OUTLINE – see TABLES for summaries

I. Common disease conditions – Spontaneous or Non infectious [1] [2] [3] [4] [5] [6] [7] [8] [9]

Common clinical complaints in laboratory mice are readily observable findings such as

- Skin wounds, usually ulcerative dermatitis or fighting;
- Superficial or external mass lesions, usually abscesses or tumors;
- Abdominal enlargement, usually from organomegaly such as enlarged uterus, kidney or liver, or excessive fluid in the abdomen (ascites), possibly a distended urinary bladder;
- Abnormal posture, e.g. hunched posture or head tilt;
- Abnormal activity e.g. reduced activity, posterior weakness, spinning, rolling, seizures;
- Obvious change in body condition, usually wasting, or obesity.

Likely causes of these conditions vary with the age and sex of the mice, genetic background and immune status of the mice, microbial status, diet and other factors. Different disease conditions are likelier to manifest at different ages. Careful clinical examination, observation and palpation can help to identify disease conditions, or develop a list of likely conditions and causes. Infectious causes should be considered also (next section).

Sexual dimorphisms in body weight, size and morphology of salivary glands, adrenals, kidneys, mammae, should be recognized as such and not as important findings. Possibly the absence of sexual dimorphisms may be a significant finding.

In young animals malocclusion and hydrocephalus are life threatening conditions that should be identified at or before weaning. Microphthalmia is not life threatening, but may interfere with some studies. In adult animals of various ages, extensive dermatitis or wounds from fighting, abdominal enlargement, or neurologic signs probably are the most common conditions that are life threatening, or likely to compromise breeding or research. Any mice that suffer a decline in body condition should be evaluated for likely non infectious causes and infectious causes (next section). Likely non- infectious causes of progressive decline, or wasting, in older mice (more than 6 months old in some strains, more than 12 or 18 months old in long lived strains) include systemic amyloidosis, severe renal disease, acidophilic macrophage pneumonia, and neoplasia. Arteritis (polyarteritis), mild cardiac changes, and hyalinosis also are likely in old mice, but not usually life threatening. Obesity in overfed older animals is a management problem, but also may reflect underlying genetic predisposition. Neoplasms should be expected in aging mice, and mouse strains vary in the tumor types that are likeliest to develop. Knowledge of genetic background should inform what tumors and other phenotypes to expect, and what phenotypes may be unusual or important. The most common neoplasms reported in common mouse strains involve the hematopoietic system (lymphomas and histiocytic sarcoma), lungs, mammary glands, and liver. But like other species, mice may develop neoplasm in almost any tissue. Some expected neoplasms and other expected or likely phenotypes in common strains are summarized in

Spontaneous (non infectious) conditions (by system)

1) Alimentary System (digestive, enterohepatic)

Dental disease or periodontal disease

Periodontal inflammation involving molar teeth, sometimes with protruding hairs, usually is an incidental finding, not contributing to morbidity mortality. Especially in older mice, the inflammation can be substantial, and accompanied by alveolar bone loss and remodeling.

Incisor dysplasia

Incisor dysplasia (abnormal or disrupted incisor growth) usually is an incidental histopathology finding not associated with clinical signs or disease. The condition is more common in older mice, has been associated with feeding of soft or powdered food. Primary tumors of the teeth such as odontomas, can occur but are not likely in common mouse strains.

Malocclusion, incisor overgrowth

At (or before) weaning, mice should be examined for overgrowth and misalignment of incisor teeth that will prevent these mice from eating hard food. Mice that fail to thrive after weaning should be examined for the condition also. Usually these mice should be culled from a breeding or research program. If they are genetically valuable, they may be maintained by regular trimming, but the teeth may be damaged by the procedure and develop chronic infections.

Megaesophagus

Esophageal dilatation, or megaesophagus, sometimes is identified at necropsy. When severe, it may be a cause of death.

NEOPLASIA, Intestine [10] [11]

Spontaneous, primary neoplasms of the intestine are not common spontaneous lesions in most mouse strains. In susceptible strains or genetically engineered mice, they can be induced or increased by chemicals such as Dextran Sodium Sulfate (DSS) or by infections with certain Helicobacter species.

NEOPLASIA, Liver [12] [11]

Spontaneous, primary neoplasms of hepatocytes are expected with variably high incidence in aging male mice of certain strains, especially C3H, CBA, B6C3F1. There may be single or multiple nodules. Hepatocellular adenoma, hepatocellular carcinoma, are more likely than hepatoblastoma. Foci of altered hepatocytes, with primarily eosinophilic, basophilic, clear cell, or mixed cytoplasmic staining, are considered to be preneoplastic lesions in rodent livers. In susceptible strains or genetically engineered mice, hepatocyte neoplasms can be induced or increased by liver carcinogens or toxins, or by infections with certain Helicobacter species. Cholangioma, cholangiocarcinoma, Ito cell tumors, hemangiomas, hemangiosarcoma, and metastatic neoplasms also occur in mouse livers.

NEOPLASIA, Salivary glands

Spontaneous, primary neoplasms of the salivary glands in mice are not very common. Primary adenomas or carcinomas or myoepitheliomas of the salivary gland are possible. Myoepitheliomas may be more common in BALB/c and related strains, compared to other strains.[13] Large tumors present as mass lesions around the neck. Enlarged lymph nodes (lymphoma), and mammary tumors also may present as 'neck masses'. Salivary gland tumors related to polyomavirus infection are unlikely in contemporary colonies unless infected biological materials are inoculated into mice.

NEOPLASIA, Stomach Pancreas

Spontaneous, primary neoplasms of the pancreas or stomach in mice are unusual. Papillomas in the stomach are sometimes reported, usually as incidental findings.

2) Cardiovascular system

Arteritis, polyarteritis

Arteritis, polyarteritis or periarteritis usually is an incidental histopathology finding not associated with clinical signs or disease, and is more likely in older mice. Arteries at multiple anatomic sites can be involved (polyarteritis). Periarterial inflammation and fibroplasia may be substantial in advanced disease (periarteritis). Arteries in the mesentery, pancreas, heart, head and other sites may be affected. Severe involvement of heart, and around brain may contribute to morbidity or mortality.

Atrial thrombi, cardiac thrombi

Cardiac thrombi (intravascular blood clots that form in vivo) usually involve the left atrium in mice. They are not especially common in unmanipulated mice, but BALB/c mice are among the most likely to develop cardiac pathology including atrial or auricular thrombi, cardiac calcinosis and degenerative myocardial changes. Small thrombi may be identified by histology without apparent clinical significance. When large thrombi are accompanied by cardiomegaly, cardiac dilatation or hypertrophy, it may be

difficult to determine if cardiac dysfunction preceded and contributed to thrombus formation, or if the thrombus preceded and contributed to cardiac dysfunction.

Cardiac calcinosis, dystrophic cardiac calcinosis, mineralization [14]

Mineralization of cardiac myofibers or epicardium, is expected in BALB/c, C3H and DBA mice, but is unusual in most other strains. Several genetic contributors are identified in these strains. In BALB/c (and BALB/c derived strain) mineralization commonly involves the epicardial surface of the right ventricular free wall. In C3H and DBA mice, other areas of myocardium, and other soft tissues, including tongue, may be affected.

Cardiomyopathy, myocardial degeneration

Cardiovascular causes of clinical disease are uncommon in mice, but pathology findings including myofiber degeneration, loss, replacement fibrosis, sometimes accompanied by inflammation, or hypertrophic fibers may be fairly common in some studies, and are likely to increase with age. These and other cardiac changes including cardiac thrombi and calcinosis, sometimes have been referred to collectively as 'cardiomyopathy'. Specific characterization of cardiac findings (and heart weight), is likely to be more useful to understanding a condition and its relevance to genetic background, experimental manipulation or other causes.

NEOPLASIA, vascular (hemangioma, hemangiosarcoma) [12]

Hemangioma and hemangiosarcoma are benign and malignant primary neoplasms of the vascular system. They are not especially common in most mouse strains, but are encountered in various tissues in aging mice on long term studies. Especially in highly vascular tissues such as liver and spleen, it can be challenging to distinguish these neoplasms from large areas of angiectasis (sometimes referred to as telangiectasis or peliosis). Angiectasis refers to abnormally dilated vascular spaces, and usually is an incidental histopathology finding in older mice. Bloody tumor masses in liver, spleen, less commonly in skin or other tissues, suggest hemangioma or hemangiosarcoma.

