NOTES

ON

DISEASES OF LABORATORY ANIMALS

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1. TYZZER'S DISEASE

Tyzzer's disease is named for Ernest Tyzzer, who first described it in a colony of Japanese waltzing mice. The causative organism, ***Bacillus piliformis***, is a long, thin, gram-negative spore-forming bacterium that appears to infect only living cells.

Clinically, Tyzzer's disease is frequently expressed as acute death that may be preceded by diarrhea. Outbreaks can be explosive, with high morbidity and mortality, but serological surveys indicate that subclinical infection also occurs.

Stresses, such as overcrowding, high temperature and humidity, moist food, and immunosuppression, may predispose mice to Tyzzer's disease, and there is evidence that susceptibility and resistance is influenced by host genotype. Tyzzer's disease has been found in many species of laboratory animals and in domestic and free-living species, but the reservoir of environmental infection remains unknown. Because the vegetative form of Bacillus piliformis is unstable, the spore form probably constitutes the surviving form in the environment and the primary means of spread.

Feces-contaminated food seems to be a likely source of infection, and soiled bedding can harbor infectious spores for long periods. In utero infection can be induced by intravenous inoculation of pregnant dams, but the prevalence of prepartum transmission in nature has not been determined.

Macroscopically, the **ileum and colon** may be normal or red and dilated with watery, fetid contents. The **liver** often contains one or more gray-white foci.

Histologically, lesions are characterized by necrosis. In the intestine, necrosis of mucosal epithelium may be accompanied by acute inflammation and hemorrhage. In the liver, foci of coagulation necrosis are generally distributed along branches of the portal vein; a finding compatible with embolie infection from the intestine. Peracute lesions are largely free of inflammation, but neutrophils and lymphocytes may infiltrate less fulminant lesions. **Myocardial necrosis** occurs in some species (e.g., rabbit and rat), but is not commonly seen in the mouse. Bundles of long, slender rods can be found in the cytoplasm of viable hepatocytes bordering necrotic foci. Organisms are found more easily during early stages of infection.

Organisms in tissue sections do not stain well with hematoxylin- eosin stain. Special preparations such as silver stains (Warthin-Starry), Giemsa stains, or periodic acid-Schiff stains are usually required. Bacilli can also be found in the epithelial cells of the intestine especially in association with **focal necrotizing enterocolitis**.

Tyzzer's disease is diagnosed most frequently by the demonstration of characteristic organisms in tissue sections of liver and intestine. Supplemental procedures include inoculation of cortisonized mice or embryonated eggs with suspect material followed by histological or immunocytochemical demonstration of organisms in tissues. Asymptomatic infection can be detected serologically with an immunofluorescence technique.

The detection of organisms at the periphery of necrotic foci is key to differentiating Tyzzer's disease from other infections that can produce similar signs and lesions, especially mouse pox, corona viral hepatitis, reoviral hepatitis, and salmonellosis.

2. SALMONELLOSIS

Salmonellosis has been studied thoroughly in mice as a natural and as an experimentally induced infection (see review by Ganaway, 1982). The mouse is also used to test the potency of vaccines used for protection of humans against typhoid fever..

There are approximately 1600 recognized serotypes of Salmonella. The Salmonella most commonly isolated from mice is S. enteriditis serovar typhimurium, a gram-negative, slow lactose-fermenting rod. Salmonellae are primarily intestinal microorganisms and can contaminate food and water supplies. Infection occurs primarily by ingestion. In a colony where vermin, birds, and feral animals are excluded, human carriers may be a source of infection.

The induction and course of infection are influenced by the virulence of the organism, route of infection, dose of organism, age, sex, genetic factors, nutrition, and intercurrent disease. Stresses that suppress immunity such as X irradiation, corticosteroid administration, and exposure to heavy metals, and environmental factors such as temperature can alter expression of disease.

