# Cytomegalovirus Infection, Salivary Glands, Mouse, Rat, and Hamster

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*Synonyms.* Salivary gland virus infection, cytomegalic inclusion disease

## Gross Appearance

Under most circumstances there are no grossly visible lesions. During acute, generalized infections in mice, the liver may be enlarged and pale with hemorrhagic foci. Intestinal serosa can be irregularly reddened and mucosa congested (McCordock and Smith 1936). Mineralization of skeletal muscle and brown fat (Lussier 1975) and blood-tinged ascitic fluid (Olding et al. 1976) have also been observed. Mice infected as neonates are runted with thymic and splenic involution (Schwartz et al. 1975).

## Microscopic Features

Acute generalized infections in susceptible (especially if immunosuppressed) mice are characterized by focal necrosis, cytomegaly, intracytoplasmic and intranuclear (type A) inclusion bodies, and nonsuppurative inflammation of multiple organs. Lesions can be found in salivary and lacrimal glands, brain, liver, spleen, thymus, lymph nodes, paritoneal connective and adipose tissue, lungs, skin, renal glomeruli, bowel, pancreas, adrenals, skeletal and cardiac muscle, cartilage, and brown fat (Brody and Craighead 1974; Gardner et al. 1974; Jordan 1978; Lussier 1975; McCordock and Smith 1936; Mims and Gould 1979; Olding et al. 1976; Schwartz et al. 1975). Lesions may be restricted to salivary glands in natural infections of mice, rats, and hamsters (Gardner et al. 1974; Lussier 1975; Lyon et al. 1959; Priscott and Tyrrell 1982). Submaxillary salivary glands are preferentially infected, the sublingual glands less so, and the parotids least of all (Mims and Gould 1979; Ruebner et al. 1966). In mice, inclusions are most apt to be found in acinar epithelium (Fig. 212), whereas they occur in ductal epithelium in rats, guinea pigs, humans, and most other species (Bruggeman et al. 1985). Eosinophilic intracytoplasmic and intranuclear inclusions are present in acinar and ductal epithelial cells. Intranuclear inclusions are Feulgen positive, and intracytoplasmic inclusions are periodic acid-Schiff (PAS) and Feulgen positive. Infected cells can become atypically large (cytomegaly; Fig. 212). This is accompanied by infiltration of the surrounding interstitium with lymphocytes and plasma cells. In the acute phase of generalized infections, other organs, particularly liver (Fig. 213), are more apt to possess lesions than salivary glands, which develop lesions later in the course of infection (Brodsky and Rowe 1958; Gardner et al. 1974; Henson and Strano 1972; Ruebner et al. 1966).

## Ultrastructure

Initially, nuclei of acinar cells of salivary glands become enlarged with chromatin uniformly dispersed. Nucleoli enlarge and are partially surrounded by fibrillar structures identical to those of the virus membrane. Pleomorphic dense cores become surrounded by these fibrils, followed by the appearance of cores, fibrils, and virions throughout the nucleoplasm. Virus particles acquire a second membrane by passing through the nuclear membrane into the cytoplasm. Particles make contact with membranes of dilated Golgi vesicles and, to a lesser extent, endoplasmic reticulum, acquiring a third membrane or envelope by the process of invagination. Vesicles enlarge and are filled with virus particles as they approach the cell apex and are extruded into the lumen. Intranuclear inclusions observed by light microscopy correspond to aggregates of granular and fibrillar material intermixed with virus parti-

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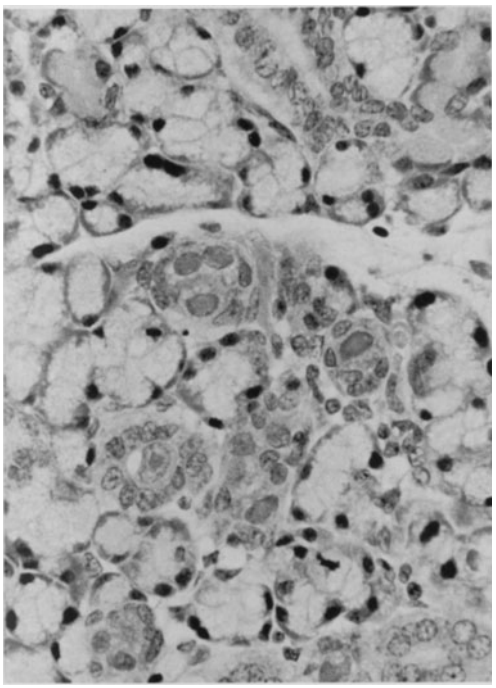

