Murine Respiratory Mycoplasmosis, Upper Respiratory Tract, Rat

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Synonyms. Murine chronic respiratory disease; infectious catarrh.

Gross Appearance

Some affected rats have mucopurulent nasal exudate or pink, porphyrin-tinted oculonasal discharge, but gross lesions in the upper respiratory tract are, in many cases, not detectable. Exudate can sometimes be found in the nasal passages, trachea, and tympanic cavities. These structures should be disturbed as little as possible during dissection and collection of specimens for culture so as to preserve the quality of the tissues for microscopic examination.

Microscopic Features

The principal lesions of murine respiratory mycoplasmosis in the upper respiratory tract are, in decreasing order of frequency, rhinitis, otitis media, laryngitis, and tracheitis. All are characterized by: (a) epithelial changes including hypertrophy, hyperplasia, metaplasia to nonkeratizing squamous or stratified squamous epithelium, and goblet cell hyperplasia; (b) neutrophilic exudation; and (c) accumulation of lymphocytes and plasma cells.

Rhinitis. Normal rat nasal mucosa (Fig. 114) contains few lymphocytes except for small numbers around and just anterior to the nasopharynx. In murine respiratory mycoplasmosis, lymphoid cells accumulate diffusely in the subepithelial stroma. Loss of cilia, pseudoglandular epithelial hyperplasia, and goblet cell hyperplasia can be extensive and severe (Fig. 115).

Otitis Media. The middle ears are nearly as frequently affected as the nasal passages. The tympanic cavity may be completely filled with neutrophils. The lining epithelium, normally simple squamous or low cuboidal, becomes hyperplastic. Goblet cells are often numerous. In many cases the lumen becomes filled with immature collagenous connective tissue, leaving only a few glandular spaces containing neutrophils at the boundary representing the original lining (Fig. 116). The cavity may eventually clear but the lining membrane remains thickened by connective tissue.

Laryngitis and Tracheitis. The laryngeal submucosal glands are in many cases dilated with mucopurulent exudate. Epithelial changes are as in other tissues, and the tracheal mucosa can become extremely thickened by epithelial hypertrophy and hyperplasia, with formation of gland-like crypts and severe accumulation of lymphoid cells (Figs. 117 and 118).

Ultrastructure

Mycoplasma pulmonis parasitizes the surface of respiratory epithelial cells (Fig. 119). Various degenerative changes occur, ranging from loss of cilia and vacuolation of cytoplasm to necrosis of scattered individual cells. The mechanisms for these changes are unknown, although damage by the accompanying inflammatory response probably contributes.

Differential Diagnosis

The characteristic respiratory sounds (snuffling) are not consistently present, but in many cases are the only clinical manifestation of the disease. For unknown reasons, in some affected rats porphyrin secretion from the Harderian glands results in accumulation of red material around the eyes and external nares. Some authors have mistakenly identified this pigment as serosanguinous exudate. In the natural disease, most rats with these signs are infected with *M. pulmonis* and one or

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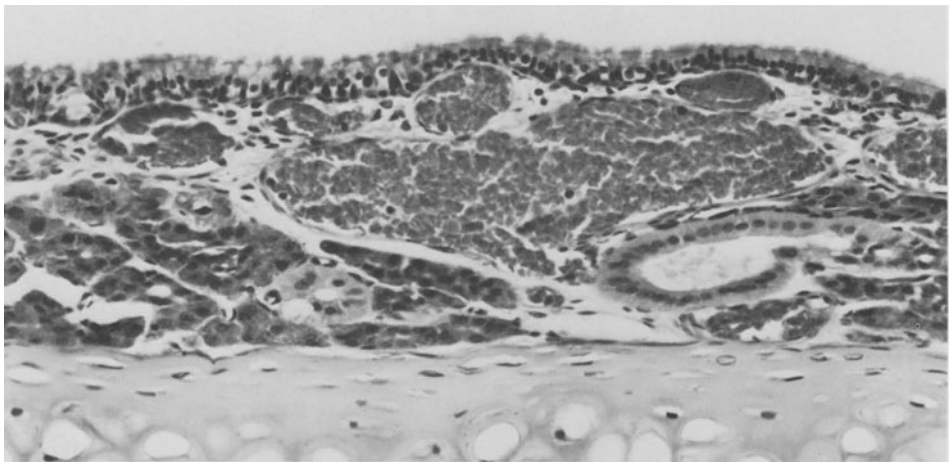