3) **Endocrine System**

Adrenal gland, accessory cortical nodules, X zone degeneration [15]

Small accessory adrenal cortical nodules, not neoplastic, are fairly common in some mouse strains and may not increase with age. In female mice vacuolar degeneration of the perimedullary X zone can be a conspicuous histology finding.

Ectopic thyroid, parathyroid (and thymus)

The thyroid and parathyroid glands, and the thymus all develop from embryonic structures called pharyngeal pouches in the embryonic pharynx. Fragments of thyroid or parathyroid may fail to migrate completely, and can be identified by histopathology on the midline between the intrathoracic thymus and their usual location near the larynx. Fragments of thymus also, may be found on the midline beyond the thorax, or near the thyroid and parathyroid glands. Ectopic fragments of these structures usually have no clinical significance. Residual activity from the ectopic fragments can frustrate studies in which these tissues were thought to have been ablated or removed.

NEOPLASIA and proliferative lesions, endocrine system [16]

Most lesions in small endocrine tissues (adrenals, thyroid, pancreatic islets, pituitary) are identified by histology as mild or incidental findings. Grossly evident large neoplasms of adrenal or thyroid glands are not common in most strains.

Adrenal cortical subcapsular cell hyperplasia is a common in aging mice. Adrenal cortical tumors may be fairly common in some strains, usually as incidental histopathology findings.[13] Adrenal medullary tumors (pheochromocytoma) are less common in mice.

Pancreatic islet tumors (insulomas, islet cell tumors) are unusual in mice. Large or hyperplastic islets may be identified in obese mice and in some diabetic model mice.

Pituitary neoplasms can be common in long term studies of aging mice, usually identified by histologic examination, and not obvious on gross examination unless lesions are large and the head is examined carefully. Proliferative and neoplastic pituitary lesions in mice seem to involve the pars distalis most commonly, may secrete prolactin, and may be associated with proliferative mammary lesions in some strains, especially FVB/N.[17]

Thyroid tumors are not commonly reported spontaneous lesions. In mice, follicular cysts, or follicular hyperplasia and tumors are more common than interstitial cell (C cell) proliferative lesions. Hypothyroidism and proliferative changes can be induced by treatment with the antibiotic trimethoprim-sulfamethoxazole.

4) Hematopoietic (and immune) System

Anemia [18]

Anemia refers to reduced circulating red blood cells. Iatrogenic anemia related to bleeding for research purposes may be the most common cause in research mice. Anemia due to reduced production can occur when hematopoietic tissue is responding to a severe or chronic infection, when hematopoietic neoplasms take over much of the bone marrow, or damage to marrow by toxins or irradiation. Pallor (pale paws, ears, and eyes), 'watery' blood, due to anemia, and failure of blood to clot suggest severe compromise to hematopoietic tissue. Anemia due to primary destruction of red cells (hemolytic disease), or due to a primary failure of red cell production is possible, but is not very likely in common inbred strains, and contemporary husbandry conditions.

Reactive myeloid or lymphoid hyperplasia

Infections are likely causes of reactive immune cell hyperplasia in mice. Reactive hyperplasia of inflammatory cell precursors, followed by increased numbers of circulating leukocytes are expected responses. Increased circulating neutrophils are expected in bacterial infections. Increased circulating eosinophils are expected with parasitism. Increased lymphocytes and or monocytes are expected in chronic infections. Characteristic gross findings include enlarged spleen (splenomegaly), and lymph nodes (lymphadenomegaly) near affected sites. Characteristic histopathology findings include: increased immature and mature granulocytes in bone marrow, spleen and sometimes liver; and increased immature and mature lymphocytes and plasma cells in enlarged lymph nodes and spleens. Extreme reactive proliferative responses sometimes can be difficult to distinguish from hematopoietic neoplasia. Identification of the infection can help to characterize the proliferation as reactive (inflammatory), or neoplastic.

Stress responses

The hematopoietic and immunopoietic system responds to stress, and to inanition or starvation (see below, systemic and multisystem). Stress responses in mice are (and rats) are mediated largely by corticosterone. Glucocorticoids including corticosterone induce lymphocyte death. Lymphocyte depletion or loss in lymphoid organs (thymus, spleen, lymph nodes), may be a manifestation of stress from various sources including disease, transportation, starvation, and other environmental factors.

NEOPLASIA, lymphoma, histiocytic sarcoma, leukemia, myeloid neoplasms, mast cell [16] [19]

Hematopoietic neoplasms are common in mice, and are the likeliest causes of death in several strains. Thymic lymphomas are a likely cause of death in AKR, C58, NOD/scid and related mice before they are one year old. Other lymphoma types and histiocytic sarcoma usually occur in older mice, and are a significant cause or contributor to death in SJL/J, C57BL/6 and other mice. In advanced disease some lymphomas and histiocytic sarcoma can involve bone marrow and circulation, in a leukemic phase. But primary leukemias, myeloid neoplasms and mast cell tumors are not common in common mouse strains. Marked leukocytosis (high white cell count), especially neutrophilic leukocytosis, in mice, is much more likely to be due to infection than to leukemia. Advanced or disseminated hematopoietic neoplasia is likely to present clinically as a decline in body condition. Peripheral lymphadenomegaly may be

palpable, or obvious as enlarged symmetric neck masses. Enlarged thymus, lymph nodes, spleen or liver usually are obvious at necropsy. With advance disease and severe organomegaly, a 'normal' body weight may be misleading due to neoplastic infiltration and enlargement of lymph nodes, spleen and other organs. Pallor (pale paws, ears, and eyes) and 'watery' blood, due to anemia, are good indicators that the marrow is affected, and unable to produce red cells.

5) Integument, skin and adnexae (mammary, lacrimal, clitoral and preputial glands)

Barbering

Barbering by one or more mice on their cage mates is a likely cause of symmetric, cage or strain specific patterns of alopecia (baldness). Hair removal usually is by nibbling, without associated skin trauma. Vibrissae (commonly but incorrectly called whiskers) are important sensory organs in mice. Loss of vibrissae may affect some behavioral tests.

Ulcerative dermatitis, mouse ulcerative dermatitis (MUD)

Ulcerative dermatitis usually is progressive and refractory to treatment, and can interfere with many research areas. Severe progressive ulcerated lesions can be life threatening (from overwhelming opportunistic infections) or warrant euthanasia for humane reasons. Secondary phenotypes related to chronic inflammation and infections can interfere with diverse studies. Pruritus and scratching can be unrelenting and likely to interfere with behavioral tests.

Wounds

Skin wounds due to conspecific (usually male on male) aggression usually are on the back, rump and around the genitals. The extent of the wounds may not be obvious from casual observation, but necrotic dry skin may overlie extensive wounds. BALB/c and SJL/J male mice are notoriously likely to kill each other, but male aggression can be a problem in many strains, and require single housing to maintain male mice to complete a study.

NEOPLASIA of skin and adnexae [16]

Primary spontaneous skin neoplasms are not very common in most mouse strains. Papillomas, carcinomas, and subcutis sarcomas can occur. In susceptible strains or genetically engineered mice, these can be induced or increased by carcinogens, or by ear tags or implanted materials such as transponders. [20] [21]

Clitoral or preputial gland neoplasms are possible causes of enlarged clitoral or preputial glands, but far less likely than abscesses in these perigenital sebaceous glands in mice. In older mice, these glands may be come cystic, with mild proliferative changes, usually associated with inflammation.

Harderian gland neoplasms are not very common, but are more likely in BALB/c mice.[22] Large tumors may present clinically as exophthalmos due to a mass lesion behind the eye. Orbital or retroorbital abscess is an important diagnostic consideration for exophthalmos.

Mammary neoplasms,[23] [24] **mammary adenoma or carcinoma,** are the most common spontaneous tumors of adnexae, expected especially in aging female mice of C3H and GR mice, and related mice. Exogenous mammary tumor virus (Bittner agent) contributed to incidences of close to 100% in older reports (e.g. before 1980), but has been eliminated from most contemporary colonies. Mouse mammary tissue is widely distributed from the tail to the ears, so neoplasms may arise almost anywhere in the subcutis. FVB/N female mice develop mammary hyperplasia that may complicate mammary tumor models based in this strain.[17] Myoepitheliomas may arise in any tissues with myoepithelial cells, but especially in salivary and mammary glands, and seem to be more common in BALB/c than in other strains.

