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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

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lesions resolve uneventfully, but if necrosis is severe the liver may become firm or nodular due to stromal collapse,, fibrosis, and compensatory hepatocytic and biliary hyperplasia. Small, red capsular cysts or elevations resembling those of peliosis hepatis may also develop (Bergs and Scotti 1967).

Microscopic Features

Viral-induced hepatocytic necrosis is the central lesion. Basophilic type A parvoviral inclusions may develop in hepatocytic nuclei as early as 24 h after infection and can persist for up to 3 weeks (Fig. 153; 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. Immunohistochemical staining and in situ molecular hybridization have revealed viral antigen and DNA, respectively, in these cell types (Jacoby et al. 1987; Gaertner et al. 1993). Nuclear chromatin in infected cells is often concentrated at the nuclear envelope. The cytoplasm of infected hepatocytes often becomes increasingly dense and eosinophilic or may undergo ballooning degeneration. Cell nuclei become pyknotic and karyorrhectic.

Necrosis can occur among individual cells or groups of cells, but is in random distribution with respect to lobular zones. During severe necrosis, large segments of one or more lobules may be destroyed. Inflammation develops during convalescence (see below), especially in portal triads, and consists primarily of mononuclear cells and some polymorphonuclear leukocytes (Ruffolo et al. 1966). Bile stasis can be observed in icteric livers and may be accompanied by bile thrombi.

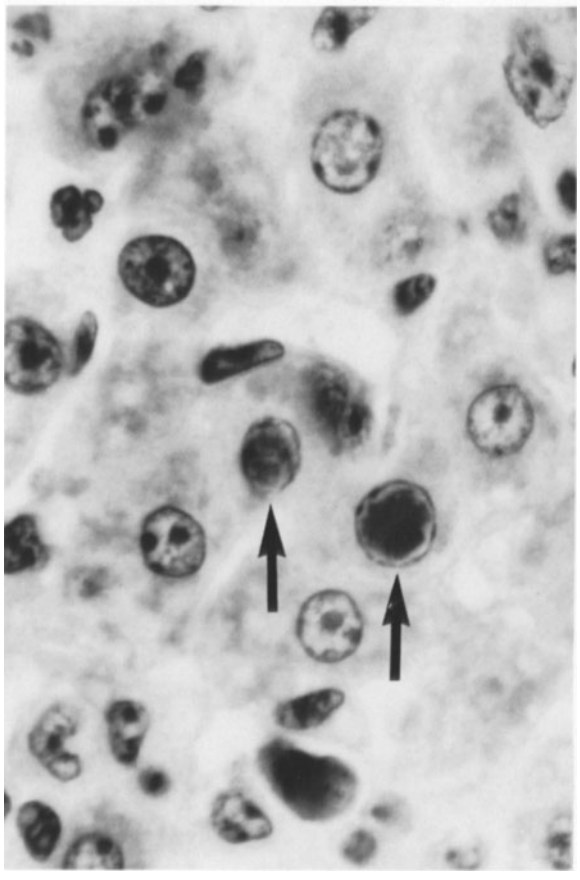


Fig. 153. Liver of a 4-day-old rat with natural RV infection. Several phases of inclusion body formation in hepatocytes are demonstrated (*arrows*). A necrotic hepatocyte is located at the *center bottom* of the field. (Courtesy of Dr. G. Margolis). H&E, ×900