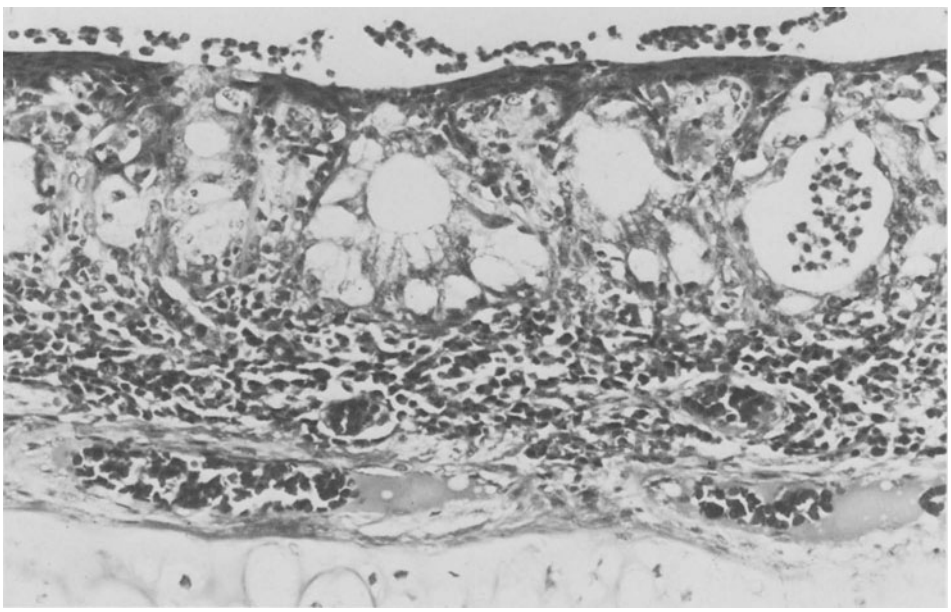

Fig. 114 *(Above).* Normal nasal septal mucosa. H and E, x 220

Fig. 115 *(Below).* Nasal septal mucosa in severe murine respiratory mycoplasmosis with neutrophilic exudate, flattening of the superficial epithelium, loss of cilia, extensive goblet cell hyperplasia with formation of glandular epithelial infoldings, and diffuse accumulation of lymphocytes and plasma cells. H and E, × 220

more other agents such as Sendai virus, sialodacryoadenitis virus, rat coronavirus, *Streptococcus pneumoniae, Corynebacterium kutscheri, Bordetella bronchiseptica, Klebsiella pneumoniae, Pseudomonas aeruginosa, Pasteurella pneumotropica,* or *Streptobacillus moniliformis*. Uncomplicated infections seldom occur. However, *M. pulmonis* alone is sufficient to produce the full spectrum of lesions of respiratory mycoplasmosis and no other organism has been shown to produce its characteristic lesions in pathogen-free rats. *M. pulmonis* is therefore the primary pathogen, but clearly other agents do modify the course of the natural disease.