Weanling mice are more susceptible to infection than older mice. Frank salmonellosis is rare in mice. If acute disease occurs, it is especially severe in young mice and is characterized by anorexia, weight loss, lethargy, dull coat, humped posture, and occasionally, conjunctivitis. Gastroenteritis is a common sign, but feces may remain formed. Subacute infection can produce distended abdomens from hepatomegaly and splenomegaly.

Chronic disease is expressed by anorexia and weight loss. If salmonellosis is enzootic in a production colony, there are alternating periods of quiescence and high mortality, the

latter being associated with diarrhea, anorexia, weight loss, roughened haircoat, and reduced production.

The virulence of *S. enteriditis serovar typhimurium* depends on its ability to penetrate intestinal walls, enter lymphatic tissue, multiply and disseminate. Organisms reach Peyer's patches within 12 hr after inoculation and spread quickly to the mesenteric lymph nodes. Bacteremia results in spread to other lymph nodes, spleen, and liver within several days. In chronic infections, organisms persist in the spleen and lymph nodes as well as the liver and gallbladder and from the latter are discharged into the intestinal contents. Bacteria reaching the intestine can reinvade the mucosa and can be shed intermittently in the faeces for months. Chronic arthritis associated with *S. enteriditis* infection has been reported.

In animals dying acutely there may be no gross lesions, but visceral hyperemia, pale livers, and catarrhal enteritis are common. If mice survive for up to several weeks, the intestine may be distended and reddened, while the liver and spleen are enlarged and contain yellow-gray foci of necrosis. Affected lymph nodes are also enlarged, red, and focally necrotic. Focal inflammation can develop in many organs including the myocardium.

Microscopically, lesions reflect bacterial invasion, and the extent of lesions is proportional to the course of disease and the number of bacteria in the tissues. Necrotic foci are found in the intestine, mesenteric lymph nodes, liver, and spleen. Neutrophilic leukocytes and histiocytes accumulate in lymphoid tissues. Thrombosis from septic venous embolism may occur especially in the liver. Granulomatous lesions are particularly characteristic of chronic salmonellosis.

Diagnosis is based on isolation of salmonellae together with documentation of compatible clinical signs and lesions. In mice with systemic disease, bacteria may persist in the liver and spleen for weeks. During acute stages, bacteria can also be isolated from the blood. Asymptomatically infected animals can be detected by fecal culture using selective enrichment media.

Confirmation of infection can be made serologically. Serotyping reagents aid speciation and can be obtained commercially.

Salmonellosis can be prevented by proper husbandry and sanitation. Contact between mice and potential carriers, such as nonhuman primates, dogs, and cats, should be prevented.

3. PSEUDOTUBERCULOSIS

Corynebacterium kutscheri, a short gram-positive rod, is a cause of pseudotuberculosis in laboratory animals. Latent infections may be common in conventionally housed mice. Active disease is precipitated by immunosuppression or environmental stresses. Clinical signs include inappetance, emaciation, rough haircoat, hunched posture, hyperpnea, nasal and ocular discharge, cutaneous ulcération, and arthritis.

Lesions develop in various internal organs, such as kidney, liver, lung, and brain, from hematogenous spread. They are characterized by coagulative or caseous necrosis bordered by intense neutrophilic infiltration. Colonies of short gram-positive rods can usually be demonstrated in caseous lesions. Mucopurulent arthritis of carpal, metacarpal, tarsal, and metatarsal joints are related to bacterial colonization of synovium accompanied by necrosis, cartilage erosion, ulcération, and eventually ankylosing panarthritis.

Corynebacterium kutscheri is not a primary skin pathogen, but skin ulcers or fistulae follow bacterial embolization and infarction of dermal vessels. Subcutaneous abscesses have also been reported.

Diagnosis depends on isolation and identification of C. kutscheri. Agglutination serology is available, and immunofluorescent and immunodiffusion tests have also been reported.

4. Murine Respiratory Mycoplasmosis (MRM)

Murine respiratory mycoplasmosis is a syndrome characterized by suppurative rhinitis, otitis media, and chronic pneumonia caused by ***Mycoplasma pulmonis***.

