INFECTIOUS AGENT EXCLUSION LIST FOR MICE

Division of Comparative Medicine

Specific examples of interference to research caused by infectious agent exposure are viewable at http://www.lal.org.uk/pdffiles/GVSOLAS.pdf.

I. DNA VIRAL DISEASES

A. ADENOVIRUS

MOUSE ADENOVIRUS-1
Etiology: MAV-1 (FL), nonenveloped, polytropic.
Transmission: urine, feces, nasal secretions.
Clinical: naturally asymptomatic; experimentally fatal, multisystemic, prolonged viruria.
Pathology: thymic involution; foci of endothelial and epithelial necrosis with hemorrhage, and type A intranuclear inclusions in renal tubules, adrenal cortex, also spleen, intestine, brain, salivary glands, myocardium.
Ddx:.polyoma virus, cytomegalovirus.
Significance: rare multisystemic infection, neonatal encephalitis, SCID or nude enteritis; model for adrenal necrosis.

MOUSE ADENOVIRUS-2
Etiology: MAV-2 (K87), nonenveloped, enterotropic.
Transmission: feces.
Clinical: none, enterotropic, runting in sucklings, recover.
Pathology: runting may occur; intranuclear inclusions in small intestinal and cecal mucosal epithelium.
Dx: antiserum to MAV-2 reacts with MAV-1, use MAV-2 antigen in serological tests; intranuclear intestinal inclusions are pathognomonic.
Significance: moderate prevalence, rare suckling runting.

B. HERPESVIRUS

MOUSE THYMIC VIRUS
Etiology: Mouse Thymic Virus; salivary tropism, true latency possible.
Transmission: saliva shedding for months, possibly trans-mammary.
Clinical: natural subclinical; experimental exposure neonatal thymic necrosis, adults no clinical signs, tropism for salivary glands and CD4+ T cells.
Pathology: necrosis of thymocytes, possibly lymph nodes or spleen, intranuclear inclusions; no salivary gland lesions.
Significance: rare; immunosuppression, autoimmunity; frequent contaminant of MCMV stocks.

MOUSE CYTOMEGALOVIRUS
Etiology: MCMV, species specific betaherpesvirus; salivary tropism, true latency possible.
Transmission: oronasal via saliva, tears, urine.
Clinical: none, naturally; maternal antibodies protective; experimentally exposed or immunocompromised mice develop disseminated cytomegalic inclusion disease.
Pathology: preferentially replicates in submandibular salivary gland; experimentally, multisystemic dissemination, infants develop focal necrosis, cytomegaly, lymphoplasmacytic infiltration, and inclusions in many tissues; young adults develop subclinical pulmonary infection with alveolar septal thickening and edema; eosinophillic intranuclear and intracytoplasmic inclusions particularly in salivary gland acinar epithelial cells.
Ddx: polyoma virus-associated sialoadenitis with inclusion bodies.
Significance: seldom overt disease; synergism with *Pseudomonas aeruginosa*; severe disseminated disease with mortality in SCID, nude, or aging mice possible; model.

C. PAPOVAVIRUS

MOUSE K VIRUS
Etiology: Mouse K virus; endothelium tropism.
Transmission: orofecal, urine; intestinal endothelium, dissemination to liver, lung, spleen, adrenal, renal tubular endotheliums.

Clinical: neonatal or immunocompromised mice, viremic, dissemination to pulmonary vascular bed results in sudden onset of dyspnea, death; none in mice >18 days, resistance.
Pathology: intranuclear inclusions in vascular endothelium of jejunum, ileum, lung, liver; pulmonary congestion, edema, hemorrhage, atelectasis, alveolar septal thickening.
Ddx: MAV-1, MCMV, or polyoma virus-associated multisystemic infection with intranuclear inclusions.
Significance: low natural prevalence.

POLYOMAVIRUS
Etiology: Polyomavirus, Papovavirus; "many tumors", especially salivary gland tumors, experimentally develop in neonates <24 hours old parenterally administered high titers of oncogenic strains of virus, similar to SV40, BK and JC viruses.
Transmission: intranasal urine, environmentally stable, but inefficient transmission can be broken by husbandry practices.
Clinical: natural infection rare; neonatal inoculation of nasal mucosa to submandibular salivary gland to lung, then dissemination especially kidney with high mortality; persists in lungs and kidneys; cleared in older mice; nude mice develop multisystemic wasting, paralysis associated with demyelination progressive multifocal leukoencephalopathy, and vertebral tumors; tumors of uterus and bone.
Pathology: nude mice develop multifocal inflammation and necrosis, tumor formation; multiple tissues affected including bronchial, renal pelvic, ureteral epithelium; oligodendroglia with demyelination, intranuclear inclusions.
Ddx: nude wasting – MHV, *Pneumocystis carinii*, Sendai, PVM; intranuclear inclusions – K virus, adenovirus, MCMV.
Significance: minimal, rare, contamination of transplantable tumors; prevalence may increase with use of polyoma middle T (Py V-MT) transgene.

D. PARVOVIRUS

MINUTE VIRUS OF MICE
Etiology: MVM, Parvovirus; lytic replication cycle, lymphoid tropism, 2 strains.
Transmission: direct contact, urine, feces; infant mice, tropism for small intestine, lymphoid tissue, and kidney, but mouse enterocyte lacks receptor for parvovirus present in other species.
Clinical: acute self-limiting, common seroconversion, asymptomatic.
Pathology: none naturally; experimentally infects germinal centers of cerebrum, and results in cerebellar hypoplasia, erythrocyte-associated viremia, anemia; in SCIDs fatal leukopenia, hematopoietic dyscrasia.
Significance: common, lymphoid tissue tropism, possible immunomodulation, immunosuppression, oncolysis.

