

Mouse Hepatitis Virus Infection, Intestine, Mouse

Stephen W. Barthold

Synonym. Lethal intestinal virus of infant mice (LIVIM).

Gross Appearance

Neonatal mice suffer high mortality. They become dehydrated with soiling of the perineum with yellow, diarrheic feces. Their stomachs are usually empty and intestines are thin-walled, flaccid, and contain watery yellow digesta and gas. Juvenile mice are less severely affected, but are often runted with pot bellies and oily-appearing hair. Careful examination of weaning-age or adult mice may reveal dark, sticky feces and opaque, thickened segments of bowel. Livers, if affected, have few to many small pale or hemorrhagic foci (see p. 134, this volume) (Barthold 1985; Barthold and Smith 1984; Barthold et al. 1982; Hierholzer et al. 1979; Ishida and Fujiwara 1979; Ishida et al. 1978; Kraft 1962, 1966).

Microscopic Features

The quality and location of intestinal lesions vary widely, depending on virus strain and host age. The virus characteristically causes mucosal epithelial necrosis and syncytium formation, while host responses include inflammation and compensatory mucosal hyperplasia. In susceptible hosts, such as neonates, viral effects are severe. Syncytia can be pronounced in the small intestine, since they tend to be retained at villus tips or are detached within the lumen. These large, multinucleate cells have been termed “balloon cells” because of their appearance (Fig. 295). Infected enterocytes can have poorly defined eosinophilic intracytoplasmic inclusions, but these are of little diagnostic value. When cytolysis predominates, villi become markedly attenuated (Fig. 296). Syncytia tend to form as large masses in the surface mucosa of the large bowel (Fig. 297), but the mu-

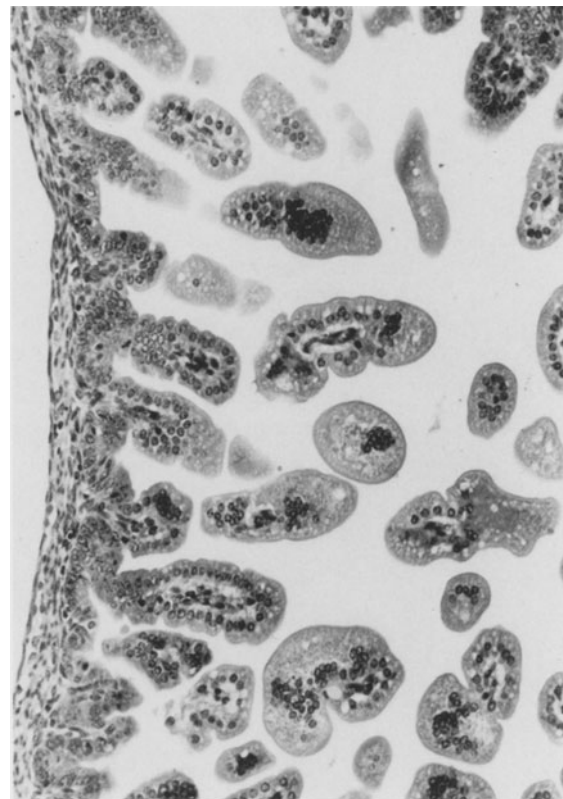
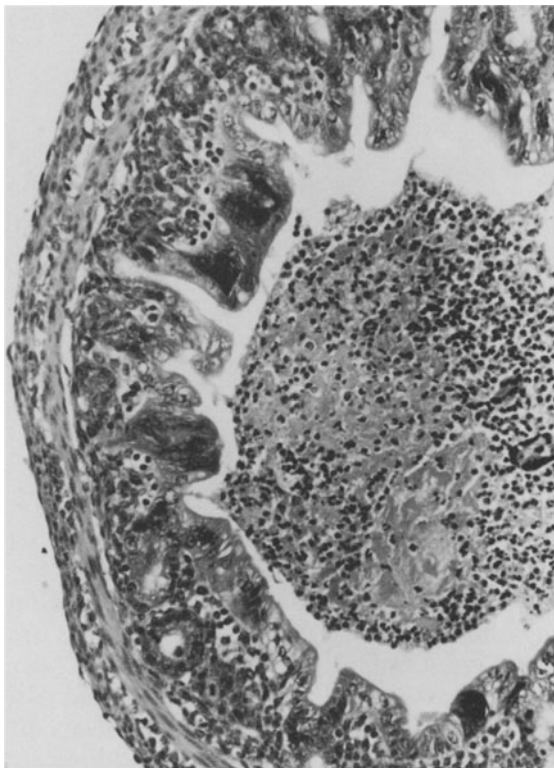
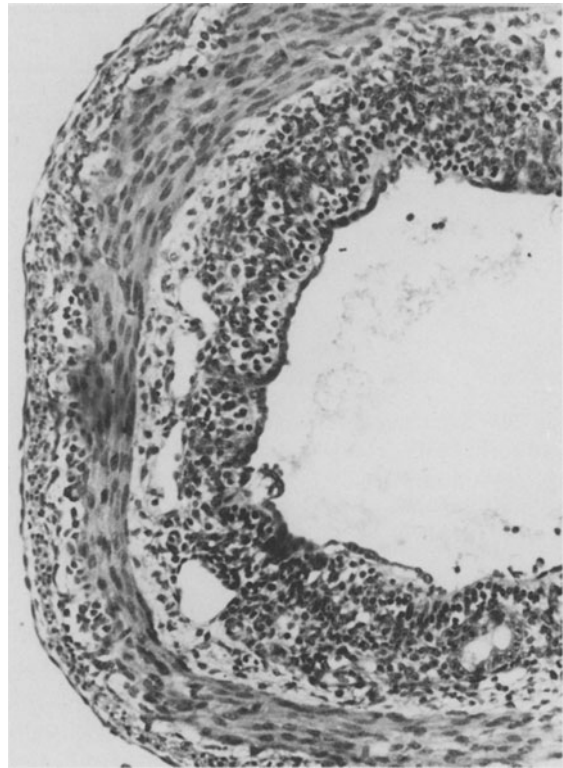
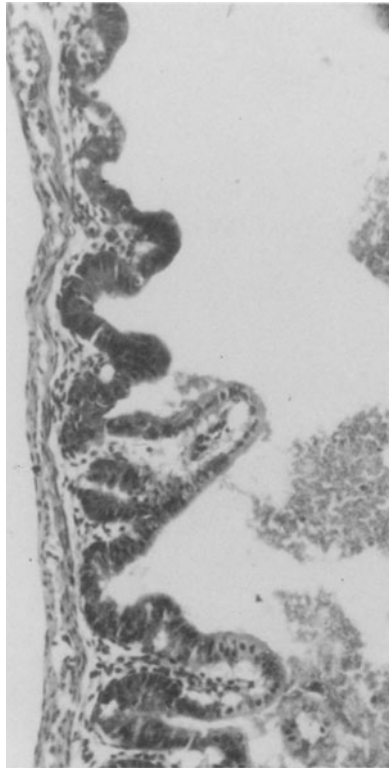


