Pneumonia Virus of Mice Infection, Lung, Mouse, and Rat

David G. Brownstein

Synonyms. Mouse pneumonia virus, pneumonia virus

Gross Appearance

Mice. Gross lung changes are not seen in mice naturally infected with pneumonia virus of mice (PVM). Pulmonary consolidation has been produced experimentally using tissue culture adapted virus (Harter and Choppin 1967; Tennant et al. 1965) or serially blind-passed PVM-infected lung tissue (Horsfall and Hahn 1940; Curnen and Horsfall 1947). Initially, consolidation is hilar in distribution with subsequent radiation along bronchioles. Consolidated foci are dark red and exude sanguinous fluid when cut. Later these foci become gray. Athymic mice, which are susceptible to persistent PVM infection, develop lobar consolidation or diffuse pulmonary edema (Weir et al. 1988).

Rats. Naturally infected adult rats usually have no gross lung changes but may have focal or multifocal plum-colored to gray foci less than 2 mm in diameter. These may occur in any lobe.

Microscopic Features

Mice. Histopathological lung changes are rare in naturally infected mice. Lesions produced experimentally with tissue culture adapted (Carthew and Sparrow 1980a; Vogtsberger et al. 1982) or serially blind-passed infected lung tissue (Horsfall and Hahn 1940) include both airway and parenchymal changes. PVM adapted to BHK-21 cells and inoculated at high doses (10^4–10^5 $TCID_{50}$) intranasally causes a mild erosive bronchiolitis and interstitial pneumonia. Bronchiolar epithelium first develops granular eosinophilic cytoplasm followed by lifting from the basal lamina. Desquamated epithelium and neutrophils may plug affected airways. Alveolar changes generally lag behind those in the airways. Alveolar septa are edematous, congested, and infiltrated with neutrophils and macrophages. There is some necrosis within alveolar walls. By the time bronchiolar epithelium has regenerated and returned to a normal appearance, alveolar septa are thickened by dense infiltrates of lymphocytes, macrophages, and scattered neutrophils. Alveolar spaces may contain an exudate with a similar inflammatory cell composition. Inflammatory changes in the parenchyma peak near the end of the 2nd week of experimental infection and are usually resolved by the end of the 3rd week.
Lower doses ($<10^3$ $TCID_{50}$) of tissue culture adapted PVM cause vascular-oriented inflammation and interstitial pneumonia (Vogtsberget et al. 1982). The vascular component has been described as an acute vasculitis with infiltrates of neutrophils and lymphocytes followed by a mild nonsuppurative vasculitis, which persists to the end of the 3rd week of infection. The interstitial pneumonia is acute, but its duration and histological features have not been reported.
Mild rhinitis is a constant feature in mice infected intranasally with tissue culture adapted PVM, even at doses that fail to produce pulmonary histological lesions. The nasal mucosa is edematous with multifocal erosions. Neutrophils and lymphoid cells infiltrate the lamina propria. A sparse exudate rich in neutrophils and desquamated epithelium is occasionally present.
Changes in the lung of athymic mice infected with PVM consist of thickening and hypercellularity of alveolar walls, intra-alveolar hemorrhage and fibrin deposition, and accumulations of macrophages and desquamated alveolar type II cells in alveolar spaces (Weir et al. 1988).

Rats. Histopathological changes in lung have been observed in naturally and experimentally infected rats. Naturally infected weanling Lewis rats develop hyperplasia of bronchus-associated lymphoid tissue (BALT), perivascular mononuclear cell infiltrates, and multifocal interstitial pneumonia (Fig. 353). Prominent germinal centers form within the expanded BALT. The overlying airway epithelium is intact but bulges into the lumen. Transepithelial lymphocytes are increased near these reactive lymphoid nodules. Pulmonary venules, small veins, and aterioles con-

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tain dense, usually symmetrical, adventitial infiltrates of plasma cells, lymphoid cells, and macrophages (Fig. 354). The endothelium of these vessels may be hypertrophied, and leukocyte pavementing may be prominent. Perivascular infiltrates often occur in areas of interstitial inflammation. Alveolar septa are congested, edematous, and infiltrated with lymphocytes, plasma cells, and macrophages. Alveolar lining cells are swollen or hypertrophied. Alveolar spaces contain variable numbers of foamy macrophages, desquamated pneumocytes, lymphocytes, and neutrophils (Fig. 355).