MOUSE PARVOVIRUS
Etiology: MPV, Parvovirus; T-cell tropism.
Transmission: orofecal, adult mice, parvo-tropism for small intestine and lymphoid tissue, but mouse enterocyte lacks receptor for parvovirus present in other species.
Clinical: persists in lymphoid tissue, common seroconversion, asymptomatic.
Pathology: none naturally.
Dx: no common structural antigens with MVM, but shares common cell-associated, nonstructural antigens with MVM; consequently, diagnostic use of MVM-infected cells as target in IFA began in FY 2001-02.
Significance: common, persists in adults, lymphotropism results in significant immunomodulation, immunosuppression.

E. POXVIRUS

MOUSEPOX
Etiology: Ectromelia virus, *Orthopoxvirus*, many strains, vary in virulence.
Transmission: contact, urine, orofecal; cutaneous trauma, skin to lymph nodes to spleen & liver to other organs; not highly contagious; contaminated commercial mouse sera.
Clinical: susceptible strains C3H, A, DBA, SWR, BALB/c die acutely; others develop cutaneous lesions; B6 mice become subclinically infected and resistant to disease.
Pathology: susceptible mice develop cutaneous erythema and erosions, multifocal coagulative necrosis in liver, spleen, lymph nodes, Peyer's patches, thymus, erosive enteritis and hemorrhage of small intestine; type A pox inclusions or Marchal bodies especially in hepatocytes, skin and conjunctival mucosa; recovered mice may have splenic fibrosis and amputated tails and digits (ectromelia – shortening of extremities, dry gangrene).
Ddx: hepatitis in adults – MHV, Tyzzer's, salmonellosis; skin – bites; gangrene – "ringtail", trauma.

Significance: high mortality in adult immunocompetent strains; polytropic, subclinical active infection, contamination of commercial mouse sera and other biologics; rare; vaccine IHD-T available but a modified live preparation that prevents mortality but not infection and sero-conversion, not recommended.

II. RNA VIRAL DISEASES

A. ARENAVIRUS

LYMPHOCYTIC CHORIOMENINGITIS

Etiology: LCMV, Arenavirus; mouse is the natural host, lytic cycle in lymphoid subpopulations, but typically considered budding non-lytic replication cycle.
Transmission: labile virus, *in utero* major means of transmission in colonies, cesarean rederivation of no value; nasal secretions, saliva, urine; persistent viral shedding possible especially in urine; wide host range (rats refractory).
Clinical: minimal to subclinical in natural infections; adult immunocompetent recover rapidly without overt disease; infant and immunodeficient mice develop disseminated infection, runting, wasting; experimentally tolerant, multisystemic, persistent, subclinical, infection (budding, not cytolytic); break in tolerance results in "late disease".
Pathology: late disease comprised of immune complex glomerulonephritis, vasculitis and lymphocytic infiltration in brain, liver, adrenal, kidney, lung; experimental intracerebral inoculation causes fatal lymphocytic choriomeningitis in adult mice, but not neonates.
Significance: polytropic, wide host range, contaminated transplantable tumors, immune suppression; zoonotic potential; adult Syrian hamsters can be persistently infected, shed, and serve as source of interspecies transmission.

B. ARTERIVIRUS

LDH-ELEVATING VIRUS

Etiology: LDV, lactate dehydrogenase-elevating virus; monocyte tropism.
Transmission: inefficiently transmitted in saliva naturally, bite wounds; cell tropism for macrophages, monocytes, and neural tissue; contaminated biologics, transplantable tumors, hybridomas.
Clinical: asymptomatic, lifelong infection, but brief inefficient shedding; experimentally in C58 and AKR mice with N-ecotropic MuLV and homozygous at the Fv-1 locus results in cytolytic infection of ventral horn neurons of spinal cord and paralytic syndrome.
Pathology: none, naturally; experimentally in C58 and AKR mice age-dependent poliomyelitis neuronolysis, mononuclear perivasculitis of ventral horns of spinal cord.
Ddx: MHV, MEV.
Significance: altered macrophage/monocyte function; immunomodulation; common contaminant of biologics, eliminate from biologics *in vitro* or by passage through nude rats.

C. CALICIVIRUS

MURINE NOROVIRUS

Etiology: MNV, genus *Calicivirus*; "Norwalk-like"; non-enveloped; multiple serotypes; tropism for macrophages and dendritic cells.
Transmission: fecal shedding, possibly oral and respiratory; very low infective dose, persistent in environment, requires ≥ 10 mg/liter of chlorine to inactivate; widespread serologic evidence of exposure in conventional colonies (>20%).
Clinical: disease described only in strains lacking components of the innate immune system (i.e., STAT1, α/β and γ-interferon receptors).
Pathology: STAT1 nullizygous mice develop pneumonia, liver fibrosis, and loss of splenic architecture; RT-PCR detection of virus in multiple organs including the intestines, and in feces; RAG2 nullizygous mice become persistently infected, but with limited mortality following oral innoculation; wild-type 129 mice remain asymptomatic and lack tissue pathology after oral inoculation.
Significance: newly recognized pathogen; widespread serologic evidence of exposure; interference with inter-institutional transfers.