**Fig. 212.** Intranuclear inclusions in submaxillary salivary gland of a mouse experimentally infected with mouse cytomegalovirus. H&E, ×485

cles. Intracytoplasmic inclusions correspond to virus-filled vesicles (Fig. 214; Henson and Strano 1972; Ruebner et al. 1966). Similar viral replicative changes have been described in pulmonary macrophages (Brody and Craighead 1974), splenic reticulum cells, and hepatocytes (Ruebner et al. 1964, 1966).

## Differential Diagnosis

In mice, sialoadenitis is also caused by polyoma virus and reovirus type 3. Polyoma virus induces intranuclear inclusions, but not cytomegaly or intracytoplasmic inclusions, and preferentially infects the parotid salivary gland. Reovirus type 3 can cause necrotizing sialoadenitis without inclusion bodies. Furthermore, mouse salivary gland is a primary target organ for another herpesvirus, mouse thymic virus, but salivary gland lesions have not been described (Cross et al. 1979). Murine mammary tumor virus also replicates in and is shed from salivary glands, but is not associated with light microscopy changes (Bentvelzen and Hilgers 1980). Sialoadenitis can be caused by coronavirus and polyoma virus in rats. Coronavirus produces necrotizing lesions without inclusions in submandibular and parotid salivary glands, as well as lacrimal glands. Polyoma virus induces inclusions in parotid salivary glands. Papovavirus also induces very similar inclusions and sialoadenitis in parotid salivary glands of athymic nude rats (Ward et al. 1984).

## Biologic Features

### Natural History

Infections with cytomegalovirus in mice under natural conditions are almost invariably subclinical. Virus is transmitted by direct contact through inhalation or ingestion and is excreted in saliva, tears, and urine (Brodsky and Rowe 1958; Lussier 1975). In utero transmission does not play

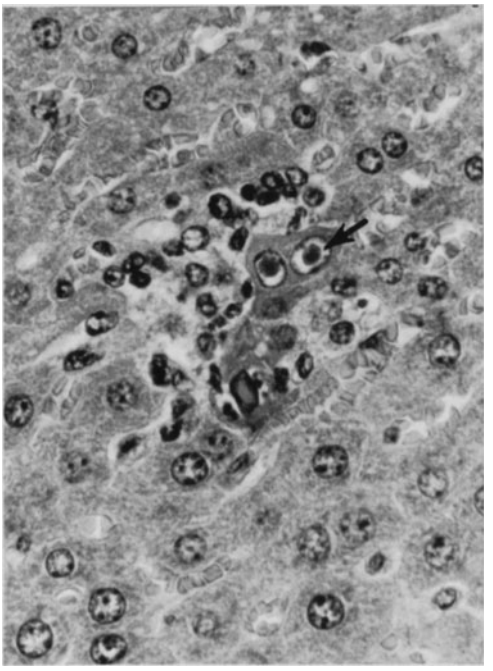

**Fig. 213.** Focal hepatitis, liver, mouse. Intranuclear inclusions (*arrow*); experimental mouse cytomegalovirus infection in a neonatal mouse. H&E, ×440

