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# Sialodacryoadenitis (SDA) Infection, Rat

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Synonyms. Rat coronavirus infection.

Gross Appearance

Lesions develop during the 1st week after infection and occur primarily in the submaxillary and parotid salivary glands, which are located on the anteroventral and anterolateral aspects of the neck, respectively (Fig. 175). The glands are unilaterally or bilaterally enlarged ans pale yellow to white in contrast to their normal tan color (Fig. 176). Periglandular connective tissue is often edematous and, together with glandular enlargement, may cause grossly visible cervical swelling in the living rat. The parotid salivary gland of the rat is lobulated and sometimes difficult to delineate from surrounding adipose tissue when inflammatory edema is severe. The cervical lymph nodes may also be enlarged and edematous. They are frequently congested, especially early in infection, and occasionally flecked with red spots. Gross lesions of the oropharynx and tubular portions of the gastrointestinal tract have not been reported.

Microscopic Features

The lesions of SDA are characterized by necrosis and inflammation during acute stages of disease and by squamous metaplasia as tissues are repaired (Jonas et al. 1969; Jacoby et al. 1975). Serous and miced salivary glands in the oropharynx and neck can be affected, but mucous salivary glands are resistant. Earliest lesions are detected in the submaxillary salivary glands, where necrosis of ductular epithelium can begin by 4 days postinfection (Fig. 177). Immunohistochemical stains reveal viral antigen in the cytoplasm of infected epithelial cells. Infection and necrosis of adjacent acinar parenchyma begins shortly thereafter and spreads quickly to involve large areas of the parenchyma (Fig. 178). Necrosis is accompanied by inflammatory edema which engulfs periglandular connective tissues. The inflammatory cells consist of small and large mononuclear cells and polymorphonuclear leukocytes. Necrosis and inflammation in the parotid salivary glands develop in a similar pattern and lesions are sometimes found in salivary tissues of the oropharynx. The sublingual salivary glands, which are mucin-secreting glands in the rat and which lie at the ante-
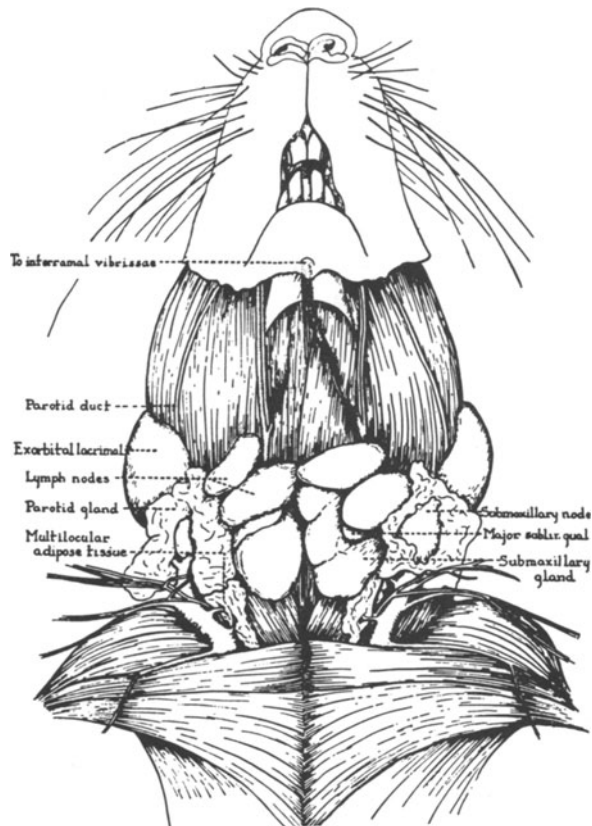
Fig. 175. Gross anatomy, ventral aspect of the neck, rat. (Adapted from Greene 1959 with permission of Hafner Publ. Co.)
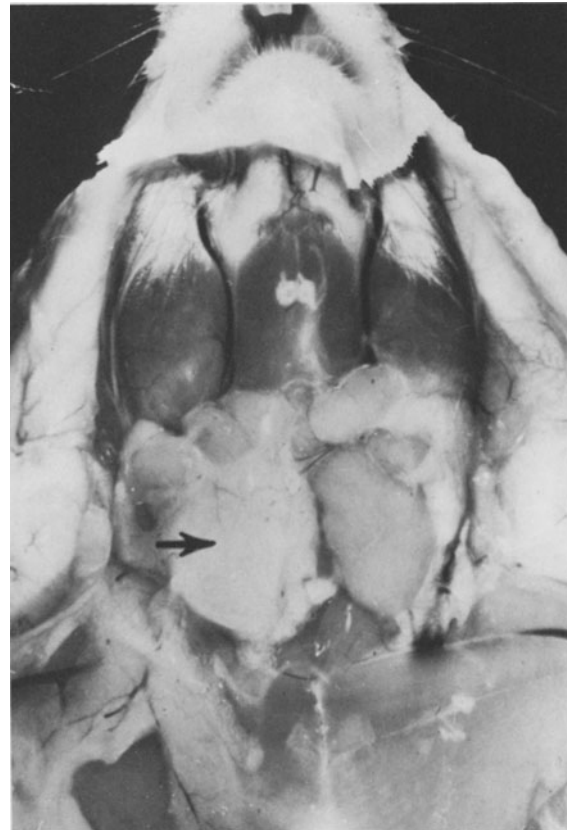
Fig. 176. Submaxillary gland *(arrow)*, rat inoculated intranasally with sialodacryoadenitis virus 5 days previously. The gland is swollen and pale. Cervical lymph nodes are also enlarged. (From Jacoby et al. 1979 with permission of Academic Press)