D. CORONAVIRUS

MOUSE HEPATITIS VIRUS

Etiology: MHV, syncytia; 2 biotypes – respiratory/polytropism and enterotropism; Coronavirus; numerous highly mutable strains, repeat infections; constantly evolving, varied virulence and varied organotropisms.
Transmission: orofecal, nasal, highly contagious; primary tropisms for either upper respiratory (MHV-1, 2, 3, or JHM) or enteric (formerly LIVIM) mucosal epithelium; respiratory tropism (polytropic) initially replicate in nasal mucosal epithelium then disseminate to endothelium and parenchyma of liver, brain, lymphoid organs; enterotropic strains selectively infect intestinal mucosal epithelium with little dissemination.
Clinical: typically subclinical; cleared within 3-4 weeks, no persistence or carrier state; "burn-out"; high mortality among neonates possible; immunodeficient strains cannot clear, die acutely or develop chronic wasting disease.
Pathology: focal necrosis with syncytia; natural infections mild or no discernable lesions; respiratory tropism – multifocal necrosis with syncytia in liver, splenic red pulp, lymph nodes, gut-associated lymphoid tissue and bone marrow, splenomegaly compensatory hematopoiesis; neonatally infected mice vascular-oriented necrotizing encephalitis with spongiosis and demyelination in brain stem; experimentally nasoencephalitis via olfactory nerves, bulbs and tracts; enterotropism – (neonates) terminal small intestine, cecum, ascending colon, villus attenuation, enterocytic syncytia, eosinophillic intracytoplasmic inclusions, necrotizing enterocolitis, syncytia in mesenteric lymph nodes and endothelium; (adults) minimal lesions with enterotropic strains due to quicker mucosal kinetics.
Ddx: enteritis – EDIM, salmonellosis, Tyzzer's, reovirus; demyelinating lesions – mouse encephalomyelitis virus, LDV, polyoma virus.
Significance: very common; polytropic, highly contagious, immunomodulating; contaminant of biologics, tumors, cell lines; altered biological responses; novel manifestations in GEM (e.g., "FIP" granulomatous serositis in αIFN-KO mice; increased prevalence of *Spironucleus muris* with MHV; model of multiple sclerosis.

E. PARAMYXOVIRUS

PNEUMONIA VIRUS OF MICE

Etiology: PVM, genus *Pneumovirus*, Paramyxovirus; tropism for bronchiolar epithelium and type II pneumocytes.
Transmission: respiratory, labile, low degree of contagion requiring close contact, focal colony infection.
Clinical: subclinical, acute self-limiting, upper respiratory infection; morbidity in immunodeficient strains progressive interstitial pneumonia, wasting, confined to alveolar type II pneumocytes and bronchiolar epithelium; complicated by *Pneumocystis carinii.*
Pathology: rare lesions except immunodeficient strains, thick, edematous alveolar septa with infiltrating macrophages and leukocytes, alveoli filled with fibrin, blood, macrophages, and large polygonal sloughed alveolar type II cells.
Ddx: pulmonary and wasting in immunodeficient strains – Sendai, *Pneumocystis carinii*.
Significance: common; morbidity in immunodeficient strains, wide rodent host range, interspecies transmission.

SENDAI VIRUS

Etiology: *Parainfluenza 1*, (Sendai, Japan), Paramyxovirus; tropism for bronchiolar epithelium and type II pneumocytes; nonlytic replication cycle; contributes to inefficient ciliary clearance; delayed exuberant immune response.
Transmission: highly contagious, close contact transmitted by aerosol, labile, also affects rats and hamster, descending respiratory infection; DBA/2 and infant mice highly susceptible due to delayed zealous immune response deep in lung; B6 mice subclinical; acute infection with no persistent carrier state except in immunodeficient strains, virus cleared in 8-12 days; soiled bedding does not reliably seroconvert sentinels.
Clinical: subclinical, dyspnea, necrotizing rhinitis, tracheobronchitis, bronchiolitis, interstitial pneumonia; predispose to otitis media and interna, precipitate *Mycoplasma* pneumonia.
Pathology: plum-colored consolidation of anteroventral lung; hypertrophic, hyperplastic, and sloughed bronchiolar epithelium with syncytia, intracytoplasmic eosinophillic inclusions, squamous metaplasia of bronchiolar epithelium, interstitial pneumonia, proliferative alveolitis, cuboidal metaplasia of alveoli, focal alveolar fibrotic scarring; SCID and nude proliferative rather than necrotizing lesions.
Ddx: *Mycoplasma* and *Corynebacterium kutscheri*; in immunodeficient strains lesions are similar to PVM infection.
Significance: major concern; virus most likely to cause clinical disease in adult, immunocompetent mice, mortality in susceptible and immunodeficient strains; predispose to bacterial respiratory infections; immunomodulation; delayed wound healing; altered incidence of pulmonary neoplasms.