Fig. 295. Small intestine, neonatal mouse infected with enterotropic MHV. Villi possess several large multinucleate syncytia (“balloon cells”) which are typical for mouse hepatic virus. H and E, $\times 150$

cosal epithelium is often nearly completely effaced (Fig. 298). Large-bowel syndromes seem to preferentially involve cecum and ascending colon. Surviving mice or weaning-age mice respond to infection with marked mucosal hyperplasia of the involved segment of bowel (Fig. 299). Lesions in adult mice are marginal, consisting of only a few scattered syncytia and modest crypt hyperplasia (Barthold 1985; Barthold et al. 1982; Biggers et al. 1964; Hierholzer et al. 1979; Ishida and Fujiwara 1979; Ishida et al. 1978; Kraft 1962, 1966).



Athymic nude mice develop chronic, hyperplastic enteritis with characteristic mouse hepatitis virus (MHV) syncytia (Barthold 1985).

Ultrastructure

Infected enterocytes often have nonspecific degenerative changes or are undergoing necrosis. The endoplasmic reticulum contains 80- to 120-nm coronaviral particles and the cytoplasm may possess one or more amorphous electron-dense bodies and complexes of reticular structures (Fig. 300). These changes are seen in other infected tissues as well (see p. 135, this volume). Virus particles can also be found within macrophages of the lamina propria. Ultrastructural correlates of inclusions seen by light microscopy have not been found (Barthold et al. 1982; Hierholzer et al. 1979; Ishida and Fujiwara 1979; Ishida et al. 1978).

Differential Diagnosis

Enteric disease in mice can be caused by a number of viruses, bacteria and protozoa, but histologic changes in mice infected MHV with mouse hepatitis virus are diagnostic. Because lesions are often segmental, all levels of bowel should be examined.