6) Musculoskeletal

Arthritis [25] [26] [27]

Arthritis, inflammation of or in joints, occurs spontaneously in some mouse strains and can increase with age and obesity. Strains vary in susceptibility to collagen induced arthritis, proteoglycan induced arthritis, adjuvant induced arthritis, as models of autoimmune disease. [28] Mice also are used to model various types of infectious arthritis. Infectious causes of arthritis should be suspected in spontaneous outbreaks, especially in strains where spontaneous arthritis is not expected.[29]

Bone, fibroosseous lesion [25] [30]

Fibroosseous lesion describes a variably common lesion in medullary cavities of aging, usually female mice. In various bones, hematopoietic tissue can be mildly to markedly replaced by fibrovascular proliferation with or without osseous (boney) contributions. Usually this is an incidental finding, and may increase with age and estrogen influences.

Muscular dystrophy [31] [32] [33]

Muscular dystrophy due to mutations in the dysferlin gene occurs in A/J and SJL/J mice. Clinical signs of weakness may be subtle until the mice are challenged in neurobehavioral tests. Histopathology findings of myofiber degeneration, regeneration and fibrosis increase with age. Other spontaneous and genetically induced models are used to model human muscular dystrophies. Heart muscle can be involved in some of these models.

Osteoporosis/osteopenia [34] [35] [36] [37] [38]

Bone quality, density, mass and strength vary among mouse strains, and can be influenced by factors such as diet, obesity and estrogen levels. Spontaneous fractures in mice are unusual, and suggest a primary bone phenotype.

NEOPLASIA, leiomyoma, leiomyosarcoma, rhabdomyoma, rhabdomyosarcoma [39]

Spontaneous, primary neoplasms smooth muscle, leiomyoma (benign), leiomyosarcoma (malignant), or of skeletal muscle, rhabdomyoma (benign), rhabdomyosarcoma (malignant), are unusual in mice. Smooth muscle neoplasms usually are reported in uterus or urinary bladder, where they can be difficult to distinguish from other mesenchymal (non epithelial) tumors. Rhabdomyosarcomas presenting as subcutaneous masses of the trunk or limbs, have been reported most commonly in A/J and BALB/c mice.

NEOPLASIA, osteoma, osteosarcoma [40] [41] [42] [43] [30]

Spontaneous, primary neoplasms of bone, osteoma (benign), osteosarcoma (malignant), in mice are uncommon. Occasional occurrence of multiple osteomas, especially in skull and larger limb bones, has been associated with retroviruses. Osteosarcomas can be common in some Trp53 deficient mice, and among common inbred mice seem to be most common in BALB/c.

7) Nervous system, also Neuromuscular, Special Senses

Acallosity/hypocallosity

Absent or reduced corpus callosum (normal neural connection between brain hemispheres) is expected (with variable incidence) especially in mice of BALB/c and 129 strains. Associated disease signs are not expected. Some behavioral tests may be affected. The condition should be recognized as a possibly normal anatomic variation for the genetic background when it is identified by dissection, imaging or histology.

Artifacts

CNS histology findings that should not be over interpreted include dark neurons and vacuolation of the white matter. Dark neurons artifact can result from perimortem handling of unfixed CNS tissue, and should not be confused with dark necrotic neurons. Vacuolation artifact usually is in white matter, sometimes with pale basophilic acellular material in the vacuoles. It is frequently associated with prolonged exposure to alcohols during fixation and processing. These vacuoles should not be confused with spongiosis or edema of the neuropil, or with distended myelin sheaths as in demyelinating

conditions. For CNS studies it can be very important for specimens from experimental and control mice to be dissected, handled, and processed identically or concurrently.

Blindness [44]

Many of common laboratory mouse strains, including C3H, FVB/N, SJL/J, SWR and some outbred Swiss mice, are blind due to homozygosity for the recessive mutation *rd1* (in *Pde6b* gene), that causes retinal degeneration and loss of photoreceptors by about the time of weaning. Mice with microphthalmia (see above) have variably severe abnormalities in retina, lens and other structures. DBA/2 mice develop glaucoma as they age. Blindness should be expected to affect some behavioral tests.

Cataracts and corneal opacities[45] [46] [47] [48]

Cataracts and corneal opacities can present similarly as pale areas within or on the anterior globe. Careful examination should reveal if the abnormal lens (in the eye), or the abnormal cornea (the anterior surface) is involved. Cataracts, lenticular opacities, may be genetically determined, or may be induced by irradiation or other treatments, and some may be transient. Corneal opacities can occur in various strains, but are more likely in C3H, DBA, BALB/c, and related strains.

Hearing loss, deafness [49] [50]

Many common mouse strains develop hearing loss, indicated by increased Auditory Brain Response (ABR) thresholds, by a few months of age. Noise and otitis (ear infections) can contribute to hearing loss. Poor hearing should be expected to affect some behavioral tests.

Hydrocephalus

At (or before) weaning, mice should be examined for a domed and relatively enlarged head that indicates dilated brain ventricles (hydrocephalus). These mice are usually smaller than unaffected mice, and are likely to do poorly and die. Affected mice usually should be culled from breeding or research populations, unless there is scientific justification to retain them. The condition can be fairly common in C57BL/6 or C7BL/10 strain mice. With later onset hydrocephalus, the head is not enlarged or domed because cranial sutures closed before the onset of ventricle enlargement. Markedly enlarged ventricles can be identified post mortem when the head or brain (fresh or fixed) is sectioned. Ventricle size varies among strains, with C57BL/6 having relatively large ventricles. Mild enlargement identified with imaging techniques may not be as obvious in post mortem specimens if the cortex collapses in, after the CSF drains from the ventricles.

Microphthalmia

At (or before) weaning, microphthalmia can be recognized, as small or inapparent eyes. The condition is reported to be most common in C57BL/6 and related mice, in females, and in the right eye. Usually these mice should be culled from a breeding program. If they are genetically valuable, retention for breeding may be justified, but blindness can affect some behavioral tests.

Paresis, paralysis [51]

Abnormal gait, posterior weakness (paresis), or (inability to move limbs) may be related to a primary neurologic problem, possibly a musculoskeletal problem, or other illness. Traumatic damage to limbs or spine should be considered. In older mice, or in susceptible trains or mutants, neoplasia involving the spine is a primary consideration. Muscular dystrophy may contribute to weakness in susceptible strains such as A/J and SJL/J, or in other dystrophic mutant mice. Infectious causes of paresis or paralysis in contemporary clean colonies are unlikely but should be considered.[52]

Seizures [53]

Mouse strains vary in their susceptibility to seizures. Sudden death in FVB/N mice may be due to seizures. Seizure activity such as facial grimace, chewing, ptyalism or convulsions may be observed. DBA/2 mice are susceptible to noise induced seizures until they become deaf.

Vestibular signs [54]

Clinical signs such as rolling, spinning or head tilt usually indicate damage to the vestibular system. Otitis interna, arteritis, infarcts or other lesions of or near vestibular nuclei or nerve tracts are possible causes. Infectious causes of otitis and upper respiratory tract infections are discussed below.

NEOPLASIA nervous system, neuromuscular [16]

Spontaneous, primary neoplasms of the nervous system in mice are uncommon. Neoplasms involving the spine or head, such as osteosarcoma or hematopoietic neoplasms, may present with neurologic signs by compressing or invading spinal cord or brain. Primary spontaneous bone tumors (osteosarcomas), or skeletal muscle tumors (rhabdomyosarcomas) are unusual in common mouse strains. But rhabdomyosarcoma may be likeliest to develop in A/J or BALB/c mice.[39]

8) Respiratory system

Acidophilic Macrophage Pneumonia (aka eosinophilic crystalline pneumonia) [55]

Acidophilic Macrophage Pneumonia or eosinophilic crystalline pneumonia can be a common and important cause of death in susceptible mouse strains, such as such as 129, C57BL/6 Swiss and related mice. In advanced disease, lungs can be grossly consolidated and pale, with corroborating histopathology findings of engorged acidophilic macrophages and crystals filling airways. In mild conditions, scattered macrophages laden with eosinophilic granular or crystalline material, and scattered extracellular eosinophilic crystals may be an incidental histopathology finding. Infectious pneumonia conditions can accompany acidophilic macrophage pneumonia. The acidophilic material has been identified as a chitinase like protein (YM1) that is associated with various immune stimulated conditions. When these chitinase like proteins are produced by epithelia at other anatomic sites, usually in older mice, the condition has been referred to as hyalinosis (see below).