Mycoplasma pulmonis is a pleomorphic bacterium of the sterol-requiring family Mycoplasmataceae. It lacks a cell wall and has a single outer limiting membrane. Colonies growing on agar have a fine granular appearance and may resemble fried eggs when viewed at low magnification. Mycoplasma pulmonis can ferment glucose but not arginine. Most isolates have up to three common antigens. Asymptomatic infection may occur, but mice commonly display chattering, inactivity, weight loss, rough haircoat, and dypsnea. Chattering and dypsnea are due to accumulations of purulent exudate in nasal passages together with inflammatory thickening of nasal mucosa.

In mouse, lower doses of infectious agent causes mild transient disease involving the upper respiratory tract and middle ears, whereas higher doses often cause death from acute pneumonia that accompanies upper respiratory lesions. Survivors develop chronic bronchopneumonia with bronchiectasis and pulmonary abscesses and can spread disease to other mice. Rarely, abscesses in the brain and spinal cord may cause flaccid paralysis. Naturally occurring genital disease due to M. pulmonis has not been reported in mice, but experimental parenteral inoculation has caused oophoritis, salpingitis, and metritis. Mycoplasma pulmonis reportedly can also cause infertility or fetal deaths.

Transmission can occur between cage contacts and between adjacent cages. The offspring of infected dams probably acquire infection by aerosol transmission early in life. In utero infection of fetuses has been demonstrated in rats, but not in mice. Mycoplasma pulmonis is a serious pathogen of rats and has been isolated from hamsters, guinea pigs, and rabbits. Among these species only rats are significant reservoirs of infection for mice.

The primary lesion early in experimental or natural disease is suppurative rhinitis, which can progress to prominent squamous metaplasia. Transient hyperplasia of submucosal glands may occur, and lymphoid infiltration of the submucosa can persist for weeks. Syncytia can sometimes be found in nasal passages in association with purulent exudate. Affected mice usually have suppurative otitis media and chronic laryngotracheitis with mucosal hyperplasia and lymphoid cell infiltrates.

The lung lesion is chronic bronchopneumonia that spreads from the hilus. Neutrophils accumulate in bronchial lumens, and large peribronchial clusters of lymphoid cells (primarily

plasma cells) develop. Bronchial exudate can cause atelectasis, bronchiectasis, bronchiolectasis, and abscesses. Advanced lesions may be expressed macroscopically as a **cobblestone appearance** of the lung. Cuboidal epithelium often lines alveoli immediately surrounding affected airways, but pleuritis is rare.

The pathogenesis of cell injury in MRM is not well understood, although it is known that M. pulmonis attaches or adheres to host cell membranes as an initial event. This attachment to respiratory epithelium occurs anywhere from the anterior nasal passages to the alveoli and may be mediated by surface glycoproteins. The organism may injure host cells through competition for metabolites such as carbohydrates and nucleic acids or by release of toxic substances such as peroxides. Ciliostasis, reduction in the number of cilia, and ultrastructural changes leading to cell death have also been described in MRM.

Prior infection with Sendai virus enhances the growth of M. pulmonis and the severity of lung lesions. Pasteur ella pneumotropica is thought by some to exacerbate the severity of respiratory disease from M. pulmonis, but this has not been confirmed experimentally.

Clinical signs may not be pathognomonic during acute outbreaks because they may be mimicked by other respiratory infections, including Sendai virus pneumonia. Lesions are fairly characteristic, especially in advanced disease. The upper respiratory tract should be cultured since it is a common site for natural infection. Buffered saline or Mycoplasma broth can be used to lavage the trachea, larynx, pharynx, and nasal passages. Genital tract infection may occur in the absence of respiratory infection, therefore, culturing at this site also is prudent.

Mycoplasmas can generally be cultured in standard Hayflick's broth or Mycoplasma agar at 37°C. Cultural isolation can give good results if it is carefully done. Organisms can be identified by colony morphology, but M. pulmonis has little tendency to produce typical fried egg colonies under less than optimal growth conditions. Speciation can be accomplished by immunofluorescence or immunoperoxidase staining or by growth inhibition.