◁ **Fig. 296 (upper left).** Small intestine, neonatal mouse infected with enterotropic MHV. Villi are markedly attenuated and crypts are hypercellular. (Courtesy of Dr. S. W. Barthold and Hemisphere Publishing Corp.). H and E, $\times 150$

Fig. 297 (lower left). Colon, neonatal mouse infected with enterotropic MHV. The lumen contains leukocytes and cellular debris. The surface mucosa has multiple prominent epithelial syncytia. H and E, $\times 150$

Fig. 298 (upper right). Cecum, neonatal mouse infected with enterotropic MHV. The mucosal epithelium has been almost completely effaced, leaving only the lamina propria, except for an incomplete layer of surface epithelium. H and E, $\times 150$

Fig. 299 (lower right). Cecum, neonatal mouse recovering from enterotropic MHV infection. The mucosa is distorted due to hyperplasia of the crypt epithelium. H and E, $\times 150$

Biologic Features

Natural History. Enterotropic strains of the virus are highly contagious. When first introduced to a breeding population of mice, epizootics of enteritis with diarrhea are associated with high morbidity and mortality among infant mice. Once enzootic within a population, signs of disease are less obvious, since pups from recovered dams are partially protected by maternal antibody (Hierholzer et al. 1979; Ishida and Fujiwara 1982; Ishida et al. 1978). Under these circumstances, reduced litter survival and runting occur, but may not be noticed. Infection among adults is usually subclinical. With the exception of athymic nude mice which develop persistent infections, mice recover within 2 weeks of infection (Barthold and Smith 1984; Barthold et al. 1982; Barthold 1985; Biggers et al. 1964).

Pathogenesis. Two patterns of infection occur in susceptible mice, depending on virus strain: enteric and nonenteric. Nonenteric strains have been extensively studied and are known to be influenced by host genotype, age, and lymphoreticular function. These viral strains have little or no tropism for bowel (see p. 135, this volume). Enterotropic strains cause infections largely limited to bowel, although dissemination to other organs may take place (Barthold and Smith 1984; Hierholzer et al. 1979; Ishida and Fujiwara 1979; Ishida et al. 1978). Host age is important in determining the outcome of enteric infections, but the roles of genotype and immune response have not been thoroughly investigated. Neonatal mice develop severe enteritis, resulting in malabsorption and diarrhea. As mice mature, intestinal cell turnover rate is accelerated, allowing a compensatory proliferative response to viral damage (Biggers et al. 1964). Maturation of immune response no doubt also influences infection. Colostral IgG antibody from immune mothers is protective against fatal infections in neonatal mice (Ishida and Fujiwara 1982). Athymic nude mice develop persistent enteric infections, with chronic mucosal hyperplasia (Barthold 1984).

The distribution of lesions within the intestine is probably determined by virus strain. Severe small intestinal involvement has been noted with some strains, such as LIVIM, MHV-S/CDC, and MHV-D (Biggers et al. 1964; Hierholzer et al. 1979; Ishida and Fujiwara 1979; Ishida et al. 1978). Predilection for large bowel has been noted with other mouse hepatitis virus isolates, such as MHV-Y (Barthold et al. 1982; Barthold and

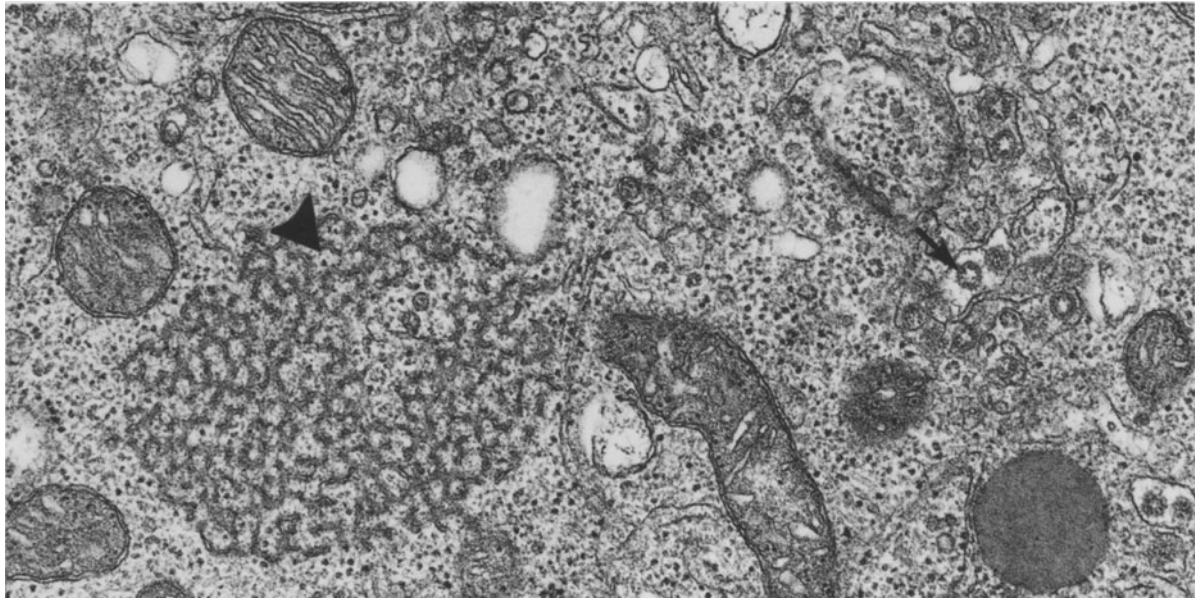


Fig. 300. Electron micrograph of cecal mucosal epithelium of a neonatal mouse infected with MHV. The cytoplasm contains an electron-dense reticular structure. Virus

particles are present in cisternae of the endoplasmic reticulum. (Courtesy of Dr. S. W. Barthold and Laboratory Animal Science). Uranyl acetate and lead citrate, $\times 225\,000$

Smith 1984). Intestinal bacteria and protozoa may influence the course of enteric MHV infections, but little work has been done in this regard.