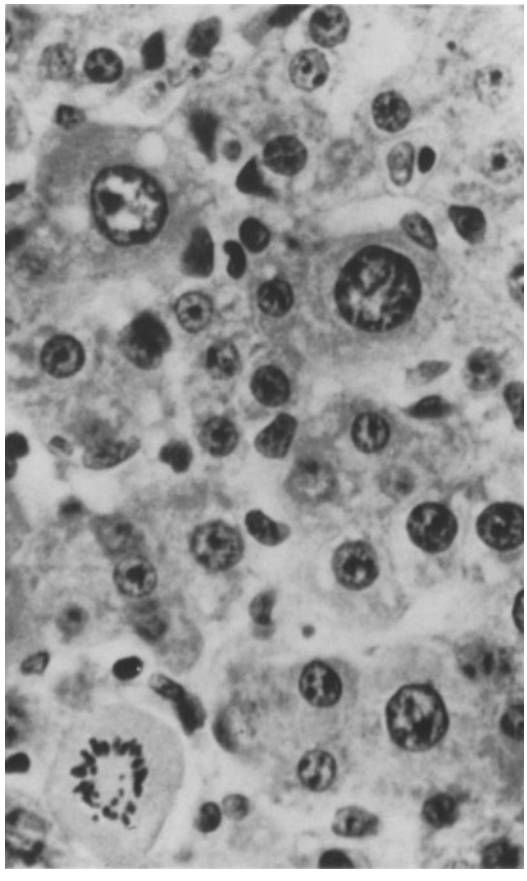


Fig. 154. Giant hepatocytes in the liver of a rat with rat virus infection. (From Margolis et al. 1968, with permission of Dr. G. Margolis and *Experimental and Molecular Pathology*) H&E, ×910

Liver lesions in convalescent rats occur in four patterns, either individually or in varying combinations (Margolis et al. 1968). These include the following: (1) giant cell transformation, (2) nonsuppurative portal hepatitis and biliary hyperplasia, (3) sinusoidal dilatation, and (4) postnecrotic stromal collapse, fibrosis, and nodular hyperplasia. These changes usually develop over several months. Giant cell transformation is characterized by cytomegaly, nuclear enlargement, and polyploidy (Fig. 154). Enlarged cells may contain multiple nuclei. Lesions of the type pictured in Fig. 154 have been detected at 16–43 days in rats inoculated experimentally as neonates or sucklings. Nonsuppurative portal hepatitis and biliary hyperplasia can begin as early as 8 days after infection and affect primarily small ducts (Fig. 155). Sinusoidal dilatation peliosis hepatis (Yanoff and Rawson 1964) is characterized by irregular blood-filled spaces enclosed by distorted plates of hepatocytes that may be one cell thick (Fig. 156). Postnecrotic stromal collapse and fibrosis, together with nodular hepatocytic hyperplasia, produce irreversible distortion of hepatic architecture (Fig. 157).

Ultrastructure

The ultrastructure of naturally occurring rat parvovirus infection has not been thoroughly described. Ruffolo and coworkers (Ruffolo et al. 1966) have, however, studied responses of partially hepatectomized rats to H-1 virus (Fig. 158). Viral particles were found primarily in nuclei of hepatocytes and Kupffer cells. Nuclear degeneration was marked by increased density and confluence of chromatin, especially adjacent to the