NEOPLASIA lung [16] [56]

Spontaneous, primary lung tumors are common and a likely cause or contributor to death in certain strains, especially A, 129, BALB/c and FVB. Multiple tumors, usually more adenomas than carcinomas, can occur before 1 year of age in susceptible strains. Metastatic involvement of lungs by liver, mammary, hematopoietic or other neoplasms may occur. Dyspnea and clinical deterioration may be evident in severely affected mice.

9) Urogenital System

Hydrometra or Mucometra, **Imperforate vagina, vaginal septa** [57] [58] [59]

Imperforate vagina results in progressive enlargement of the uterus with fluid or mucoid material (hydrometra or mucometra). Progressive abdominal swelling often with a bulging perineum, and infertility are characteristic clinical findings. Pyometra (pus in the uterus) is possible. The condition should be suspected in female mice with progressive abdominal distention for longer than a mouse gestation period. Imperforate vagina has been attributed to occlusive fibrous vaginal septa. Surgical removal of the septa should relieve the condition.

Nephropathy, chronic renal disease, glomerulonephritis

Mild kidney changes including combinations of tubule degeneration and regeneration, glomerular changes, and interstitial inflammation, can be incidental histopathology findings, and tend to increase with age. Severe renal disease can result in protein loss, uremia, and clinical deterioration. Grossly, kidneys can be enlarged or shrunken, with a granular or pitted surface. Histopathology findings can include hypercellular expanded glomeruli, and/or shrunken sclerotic glomeruli (glomerulonephritis, glomerulosclerosis), marked tubule dilatation, proteinosis, degeneration, regeneration; and interstitial inflammation and fibrosis.

Urinary Obstruction (Mouse Urologic Syndrome, MUS)[60]

Chronic urinary obstruction (sometimes known as mouse urologic syndrome or MUS) can result in enlarged bladder, hydroureter, hydronephrosis. Hydronephrosis can progress to cause abdominal enlargement. Chronic urinary obstruction leading to uremia can contribute to mortality.

NEOPLASIA Urogenital [61]

Spontaneous primary urinary tract (kidney and urinary bladder) neoplasms are uncommon in mice. Hematopoietic neoplasms, malignant adrenal neoplasms or vertebral neoplasms may involve the kidney and urogenital tissues in advanced disease.

Spontaneous primary reproductive tract neoplasms (ovarian, uterine, testicular, etc.) are found in aging animals in long term studies, but usually are incidental findings, not usually identified as significant contributors to mortality. Endometrial hyperplasia can be common in aging mice. Hematopoietic neoplasms and other invasive neoplasms may involve reproductive organs, and the uterus is a fairly common site for histiocytic sarcoma.[19]

10) Systemic or multisystem conditions

Amyloidosis [62] [63] [64] [65]

Systemic amyloidosis can be a significant cause or contributor to mortality to mice on long term studies. Mild or early amyloidosis may be an incidental histopathology finding, but clinical deterioration or wasting is characteristic of extensive involvement. Gross lesions may be unremarkable, or severe deposition may expand affected organs resulting in organomegaly, especially hepatosplenomegaly. Histopathology reveals deposition of acellular fibrillar to amorphous pale eosinophilic material in various tissues. Deposition usually is earliest in distal small intestine, progressing to other areas of gastrointestinal tract, involvement of spleen, liver, kidney, adrenal gland, parotid salivary gland, gonads, with heart and lung usually involved in senile amyloidosis. Congo red stain is used to confirm the presence of amyloid. Further characterization as reactive (serum amyloid A, or SAA) type, or senile (ApoA) type can be achieved by immunohistochemistry if that should be necessary. Amyloidosis used to be a common problem and cause of death in studies of aging mice, especially of C57BL/6, Swiss mice and related mice, but has become less common as colonies have become 'cleaner'.

Hyalinosis [66] [67] [68]

Hyalinosis has been used to refer to eosinophilic cytoplasmic change, due production of eosinophilic chitinase like protein in epithelia of the glandular stomach, respiratory tract, bile duct, and gall bladder. Usually this is an incidental finding in susceptible strains. The eosinophilic crystals in and near epithelial cells can be striking, and may be associated with inflammatory conditions. These chitinase like proteins, especially YM1 crystals are also found in acidophilic macrophage pneumonia, are produced by neutrophils or macrophages, and can be found in bone marrow and in sites of chronic inflammation.

Nutritional status, inanition (not eating), obesity

Nutritional status is mentioned here because it can impact various systems, influence various illness or disease phenotypes, and contribute (positively) to, or confound experimental outcomes. Influences of nutritional status and body condition on experimental parameters should be considered in experimental design, and in analysis of results. Types of diets are discussed elsewhere in this text.

Diet restriction and inanition[69] [70] [71] [72]

While intentional diet restriction in mice may improve life span and reduce age associated morbidities, inanition or starvation, for only one to few days, can affect body temperature, size, fat deposits, liver and hepatocyte size, and immune responses. Immune effects including thymic atrophy, and B and T cell suppression, at least in part, are mediated by stress and corticosterone. Some immune responses such as natural killer cells, macrophages and granulocytes, increase with short term inanition. Longer term inanition also affects multiple systems. Clinically and grossly, mice that don't eat for any reason are expected to be smaller with lower subjective body condition scores, and discernibly and measurably less

fat, e.g. by dexa or QNMR analyses (see chapter 6, Phenotyping), and diet restricted mice have lower fertility. Expected microscopic (histology) changes include less fat and smaller adipocytes (fat cells), smaller hepatocytes, smaller muscle fibers, lymphocyte depletion, small spleen, thymus, lymph nodes. Thus these changes should be interpreted carefully in mice that may not be eating adequately.

Obesity [73] [74] [75] [76]

Obesity, metabolic syndrome and type II diabetes are important areas of research in mouse models, often intentionally induced or exacerbated by diet in genetically susceptible strains. Obesity is expected to have physiologically significant sequelae, such as alterations in cytokines and chemokines, insulin, glucose and fat metabolism, and potentially morbid sequelae such as systemic inflammation, hepatic lipidosis or steatosis, hypertension, nephropathy with albuminuria. Standard ad libitum feeding of laboratory rodents leads to obesity in some strains, and age associated morbidities are increased or accelerated compared to diet restricted rodents.

Stress [77] [78] [79]

Stress is mentioned here because it can impact various systems, influence various illness or disease phenotypes, and contribute (positively) to, or confound experimental outcomes. Potential influences of stressful handling or environmental conditions on experimental parameters should be considered in experimental design, and in analysis of results. Sources of stress include disease, diet or water restriction, transportation, social structures, noise, light cycle alteration, temperature extremes, and other changes in environment. Endogenous glucocorticoids, especially corticosterone in rats and mice, are produced during stress, and notably affect the immune system. Glucocorticoids induce apoptosis in precursor T and B cells, and alter lymphopoiesis. Thymic atrophy can be induced by endogenous or exogenous (administered) glucocorticoids, and apoptosis can be identified by histopathology in lymphoid tissues (thymus, lymph nodes, spleen). In addition myelopoiesis is stimulated, and blood neutrophil counts elevated, while blood lymphocyte counts decline in short term responses to glucocorticoids. Responses vary with mouse strain, and are more complex and variable depending on the duration and types of stressors.

II. Common diseases – Infectious [5] [80] [81] [82] [83] [84] [7] [85] [86] [87]

Given the relatively low prevalence of pathogenic microbes in contemporary colonies compared to a few decades ago, clinically obvious infectious disease conditions are not common in competent mice in reasonably 'clean' facilities. Overt enterohepatic disease with diarrhea or severe hepatitis, overt respiratory disease with pneumonia and respiratory noise (chattering) heard in the mouse room, or epizootics with devastating mortality are unusual today. The infectious agents that persist or lurk in contemporary colonies are not as likely to cause substantial morbidity or mortality that raises concern and leads to further investigation. Infections in contemporary colonies are more likely to be detected by surveillance or quarantine testing of animals without overt clinical disease. However even inapparent infections modulate the immune system and may interfere with diverse research areas. Obvious or clinical infectious disease problems may signal that

a. the affected mice are not as competent as they are expected to be, and may require special handling to protect them from opportunists;
b. disease is due to a familiar agent that should be identified promptly to protect vulnerable animals, experiments or personnel;
c. disease is due to an emerging agent that should be characterized to protect vulnerable animals, experiments or personnel.