Disease caused by Sendai virus is usually subclinical in adult rats and is characterized by necrotizing bronchiolitis (Jacoby et al. 1979). Sialodacryoadenitis virus and coronavirus do not cause serious respiratory disease in adult rats and do not appear to be important respiratory pathogens, but they can cause focally necrotizing rhinotracheitis and multifocal interstitial pneumonia (Jacoby et al. 1979). These viral lesions, if found, should not be difficult to differentiate from those of respiratory mycoplasmosis. *S. pneumoniae* and *C. kutscheri* have been associated with rhinitis and otitis media, although in most cases *M. pulmonis* is probably also present. Other bacteria are

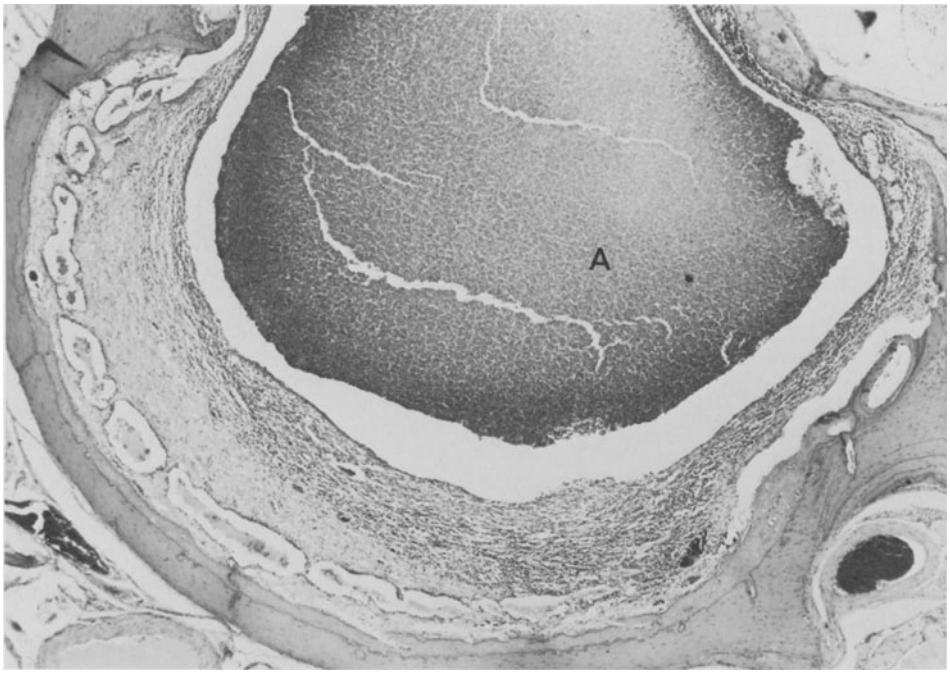

Fig. 116. Tympanic bulla with purulent exudate in lumen *(A)* and fibrosis of the lining membrane. H and E, × 35

probably little more than opportunistic pathogens.

Diagnosticians must diligently gather all information necessary to identify all agents present in affected rats. Results of histological studies, bacterial and mycoplasmal cultures, and serological tests must be carefully considered in making diagnoses.

A diagnosis of murine respiratory mycoplasmosis can be supported by enzyme-linked immunosorbent assay (ELISA) of serum antibodies (Horowitz and Cassell 1978) and by cultural recovery of the organism. Failure to isolate the organism does not rule out the diagnosis, as the organism can be quite difficult to grow by routine culture methods. Among the difficulties which can be encountered is growth inhibition by certain tissue and medium components (Del Giudice et al. 1980; Kaklamanis et al. 1971; Mardh and Taylor-Robinson 1973; Tauraso 1967). Davidson et al. (1981) have reported that cultural isolation and ELISA both detected a high percentage of infected rats, and that combinations of methods increased the detection rate. Culturing multiple sites in the respiratory tract also increased the rate of recovery of organisms, but of individual sites the organism was most frequently isolated from the nasopharyngeal duct.

Biologic Features

Several aspects of the natural history of murine respiratory mycoplasmosis need to be clarified. The major mode of transmission is probably via aerosol from affected mothers to neonates, but *in utero* transmission apparently occurs also. Infection results in a slowly progressive respiratory disease which persists throughout the animal's life. Infected rats can transmit the infection to others but horizontal transmission is slow, even within a cage, and is considerably reduced by increasing the space between cages. Transmission of *M. pulmonis* via food, water, bedding, and other materials has been suggested but not proved. Inasmuch as *M. pulmonis* has been isolated from wild rats, cotton rats, rabbits, Syrian hamsters, and guinea pigs, these animals could be potential sources of infection.