A rapid presumptive test is the hemadsorption test, but some strains of M. pulmonis do not hemadsorb. Immunofluorescence and immunoperoxidase techniques can also be used to identify mycoplasmal antigen in tissue sections or in cytological preparations of tracheobronchial or genital tract lavages. Conventional serological tests, such as complement fixation (CF), hemagglutination inhibition (HAI), and growth inhibition, have limited value for serological detection of mycoplasmosis because serum titers are usually low. More recently, a sensitive enzyme-linked immunosorbent assay (ELISA), a radioimmunosorbent assay, and a solid phase radioimmunoassay show promise of increasing the sensitivity and speed of serological detection (Cassell et al., 1981).

5. Neurotoxic Mycoplasmosis (Rolling Disease)

Mycoplasma neurolyticum is the etiological agent of rolling disease. Its natural prevalence in mice is rare. Clinical signs appear, however, within 1 hr after intravenous inoculation of M. neurolyticum exotoxin. They include spasmodic hyperextension of the head and raising of one foreleg followed by intermittent rolling on the long axis of the body. The rolling becomes more constant, but mice occasionally leap or move rapidly. Mice of all ages appear to be susceptible.

Mycoplasma neurolyticum exotoxin enters the brain from the vascular system and fixes to receptors on glial cells. Lesions are not striking in animals that die peracutely. If mice survive for 8 hr or more, astrocytes can undergo spongiform degeneration from intracellular accumulation of fluid. The disruption of fluid transport with concomitant compression of neurons by swollen astrocytes may be responsible for the neurological signs. Mycoplasma pulmonis has been recovered from the brain of mice, but it does not seem to cause overt neurological disease.

Diagnosis can be made from the appearance of typical clinical signs, astrocytic swelling, and isolation of the causative organism. Clinical signs must be differentiated from rolling associated with Pseudomonas-caused otitis.

6. Mousepox (Infectious Ectromelia)

Mousepox is a devastating disease of mice caused by **Ectromelia virus**, an **orthopoxvirus** that is closely related antigenically and physicochemically to vaccinia virus. Mousepox was first reported by Marchai in England, and the causative virus was detected soon after by Barnard and Elford. Field strains of ectromelia virus have been isolated in many countries, but two strains, **Hampstead** (low virulence) and **Moscow** (high virulence), have been extensively known.

Mousepox usually takes one of three clinical courses: acute infection with high mortality, chronic infection with variable mortality, or asymptomatic infection. The expression of clinical signs reflects an interplay between virus-related factors, such as virulence, and dose- and host-related factors, such as age, genotype, immunological competence, and portal of entry.

Acute lethal infection occurs in genetically susceptible mice and may produce clinical signs, such as ruffled fur or prostration, for only a few hours before death. The rapidly fatal form of mousepox is associated with extensive necrosis of lymphoid tissue and liver and with intestinal hemorrhage.

Mice that survive acute infection often develop a skin rash whose severity depends on the extent of secondary viremia after infection of parenchymal organs. The pox rash can develop anywhere on the body and may be solitary or generalized (Fig. 18). In some mice, conjunctivitis also occurs. The rash often recedes within several weeks, but hairless scars can remain.

Severe viral infection of the feet and tail can lead to amputation; hence the name infectious ectromelia. **Natural exposure** is thought to occur through small abrasions of skin, but experimentally, oral exposure can cause **chronic** inapparent infection of Peyer's patches, prolonged excretion of virus in feces, and occasional chronic tail lesions. Mice with chronic intestinal infection appear not to readily transmit infection by contact, but carrier mice can be a source of contaminated tissue suspensions. Arthropod transmission is important for some pox viruses, but this appears not to apply to ectromelia virus, although the blood-sucking rat mite ***Ornithonyssus bacoti*** may be a passive vector.

The laboratory mouse is the primary host for ectromelia virus, although infection of wild mice has been reported. Natural infections in other laboratory animals have not been confirmed, but poxlike viruses have been found in rats. Highly susceptible mice die from visceral infections before a skin rash develops; therefore they are a relatively small hazard for dissemination of virus. Resistant mouse strains are dangerous because they can develop enzootic asymptomatic infections.