Sources of rodent pathogens exist within and near rodent facilities, as indicated by results from biological materials testing (Chapter 5), and surveys of pet shop rodents,[88] and of wild rodents near research rodent facilities.[89] [90] [91] [92] These risks should be assessed in the development of surveillance, quarantine and diagnostic testing strategies.

Table II summarizes viral, bacterial and larger infectious agents in mice by whether the digestive (enterohepatic) system, respiratory system or other systems are primarily involved. Significantly in mice, strains vary in their susceptibilities to infections, and in their manifestations of infectious diseases, which can be considered to be disease phenotypes. These variations in disease phenotypes may confound recognition or diagnosis of disease, but also represent opportunities to dissect genetic mechanisms of disease susceptibility and resistance. Notably, several strains lack hemolytic complement (c5); C3H/HeJ mice lack functional Tlr4, while closely related C3H strains do not; and SJL/J lack functional Ceacam1 which is a receptor for some strains of MHV.

Spontaneous (infectious) conditions (by system)

1. **Conditions infectious: Alimentary, digestive, enterohepatic**
   a. **Intestine –** Clinical signs of intestinal disease are diarrhea and rectal prolapse. Failure to thrive or wasting may occur with chronic enteric disease. Pathology findings include inflammation, ulceration, hyperplasia. Likely infectious agents in contemporary colonies are helicobacters, maybe rotavirus diarrhea in neonates. Historically important agents have included MHV, Citrobacter rodentium (C freundii 4280), Clostridium piliforme (Tyzzer's disease), Salmonella enteritidis typhimurium. Pinworms and common protozoa in mice usually are subclinical.
   b. **Liver –** Clinical signs of hepatitis in mice often are non specific. Icterus may occur with severe hepatobiliary disease (or with severe hemolysis). Clinical pathology may indicate inflammation (increased WBC), or hepatocyte or biliary damage (increased ALT, AST, LDH, AP). Likely infectious agents in contemporary colonies are helicobacters, maybe MHV. Historical and potentially important agents include MHV, Clostridium piliforme (Tyzzer's disease), Ectromelia virus, Salmonella enteritidis typhimurium, and Cytomegalovirus (MCMV) especially in immunodeficient mice.
2. **Conditions infectious, Hematopoietic system, immunohematopoietic system**
   a. **Reactive responses, immunomodulation -** The immune system, comprising immune cells, antibodies, cytokines, chemokines, defensins, and other factors involved in immune responses

are said to be 'modulated' by infections. Immune responses have been classified as primarily innate responses, or primarily adaptive responses, with considerable overlap and synergism between these types of responses. Innate immune responses are the more immediate and not so specific responses, especially involving neutrophils, phagocytic cells, various cytokines and defensins. Adaptive or acquired immune responses are generally slower but more specific, especially involving T and B lymphocytes, antibodies, and other cytokines.
Clinical manifestations of infections include leukocyte responses, increased white blood cell counts (WBC), especially increased neutrophils in acute infections and bacterial infections, increased eosinophils in parasitic infections, and usually increased lymphocytes and monocytes in more chronic infections. Especially with bacterial infections, bone marrow and spleen respond with increased production of granulocytes (granulopoiesis). The resulting leukocytosis and splenomegaly can be dramatic. In more chronic infections lymph nodes and spleens are enlarged (lymphadenomegaly, splenomegaly) by reactive lymphoid hyperplasia, normally including many plasma cells and specific antibodies. The source of infection may be obvious. Or it may be important to distinguish these phenotypes from leukemia or lymphoma, or from other experimentally relevant alterations in cell responses, cytokines, or gene expression.
Some agents such as some Parvoviruses and mouse thymic virus specifically target immune cells, immunomodulate by destroying immune cells. These infections usually are subclinical, but may alter various research results.

3. **Conditions infectious, Integument (skin)** [93]
   a. **Abscesses** in mice frequently present as masses around the face, in the preputial glands, or anywhere on the body. Skin abscesses may develop from furunculosis (inflammatory destruction of follicles), or folliculitis (inflammation of the follicles). Staphylococcus aureus is a common isolate from abscesses in mice. Coagulase negative staphylococci, (S hominus, S xylosus etc) that are commonly considered to be commensal, may be identified (by culture or PCR) in abscesses especially in immunodeficient mice. Various gram positive or gram negative opportunist agents (e.g. *Pasteurella pneumotropica*) also can be isolated from these lesions. Streptocobacillus moniliformis and Corynebacterium kutscheri (the agent of pseudotuberculosis in mice and rats) have been historically important causes of abscesses in various tissues and reactive lymphadenomegaly, but thee agents are uncommon in contemporary colonies.
   b. **Conjunctivitis, Blepharoconjunctivitis** (inflammation of the conjunctiva and or eyelids) can be a clinical problem in some colonies or strains. Trauma, abnormal eyelids, eyelashes, eye or orbit morphology, may contribute to the condition. Various gram positive or gram negative opportunist agents, including Pasteurella pneumotropica, Staphylococcus sp, Corynebacterium species, may be isolated from these lesions.[94] Conjunctivitis has been reported as a clinical finding in mousepox (ectromelia virus infection).[95] Ectromelia virus is an unlikely cause, but may be a concern when conjunctivitis is associated with a history of inoculation of biological materials, and morbidity or mortality of ectromelia virus susceptible mouse strains.
   c. **Ulcerative dermatitis (MUD)** can contribute substantially to mouse loss in some colonies and studies. In chronic lesions, various and multiple bacteria can be identified, especially Staphylococcus sp. Usually they are considered to secondary opportunists that contaminate and colonize a wound or lesion, rather than a primary or inciting cause of the condition.
   d. **Hyperkeratosis** (flakey skin), with histopathology findings of acanthosis, hyperkeratosis and intracorneal gram positive bacterial colonies, especially in immunodeficient mice, has been shown to be due to *Corynebacterium bovis*.

4. **Conditions infectious, Musculoskeletal**
   a. **Arthritis** primarily due to infectious causes is not expected in competent mice in contemporary colonies. Natural infections that have been implicated in arthritis include *Mycoplasma arthritidis, M arginini, M pulmonis, Streptobacillus moniliformis,* and *Staphylococcus aureus*. Swollen paws or hock joints are typical clinical signs in natural or experimental arthritis. Radiography and histopathology are primary diagnostic tests. Degenerative joint lesions (osteoarthritis) occur in old or obese mice. Auto immune arthritis occurs in some 'auto immmune' mice, such as MRL^{lpr}, but Inflammatory lesions should be tested for infectious agents
5. **Conditions infectious, Nervous system**
   a. **Hydrocephalus and cerebellar hypoplasia** have been caused by experimental infections with various viruses. In contemporary colonies, strain related hydrocephalus is more likely than infectious causes.
   b. **Paralysis**, specifically posterior paralysis, was an occasional consequence of demyelination in TMEV-infected mice. Both TMEV and MHV viruses have been used in experimental models of demyelinating disease (such as multiple sclerosis) in mice. Lactate dehydrogenase elevating virus (LDV) and retroviruses occasionally are implicated in paralytic poliomyelitis, or neurodegeneration.[52] Neoplasia or trauma involving the spine probably is a more common cause of paresis or paralysis in contemporary colonies.
   c. **Vestibular signs** (rolling, spinning, head tilt) may be due to otitis interna in mice. Otitis can be diagnosed by histopathology. Various bacteria have been identified in otitis in mice. *Klebsiella oxytoca* has been identified in susceptible mice in recent reports.[96] Historically, Pseudomonas aeruginosa was a likely cause, especially in immunodeficient or immunosuppressed mice, and upper respiratory infections by *Mycoplasma pulmoni*s included otitis. 'Rolling disease' in mice or rats due to *Mycoplasma neurolyticum*, is attributed to neurotoxins of this agent, which is not expected in contemporary colonies.
6. **Conditions infectious, Respiratory system.** Clinical respiratory tract infections are much less likely in contemporary colonies than when *Mycoplasma pulmonis*, CARbacillus, Sendai virus and Pneumonia virus of mice were prevalent. However especially in immunodeficient or otherwise compromised mice, a variety of opportunistic agents may be implicated by histopathology, cultivation, or PCR, in upper respiratory tract disease or pneumonia.
   a. **Upper respiratory infections (URI):** rhinitis, otitis, laryngotracheitis
   Rhinitis and laryngotracheitis are potentially life threatening conditions. Mice are obligate nose breathers, so obstruction of the nose or trachea by inflammation or exudate can lead to suffocation. Otitis may be fairly common in mice without obvious clinical disease. Upper respiratory lesions are identified readily by histopathology of head and trachea, but will be missed if these tissues are not evaluated. Pasteurella pneumotropica, Bordetella sp., Klebsiella sp. and other agents may be implicated.[97] [98] [99] Of these P pneumotropica is the most commonly identified in mouse specimens.[80] Mycoplasma pulmonis was an important cause of respiratory disease, including upper respiratory disease, [100] but is not prevalent in contemporary colonies. **Lungs: Pneumonia** is a life threatening disease in mice and other species.
   Mycoplasma pulmonis, CARbacillus and Sendai virus were common culprits when these agents were prevalent. [100] [101] Pneumocystis murina is a likely cause in immunodeficient mice, and can cause wasting, dyspnea and mortality.[102] [103] In contemporary colonies, Pasteurella pneumotropica, Bordetella sp., Klebsiella sp. and other agents may be implicated, especially in immunodeficient mice. [98] [104] [105]