In conventional and experimentally infected rats, the nasal passages and middle ears are the most commonly infected sites; lung lesions are less consistently found. Thus the upper respiratory tract seems to be the source of infection for the distal tract. The extent to which the distal airways and lungs become affected seems to depend on complex interactions among host, organism, and environment. Exposure to ammonia from soiled cage bedding or to purified ammonia increases the severity of upper respiratory lesions and both

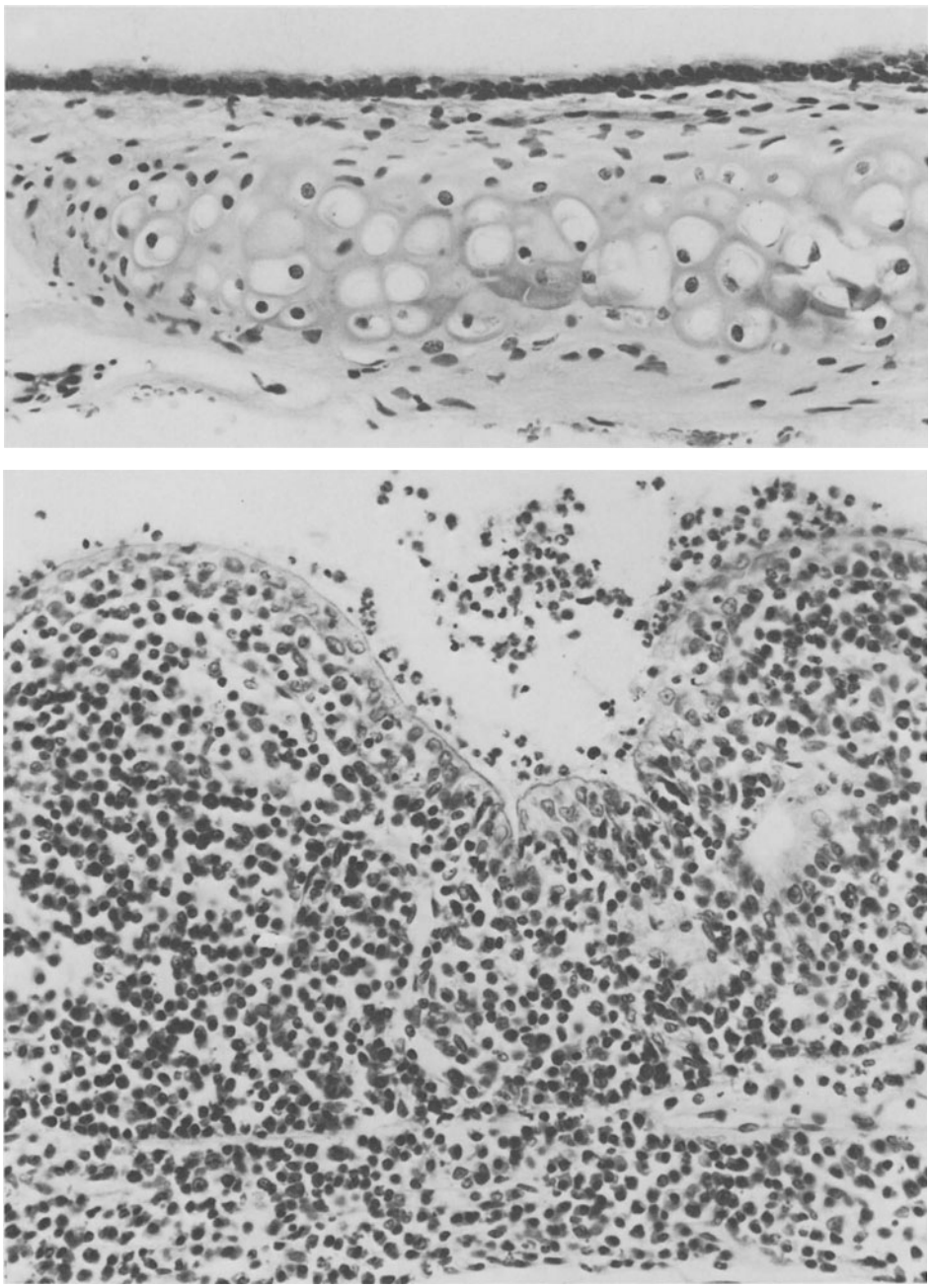

Fig. 117 *(Above).* Normal rat trachea. H and E, × 330

Fig. 118 *(Below).* Tracheal mucosa in severe chronic murine respiratory mycoplasmosis, with neutrophilic exudate, epithelial hyperplasia, loss of cilia, and mucosal thickening with accumulation of many lymphocytes and plasma cells. The *dark line* at the epithelial surface represents numerous mycoplasmas adherent to the cells (see Fig. 119). H and E, × 330