Addition of susceptible strains to an enzootically infected colony can provoke explosive lethal outbreaks. Intermediately resistant (or susceptible) mice frequently survive long enough to develop skin lesions that, aside from being extensive and unsightly, also can shed virus and serve as a major reservoir for spread of infection. Very young and aged mice seem to be more susceptible to lethal infection than are young adult mice.

Mousepox has been a common disease of mouse colonies in Europe, Japan, and China since 1930. Maternal immunity may perpetuate infection by protecting young mice from death, but not from infection. Such mice can infect other mice by contact exposure. Ectromelia virus multiplies in the cytoplasm and produces two types of inclusion bodies. The A type (**Marchai body**) is acidophilic and is found primarily in epithelial cells of skin or mucous membranes. The B type inclusion is basophilic and can be found in all ectromelia-infected cells if they are stained intensely with hematoxylin.

The pathogenesis of infection following skin invasion begins with viral multiplication in the draining lymph node and a primary viremia. Splenic and hepatic involvement begins within 3 to 4 days, whereupon larger quantities of virus are disseminated in blood to the skin. This sequence takes approximately 1 week and, unless mice die of acute hepatosplenic

infection, ends with the development of a primary skin lesion at the original site of viral invasion. The primary lesion is due ostensibly to the development of antiviral cellular immunity.

Focal or confluent hepatocellular necrosis occurs in susceptible mice during acute stages of mousepox. White spots indicative of necrosis are seen grossly throughout the liver. In nonfatal cases, regeneration begins at the margins of necrotic areas, but inflammation is variable. Splenic necrosis in acute disease commonly precedes hepatic necrosis but is at least equally severe. Necrosis and scarring of red and white pulp can produce a gross "mosaic" pattern of white and red-brown. Necrosis of the thymus, lymph nodes, Peyer's patches, intestinal mucosa, and genital tract also have been observed during acute infection, whereas resistant or convalescent mice can develop lymphoid hyperplasia.

The primary skin lesion, which occurs 6-10 days after exposure, is a localized swelling that enlarges from inflammatory edema. Necrosis of dermal epithelium provokes a surface scab and heals as a deep, hairless scar. Secondary skin lesions (rash) develop 2 to 3 days later, are often multiple and widespread, and can be associated with conjunctivitis, blepharitis, and, in severe cases, with buccal and lingual ulcers. Secondary skin lesions also ulcerate and scab before scarring.

Mousepox can be diagnosed from clinical signs, lesions, serological tests, and demonstration of virus or viral antigen in tissues. Characteristic intracytoplasmic eosinophilic inclusions aid histological confirmation, and typical poxvirus particles can be found in tissues by electron microscopy. Fenner has suggested that demonstrating poxvirions in homogenized tissues or scabs from suspected cages could be a rapid method to diagnose mousepox. Virus can be isolated from infected tissues by inoculation of cell cultures (B-SC-1) or embryonated eggs.

Mousepox must be differentiated from other infectious diseases associated with high morbidity and high mortality. These include mouse hepatitis, Tyzzer's disease, and reovirus 3 infection. Each can be expressed by acute necrosis in parenchymal organs, but they can be differentiated by morphological, serological, and virological criteria. The skin lesions of chronic mousepox must be differentiated from other skin diseases caused by opportunistic or pathogenic bacteria, acariasias, and bite wounds.

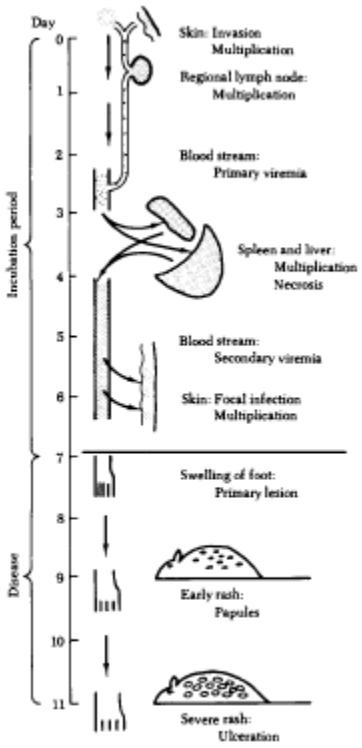

Fig. 20. Diagram illustrating the pathogenesis of mousepox. (From Fenner, 1948.)