rior pole of the submaxillary glands (Greene 1959), are not affected despite the fact that they are separated from the submaxillary gland by only a thin wall of connective tissue (Fig. 179). Cervical lymph nodes are congested during the first 4–5 days of infection, but they enlarge primarily from hyperplasia.

By the end of the 1st week, active germinal centers appear in the cortex and medullary cords begin to fill with plasma cells. Mild focal necrosis and an occasional focus of hemorrhage may be detected during this period.

Reapair begins during the 2nd week of infection and is normally complete by the end of the 3rd week. It proceeds efficiently because the basement membranes of acini and ducts are not destroyed during acute phases of infection.

Fig. 177 *(upper left)*. Submaxillary salivary gland, rat, 4 days after intranasal inoculation of sialodacryoadenitis virus. Note necrosis of a large salivary duct and mild interstitial inflammation. Early signs of degeneration in adjacent acini are indicated by intracytoplasmic vacuoles. (From Jacoby et al. 1975 with permission of *Veterinary Pathology*). H and E, × 400

Fig. 178 *(lower left)*. Submaxillary gland, rat infected intranasally with sialodacryoadenitis virus 5 days previously. Note widespread necrosis and inflammation. (From Jacoby et al. 1975 with permission of *Veterinary Pathology*). H and E, × 160

Fig. 179 *(upper right)*. Submaxillary gland, rat, effaced by ▷ severe sialoadenitis 6 days after infection with SDA virus. Squamous metaplasia is evident in a salivary duct. The adjacent sublingual gland is normal. (From Jacoby et al. 1975 with permission of *Veterinary Pathology*). H and E, × 160