the incidence and severity of lung lesions (Broderson et al. 1976). The mechanisms of this effect remain unclear, but ammonia greatly increases the growth of *M. pulmonis* in rat respiratory tracts, particularly in the nasal passages, probably through effects on the host rather than on the organism itself (Schoeb et al. 1982).

Other microbial agents are frequently found in colonies and it is likely that some of them can affect the expression of mycoplasmosis. Sendai virus is a likely contributor because, although no such studies in rats have been reported, Sendai virus infection in mice enhances intrapulmonary growth of *M. pulmonis* (Howard et al. 1978), and

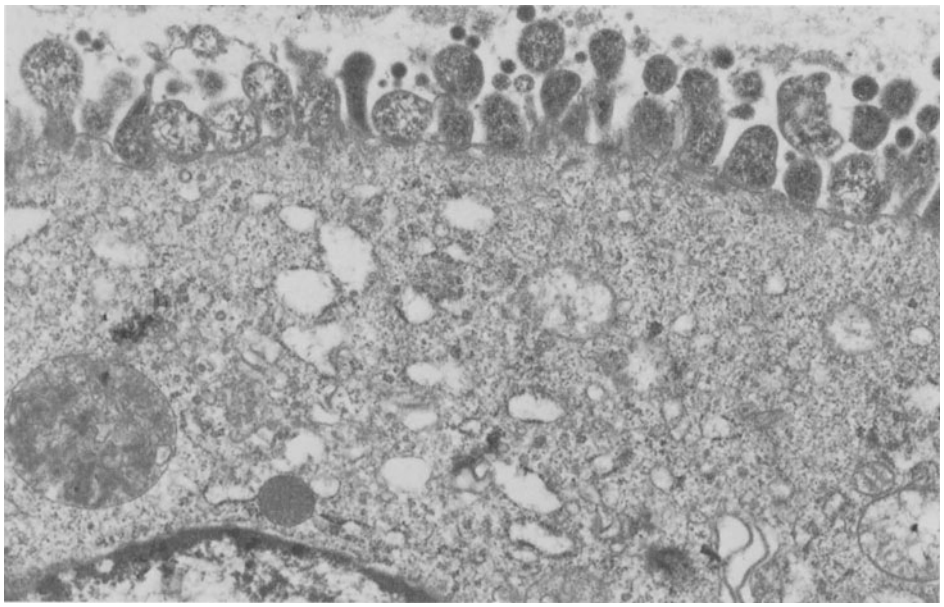

Fig. 119. Tracheal epithelial cell with numerous *M. pulmonis* organisms on its surface. TEM, × 12000

alters functions of alveolar macrophages and inhibits pulmonary bacterial clearance (Jakab 1981). Increased susceptibility is also associated with advancing age, possibly as a result of decreased immune responsiveness (Cassell et al. 1979). Genetically determined factors are also important inasmuch as LEW rats are more susceptible than F344 rats (Davis and Cassell 1982; Davis et al. 1982).