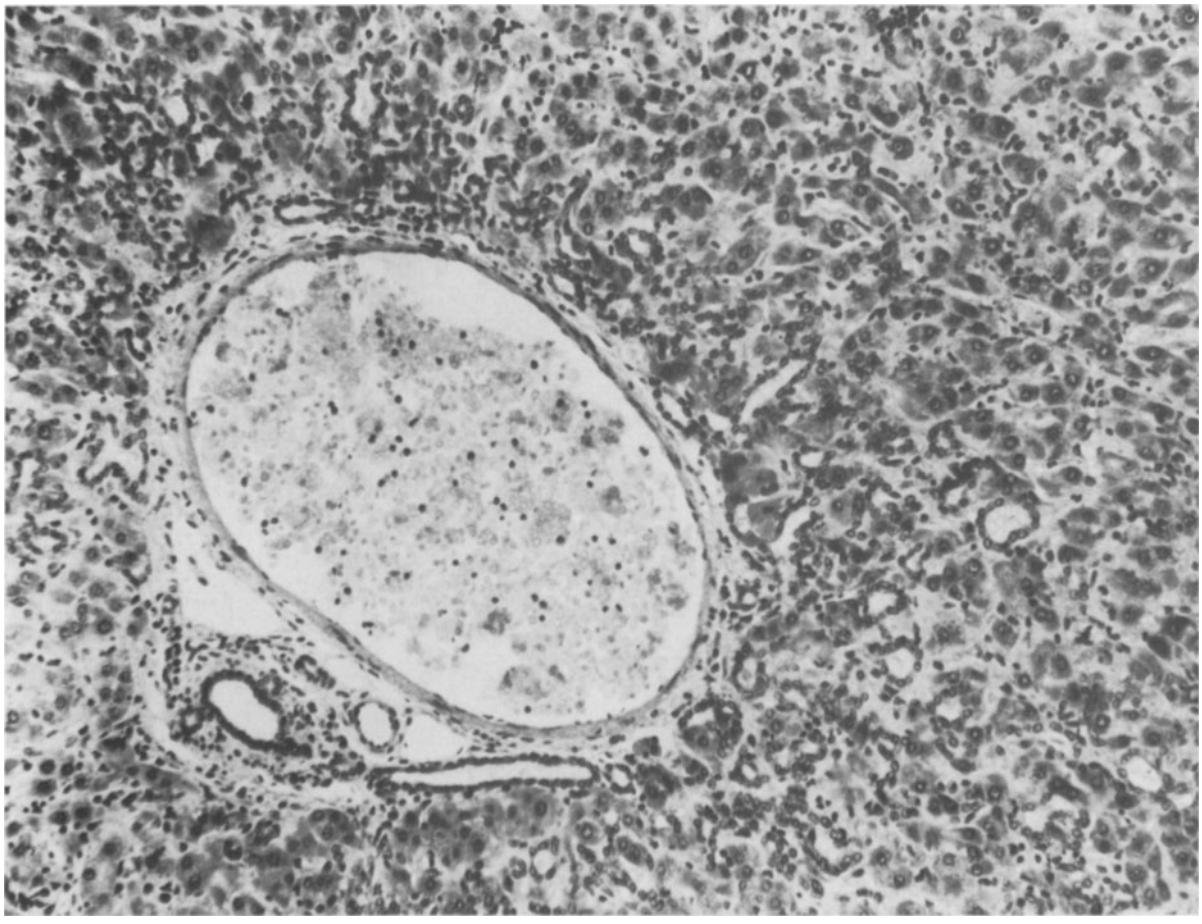
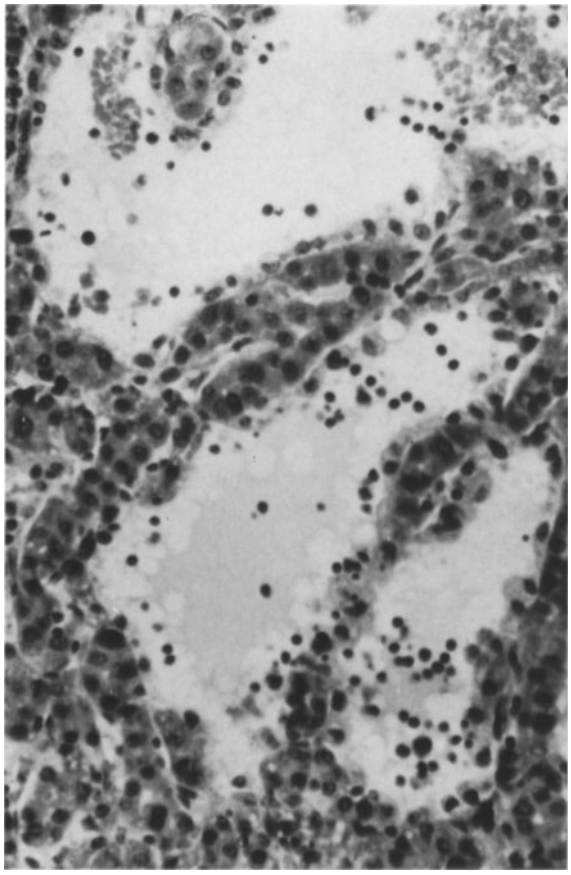
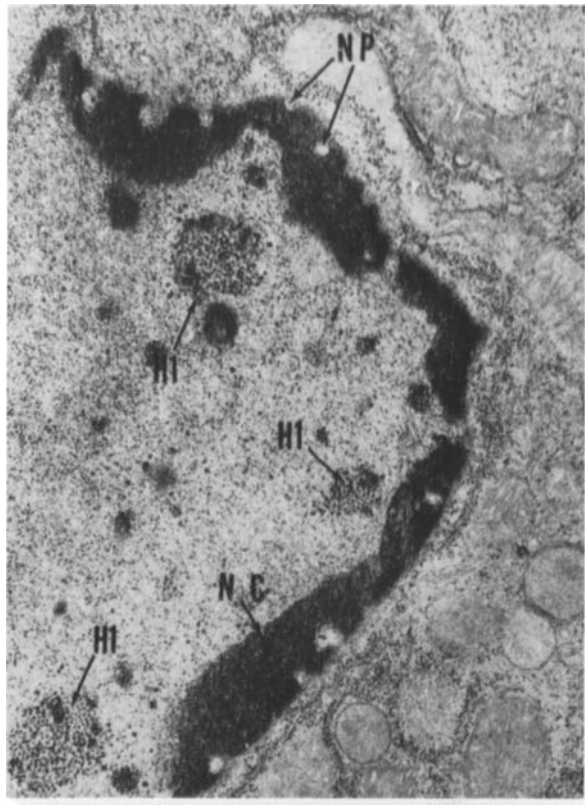