Etiology. Many strains of this virus exist which can be partially differentiated antigenically, but all share common antigens among themselves, as well as with coronaviruses of rats and humans (Barthold 1985). Antigenic composition does not predict virulence or organotropism (Barthold and Smith 1984). It is not known if rats are experimentally susceptible to enteric strains as they are to nonenteric strains.

Frequency. As discussed in "Mouse Hepatic Virus Infection, Liver" (p. 317, MHV is among the most common viruses of laboratory mice. Enterotropic strains seem to be more prevalent than nonenteric strains, but this may be influenced by the relative ease of diagnosing enterotropic infections. Enteric lesions are always present in actively infected mice, but are detected most easily in young mice. Lesions are present for only 1–2 weeks and are absent when seroconversion takes place.

Comparison with Other Species

Enterotropic mouse hepatitis virus infections are analogous to enteric coronavirus infections in many other species of birds and mammals. Enter-

ic coronaviruses have been described in humans, nonhuman primates, turkeys, swine, cattle, sheep, horses, dogs, rats, cats, and rabbits. As in mice, these viruses are generally associated with disease in neonates. Small intestinal changes in neonates usually include villus "atrophy," resulting in malabsorption and diarrhea (Barthold 1985).

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Murine Rotavirus Infection, Intestine, Mouse

Stephen W. Barthold

Synonyms. Epidemic diarrhea of infant mice; epizootic diarrhea of infant mice, EDIM.

Gross Appearance

Mice less than 18 days of age have mustard-colored to dark sticky feces, which adhere to the perineum and give an oily appearance to the hair. Rarely, dried feces obstructs the anus, resulting in obstipation. Affected mice are pot-bellied and runted, but recover their rate of gain in weight by 8 weeks of age. The stomach is full of ingesta and the intestines are distended with copious mucoid yellow digesta and gas. Older mice do not manifest signs or lesions (Cheever 1956; Cheever and Mueller 1947; Kraft 1957, 1958, 1962; Sheridan et al. 1983).

Microscopic Features

Light microscopic lesions are difficult to recognize and are often absent, particularly in older mice. Tips of small intestinal villi, especially in the jejunum and ileum, appear bulbous due to swelling of epithelial cells, vascular congestion, and dilatation of lymphatics (Fig. 301). Columnar epithelial cytoplasm is swollen due to diffuse, fine vesiculation. Severely affected cells develop large cytoplasmic vacuoles and 1- to 4- μ m acidophilic inclusions may be randomly distributed within the cytoplasm. Minimal or no inflammation is present (Adams and Kraft 1967; Kraft 1957, 1962; Pappenheimer and Cheever 1948).

Ultrastructure

Enterocytes infected with the virus contain numerous vesicles arising from rough endoplasmic reticulum. These vesicles contain many virus particles, electron-dense granular material, and lipid. The cytoplasm also has aggregates of dense granular material with nascent virus particles that range from 65 to 80 nm in diameter (Fig. 302). The largest particles possess a double set of membranes; the outer membrane is acquired by budding into the lumen of the endoplasmic reticulum. Smaller particles with only a single membrane are also present in vesicles, as well as in cytoplasmic matrix. Tubular structures, which possess single or double sets of membranes, may be present in the cytoplasm, endoplasmic reticulum, and, occasionally, the nucleus. These structures apparently represent products of abnormal virus assembly (Fig. 303). No structures corresponding to the intracytoplasmic inclusions seen by light microscopy can be found ultrastructurally. Virus is present in enterocytes at all levels of the small and large intestine. In the small intestine, there appears to be a gradient of cellular susceptibility toward villus tips. Virus is released into the intestinal lumen by cell disruption and exfoliation (Adams and Kraft 1963, 1967; Banfield et al. 1968; Holmes et al. 1975; Kraft 1962).

Differential Diagnosis

Agents which produce diarrhea in young mice include: enteric mouse hepatitis virus, reovirus type 3, *Salmonella*, and *Spiroplasma muris*, among others. Coinfection among these agents is frequent. Murine rotavirus infection is difficult to diagnose, since morphological lesions are often subtle or absent, even in the presence of clinical