7. **Conditions infectious, Urogenital**
   a. **Reproductive tract infections**: Metritis, oophoritis in females, urethritis in males may not be obvious in contemporary colonies of competent mice, but subclinical infections may contribute to reduced fertility. Pasteurella pneumotropica, Pseudomonas, Klebsiella, Enterococcus, may be implicated, especially in immunodeficient mice. [99] [106] Vaginal swabs are useful diagnostic specimens for females, and may implicate their male cage mates as well . Mycoplasma or Ureaplasma species were potential causes or contributors when these agents were more prevalent. [107] Severe balanoposthitis may present as preputial swelling and paraphimosis (penile prolapse) with colonization by various opportunists.
   b. **Urinary tract infections (UTI):** UTI especially nephritis and cystitis are not expected in competent mice in reasonably clean contemporary colonies. Infectious causes of nephritis may be blood borne, or may ascend from the lower urinary tract. Inflammation with bacteria in the cortex, and bacterial emboli (intravascular bacterial colonies) in vasa rectae or glomeruli are consistent with bacteremia and blood borne infections. Pyelonephritis (inflammation in the renal pelvis) suggests ascending infection. Infectious causes of cystitis usually ascend from the distal intestine or environment via a compromised or damaged urethra. Thus likely agents are enteric or environmental opportunists. Diabetic mice or hyperestrogenized mice may be especially susceptible. Diabetic mice are polyuric and glucosuric contributing to a damp that favors microbial proliferation. They may be obese and unlikely to groom or move external genitalia from contaminated areas. Estrogenized mice may develop squamous metaplasia in the urogenital tract, urethral obstructions, enlarged bladder, and cystitis. Opportunists including *Klebsiella oxytoca, Enterococcus faecalis,* staphylococci*, Proteus mirabilis, E coli* are identified in mouse UTI.[108] [109] [110]
8. **Conditions infectious, systemic-multisystem** [93] [110] [111] [112] [113] [114] [115]
   a. **Bacteremia**, refers to bacteria in the blood. **Septicemia** refers to systemic disease due to microorganisms and or toxins in the circulating blood. Sepsis and septicemia frequently are used interchangeably, but in current usage sepsis refers more specifically to the systemic response to infection, defined as the presence of systemic inflammatory response syndrome (SIRS) in addition to a documented or presumed infection.[116] These conditions are not expected in competent mice, unless bacteria or toxins have been introduced iatrogenically or experimentally. Especially in immunodeficient mice, sepsis, septicemia or bacteremia may be suspected when there are no specific signs or lesions to suggest other causes. In immunodeficient, sick or compromised mice, almost any organism or toxin that gains entry to systemic circulation may cause bacteremia or septicemia. Histopathology findings of intravascular and perivascular bacterial colonies with associated inflammation or necrosis to indicate antemortem effects, are good evidence for a bacteremic cause of death. But the bacteria and antemortem changes are not always obvious, especially when animals die quickly. Prolonged post mortem intervals before evaluation allow post mortem degeneration of tissues, proliferation of bacteria, and migration of motile bacteria into vasculature and other tissues. Promiscuous, motile and rapidly dividing bacteria may be the most abundant and obvious in autolyzed specimens, but not relevant to death. Likely enteric and environmental flora involved in bacteremia include gram negative pseudomonads, coliforms, *Klebsiella* species; and gram positive streptococci, enterococci, staphylococci. While mice are used experimentally to model pathogenic effects of microbial toxins, naturally occurring disease due to endotoxemia and enterotoxemia are challenging to prove definitively. Hemorrhage and gas in intestines may suggest enterotoxins, and *Clostridium* species, *E. coli* and other bacteria may be identified and implicated by association, but a causal relationship is difficult to establish.

III. Diagnostic methods for infectious agents [80] [84] [85] [86]

A variety of methods are used to diagnose infectious agents in mice. Each has strengths and weaknesses. Different methods or combinations of methods offer advantages for quarantine, surveillance, or diagnostic testing. Optimal testing strategies can depend on the type of facility, microbial exclusion lists of the facility, strains and immune status of the mice, value of the mice, and the cost and time involved.

1. **Pathology**. **Gross examination** of tissues, and **histopathology** (microscopic examination of tissue sections), are used to detect the damage done by infectious agents to the host tissues. Compared to serology tests and PCR that assess only the agents specified, pathology assesses broadly for responses to agents, and for other causes or contributors to disease. Bacterial colonies, fungi and larger agents (fungi, protozoa, metazoa) can be identified in tissue sections. Some viruses, such as adenoviruses, herpesviruses, papovaviruses, poxviruses can leave distinct "footprints" such as intranuclear inclusion bodies. Cytomegaloviruses can cause bizarrely enlarged "cytomegalic" cells. MHV infection can produce multinucleated cells called syncytia. Agents may not leave such specific and distinctive "footprints," but the changes or lesions signify the response to an agent. To further complicate matters, mice of different strains, ages, or sex may respond differently to pathogens, and different strains a virus can elicit different responses and cause different lesions. For example: liver and intestine lesions due to Helicobacter hepaticus infection vary with the sex and strain of mice;[117] [118] enterotropic MHV strains may cause no signs or lesions in adult B6 mice but lethal intestinal disease in young B6 mice; and in nude mice enterotropic MHV strains can cause severe typhlocolitis, but polytropic MHV can cause hepatic necrosis.[119] [120] [121]

   Electron microscopy can play important roles in detecting and characterizing viruses, but is not practical in high throughput detection of agents in surveillance or quarantine programs, or for routine diagnostic efforts.

   Immunohistochemistry can play important roles in detecting and characterizing many infectious agents, but usually is not practical in high throughput detection of agents in surveillance or quarantine programs, or for routine diagnostic efforts.

   Special stains (histochemistry)[122] can be useful for identifying bacteria, fungi and other agents, common stains include

   a) Acid fast stains (e.g. Ziehl Neelsen, Fite Faraco, Kinyoun) stain mycobacterial cell walls red, and may distinctively stain structures in other agents such as cryptosporidia.
   b) Gram stains (e.g. Brown Brenn, Brown Hopps) stain gram positive bacteria purple, gram negative bacteria red.
   c) Giemsa stain can highlight features or structures of some protozoa and bacteria.
   d) Silver stains for bacteria (e.g. Warthin Starry or modified Steiner's stain) render bacterial cell walls black, and are useful to identify bacteria such as spirochaetes and helicobacters that do not stain well with gram stains.
   e) Silver stains for fungi such as Gomori Methenamine Silver (GMS) render fungal cell walls black by silver deposition. GMS also stains some bacteria.
   f) Periodic Acid Schiff (PAS) stains certain polysaccharide structures violet-pink, and is useful for identification of fungi.