Fig. 155. Liver of a 19-day-old rat inoculated 8 days postnatally with H-1 virus. Numerous small, dilated, proliferated biliary ducts extend from the portal areas deep into the hepatic lobules. The hypocellular areas are remnants of necrotic foci. Note the chronic inflammatory responses. (Courtesy of Dr. G. Margolis.) H&E, ×80





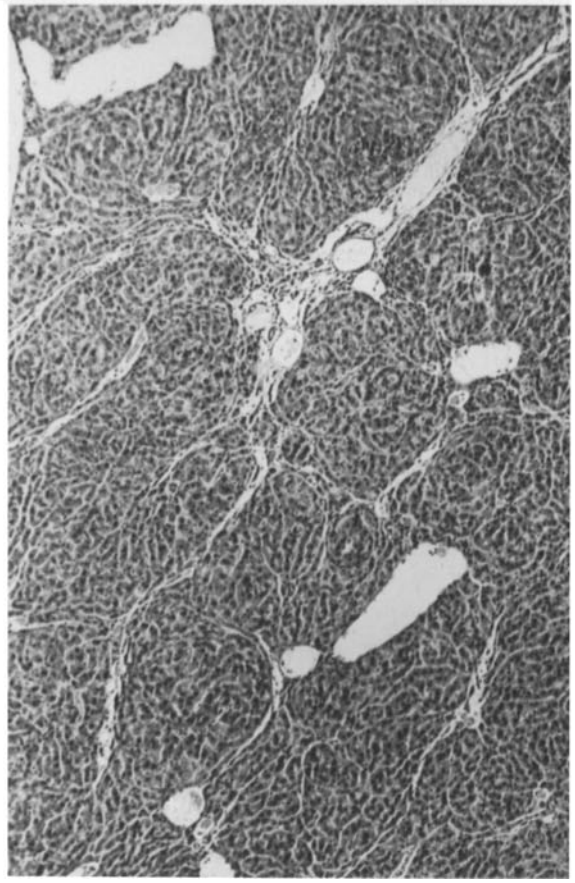


Fig. 156. (*upper left*) Peliosis hepatis in a rat inoculated with rat parvovirus. (From Margolis et al. 1968, with permission of Dr. G. Margolis and *Experimental and Molecular Pathology*) H&E, ×250

Fig. 157. (*below*) Nodular hyperplasia and fibrosis in the liver of a rat infected with rat virus about 7 weeks previously. (From Margolis et al. 1968, with permission of Dr. G. Margolis and *Experimental and Molecular Pathology*) H&E, ×46