7. Sendai Viral Pneumonia

Sendai virus is a paramyxovirus that was isolated in Japan in the early 1950's and is closely related antigenically to parainfluenza 1 virus of humans. There is no firm evidence, however, that cross-infection occurs between humans and mice. Viral particles are pleomorphic, contain single-stranded RNA, and have a lipid solvent-sensitive envelope that contains glycoproteins with hemagglutinating, neuraminidase, and cell fusion properties.

Sendai virus grows well on embryonated hen's eggs and in several mammalian cell lines [e.g., monkey kidney, baby hamster kidney (BHK-21) and mouse fibroblast (L)]. Virus replicates in the cytoplasm and by budding through cell outer membranes.

Natural infections occur in mice, rats, hamsters, and guinea pigs, but the latter three species rarely show clinical signs. Ferrets and nonhuman primates can be infected intranasally, but only the former species can develop severe pneumonia. Acute epizootics are common in previously uninfected mouse colonies and are characterized by respiratory distress, neonatal mortality, retarded growth, and prolonged gestation. Weaning rates can decrease dramatically until infection subsides.

Susceptible adult mice typically sit in a hunched position and have an erect haircoat. Rapid weight loss and dyspnea occur, and there may be crusting of the eyes and chattering. Severely affected adults may die.

Infection is commonly more lethal in suckling mice and, to some extent, is more severe in aged mice than in young adults. Sex differences in susceptibility have not been found. Sendai virus is highly infectious, and morbidity in infected colonies is commonly 100%. Mortality in natural epizootics can vary from 0 to 100% partly because strains of mice vary greatly in their susceptibility to lethal Sendai virus infection.

Sendai virus is transmitted by aerosol or by contact. Airborne infection is promoted by high relative humidity and by low air turnover. It may be inapparent or it may be expressed as acute clinical disease or inapparent enzootic infection. Enzootic infection is commonly detected in postweaned mice (5-7 weeks old) and is associated with seroconversion and persistence of circulating antibody for at least a year. There is no evidence for chronic or persistent infection in imunocompetent mice.

Gross lesions are characterized by partial to complete consolidation of the lungs. Individual lobes are meaty and plum-colored, and the cut surface may exude a frothy serosanguinous fluid. Demarcation between normal and pneumonic zones is usually distinct. Pleural adhesions or lung abscesses caused by secondary bacterial infection are seen occasionally, and fluid may accumulate in the pleural and pericardial cavities.

Histologically, typical changes begin with inflammatory edema of bronchial lamina propria, which may extend to alveolar ducts, alveoli, and peri vascular spaces. Necrosis and exfoliation of bronchial epithelium ensues, frequently in a segmentai pattern. Alveolar epithelium also may desquamate, especially in severe disease, and necrotic cell debris and inflammatory cells can accumulate in airways and alveolar spaces.

Alveolar septae are usually infiltrated by leukocytes to produce interstitial pneumonia. Lymphoid cells also invade epibronchial and perivascular spaces. Regeneration and repair begin shortly after the lytic phase and are characterized by hyperplasia and squamous metaplasia of bronchial epithelium, which may extend into alveolar septae (Fig. 25). Proliferation of cuboidal epithelium may give terminal bronchioles an adenomatoid appearance.