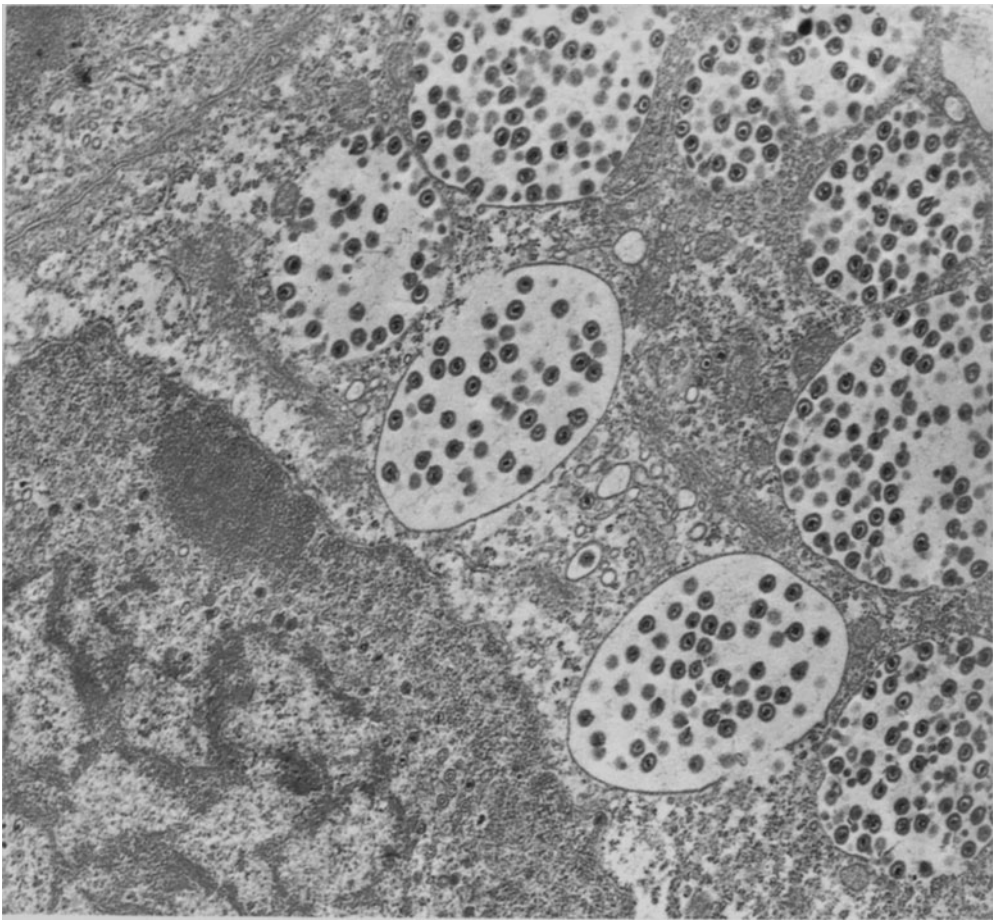

**Fig. 214.** Salivary gland, mouse, 16 days after infection with mouse cytomegalovirus. Viral particles are in the nucleus and in cytoplasmic vesicles. (Courtesy of Ruebner et al. 1964 and *American Journal of Pathology*) Uranylacetate, TEM, ×16300

an important role in natural murine infections, but transmission from dam to fetus can occur in latent form under experimental conditions (Chantler et al. 1979). Suckling pups are protected from infection by maternally derived antibody (Mannini and Medearis 1961; Medearis 1964). In susceptible mice, infection is followed by one of four outcomes: death, recovery, chronic localized replication in salivary glands, or latency, in which virus is harbored in tissues in a nonreplicative state (Olding et al. 1976). Considerably less is known about cytomegaloviruses of hamster and rat. In these species, infection appears to be largely restricted to salivary glands (Lussier 1975; Lyon et al. 1959; Priscott and Tyrrell 1982).

## Pathogenesis

Most studies on pathogenesis of cytomegaloviruses have been done with the mouse virus. The course of infection is dependent on route of inoculation, host age and genotype, virulence of the agent, and immune status of the host (Hudson 1979; Lussier 1975; Mannini and Medearis 1961). Within a week of inoculation, young mice develop leukocytosis and viremia with dissemination to multiple organs. Hematocrit, leukocyte, and platelet counts decrease, but return to normal by 15 days (Lussier 1975; McCordock and Smith 1936; Osborn and Shahidi 1973). Intranasal or oral inoculation of low doses into young adult mice re-