Multifocal nonsuppurative vasculitis and acute interstitial pneumonia have been described in experimentally infected Fischer 344 rats (Vogtsberger et al. 1982).

Ultrastructure

The fine structure of PVM infection has been described in cell cultures (Compans et al. 1967; Berthiaum et al. 1974) and in naturally infected athymic mice (Weir et al. 1988). Nucleocapsid assembly occurs in the cytosol. Pleomorphic inclusions, which may be seen by light microscopy in the vicinity of the nucleus, are composed of electron-dense dots or threads approximately 12 nm in diameter. Virus maturation occurs at the plasma membrane, where budding particles have round or filamentous profiles about 80–120 nm in diameter, with filamentous forms predominating. The viral envelope contains surface projections approximately 12 nm in length. Within the envelope are four to eight electron-dense dots or strands identical to those seen in the cytosol. Strands are usually coiled in filamentous forms. Terminal swellings 150–300 nm in diameter are usually present on filamentous forms.

In negatively stained preparations filamentous forms predominate with lengths up to 3 μm and diameters of approximately 100 nm. Alveolar type II cells, the principal targets of PVM infection, degenerate and detach. Most budding virions can be seen in detached and degenerate alveolar type II cells.

Differential Diagnosis

Mice. Naturally occurring PVM apparently rarely causes pneumonia. Until there is evidence to the contrary, PVM should be considered an unlikely cause of inflammatory lung disease in mice under natural conditions, but should be regarded as a cause of mild erosive rhinitis. PVM is one of the causes of "wasting disease" in athymic mice and must be distinguished from other causes which include infections with Sendai virus or mouse hepatitis virus (Hou et al. 1992).

Rats. The pulmonary changes in PVM infection must be distinguished from those caused by Sendai virus, rat coronaviruses, *Mycoplasma pumonis*, and pathogenic bacteria. The lesions caused by PVM most closely resemble those caused by pneumotropic strains of rat coronaviruses (Parker's rat coronavirus). Generally the latter causes milder lesions than PVM.

Biological Features

Natural History. PVM causes acute, limited infections in immunocompetent rodents. Virus peristence (over 20 days) has been reported in germ-free athymic (nu/nu) mice (Carthew and Sparrow 1980b). Enzootic and epizootic forms exist, and both are asymptomatic in mouse and rat colonies.

Transmissibility in mouse colonies is low; infections may therefore be focal (Tennant et al. 1966). Attack rates in 59% of infected mouse colonies are reported to be 25% or less. This is the lowest attack rate for any indigenous murine virus (Tennant et al. 1966). Various age groups may harbor the infection, depending on management practices. In one colony antibody was first detected in 8-week-old mice, while in a second colony mice did not seroconvert until the age of 7 months (Parker et al. 1966).

Attack rates are apparently higher in rat colonies. We frequently find a 100% prevalence of serum antibodies (hemagglutination inhibition test) in weanling rats from enzootically infected colonies.

Clinical signs have not been reported for naturally infected mice or rats. Depression, anorexia, weight loss, ruffled fur, hunched posture, and labored respiration have been reported in experimentally infected mice (Horsfall and Hahn 1940).

Pathogenesis. Viral replication is restricted to the epithelium of the respiratory tract (Carthew and