Fig. 158. (*upper right*) Early changes in a hepatocyte of a partially hepatectomized rat infected with H-1 virus. Clusters of H-1 virus (*H1*) and nuclear pores (*NP*). The nuclear chromatin (*NC*) is denser than normal and condensed at the nuclear envelope. The cytoplasm is devoid of glycogen. (From Ruffolo et al. 1966, with permission of Dr. G. Margolis and the *American Journal of Pathology.*) TEM, ×20300

nuclear membrane, and by clear spaces and membrane-bound vesicles containing nuclear debris. Cytoplasmic changes occurred when nuclear degeneration was advanced. There was a relative increase in smooth endoplasmic reticulum. Cells were shrunken and the number of phagolysosomes was increased. Mitochondrial cristae were lost and intracristal spaces widened. Amorphous or granular material accumulated in cell matrices, and the cellular limiting membrane underwent lysis.

Differential Diagnosis

The hepatic lesions of parvovirus infection are not found in other viral infections of rats. Liver necrosis can occur in Tyzzer's disease (Jonas et al. 1970), but the causative organism *(Clostridium piliforme)* can usually be demonstrated with silver impregnation stains at the margin of necrotic foci. Liver necrosis and its sequelae can potentially follow inadvertent exposure to hepatotoxins that may contaminate the environment (e.g., food, bedding), but such lesions are rare among laboratory rats. Biliary hyperplasia, portal fibrosis, and peliosis hepatis occur in aged rats, but the etiology and pathogenesis of these lesions are not clear.

Physical or chemical hepatic injury can render even adult rats susceptible to parvoviral hepatitis, as noted above. Conversely, infection could potentially exacerbate effects of hepatotoxins and complicate interpretation of drug-induced lesions. In addition, the predilection of parvoviruses for mitotically active cells (Margolis and Kilham 1965) has the potential for altering the kinetics of hepatic neoplasia and immunologic responses (Campbell et al. 1977; McKisic et al. 1995).

Biologic Features

Prenatal infection can cause fetal deaths and resorption, but the propensity for in utero infection appears to depend on virus strain as well as dose and route of inoculation (Kilham and Margolis 1969; Margolis and Kilham 1972; Jacoby et al. 1988). During natural infection, virus appears to enter through the respiratory tract and is widely disseminated by viremia (Gaertner et al. 1993). Clinical disease is rare, but can be severe or lethal. It occurs most commonly among sucklings as the result of hepatic necrosis, granuloprival cerebellar hypoplasia from cytolytic infection of external germinal cells, and hemorrhagic infarction from infection of vascular endothelium and megakaryocytes (Kilham and Margolis 1966; Jacoby et al. 1987; Gaertner et al. 1993). Infection of adult rats is usually asymptomatic, although hemorrhagic infarcts can occur, especially in the central nervous system (Coleman et al. 1983). Chemical immunosuppression appears to be at least one factor that predisposes adults to hemorrhagic disease (Eldadah et al. 1967).

Infection of the liver results from viremia. The highly fenestrated sinusoidal endothelium of rat liver may facilitate direct infection of hepatocytes (Burkel and Low 1966; Margolis and Kilham 1965). Additionally, mitotic activity among rat hepatocytes remains high for up to 6 weeks postpartum (Steiner et al. 1966). Because rat parvovirus has a predilection for dividing cells, susceptibility to liver damage is predictably greater in young rats (Margolis et al. 1968). A predilection for mitotically active cells has also been used to explain prolonged hepatic infection, i.e., mitotic activity in response to virus-induced liver injury could initiate repeated cycles of hepatocytic infection (Margolis et al. 1968).

Rat parvoviruses are small (18–30 nm), single-stranded, negative-sense DNA viruses that hemagglutinate guinea pig erythrocytes and, to some extent, erythrocytes of other species (Siegl 1976). Three serogroups are distinguishable by hemagglutination inhibition or neutralization serology: the RV type, which incorporates a number of strains, including the prototype strain described by Kilham and Olivier (1959); the H-1 type discovered by Toolan (1968); and a recently discovered serotype named rat parvovirus-1 (RPV-1; Ball-Goodrich et al., unpublished data). The open reading frame encoding nonstructural proteins, which is located on the left side of the rat parvovirus genome, is highly conserved among rat parvoviruses. Thus generic assays such as enzyme-linked immunosorbent assay (ELISA), which detect both nonstructural and structural proteins do not distinguish among the viruses serologically.