2. **Serology methods** currently are the primary means to evaluate for the presence of viruses in a mouse or colony. M pulmonis, CARBacillus (bacteria) and E cuniculi (microsporidian) and other agents also may be tested for by serology. Most serology methods detect antibodies produced by the host against the infectious agent. They do not detect the agent. Serology tests may be positive in the absence of an agent, from antibody response to previous, cleared, infection. Serology tests may be negative in presence of the agent if there is not an effective antibody response, e.g. in immunodeficient mice. However serology tests are increasingly high throughput, and still the most

cost effective method for large scale surveillance. Enzyme linked immunoabsorbent assay (**ELISA**) is used frequently for primary screening, with immunofluorescent antibody (**IFA**) tests to confirm findings. **HAI**, or hemagglutination inhibition tests to detect antibody mediated inhibition of virus hemagglutination, are not as sensitive or high throughput as other test options, and not so widely used. New bead based fluorometric multiplex ELISA capabilities permit even more tests on smaller samples. Ideally, detection tests would be 100% sensitive (i.e., detect 100% of seropositive animals, with no false negative results) and 100% specific (i.e., detect 100% of the animals seropositive for a specific agent, with no false positive results). No test is 100% sensitive and 100% specific. Therefore, it is common practice to utilize the test with the higher sensitivity for screening (usually ELISA), followed by confirmation of positive results with tests of higher specificity.
Standard serology testing is not useful for certain agents. These include lactate-dehydrogenase-elevating virus (LDV), for which serum chemistry testing and PCR can be used, and for murine retroviruses, many pieces of which, sometimes called retroelements, comprise the mouse genome.

3. **Polymerase chain reaction (PCR)** methods specifically amplify probe DNA sequences to detect specific sequences of infectious agents, including viruses, bacteria, eukaryotes.[123] Reverse transcriptase PCR (RTPCR) is used to detect RNA sequences in RNA viruses. PCR can be highly specific and sensitive, but requires that the correct specimen or tissues is tested for the correct agents, and that it is not contaminated in the test environment. PCR methods are becoming increasingly accessible and time saving, and fecal specimens from live animals are proving useful for detection of viruses, bacteria, parasites, that are shed from infected animals. The testing laboratory should be consulted regarding their preferred specimens, and optimal specimen handling.
4. **Microbial cultivation** on artificial media has been a primary means to grow bacteria and fungi for identification. Cultured agents also can be tested for antimicrobial sensitivity. However isolation of an agent does not necessarily identify it as the cause of the lesion because opportunistic agents can infect secondarily, and because fastidious agents may be overgrown by faster growing agents or contaminants. Some agents, e.g. obligate intracellular agents do not grow on artificial media. Cultivation and identification of agents is labor, equipment and expertise intensive. Increasingly, PCR is used to identify diverse microbes as indicated in **tables IV V VI**
   Dermatophyte test medium (DTM) is a specialized agar medium used to selectively cultivate fungi that cause ringworm, and indicates their alkaline byproducts with Phenol red pH indicator
   Virus isolation techniques can be useful in detecting viruses, but are not practical in high throughput detection of agents in surveillance or quarantine programs, or for routine diagnostic efforts.
5. **Parasitology** [124] [125] [126] [127] [128] [129]
   a. **Direct microscopic examination for parasites,** is most frequently applied to the pelt for mites, and to different segments of the gastrointestinal tract and their contents, for metazoan parasites. A dissection microscope with a large field and magnification up to 20x facilitates examination. Positive findings are diagnostic, but negative results may not be conclusive.
   b. **Fecal flotation** refers to the use of saturated, high osmolarity solutions mixed with fecal material, to suspend protozoal oocysts and nematode eggs, such that they float and adhere to a coverslip laid on top of the mixture. The coverslip is applied to a glass slide and examined with a microscope. Centrifugation can further concentrate the eggs and oocysts, and increase the sensitivity of the test.
   c. **Fur plucks,** evaluated microscopically for ectoparasites, may be useful for detecting demodex mites. Microscopic evaluation of skin scrapings may be more sensitive for detection of fur mites.

d. **Pelt digestion** refers to removal of the pelt and digestion in basic solution, such as KOH, to dissolve skin and hair, leaving chitinized parasites including fur mites and follicle mites, and nematodes (as in filariid infections).[130]
e. **Pelt examination,** depending on the method, this can refer to microscopic examination of the pelt on the live animal, or to microscopic examination of the removed pelt.
f. **PCR – see above** – PCR testing is becoming increasingly available for detection of common parasites in mice. A significant advantage of PCR testing of fur swabs or of feces is that the diagnostic test does not kill the mouse.
g. **Skin scrape** has been found to be the most sensitive examination method to detect of fur mites. The recommended method involves scraping (with a scalpel blade) dorsal head, neck, back, plus ventral and inguinal skin, transfer of scrapings to clear tape, followed by meticulous microscopic examination.[128]
h. **Tape tests** refer to application of transparent sticky tape to the pelt or perineum to examine for ectoparasites on the skin or fur, and for Syphacia spp. pinworm egg that are deposited on the perineum. The tape is applied to a glass slide and examined with a microscope.
i. **Wet mount** refers to wet specimens, usually gastrointestinal contents. Wet mounts of fresh gastrointestinal contents permit evaluation for characteristic motility of live protozoa. High-magnification phase-contrast microscopy is preferred for these evaluations.

IV. Infectious agents, Viruses [3] [131] [132] [133]
Table IV summarizes viruses commonly tested in surveillance programs, with primary and confirmatory test methods, % positive tests from mice specimens in the US and Europe, as reported in 2009 from the prior several years, [80] and the approximate percent of positive institutions as determined by a 2006 survey of large NIH funded institutions in the US.[82] The final column indicates if PCR testing is commercially available on feces (F) or biological materials (B) such as serum or cultured cells. Many of these agents have been identified as contaminants of biological materials. [134] [135] Except for Murine Norovirus (MNV), all of these viruses are included in the 2002 FELASA recommendations for health monitoring of mice. [136] Tests for MNV became available after 2002. Although the % positive results are reassuringly low for many agents, the survey findings suggest that some agents remain prevalent in research programs. **Viruses are discussed** in alphabetical order of virus family, per **Table IV**. Some additional agents are discussed briefly because of their ubiquity (retroviruses), because of their relevance to related common agents (gammaherpesviruses, encephalomyocarditis virus (EMCV)), or because it is only recently reported (mouse papillomavirus).

Health reports with surveillance test methods, frequencies and results, for mice from large vendors are available online at sites such as
Charles River Laboratories
http://www.criver.com/en-US/ProdServ/ByType/ResModOver/ResMod/Pages/ResModels.aspx
Harlan
http://www.harlan.com/products_and_services/research_models_and_services
The Jackson Laboratory
http://jaxmice.jax.org/
Taconic
http://www.taconic.com/wmspage.cfm?parm1=26

1. **Adenoviridae; Mouse Adenoviruses (MAV1,2)** [137] [138] [139] [140] [141]

Adenoviruses are relatively large, non enveloped double stranded (DS) DNA viruses. Mouse adenoviruses 1 and 2 are not expected agents in contemporary research colonies. Natural infections are not expected to cause clinical disease. Adenoviruses replicate in nuclei, where they can produce characteristic large intranuclear inclusion bodies. MAV1 (also known as FL, Friend Leukemia agent) infects endothelial cells in lung, CNS, kidney, and is shed in the urine in experimental infections, and may cause intranuclear inclusion bodies. Mad2 (also known as K87) may cause intranuclear inclusion bodies in small intestine mucosal epithelium.

2. **Arenaviridae; Lymphocytic choriomeningitis virus (LCMV)** [142] [143] [144]

Arenaviruses are small enveloped single stranded (SS) RNA viruses. LCMV has been significant in laboratory mice as a contaminant of biological materials, and because of its zoonotic potential. LCMV can infect various species including mice, rats and hamsters, and humans. LCMV in mice usually is subclinical, but experimental infections can cause lymphocytic choriomeningitis. Infection of neonates and immunodeficient mice can result in persistent infection and shedding. Infected pet hamsters, and nude laboratory mice have been implicated in human infections.

3. **Arteriviridae; Lactate-dehydrogenase–elevating virus (LDV, LDEV)** [134] [145]

Arteriviruses are small enveloped single stranded (SS) RNA viruses. LDV infection in mice has been associated primarily with infected biological materials. There is usually no clinical disease in natural infections, although flaccid paralysis and poliomyelitis have been reported in immunosuppressed C58 and AKR mice, and scid mice that are coinfected with an endogenous murine leukemia virus. LDV infects and replicates in monocytes or macrophages that normally clear various enzymes. Infection interferes with elimination of the enzymes, and causes persistent elevations lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT), and other enzymes. LDV does elicit an antibody response, but also elicits non specific antibodies that interfere with serologic testing. Thus plasma chemistry tests for LDH activity, and PCR are the primary diagnostic test methods. Diagnosis by clinical chemistry testing is based upon elevated LDH activity in serum or plasma, e.g. levels in excess of 2500 units/ml, from a clean, non hemolyzed specimen, when the reference range is about 400-800 units/ml. LDH release by platelets during clotting increases LDH activity in serum samples, so plasma is recommended over serum as a diagnostic specimen. Hemolysis increases LDH in plasma or serum, so non hemolyzed samples should be tested. PCR testing of biological materials is a primary method to protect research mice.