Fig. 180 *(lower right)*. Submaxillary gland, rat inoculated with sialodacryoadenitis virus 9 days previously. Note the prominent squamous metaplasia of ductal epithelium and clusters of regenerating acini, especially in the upper right quadrant. (From Jacoby et al. 1975 with permission of *Veterinary Pathology*). H and E, × 160
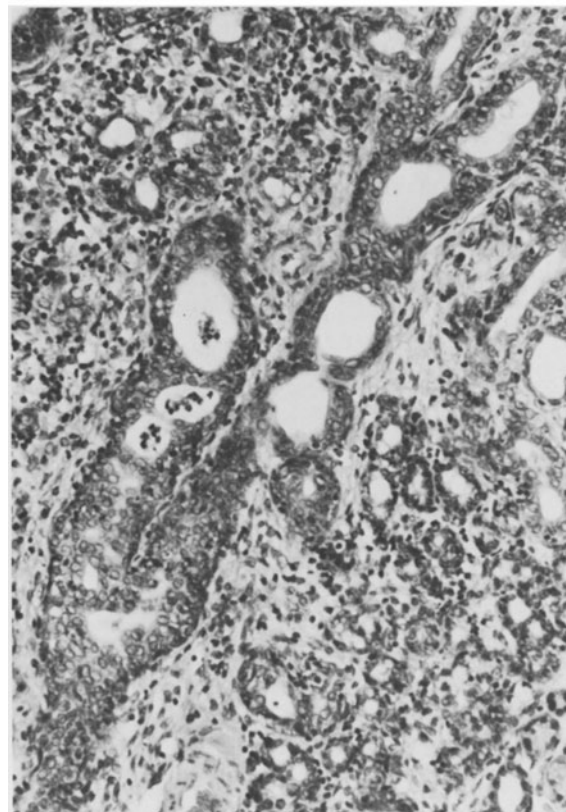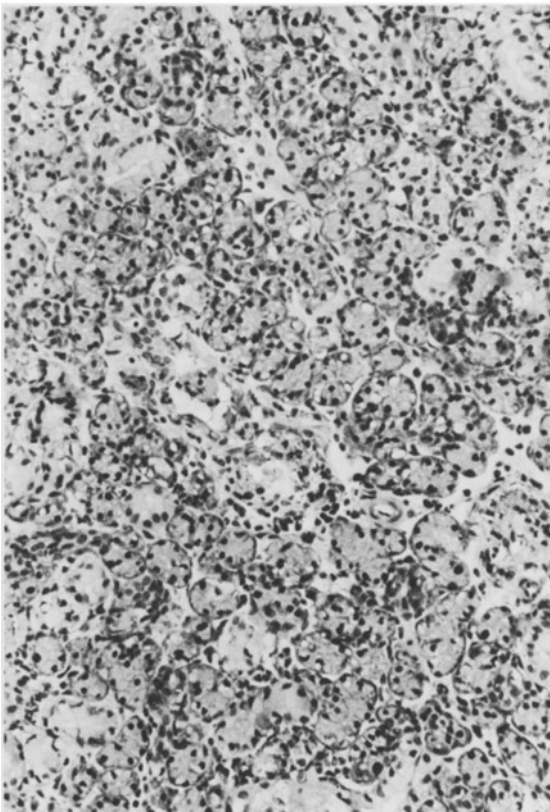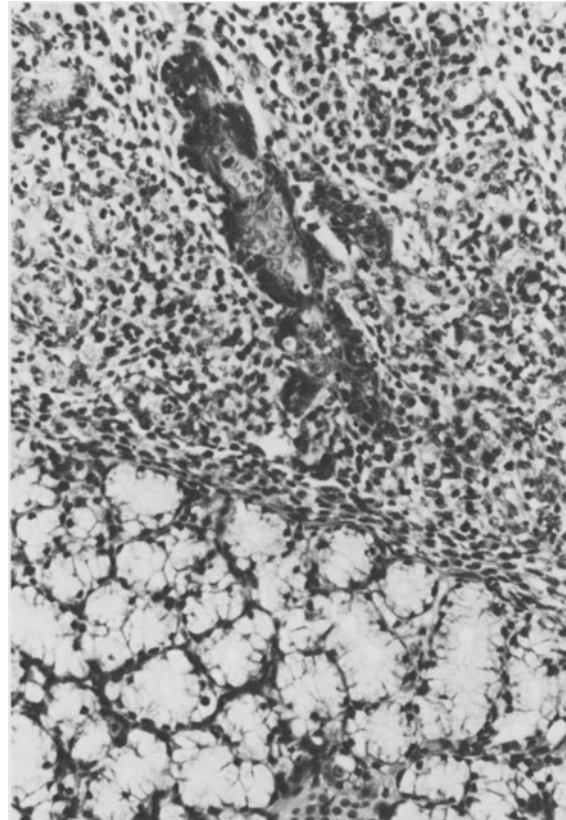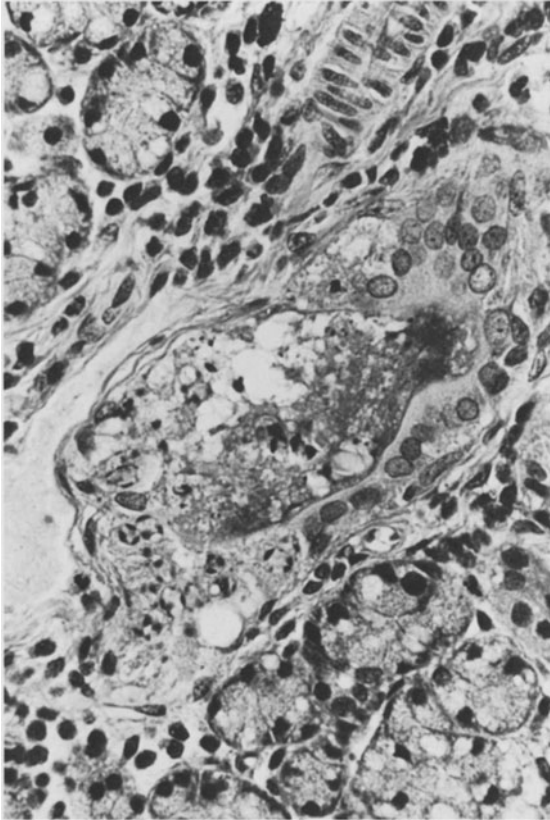
The characteristic sign of repair is squamous metaplasia of ductular epithelium (Figs. 179, 180). This is a transient lesion and is replaced by histologically normal columnar epithelium within 1-2 weeks. Acinar regeneration begins with clusters or rosettes of small hyperchromatic cells which mature into normal acini during the same interval. Inflammation and edema subside as reconstitution of glandular parenchyma occurs, but interstitial foci of residual inflammation, which usually consist of mononuclear cells, may linger after repair of acini and ducts is complete. Fibrosis is not a significant sequela of sialodacryoadenitis, but small interstitial scars can develop in some glands.