F. PICORNAVIRUS

MOUSE ENCEPHALOMYELITIS VIRUS

Etiology: MEV, *Cardiovirus*, Picornavirus; "mouse polio", 2 serogroups (i.e., TO, GDVII), numerous strains, Theiler's original, GDVII, FA, DA, etc.
Transmission: orofecal, ingestion; low, inefficient contagion; prolonged and intermittent intestinal shedding; rats and guinea pigs seroconvert.
Clinical: low virulence; enteric replication, no adverse intestinal effects; encephalitis and demyelination rare components of natural infection; rare potential endothelial access to CNS acute encephalitis, virus can persist in white matter, late-onset demyelination; presents as flaccid paralysis during acute encephalitic phase; high morbidity/mortality possible with immunocompromised strains.
Pathology: no intestinal lesions; vacuolation, neuronolysis, neuronophagia, microgliosis, nonsuppurative meningitis, perivasculitis in hippocampus, thalmus, brain stem, and ventral horns of cervical spinal cord.
Ddx: MHV, LDV, polyoma virus, neoplasia, trauma.
Significance: persistent infection with intermittent shedding; low virulence; inefficient transmission; contaminant of mouse serum; immunodeficient strain morbidity; can successfully test and cull at the cage level.

G. REOVIRUS

REOVIRUS 3

Etiology: Reo-3; respiratory, enteric, orphan.
Transmission: orofecal, aerosol, arthropod vectors, direct contact among young.
Clinical: all ages seroconvert, pups born to immune dams are protected; viral replication can occur in disseminated organs; only neonates in naïve colonies develop disease; runted, jaundiced, steatorrhea, uncoordinated.
Pathology: diffuse encephalitis with vascular distribution; focal hepatic, myocardial, lymphoid necrosis; pancreatitis, sialoacryoadenitis.
Ddx: neonatal runting with steatorrhea – MHV, EDIM, salmonellosis.
Significance: moderately prevalent; contaminant biologics, transplantable tumors; not generally significant pathogen.

EDIM

Etiology: Epizootic Diarrhea of Infant Mice; group A rotavirus of *Reoviridae* family; tropism for terminally differentiated enterocytes of villus tips of small intestinal mucosa, which are more abundant in neonates.
Transmission: orofecal, copious shedding; highly contagious; all ages susceptible to infection, but disease limited to neonates <2 weeks old; host specific, but interspecies transmission possible experimentally.
Clinical: seroconversion, asymptomatic; pups born to suckling immune dams are protected; neonates <12 days age in naïve colonies are runted, pot-bellied, mustard-colored diarrhea, steatorrhea, continue to suckle (MHV not suckling), recover at 14-17 days of age.
Pathology: hydropic swelling of villus tip epithelium, vacuolation of enterocytes, villus atrophy; (malabsorption, osmotic diarrhea, overgrowth of *Escherichia coli*); adults, including SCID and nude, do not develop lesions due to quicker mucosal kinetics.
Ddx: enterotropic MHV (formerly LIVIM), MAV, reovirus, salmonellosis, Tyzzer's.
Significance: highly contagious, copius shedding, subclinical and transient except in neonates.

H. RETROVIRUS

MuLV

Etiology: Murine leukemia viruses; 100% all mice harbor multiple copies of endogenous MuLV proviruses; exogenous MuLVs in wild mice (similar to early laboratory isolates, Gross, Friend, Moloney, Rauscher MuLVs).
Transmission: Mendelian genetic provirus transmission; up to 70 copies of ecotropic MuLVs randomly integrated; stable integration specific to strain; when expressed prone to recombination or transduction with host genes; defined by host-range polymorphisms (i.e., eco, xeno, ampho/poly), tissue tropisms, and genotype (e.g., B-ecotropic infect only mice homozygous at Fv-1^b); exogenous horizontal transmission also via saliva, milk, semen in feral mice were source of Friend, Moloney, Rauscher leukemia viruses.
Clinical: recombination, e.g., AKR endogenous, nononcogenic eco (many tissues) + xeno (thymus) = MCF mink-cell-focus forming, polytropic oncogenic virus and thymic lymphoma; random reintegration, varied consequence including altered coat color/consistency, graying, CNS disease with LDV.

Pathology: variable, genotype dependent; includes neoplasia, but most MuLV sequences are not oncogenic, instead encode strain-specific characteristics, e.g., demyelination (with LDV in C58 and AKR), dilute color (DBA), hairlessness (HR); endogenous proviruses given gene designations, e.g., AKR mice endogenous proviruses are designated *akv-1, akv-2, akv-3,* etc.; restriction genes e.g., *fv-1, fv-4* and receptors influence evolution of recombinant pathogenic isolates, in addition, numerous intracisternal A particles (IAP), virus-like 30s RNA sequences (VL30), murine retrovirus-related DNA sequences (MuRRS), tRNA glutathione-like sequences (GLN), murine repeated virus sequences on Y chromosome (MuRVY), early transposons (ET).

MMTV
Etiology: Mouse mammary tumor viruses; exogenous MMTV-S, (standard), "milk factor", Bittner agent; 100% all mice harbor multiple copies of endogenous MMTV except perhaps "Lake Casitas" mice.
Transmission: MMTV-S in milk, saliva, semen, eliminated by fostering, intentionally maintained in model strains (C3H/HeJ, C3H/HeOuJ); 0-4 copies of endogenous provirus transmitted genetically, given gene designations (*Mtv-1, -2, -8*, etc.).
Clinical: MMTV-S associated mammary tumors; varied reintegration consequence; e.g., *Mtv-29* functions as a super-antigen in SJL mice, stimulates T-cell cytokine expression, resulting in B-cell lymphoma; thymic lymphoma in GR mice.
Pathology: mammary neoplasia (C3H) or B-cell lymphoproliferative disease (SJL) or thymic lymphoma (GR) depending on strain; does not rely on recombinatorial events for oncogenesis, but instead direct insertional activation of proto-oncogenes.