sults in subclinical pulmonary infection, followed by viremia and dissemination. Virus replicates in monocytes and alveolar macrophages, with septal thickening and edema (Brody and Craighead 1974; Jordan 1978). This probably represents the natural course of infection. Salivary gland infection occurs regularly, but virus replication does not take place until later than other organs and infection persists for many months in this location after virus is cleared from other sites. Replication and excretion of salivary virus can occur in the presence or absence of discernible lesions. The affinity of the virus for salivary glands is underscored by the fact that this site is preferentially infected regardless of host age, and natural infections are localized to this site alone (Lussier 1975; Brodsky and Rowe 1958; Mims and Gould 1979; Olding et al. 1976).

Macrophages are important in early virus clearance and restriction (or replication) (Brautigam et al. 1979). Neutralizing antibody appears early after infection and provides a protective effect against challenge, but it does not seem to be involved in recovery (Hudson 1979). Cell-mediated immunity is important in host recovery (Ho 1980; Hudson 1979; Lussier 1975), and lymphocytic infiltration heralds termination of infection (Henson and Strano 1972). Immunity can result in recovery, but more often results in two types of persistent infections. In chronic infections, the virus is localized to salivary glands, where it replicates and is orally excreted for up to 1 year after infection (Brodsky and Rowe 1958). More often, latent infections develop, in which replicating virus cannot be detected (Olding et al. 1976). Salivary glands, macrophages, bone marrow-derived (B) lymphocytes, and reproductive tissues of latently infected mice harbor cytomegalovirus but not brain, thymus, liver, or kidney (Brautigam et al. 1979; Cheung et al. 1980; Olding et al. 1976). Latent infection can be reactivated in vivo and in vitro by immunosuppression and allogeneic reactions (Gardner et al. 1974; Hudson 1979; Lussier 1975; Montplaisir 1979).

Cytomegalovirus has been shown to have a number of immunosuppressive effects on infected mice due to alterations in T cell, B cell, and macrophage functions and interferon response (Hudson 1979). A synergistic effect on mouse mortality occurs in combined cytomegalovirus and *Pseudomonas aeruginosa* infections (Hamilton and Overall 1978). Chronically and latently infected mice can develop immune complex renal glomerular lesions and antinuclear antibodies (Olding et al. 1976).

Experimental inoculation of neonatal rats with rat cytomegalovirus results in disseminated infection, but without the mortality and liver disease observed in mice infected with mouse cytomegalovirus. Infection in rats is also persistent, with the salivary gland being the preferential target for virus replication, shedding, and persistence (Bruggeman et al. 1985).

### Etiology

Cytomegaloviruses are herpesviruses that are species specific in vivo. Several strains have been isolated from laboratory and wild mice and vary in virulence. Different cytomegaloviruses have been described in mice, rats, hamsters, guinea pigs, nonhuman primates, moles, pigs, dogs, feral rodents, sheep, horses, and humans (Lussier 1975). The mouse and rat cytomegaloviruses are antigenically and genetically distinct viruses (Bruggeman et al. 1985; Priscott and Tyrrell 1982).

### Frequency

Based on observation of salivary gland inclusions or isolation of virus, infection is not common among laboratory mice and is rare among hamsters and rats. With appropriate techniques, infection is found to be very common among wild mice and rats (Bruggeman et al. 1985; Lussier 1975; Mannini and Medearis 1961). Molecular hybridization techniques have revealed latent cytomegaloviral DNA in specific pathogen-free mice, in which virus was undetectable by other means. It is likely many laboratory mice may be latently infected, but presence of viral DNA does not necessarily mean that the virus can be reactivated or will interfere with experimental procedures (Cheung et al. 1980).

## Comparison with Other Species

Cytomegaloviruses frequently infect salivary glands in many species of animals and lesions are often present as incidental findings. Human infection mimics the murine disease in many ways, including its propensity for generalized infection following immunosuppression and allogeneic re-

actions. As in mice, fatal cytomegalovirus infections in humans are characterized by pneumonia and disseminated cytomegalic inclusion disease (Hudson 1979; Lussier 1975; Mims and Gould 1979; Montplaisir 1979).

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