Ultrastructure

The ultrastructure of SDA infection has not been thoroughly described. Jonas and coworkers (Jonas et al 1969) found two types of viral particles in ductal epithelium of submaxillary glands of experimentally infected rats. One type was 60-70 nm in diameter and had an electron-dense core. The second type was about 10-20 nm in diameter and occurred as cytoplasmic aggregates. Two types of cytoplasmic vacuoles were also observed. One had an electronlucent matrix, was membrane bound, and contained cytoplasmic debris, membrane fragments, and cell organelles. The other type was also membrane bound and contained the electron-dense viral particles. A similar coronavirus, "rat coronavirus" (Parker et al. 1970), was described as a pleomorphic virus 60-200 nm in diameter. The differences in measurements reported appear to be due to differences in the preparations used.

Differential Diagnosis

Necrotizing sialoadenitis in the rat is characteristic of rat coronavirus infection. Two coronaviruses have been described, SDA virus (Bhatt et al. 1972) and rat coronavirus (Parker et al. 1970). Since their properties and antigens are essentially identical, it has been proposed that they are strains of a single prototype virus (Jacoby et al. 1979). Under experimental conditions, both viruses can cause sialoadenitis although SDA virus is thought to be more sialotropic than Parker's virus (Bhatt and Jacoby 1977). Cytomegalovirus infection in the salivary glands of rats has been described; however, it is associated with enlarged ductal epithelial cells which may contain intranuclear inclusions (Lyon et al. 1959). An unclassified cytopathic agent has been isolated from the submaxillary salivary glands of rats, but it is apparently nonpathogenic (Ashe 1969). Salivary gland tumors are rare in rats and no other classes of microbial agents have been consistently associated with sialoadenitis.