Repair of damaged lungs is relatively complete in surviving mice, but lymphocytic infiltrates, foci of atypical epithelium, and mild scarring can persist. Multinucleated syncytia are occasionally seen in affected sucklings, and inclusion bodies have been reported in infected athymic mice. In the latter, mortality is often extremely high, and acute phase lesions are prolonged. After intranasal exposure, virus can be found transiently in extrahepatic

tissues, but replication is nominally restricted to the respiratory tract. Parenteral inoculation of Sendai virus can produce infection of parenchymal tissues, but this effect is considered an experimental artifact and is relèvent only because such tissues may be inadvertently contaminated with Sendai virus during experimental procedures.

Sendai virus-infected mice are less able to clear bacteria from the lung. This may be due to defective intracellular killing of phagocytized bacteria by Sendai virus-infected pulmonary macrophages.

Because only one serotype is known, serodiagnosis is an effective means to detect exposure to infection.

Sendai viral pneumonia must be differentiated from other pneumonias of mice. Pneumonia virus of mice is generally milder and asymptomatic. Bacterial pneumonias of mice are sporadic and can be differentiated morphologically and culturally. The same is true of murine respiratory mycoplasmosis. Because Sendai viral pneumonia may predispose the lung to opportunistic bacterial infections, the presence of bacteria should not deter evaluation for a primary viral insult.

8. Mouse Coronavirus Infection (Mouse Hepatitis)

Mouse coronaviruses are pleomorphic, enveloped RNA viruses with radially arranged peplomers characteristic of coronaviruses. They have been grouped for convenience under the name mouse hepatitis virus (MHV), even though hepatitis does not always occur during natural infection. Five prototype strains are commonly referred to: JHM (MHV-4), MHV-1, MHV-3, MHV-S, and MHVA59. Murine coronaviruses develop exclusively in cytoplasm and bud into cytoplasmic cisternae.

Natural transmission can occur mainly through Oral or Respiratory Routes. The respiratory tract is a major portal of entry for MHV and primary lesions (syncytia) in pulmonary vascular endothelium.

Clinical signs of MHV infection depend on a number of factors, including age and strain of mouse, virus strain and tropism, and the presence of enhancing or inhibitory factors in mice or their environment. Acute MHV is most prevalent in young mice. Suckling mice can develop diarrhoea, inappetance, dehydration, weight loss, lassitude, and ruffled hair. These signs are seen in various combinations and often terminate in death

Hepatotropic strains of MHV cause damage to liver after extension from littoral cells to hepatocytes. Neurotropic variants induce flaccid paralysis of the hindlimbs. Conjunctivitis, convulsions, and circling may be seen occasionally. Mouse hepatitis is, for all practical purposes, an infection of mice. Resistance to severe or lethal infection decreases as mice mature, but sex differences in susceptibility or seasonal periodicity have not been found.

The distribution and severity of lesions in MHV depend on multiple factors, among which are viral tropism and host age. In susceptible weanlings and adults, yellow-gray foci of hepatic necrosis are seen with varying frequency. Icterus, sanguinous peritoneal exudates, or intestinal hemorrhage may accompany hepatic lesions. In suckling mice, focal spotting of the liver may occur, but intestinal lesions are more common.

The stomach is often empty, and the intestine is filled with watery to mucoid yellowish, sometimes gaseous contents. Hemorrhage or rupture of the intestine can occur. Enterotropic strains can produce syncytia and necrosis in the intestine after oral exposure and can contaminate the hepatic portal system to produce lesions in the liver and elsewhere.

Morphologically, **syncytium formation with or without necrosis** is highly characteristic of MHV infection. **Histologically**, hepatic necrosis can be focal or confluent and may be infiltrated by inflammatory cells. Syncytia commonly form at the margin of necrotic areas and, in mild infections, may develop in the absence of frank necrosis. Intestinal lesions can be found at all levels and range from syncytium formation to necrosis and

inflammation with severe blunting of surviving villi. Syncytia can often be found in asymptomatic adults on careful examination of intestinal mucosa. Necrosis and syncytia have also been detected in spleen, stomach, lymph nodes, and pancreas. In athymic mice, syncytia occur in many tissues, and hepatic necrosis can be extensive.