HANTAVIRUS – zoonotic hazard; aerosol, contact with infected urine; no clinical disease in rats; also naturally infects *Peromyscus* mice; 2 major lineages, (HFRS) Hemorrhagic Fever and Renal Syndrome in humans with fever, thrombocytopenia, myalgia, headache, petechiae, retroperitoneal and renal hemorrhage; (HPS) Hantavirus Pulmonary Syndrome in humans with fever, pulmonary edema, shock; Bunyviridae.

III. BACTERIAL DISEASES

CITROBACTER COLONIC HYPERPLASIA
Etiology: *Citrobacter rodentium*, cocc-bacillus, (formerly *C. freundii*, strain 4280), transmissible murine colonic hyperplasia (TMCH).
Transmission: contaminated food, bedding, orofecal, direct, low contagiousness; selectively colonizes surface mucosa of cecum and colon within 4 days; locus of enterocyte attachment and type III secretion system facilitate attachment; translocated intimin receptor; recovered mice are refractory to reinfection; no carrier state.
Clinical: runted, lose weight, sticky, unformed feces; low mortality, often recover within 2 months; permanent rectal prolapse possible.
Pathology: thickened descending colon devoid of feces; marked colonic crypt hyperplasia (Th-1 response, IL-12, γIFN, TNFα, elevated keratinocyte growth factor), basophilic epithelial cells; inflammation and erosion possible among infants of some strains; hyperplasia followed by excessive goblet cells and cryptal cysts (mucin and cellular debris), normal mucosa within 2 months.
Ddx: MacConkey agar, but in 2-3 weeks can no longer isolate; enteritis in young – rota, reo, MHV, MAV-2; in older mice – Tyzzer's, *Salmonella*; rectal prolapse - *Helicobacter*
Significance: rare, no carrier state, transient, low contagiousness, low mortality, runting and rectal prolapse.

ESCHERICIA COLI
Etiology: *Escherichia coli*, coliform typhlocolitis, common intestinal organism; but atypical, non-lactose fermenting isolate.
Transmission: immunodeficient strains *nu, xid, beige*; SCIDs only.
Clinical: blood-tinged diarrhea.
Pathology: thickened, hyperplastic typhlitis and colitis, erosion.
Ddx: *C. rodentium*, *Helicobacter*, enterotropic MHV.
Significance: rare, immunodeficient strains only.

CLOSTRIDIUM PERFRINGENS
Etiology: *Clostridium perfringens*, gram positive bacilli, strict anaerobe.
Transmission: common isolate of intestinal flora.
Clinical: dilated, blood-stained fluid in small intestine.
Pathology: necrotizing enterocolitis in post-weaning mice; fibrinous exudation and effacement of small or large intestinal mucosa; hyperplastic during recovery.

Ddx: Tyzzer's, *Citrobacter, Helicobacter, Escherichia.*
Significance: sporadic.

TYZZER'S DISEASE
Etiology: *Clostridium piliforme*, spore-forming, obligate intracellular, gram negative, filamentous bacterium; propagates only in embryonated eggs or cell culture.
Transmission: orofecal, direct contact; intrauterine experimentally; fecal shed spores survive >1 year; contaminated food, bedding, environment; wide species range including rats, gerbils, hamsters, guinea pigs, rabbits.
Clinical: low morbidity, high mortality; sudden death and watery diarrhea; DBA/2 susceptible; C57BL/6 resistant; nudes as resistant as immunocompetent strains; numerous predisposing factors.
Pathology: colitis & typhlitis with dissemination to liver and heart; sudden death; miliary, 5 mm, pale hepatic foci of coagulative to caseous necrosis with polymorphonuclear infiltration, liver lesions most consistent finding in mice; segemental mucosal necrosis of terminal ileum and cecum; necrosis of mesenteric lymph nodes and focal myocardium; intracytoplasmic bundles of baccili adjacent to necrotic foci by Warthin-Starry, Giemsa, or PAS stains.
Ddx: MHV, mousepox, *Salmonella, Pseudomonaus, Corynebacterium, Helicobacter.*
Significance: depopulate; persistence of spores in environment >1 year; acute mortality; potential zoonosis for immunocompromised.

HELICOBACTER
Etiology: *Helicobacter* spp.; *H. hepaticus* & *H. bilis* most frequently described in mice; microaerobic, curved to spiral rods with flagella; *H. muridarum* perhaps associated with chronic gastritis.
Transmission: orofecal, contaminated bedding; persists in biliary canaliculi; gastrointestinal pathogen in many species.
Clinical: sticky, mucoid, unformed, bloody feces; rectal prolapse; wasting, mortality; chronic hepatitis in older males.
Pathology: hepatitis, typhlocolitis; segmental, hyperplastic typhlitis and colitis with marked mixed leukocytic infiltration, rectal prolapse; focal, 4 mm, chronic hepatitis, hepatocytomegaly and necrosis; marked hypertrophy and hyperplasia of bile ductule oval cells; organisms in biliary canaliculi, surface and crypt of colon using Steiner silver stain; increased incidence and earlier onset of hepatocellular tumors; variable strain susceptibilities, e.g., strains A, SCID, C3H/He susceptible, and strains C57BL/6 and B6C3F1 resistant to *H. hepaticus* disease.
Ddx: hepatitis – *Salmonella, Proteus, Clostridium piliforme,* MHV, ectromelia virus; typhlocolitis – *eschericia, citrobacter,* MHV.
Significance: pathogen; increased hepatocellular tumors; "inflammatory bowel disease" in interleukin, T-cell receptor, and MHC class II knockouts.