Both RV and H-1 can be cultivated in primary monolayer cultures of rat embryo cell or in continuous cell lines from other species. RV, for example, replicates in 324K cells, a line of SV40-transformed human embryonic kidney cells (Smith 1983; Jacoby et al. 1987). Productively infected cells express viral hemagglutinin, develop

intranuclear inclusions, and undergo lysis (Kilham and Oliver 1959).

RV is excreted in urine, milk, feces, and possibly in expired air (Jacoby et al. 1988; Kilham 1966; Lipton et al. 1972). Infection is therefore communicable by contact with infected rats or by airborne transmission. Prevalence rates of 100%, based on seroconversion, are not unusual in enzootically infected colonies (Robinson et al. 1971). The varied expression of infection is influenced by host age and immunological status and by virus strain. RV can persist in euthymic rats exposed as infants (Jacoby et al. 1991) or in athymic rats exposed as infants or adults (Gaertner et al. 1989, 1993). Anatomic sites that harbor persistent virus appear to include endothelium, lymphoid cells, and smooth muscle fibers. Preexisting immunity, such as maternal immunity, can protect naive rats from acute and persistent infection, but immunity is not protective once infection has been established (Jacoby et al. 1988; Gaertner et al. 1991).

Comparison with Other Species

Rat parvovirus infection among rat colonies is widespread in many areas of the world, but there is no firm evidence that species other than the rat (laboratory or wild) are naturally infected. Experimental infections have, however, been demonstrated in other species (Siegl 1976; Jacoby et al. 1979). The most notable historical model is the hamster, in which RV and H-1 produce osteolytic lesions that result in dental and skeletal deformities, giving affected animals a mongoloid appearance (Toolan 1960).

Necrotizing viral hepatitis occurs in young or fetal animals of several species. These conditions include poxviral, coronaviral, and reoviral hepatitides in the mouse, infectious canine hepatitis, equine viral rhinopneumonitis, and exotic diseases such as Rift valley fever and Wesselbron disease in sheep (Jubb and Kennedy 1970).

A number of viruses can cause necrotizing hepatitis in humans (Edington 1979; Ishak et al. 1982), including the classic syndromes of human viral hepatitis (Ishak 1976; Koff and Galambos 1982; MacSween 1980; Poulsen 1976). Because these conditions are associated with necrosis and inflammation and are variably associated with viral inclusions or chronic degenerative sequelae, they have some morphological similarities to rat parvoviral hepatitis. However, they do not appear to be sufficiently similar, etiologically or pathogenetically, to warrant using parvoviral hepatitis as a model. The rat disease has also been suggested as a model for hepatitis of intrauterine or neonatal onset (Margolis et al. 1968) and has been compared with neonatal jaundice of humans accompanied by giant cell transformation (Margolis et al. 1968; Smetana et al. 1965).

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Mousepox, Liver, Mouse

Robert O. Jacoby

Synonyms. Infectious ectromelia

Gross Appearance

The liver is a major site of viral replication in mousepox, but gross lesions, even during acute disease, are not readily apparent until shortly before death. Severely affected livers are usually swollen and friable and may occupy up to half the volume of the peritoneal cavity, whereas mildly affected livers may remain grossly normal or have sparse focal necrosis. Necrotic areas appear first as pinpoint yellow–white foci, but increase rapidly in size and number. Confluent areas of necrosis can produce a reticulated pattern of yellow–brown to pink discoloration on the surface and throughout the parenchyma. Areas of hemorrhage also may develop. The pale hue of severely affected livers is in part due to fatty change, and the fat content of such livers can be as much as four times normal. Livers from mice that survive acute infection usually have a normal gross appearance. A few small scars may be present, however, especially at