Neurotropic variants, produce central nervous system lesions after invasion of the nasal passages. Necrosis predominates in the hippocampus and olfactory lobes, whereas demyelination, secondary to viral invasion of oligodendroglia, occurs in brainstem and in peri-epdendymal areas. Neurotropic strains can also penetrate the cribiform plate to the olfactory bulbs after initial replication in nasal mucosa.

Mouse hepatitis virus must be **differentiated** from other infectious diseases that cause diarrheal illness, runting, or death in suckling mice. These include EDIM, mousepox, reovirus 3, Tyzzer's disease, and salmonellosis. Neurological signs must be differentiated from mouse encephalomyelitis, M. neurolyticum toxicosis, or non-infectious CNS lesions, such as neoplasms or musculoskeletal degeneration.

9. Minute Virus of Mice (MVM)

Minute virus of mice is a **Parvovirus**. It is highly contagious and highly prevalent in wild and laboratory mice. Because it is small and contains single-stranded DNA, it has also been studied extensively at the molecular level as a model for viral genetics and for viral pathogenetic mechanisms. Minute virus of mice is antigenically distinct from rat parvoviruses.

Natural MVM infection is essentially asymptomatic. Virus is excreted in feces and urine and is very stable to drying. Transmission occurs by oronasal exposure.

Minute virus of mice is only moderately pathogenic for mice, but it is **teratogenic** in neonatal hamsters and produces **Mongoloid deformities**. Virus also can replicate in fetal tissues without inducing lesions.

Contact exposed neonates occasionally develop cerebellar lesions. Retarded growth and granuloprival cerebellar hypoplasia can develop in neonatal mice.

10. Mouse Encephalomyelitis

The causative agent, mouse encephalomyelitis virus (MEV), is a small RNA-containing enterovirus of the family **Picornaviridae**. It was discovered by Max Theiler during his studies of yellow fever. Several strains are recognized including TO (Theiler's original) and GD strains I—VII, which are named after George Martin (George's disease), a laboratory technician who worked in Dr. Theiler's laboratory. Mouse encephalomyelitis virus is thought to be moderately to highly prevalent in conventional mouse colonies.

The biological behavior of MEV allows its separation into two subgroups: highly virulent isolates that cause **acute infection** and less virulent isolates that produce **persistent infection** of the CNS.

The characteristic observed sign of natural infection is **flaccid paralysis of the rear legs**, while the tail remains mobile. Paralysis may be preceded by weakness in the forelimbs or hindlimbs. This poliomyelitis-like disease is characterized morphologically by acute necrosis of ganglion cells neurophagia and peri vascular inflammation, particularly in the ventral horn of the spinal cord gray matter. In demyelinating disease, mononuclear cell inflammation develops in the leptomeninges and white matter of the spinal cord. Patchy demyelination is seen in areas of inflammation.

Some mice may recover from paralysis, but death frequently ensues. The course of disease may be exacerbated by a failure to obtain food or water and by urinary incontinence. Mice that recover from the paralytic syndrome are disposed to a chronic demyelinating phase, which is expressed clinically as a **mild gait disturbance.**

Virus is also known to replicates in intestinal mucosa and is excreted in feces.

11. PIN WORM of MICE

Syphacia obvelata, the common mouse pin worm, is a ubiquitous parasite of wild and laboratory mice. Infestation is diagnosed by demonstrating eggs in the perianal area or adult worms in the cecum or large intestine.

Since most eggs are deposited outside the gastrointestinal tract, fecal examination is not reliable. Eggs are usually detected by pressing cellophane tape to the perineal area and then to a glass slide that is examined by microscopy. Eggs are flattened on one side and have pointed ends. Female worms range from 3.4 to 5.8 mm in length, and male worms are smaller (1.1-1.5 mm).

Infection is usually asymptomatic, and gross lesions are not prevalent aside from the presence of adults in the lumen of the intestine. Heavily infected mice can occasionally sustain various intestinal lesions including rectal prolapse, intussusception, enteritis, and fecal impaction.

Hymenolepis nana	- the Dwarf Tapeworm
Mouse mite	Myobia musculi
Mouse louse	Polyplax serrate