It is worth noting that rat coronaviruses are antigenically related to mouse coronaviruses commonly grouped under the name mouse hepatitis virus (MHV) (Bhatt et al. 1972; Parker et al. 1970). Because, under experimental conditions, SDA virus can infect mice (Bhatt et al. 1977) and MHV can infect rats (Taguchi et al. 1979), some caution in serologic techniques and interpretation is advised when investigating coronavirus infections in these species, especially when they are housed near one another.

Several manifestations of SDA can interfere with research using rats. The most significant interference stems from chronic ophthalmologic changes which will be described elsewhere in these monographs. During acute disease, however, rats may consume less food and have transient weight loss and reduced breeding performance (Utsumi et al. 1980). Infected rats may also be at greater risk during restraining procedures. If they are restrained with head and neck extended as, for example, during general anesthesia, nasal exudates from acute rhinitis (see p.201, this volume) and swelling of cercival tissues adjacent to the larynx and trachea may combine to narrow or obstruct the trachea. Biochemical or morphological studies on affected glands would not be suitable during acute infection or convalescence. Whether squamous metaplasia of healing glands can affect the course of carcinogenicity studies has not been answered directly. There is no published evidence, however, that such lesions increase the prevalence of salivary tumors in rats treated with potential or known carcinogens, despite the probability that rats commonly sustain active infection during long-term toxicologic experiments.

Biologic Features

Sialodacryoadenitis is a common infectious disease of rats. It is acute and self-limiting and can affect rats at any age, although it usually occurs in weanlings that have recently lost maternal immunity or in sucklings of nonimmune dams. Morbidity is high, but mortality is low. Clinical disease develops by 1 week after exposure to the virus and

is characterized by one or more of the following signs: sneezing; photophobia; lacrimation including excessive secretion of porphyrin pigment (chromodacryorrhea) which imparts a red stain to periocular and perinasal skin, cervical swelling due to palpably enlarged submaxillary salivary glands and edema; transient anorexia and weight loss; and reduced breeding performance. The severity of clinical disease can vary among rat strains and mild disease may be asymptomatic (Bhatt and Jacoby 1985). Rats remain infectious for about 1 week. Recovery is associated with humoral immunity, which can be detected from 7 days postinfection by complement fixation, serum neutralization (Bhatt et al. 1972), immunofluorescence (Smith 1983), or enzyme-linked immunoadsorption (Peters and Collins 1981). Seroconversion marks the start of the healing phase and the time after which infectious virus can no longer be recovered.

Virus is spread by contact or aerosol, and infects the respiratory tract before reaching the salivary glands and lacrimal glands. The route of spread from the nasopharynx has not been determined. Attempts to demonstrate a viremic stage or to detect retrograde infection of salivary and lacrimal ducts have not been successful (Jacoby et al. 1975). Virus spread appears to be limited to the respiratory tract. salivary glands, lacrimal glands, and regional lymph nodes. Keratoconjunctivitis associated with infection has benn attributed to corneal dehydration from interrupted tear production rather than to viral invasion of the cornea (Lai et al. 1976).

As previously stated, SDA virus is closely related to a coronavirus isolated from rats by Parker and coworkers (Parker et al. 1970). This virus is relatively large (60-200 nm) and pleomorphic and can be grown in monolayer cultures of primary rat kidney (Bhatt et al. 1972). The initial cytopathic effect of SDA virus and Parker's rat coronavirus is syncytia formation.

Sialodacryoadenitis has been detected in laboratory rats in North America, Europe, and Asia and is probably one of the most common infections of laboratory rats worldwide. Its prevalence in wild rat populations has not been established. It spreads rapidly among rats, especially those housed in conventional quarters, and is difficult to eliminate until susceptible animals have become immune or until rooms with infected rats have been depopulated.

Comparison with Other Species

The lesions of SDA in rats are not duplicated in natural disease of other laboratory or domestic animal species; however, mice are susceptible to experimentally induced infection (Bhatt et al. 1977).

Sialoadenitis in humans may be infectious (e.g., mumps) or noninfectious (reviewed by Vickers and Gorling 1977), but the pathogenesis, distribution of lesions, and other manifestations of human sialoadenitis do not closely resemble SDA.

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