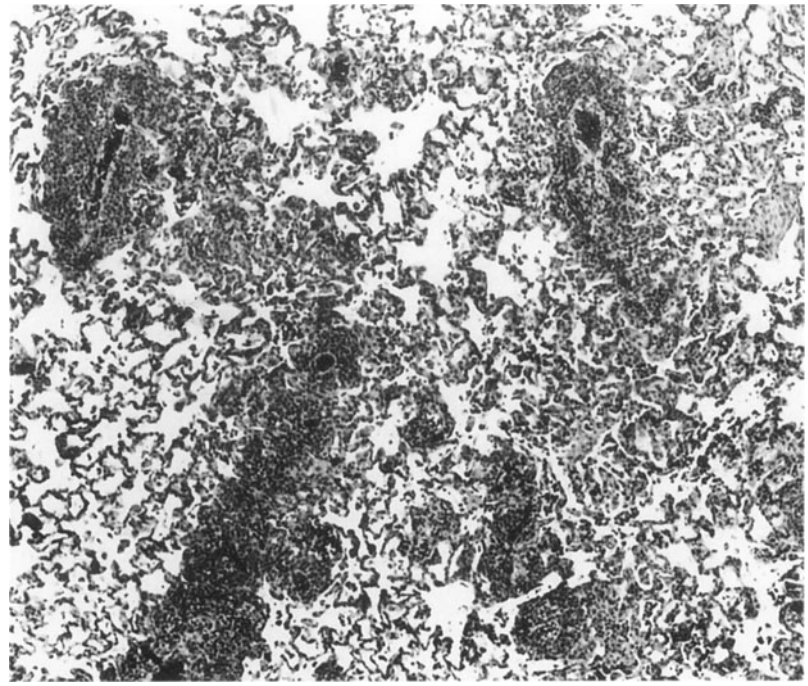

Fig. 353. (*above*) Perivascular infiltrates and interstitial pneumonia in a rat naturally infected with PVM. H&E, ×64

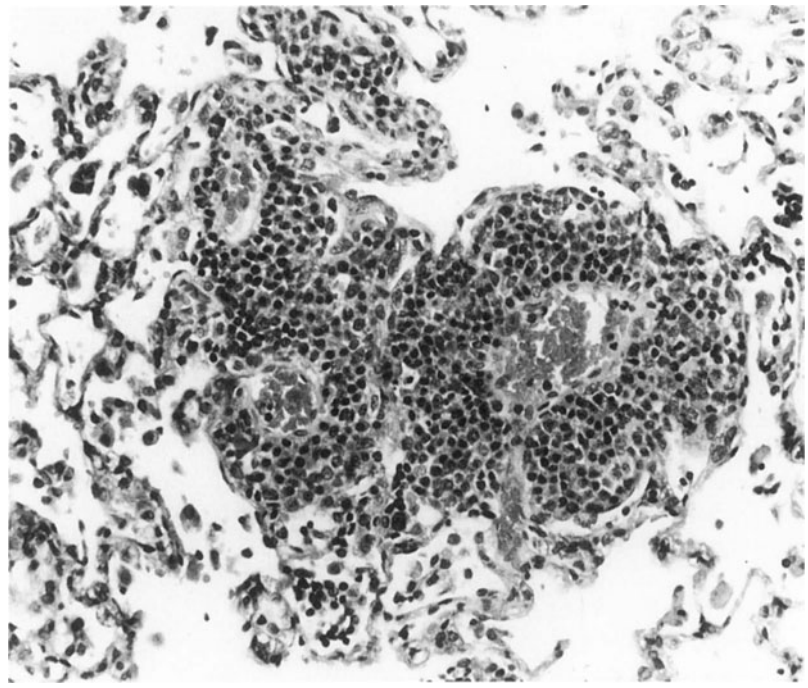

Fig. 354. (*below*). Perivascular plasma cell infiltrates in a naturally PVM-infected rat. H&E, ×217

Sparrow 1980a,b). Infectious virus can be detected up to 10 days after exposure (A.L. Smith and V.A. Carrano, personal communication). Viral antigens have not been detected in lung sections beyond day 7 in mice (Carthew and Sparrow 1980a). Virus is isolated most consistently from nasal washes in experimentally or naturally infected rodents (A.L. Smith and V.A. Carrano, personal communication).

Seroconversion [hemagglutination inhibition (HAI) complement fixation (CF)] usually occurs 9 or 10 days after exposure. CF antibody titers begin