MYCOPLASMOSIS
Etiology: *Mycoplasma pulmonis*; less commonly *M. arthritidis*, rarely *M. neurolyticum, M. collis.*
Transmission: aerosol, neonates, upper respiratory; compared to rats, mice are relatively resistant to disease.
Clinical: subclinical; dyspnea, chattering.
Pathology: suppurative rhinitis, otitis media, bronchopneumonia; peribronchial & perivascular lymphoplasmacytic infiltration to suppurative bronchiolitis, alveolitis with mobilization of alveolar macrophages, squamous metaplasia, to cranioventral consolidation, bronchiectasis; syncytia in upper respiratory tract.
Ddx: nasopharyngeal, tracheobronchial lavages, but cultures often negative; serological titers often low & cross react with *M. arthritidis*; experimentally *M. arthritidis* IV – arthritis; consider co-pathogens Sendai, MHC, CAR bacillus, *Pasteurella pneumotropica*.
Significance: immunomodulating, copathogen; test and cull can effectively eliminate; *M. neurolyticum* conjunctivitis only naturally & rare; experimentally intracerebral injection produces "rolling disease"; *M. arthritidis* – nonpathogenic naturally, antigenically related to *M. pulmonis*; *M. collis* – nonpathogenic genital isolate.

SALMONELLOSIS
Etiology: *Salmonella enteritidis*, serotype *enteritidis* or *typhimurium*; gram-negative, non-lactose fermenting; 3 species, 1600 serotypes; enterohepatic cycle.
Transmission: orofecal; contaminated feed, bedding; weanlings more susceptible; incubation 3-6 days, fimbrial attachment to M-cells to GALT to mesenteric lymph nodes, then disseminated to spleen, bile ducts, intestine; intracellular replication with macrophages avoid neutrophil attack; BALB/c and C57BL/6 susceptible, CBA and A/J resistant; intermittent shedding by carriers.
Clinical: diarrhea, conjunctivitis, variable mortality; scanty fluid intestinal lumen contents.

Pathology: multifocal necrosis and venous thrombosis with leukocyte infiltration in liver, spleen, Peyer's patches, mesenteric lymph nodes; focal hepatic granulomas as hallmark lesion; intermittent shedding.
Ddx: culture mesenteric lymph nodes; Tyzzer's, MHV, ectromelia virus, *Helicobacter, Pseudomonaus*.
Significance: depopulate, interspecies transmission, zoonotic.

OTHER GRAM NEGATIVE INFECTIONS

Pasteurella pneumotropica – gram-negative coccobacillus; commensal, common intestinal and nasopharyngeal isolate from healthy mice; subclinical, often seronegative, opportunist; purulent conjunctivitis, periorbital abscessation, abscessation of cervical lymph nodes, rhinitis, bronchopneumonia, metritis, accessory sex glands; possible dermatitis or bronchopneumonia with *Pneumocystis carinii* coinfection in immunodeficient strains; search for primary pathogen or predisposing factors.

Proteus mirabilis –SCID mice; multifocal to coalescing hepatic coagulative necrosis with thrombophlebitis; fibrinopurulent peritoneal exdudate; thrombophlebitis in intestinal serosa, pancreas; pyelonephritis; alveolar flooding and macrophage mobilization; improve sanitation, reduce densities.

Pseudomonas aeruginosa – gram-negative, nonspore-forming rod; ubiquitous, often drinking water source; not normal microflora; experimental immunosuppression or immunodeficient strains, impaired granulocyte function or neutropenia; penetration of oronasal or intestinal mucosa to regional lymph nodes to liver and spleen; vasculitis, thrombosis, necrosis, hemorrhage; prevent with acidification of drinking water to pH 2.5 – 2.8 or hyperchlorination with 10-12 ppm, although practice may contribute to dental erosion; ddx – *C. kutscheri*.

Chlamydia trachomatis – Nigg agent, discovered by Clara Nigg during intranasal inoculation of human throat wasings to attempt to isolate human influenza, also referred to as "gray lung disease" or "mouse pneumonitis"; also ***C. psittaci;*** no natural disease, subclinical and persistent; models for respiratory and genital chlamydiosis; grows intracellularly in bronchiolar epithelium and macrophages (elementary and reticulate bodies); nonsuppurative interstitial pneumonia with atelectasis, then disseminates; immunodeficient strains.

CAR Bacillus – cilia-associated respiratory bacillus; unclassified, gram-negative, motile, non-spore-forming, bacterium related to *Flexibacter* spp. and *Flavobacterium* spp.; commonly infects rabbits, pathogen in rats; experimentally induced chronic suppurative cranioventral bronchopneumonia in BALB/c; potential respiratory co-pathogen in mice; direct <u>not</u> aerosol transmission; filamentous bacterium upper airways by Warthin-Starry silver stain, "blue fuzz" on H&E.

