weiner 1981). This does not seem to play a crucial role in the natural history of the infection.

◁ **Fig. 114** *(upper left).* Mouse hepatitis virus infection, liver, mouse. Focal necrotizing hepatitis with hemorrhage. Note the large degenerating cell with dense clumped chromatin *(arrow),* a frequent finding in these lesions. H and E, × 410

Fig. 115 *(lower left).* Liver, mouse. Focal hepatitis with a characteristic syncytium *(arrow),* probably of histiocytic origin. H and E, × 660

Fig. 116 *(upper right).* Extramedullary myelopoeisis, liver, athymic nude mouse infected with mouse hepatitis virus. H and E, × 165

Fig. 117 *(lower right).* Liver, mouse recovering from mouse hepatitis virus infection. Increased hepatocellular mitotic activity. H and E, × 165

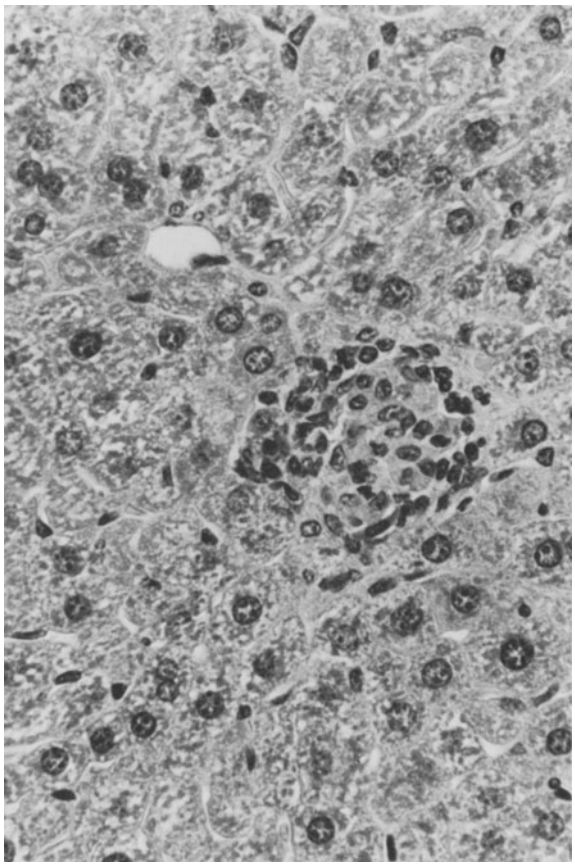


Fig. 118. Microgranuloma, liver, mouse recovering from mouse hepatitis virus infection. H and E, × 410

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; Hirano et al. 1975; Taguchi et al. 1979). Maternal antibody seems to play a protective role through this period of susceptibility under natural conditions, but this has not been well studied.

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). 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. The role of host resistance factors, such as genotype, has not been well studied with these strains. Enterotropic strains infect primarily the intestinal mucosa and are less likely to disseminate widely to other organs. Refer to p. 317 for further discussion of enterotropic infections.

Etiology. Mouse hepatitis virus is a coronavirus with many strains that possess complex antigenic interrelationships (Barthold 1985; Piazza 1969), virulence, and organotropism (Barthold and Smith 1984; Hirano et al. 1981; Piazza 1969). The antigenic composition of a strain does not predict its virulence or organotropism (Barthold 1985; Barthold and Smith 1984). This virus is closely related antigenically to the coronaviruses of the rat, and human serum often contains antibodies to it, suggesting a relationship to human coronaviruses. Rats can be experimentally infected and mice can be infected with rat coronaviruses, but the significance of natural heterologous host infection is unknown (Barthold 1985).

Frequency. Mouse hepatitis virus is an extremely prevalent virus among laboratory mice throughout the world. Mice from commercial suppliers are frequently infected. 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-linked immunosorbent assays, which are most sensitive (Smith 1985). The complement fixation test is insensitive and seldom detects antibody following natural infection.

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 are rare in naturally infected rats and only cursory descriptions are available in published reports. Acute parvovirus infection can cause hepatic necrosis. Affected livers have been portrayed as soft and pale and may contain gray-white foci (necrosis) or red foci (hyperemia and hemorrhage) (Ruffolo et al. 1966). Similar changes have been reported by Coleman and coworkers (Coleman et al. 1983), who also found ascites and yellow discoloration of the liver due to icterus. The foregoing changes should be expected primarily in suckling rats. However, mechanical or toxic injury to the livers of infected adult rats may be expressed by gross evidence of virus-induced necrosis (Margolis et al. 1968; Ruffolo et al. 1966). Mild lesions, resulting in nonfatal acute hepatic necrosis, should resolve uneventfully without residual lesions. If necrosis is severe, the liver may become firm or variably nodular. These changes correlate with stromal collapse, fibrosis, and compensatory hyperplasia to be discussed. Peliosis hepatis may also follow hepatic necrosis and is expressed as small red capsular cysts or elevations (Bergs and Scotti 1967).

Microscopic Features

Lethal infection of hepatocytes is primarily responsible for the liver lesions. The earliest change is the development of basophilic type A inclusions in hepatocytic nuclei. They can be detected as early as 24 h after infection and can persist for up to 3 weeks (Fig. 119) (Margolis et al. 1968). Inclusions also may be found in vascular endothelium, Kupffer cells, bile duct epithelium, and connective tissue fibroblasts. They vary in size and may fill the nucleus or can be separated from the nuclear membrane by a halo. Nuclear chromatin in infected cells is often concentrated at the nucle-