Mycoplasma pulmonis inhabits the surface of ciliated epithelial cells, as do other mycoplasmas affecting the respiratory tract (Cassell et al. 1978). This relationship is undoubtedly fundamental to the initiation and maintenance of infection. For example, it may enable the organism to escape elimination by the mucociliary system, cellular and noncellular inflammatory processes, and specific immune effector mechanisms (Cassell et al. 1978). It seems likely that the nonspecific mitogenic activity of *M. pulmonis* (Naot et al. 1979) alters lymphocyte responsiveness and misdirects or disrupts specific immune responses (Cassell et al. 1979). How *M. pulmonis* damages epithelial cells is unknown, but it probably competes for essential metabolites or cell components. Production of toxic wastes has been suggested but not proved to be associated with pathogenicity.

Mycoplasma pulmonis infection is ubiquitous in conventional rat colonies. Studies have shown by ELISA and cultural isolation that infection is also common in "barrier-maintained" colonies in the United States and Great Britain (Cassell et al. 1981). Rats from these colonies had mild or no lesions, not the classical lesions described here. The organism has also been found in rats thought to be germ-free (Ganaway et al. 1973).

Comparison with Other Species

With the exception of contagious pleuropneumonia *(Mycoplasma mycoides)* of cattle and goats, which is characterized by fibrinous pleuropneumonia, most respiratory mycoplasmoses are morphologically similar. In mice, lesions of murine respiratory mycoplasmosis are similar to those in rats, with a few minor differences. Middle ear fibrosis like that seen in rats does not occur in mice. Lymphoid accumulations in mice contain a greater proportion of plasma cells, as do the regional lymph nodes. Syncytial giant cells in the epithelium of the nasal passages occur in mice with the disease but not in rats.

Lesions of *Mycoplasma gallisepticum* infection in chickens include chronic suppurative rhinitis, sinusitis, tracheitis and bronchitis with epithelial hypertrophy and hyperplasia, increased mucosal mucus production, and lymphoid cell accumulation with follicle formation in the lamina propria. The lesions are thus similar to those of the murine respiratory disease. *M. gallisepticum* alone usually causes a rather mild upper respiratory disease, but infection is frequently complicated by wild or vaccine Newcastle disease virus, infectious bronchitis

virus, avian adenovirus, or *Escherichia coli,* resulting in more severe disease with extension to the lungs and air sacs.

In turkeys, *M. gallisepticum* produces a disease similar to that in chickens but with even more of a tendency for upper respiratory tract lesions, especially sinusitis, to predominate. Thus the disease is usually called infectious sinusitis. *M. meleagridis* causes a spontaneously resolving air sacculitis also characterized by chronic suppurative inflammation, lymphoid infiltration, and epithelial hyperplasia.

Swine infected with *Mycoplasma hyopneumoniae* develop lesions similar to those of murine respiratory mycoplasmosis, although bronchiectasis almost never occurs. Pneumonic lesions with macrophage and neutrophil accumulations are more prominent than in the rodent disease, and the gross lesions, discrete gray-red firm masses predominantly in the dependent parts of the lungs, are characteristic of porcine "enzootic pneumonia." The natural disease is frequently complicated by other agents such as *Pasteurella multocida, Mycoplasma hyorhinis,* and swine adenovirus.

Lesions of *M. pneumoniae* infection in humans are not well known because the disease is rarely fatal. However, available descriptions indicate that lesions include peribronchial and perivascular lymphoid infiltrates, acute bronchitis and bronchiolitis, transformation of alveolar epithelium to cuboidal type and an alveolar exudate made up chiefly of macrophages. These changes are similar to those of other respiratory mycoplasmoses.

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