Streptobacillus moniliformis – gram-negative, nonmotile, pleomorphic, filamentous rod; unlikely pathogen; normal nasopharynx microflora of rats; major reason for not co-housing rats & mice; diarrhea, hemoglobinuria, conjunctivitis; focal necrosis in liver, spleen, lymph nodes, petechial & ecchymotic subserosal hemorrhages; nephritis, polyarthritis; potential zoonosis (Haverhill or "rat-bite" fever, also *Spirillum minus*).

Eperythrozoon coccoides – transmitted by *Polypax serrata* louse; rare; Giemsa or Romanowsky stained blood smears, attached to erythrocytes or free in plasma; inapparent to anemia, splenomegaly; more closely related to mycoplasma than rickettsia, classified now as member of *Mollicutes, Mycoplasmatales*.

Klebsiella oxytoca – single report; suppurative endometritis, salpingitis, perioophoritis, peritonitis; secondary cystic endometrial hyperplasia.

Leptospira ballum – most common serotype in mice; rare; subclinical, life-long urine shedding neonates become persistently infected but do not seroconvert; zoonotic.

Mycobacterium avium-intracellularis – single report; asymptomatic, subpleural and pulmonary microgranulomas.

OTHER GRAM POSITIVE INFECTIONS

Corynebacterium kutscheri – gram-positive, diphtheroid bacillus; "psedotuberculosis"; rare significant pathogen; immunosuppressed, penetrates oral or enteric mucosa to regional lymph nodes to bacteremia to thromboembolism, caseous or liquefied purulent abscesses in liver and kidney, suppurative arthritis (carpometacarpal and tarsometatarsal); organisms seen as "Chinese letter" configurations at edge of lesions; search for subclinical carriers, improve sanitation, immunosuppression results in exacerbation of disease.

Corynebacterium bovis – "coryneform hyperkeratosis"; diffuse hyperkeratotic dermatitis of nude mice; transmitted by fomites, direct, or topical administrations; asymptomatic transient infection in immunocompetent strains, other nudes like source; high morbidity; orthokeratotic, hyperkeratotic epidermal hyperplasia; ddx: hyperkeratosis-associated with low ambient humidity.

Corynebacterium hoffmani – frequent opportunistic isolate in BALB/c conjunctivitis; ddx: *P. pneumotropica*.

Staphylococcus aureus – gram-positive, coccoid bacterium, common inhabitant of skin, mucous membranes, nasopharynx, intestine; asymptomatic; nude – periorbital abscess, furunculosis and folliculitis around muzzle, lacrimal & prepucial gland abscesses; B6 – contributes to ulcerative dermatitis, secondary to acariasis; pruritic with self-excoriation; readily identifiable bacteria, botryomycotic granules, Splendore-Hoeppli material, especially cervical lymph nodes.

Streptococcus sp. – Lancefield type G – necrotizing, ulcerative dermatitis; beta-hemolytic streptococcus – septicemia, endocarditis with mural thrombosis, myocarditis; SCIDs – alpha-hemolytic streptococcus, colonization of glomerular tufts; mice are resistant to *S. pneumoniae.*

IV. MYCOTIC INFECTIONS

DERMATOMYCOSIS
Etiology: *Trichophyton mentagrophytes* var*. quinckeanum* and var. *mentagrophytes.*
Transmission: contact; nonselective host range, other animals, human.
Clinical: typically subclinical; favus – dull yellow cuplike crusts on muzzle, face, head, ears, extremities; □lopecia, focal crusts.
Pathology: dermatitis with Schiff-positive arthrospores and mycelia; without hair shaft invasion.
Dx: culture on Sabaroud's agar.
Significance: relatively nonpathogenic; nonselective host range; zoonotic.

PNEUMOCYTOSIS
Etiology: *Pneumocystis carinii*
Transmission: widespread; saprophytic lung infection; inefficiently transmitted, direct contact.
Clinical: typically asymptomatic; dyspnea.
Pathology: lungs pale, fleshy, rubbery, collapse poorly, with patchy areas of consolidation; interstitial alveolitis with foamy proteinaceous exudation and mobilization of macrophages; methenamine silver stained 3-5 μm cysts; trophozoites attach via filapodia;
Ddx: superimposed viral or bacterial pathogens (e.g., PVM); "soap bubble" organisms do not stain with H&E.
Significance: significant pathogen of immunodeficient strains or associated with immunosuppression; high mortality; no interspecies transmission.

Candida albicans – normal flora of alimentary tract; pseudohyphae in keratinized epithelium of forestomach, incidental, or pseudomembranous, hyperkeratotic hyperplasia of gastric mucosa in immunocompromised strains.

V. PARASITIC DISEASES

A. ECTOPARASITIC INFESTATIONS

ACARIASIS
Etiology: ***Myobia musculi*** – most clinically significant, slightly elongated body, bulges between legs, single terminal tarsal empodial claw on second pair of legs; similar appearing ***Radfordia affinis*** – two terminal tarsal empodial claws of unequal length; ***Myocoptes musculinis*** – oval, suckers on tarsi, heavily chitinized, pigmented third and fourth legs.
Transmission: direct transfer; migrate from dam to sucklings at 1 week, presence of hair shaft critical, infestation persists for years; mice without pelage (nudes) are resistant; infestations are widespread and mixed; *Myobia* eggs laid on hair shaft adjacent to epidermis; larvae hatch in 7-8 days; adults evolve in 16 days; *Myobia* feed on secretions and interstitial fluid; immune sensitization, pruritic, self-inflicted ulcerative lesions, secondary *Staphylococcus* infections; *Myocoptes* feeds on superficial epidermis.