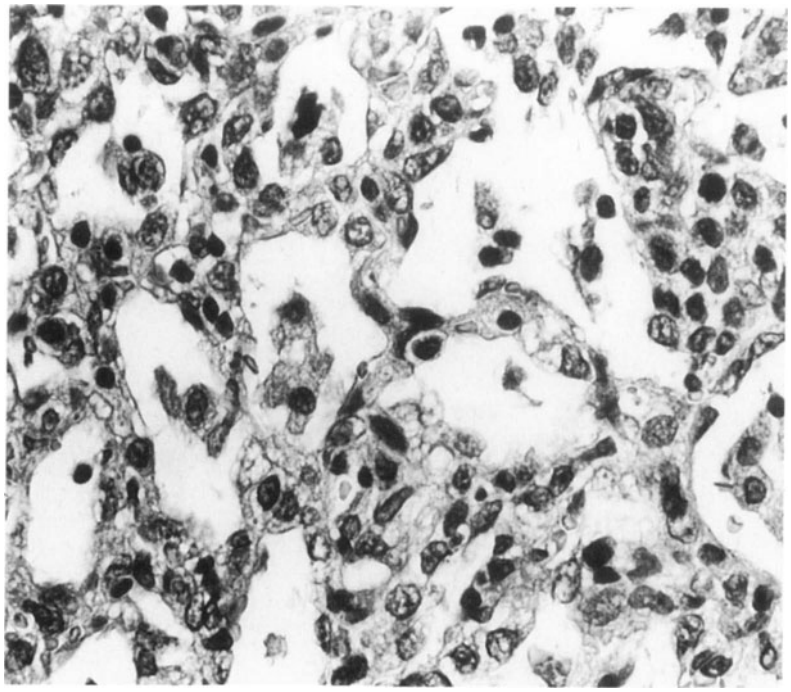

Fig. 355. Intersitial pneumonia in a naturally PVM-infected rat. Alveolar septa are congested, edematous, and infiltrated with mixed mononuclear cells. Alveolar lining cells are hypertrophied. Alveolar spaces contain large foamy mononuclear cells – probably desquamated pneumocytes and macrophages. H&E, ×536

to decline during the 3rd week of infection, while HAI antibody titers remain elevated for at least 4 months (Tennant et al. 1966).

Etiology. Pneumonia virus of mice is a *Pneumovirus* of the family Paramyxoviridae. It shares this genus with respiratory syncytial virus, which has structural and biological but not antigenic similarities (Joncas et al. 1969; Berthiaume et al. 1974). PVM is a predominantly filamentous enveloped virus containing a single-stranded RNA genome. The hemagglutinins probably occur within the fringe of envelope projections. The virus is labile in the environment and rapidly inactivates at room temperature.

Frequency. Pneumonia virus of mice is prevalent in mouse and rat colonies throughout the world. In a recent survey 63% of mouse and 68% of rat colonies from institutional and commercial sources were infected (Parker and Richter 1982).

Comparison with Other Species

Pneumonia virus of mice and respiratory syncytial virus (RSV) are the sole representatives of the genus *Pneumovirus*. PVM infects rodents naturally; RSV infects children, cattle, and sheep, and experimentally infects ferrets and cotton rats. Both of these viruses have potentially broad respiratory epitheliotropism that is expressed differently depending on the host, host age, and infecting dose of virus. Experimentally, PVM causes rhinitis, bronchiolitis, or interstital pneumonia in mice. Naturally occuring PVM infection in rats causes interstital pneumonia. RSV in humans and cattle causes rhinitis, bronchiolitis, or interstital pneumonia (Aherne et al. 1970; Mohanty et al. 1975). Experimental RSV produces rhinitis and interstitial pneumonia in infant ferrets (Prince and Porter 1976) and bronchiolitis in cotton rats (Prince et al. 1978).

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Rat Coronavirus Infection, Lung, Rat

David G. Brownstein

Synonym. Parker's rat coronavirus, rat submaxillary gland virus, sialodacryoadenitis virus

Gross Appearance

Naturally infected adult rats rarely have grossly observable lung changes. Elsewhere macroscopic lesions are absent or confined to salivary glands and periglandular tissue. Ocular changes may also occur as a consequence of keratitis sicca. Axenic rats experimentally infected with Parker's rat coronavirus (PRC) develop gross lesions in the lung on postinnoculation days 6 and 7, which consist of randomly dispersed red-brown to gray foci less than 1 mm in diameter (Bhatt and Jacoby 1977). Although PRC may cause fatal pneumonia in a high percentage of newborn and day-old rats, gross pulmonary lesions have not been described (Parker et al. 1970). Outbred young adult SPF Wistar rats experimentally infected with sialodacryoadenitis virus (SDAV) develop mild randomly dispersed red foci 5–7 days after intranasal inoculation (Wojcinski and Percy 1986).

Microscopic Features

Lung changes in young adult rats are mild and short-lived irrespective of the infecting strain. Nonsialotropic strains such as PRC produce hyperplasia of bronchusassociated lymphoid tissue (Fig. 356), perivenular lymphoid infiltrates (Fig. 357), and patchy interstitial pneumonia (Fig. 358; Bhatt and Jacoby 1977). Sialotropic strains such as SDAV produce more severe acute inflammatory changes in bronchioles and lung parenchyma (Wojcinski and Percy 1986). Random patches of bronchiolar epithelium undergo necrosis in conjunction with infiltration and exudation by neutrophils. Acute inflammation may extend from terminal bronchioles into adjacent alveoli. Affected alveolar septa are edematous, infiltrated by leukocytes, and alveolar spaces contain desquamated pneumocytes, macrophages,