Clinical: *Myobia* – head, eyelids, neck, shoulders; *Myocoptes* – all over body, primarily inguinal, abdominal.
Pathology: *Myobia* most pathogenic; *Radfordia* does not induce overt disease; hyperkeratotic epidermal hyperplasia, ulcerative dermatitis with secondary *Staphylococcus* infection.
Dx: *Myocoptes* most common; more on young; few on mice with severe lesions; pelt in petri dish for 1 hour.
Significance: B6 background strains at high risk for hypersensitivity dermatitis; cutaneous allergy in BALB/c mice.

Demodex musculi – host specific, rare, hair follicles, dorsal thorax; present on plucked hair or skin sections.

Psorergates simplex – comedones, follicular cysts on head, shoulders, lumbar areas; rare.

Ornithonyssus bacoti – "tropical rat mite", blood sucking mesostigmate mite, nonselective host range, wild rats, inhabits host only to feed, intense pruritis, zoonosis possible.

Polyplax serrata – sucking lice, anterior dorsum, direct contact, anemia and pruritis; vector of *Eperythrozoon coccoides*.

Xenopsylla – rare, but most common of fleas; ***Leptopsylla*** can serve as intermediate host for *Hymenolepis nana.*

B. ENDOPARASITIC INFESTATIONS

PROTOZOAN

Eimeria falciformis – intestinal, most significant of 6 coccidial species in mice, but rare, hyperplastic enteritis, typhlitis, colitis; diarrhea, hemorrhage, oocysts, runting in weanlings and juveniles; *Eimeria muris* – rare.

Klossiella muris – rare, subclinical, renal, eosinophilic spherical sporocysts in convoluted tubular epithelium; ingestion via blood to schizogony in glomerular endothelium, gametogony and sporogony in tubular epithelium, nonsuppurative interstitial nephritis; incidental finding.

Cryptosporidium muris – mild to nonpathogenic colonization of gastric mucosa.

Cryptosporidium parvum – marginally pathogenic, small intestine, secondary to viral infection in sucklings; ascends biliary tract of nudes & SCIDs resulting in cholangiohepatitis with peribiliary fibrosis; potential zoonosis.

Giardia muris – pear-shaped flagellate in duodenum, yellow-white watery lumenal contents; subclinical, abdominal distension, no evidence of diarrhea; morbidity in nudes; transmissible from hamsters; opportunistic, search for other primary.

Spironucleus muris – flagellate, frequently present in clinically normal mice, relatively nonpathogenic; also referred to as *Hexamita muris*; dilated crypts of duodenum filled with trophozoites, hyperplastic mucosa; PAS-positive organisms; dark red to brown watery contents; weanlings may develop diarrhea with co-pathogens (e.g., MHV); overgrowth with immunosuppression, upper small intestine; transmissible from hamsters.

ENCEPHALITOZOON (relevant due to wide host range & potential zoonosis; described below as it affects rabbits)
Etiology: *Encephalitozoon cuniculi*, obligate intracellular microsporidian protozoan, lytic cycle, spores in mononuclear cells disseminate to lung, liver, kidney, shed in urine, gram-positive.
Transmission: ingestion, inhalation, wide host range, more severe disease in monkeys and dogs, but more common in rabbits; Dwarf rabbits especially susceptible to disease.
Clinical: usually subclinical with renal lesions as incidental post mortem finding, occasionally torticollis and other nervous signs with mortality.
Pathology: focal granulomatous lesions in lung, kidney, liver, brain; granulomatous interstitial pneumonitis, granulomatous interstitial nephritis, focal granulomatous meningoencephalitis; in Dwarf rabbits uveitis and cataract formation.
Ddx: gram-positive Brown and Brenn, stain purple with carbol fuchsin, *Toxoplasma* organisms are gram-negative and do not stain with carbol fuchsin.
Significance: renal insufficiency, occasional neurological disease; seroconversion precedes renal shedding, cull; zoonosis with keratoconjunctivitis and pneumonia.

HELMINTHS

Syphacia obvelata – oxyuriasis, pinworms, common, eggs resistant to desiccation & drift; direct life cycle of 12-15 days, emerge in cecum, females migrate to deposit eggs on perineum; tape test, asymmetrical banana-shaped ova; subclinical, young particularly susceptible, rectal prolapse possible; immunodeficient strains with colitis.

Aspicularis tetraptera – oxyuriasis, pinworms, common, eggs resistant to desiccation & drift; direct life cycle of 23-25 days; emerge in cecum, lay eggs in terminal colon; flotation, bilaterally symmetrical ova; subclinical, young particularly susceptible, rectal prolapse possible; immunodeficient strains with colitis.

Hymenolepis nana – "dwarf tapeworm", direct (20-30 days) or indirect arthropod (flea) intermediate cycles possible; thread-like (1mm wide) serrated adults in small intestine the size of villi; wide host range; interspecies spread, significant hamster endoparasite; potential zoonosis; *H. diminuta* (much larger), & *H. microstoma* – no longer concern, require an intermediate arthropod host.

Cysticercus fasciolaris – *Taenia taeniaformis* cat tapeworm, mice serve as intermediate host of larval form, *Cysticercus fasciolaris*, strobilocercus in liver.