4. **Bunyaviridae; Hantaviruses (Han)** [146] [147]

Hantaviruses are enveloped single stranded (SS) RNA viruses. They are not likely natural infections in contemporary mouse colonies, but seropositivity was reported in laboratory mice in 2006.[147] They are concerning because of their zoonotic potential. Some hantaviruses (e.g. Seoul and Sin nombre virus) cause serious disease in humans, and wild rodents are important reservoirs. Hantaviruses are transmitted by urine and saliva (bites) of infected rodents, and aerosols containing infectious virus from rodent urine, feces, and saliva are important means of transmission. Infected laboratory rats and wild-caught rodents have been identified as sources of human infection in Europe and Asia.

5. **Caliciviridae; Murine Noroviruses MNV** [148] [149] [150] [151] [152]

Caliciviruses are non enveloped single stranded (SS) RNA viruses. Murine noroviruses (MNV)are caliciviruses, similar to human Norwalk viruses implicated in foodborne diarrheal disease. MNV are prevalent in research mouse colonies. There are multiple serotypes, MNV1-4, etc. Their significance in competent mice, and the need to eliminate them from research colonies, remains controversial.

Clinical signs: usually none, morbidity in severely immunodeficient mice
Gross findings: usually none
Histopathology: inconspicuous to mild inflammation in intestine, hyperplasia in spleen; inflammatory changes (hepatitis, interstitial pneumonia, pleuritis, peritonitis) in certain immunodeficient mice,
Detection: Serology, PCR
Control: These are non enveloped viruses, so are fairly resistant to routine environmental sanitation by detergents and disinfectants. Primary strategies to eliminate viruses from mice include: 1) Test, cull and decontaminate, 2) rederivation or fostering into virus free barriers.

6. **Coronaviridae; Mouse hepatitis virus (MHV)** [119] [120] [121] [153] {Compton, 2004 #1959} {Taguchi, 2012 #11432}

Coronaviruses including Mouse hepatitis virus (MHV) are enveloped single-stranded (SS) RNA viruses. Disease in mice varies with MHV strain, dose and route of administration, as well as with mouse strain, age and immune status. MHV strains have been classified as 1) primarily **enteric or enterotopic**, with infection and lesions usually restricted to the gut of young animals; and 2) **respiratory or polytropic** that infect respiratory tract initially then spread to other tissues. Historically MHV was prevalent in research colonies, and enterotropic strains were an important cause of epizootics (outbreaks) of pup diarrhea and mortality, **lethal intestinal virus of infant mice (LIVIM).** Respiratory or polytropic strains cause experimental hepatitis and encephalitis, and can cause of chronic wasting and necrotizing hepatitis in immunodeficient mice. Transmission occurs through contact with infected mice, including wild mice, fomites, airborne particles, and biological materials. Transplacental infection has been documented experimentally. Enterotropic virus is shed heavily (in feces), which tend to be very infectious. Respiratory or polytropic strains can be shed in respiratory secretions. Because respiratory or polytropic strains infect various tissues, they are more likely to be encountered in biological materials.
Enterotropic MHV strains infect intestine epithelium in all ages of mice. Naïve suckling mice are susceptible to diarrheal disease and mortality (LIVIM = lethal intestinal virus of infant mice). In contrast to rotaviral diarrhea, infected neonates stop nursing, and may die (LIVIM). Ascending colon (also distal small intestine, and cecum) is a frequent site of infection and epithelial syncytia. Older, immune sufficient mice, and Bcell deficient mice, are infected but usually do not develop disease. T cell deficient mice can develop lethal multisystem disease. Enterotropic MHV's are highly contagious, with susceptible or immune deficient mice shedding abundant virus in feces for long periods. Enzootic infection in a colony is usually subclinical, perpetuated by breeding mice that transmit the virus, along with protective immunity, to offspring.
Polytropic or respiratory strains infect the respiratory tract initially, then disseminate. Clinical disease in natural infections of competent mice is unusual, but in immunodeficient mice there can be progressive wasting and necrotizing liver disease, with characteristic syncytia in various tissues. Much of MHV research has used polytropic strains A59 and JHM. Experimental infections with these agents can cause encephalitis, spinal cord demyelination and paralysis in susceptible mouse strains, and have been used to model immune mediated demyelinating diseases especially multiple sclerosis.
Ceacam1 protein is a receptor for MHV via MHV's spike (S) protein. The N terminal 330 amino acids in S1 are responsible for receptor binding, and S2 is critical for envelope–cell membrane fusion and entry into the cell. SJL/J mice carry the *Ceacam1b* allele, which confers resistance. Most of the common inbred strains carry *Ceacam1a*, and express a functional receptor, and susceptibility to MHV. Wild mice can carry either or both alleles. Susceptibility is the 'dominant' trait. Other genes are implicated in MHV susceptibility /resistance.
Clinical signs: Vary, usually subclinical seroconversion in competent mice; chronic wasting in immunodeficient mice; historical epizootics of diarrhea and death in naive young mice, (LIVIM).
Gross findings: Often none; typhlocolitis or hepatic necrosis in susceptible mice

Histopathology: Enterotropic strains in susceptible mice: typhlocolitis with necrosis and synyctia; Polytropic strains: Syncytial cells in various tissues; in susceptible mice: necrotizing hepatitis, typhlocolitis, encephalitis, with syncytia.

Detection: Serology using multiplex or ELISA technologies, with confirmation by IFA are common in 2015. PCR of feces may be useful in shedding animals. Histopathology findings of hepatitis, necrosis or typhlocolitis, or syncytia should lead to further testing for MHV.

Control: These enveloped viruses are relatively fragile, and susceptible to common sanitation procedures, but are contagious among mice. Primary strategies to eliminate MHV include: 1) Test, cull and decontaminate, 2) rederivation or fostering into MHV free barriers.

7. Herpesviridae [89] [92] [154] [155] [156] [157] [158]

Herpesviruses are large, enveloped double stranded (DS) DNA viruses. Natural herpesviral infections are unlikely in contemporary mouse colonies.

a. Mouse Cytomegalovirus (MCMV) [89] [92] [154] [155]

MCMV is a betaherpesvirus, with many features similar to species specific cytomegaloviruses in other species. MCMV seems to be widespread in wild M musculus populations. In immune competent mice or in wild species, infection usually is subclinical with salivary glands persistently infected. In immunodeficient mice, MCMV can disseminate, causing necrosis, cytomegaly and inclusion bodies in various tissues. In nude and scid mice inoculated with contaminated biological materials, there can be mortality, and liver necrosis with cytomegaly and inclusions. Immunodeficient mice infected with MCMV, also are used to model human CMV infections.

b. Mouse Thymic Virus (MTV, murid herpesvirus 3) [156]

MTV is an unclassified Herpesvirus. It is unlikely in contemporary colonies but may be prevalent in wild mouse populations. It infects salivary glands initially and persistently, but is T lymphotropic , and causes transient lymphoid necrosis in thymus, spleen, lymph nodes of neonatal mice.

c. Herpesviridae; Gammaherpesviruses (MHV 68 etc) [157] [158]

These agents are not tested for routinely. They are viruses of wild rodents. Experimental infections in susceptible mouse strains are used to model herpesvirus mediated lymphoproliferative conditions.

8. Orthopoxviridae; Ectromelia virus (ECT) [159] [160] [161]

Poxviruses are large, enveloped double stranded (DS) DNA viruses. Ectromelia virus is an Orthopoxvirus similar to vaccinia virus, and is the agent of the disease mouse pox. Historically this agent caused epizootics in susceptible mice. Highly susceptible strains such as BALB/c or DBA can die quickly before development of characteristic lesions. Resistant strains such as C57BL/6 can harbor the agent subclinically. When present, necrosis in various tissues especially in liver and spleen, and eosinophilic intracytoplasmic inclusion bodies in the skin, are characteristic. Ectromelia refers to shortening of limbs that can occur in mice that survive severe necrotic skin lesions of the extremities. Recent 'outbreaks' have been associated with commercially available contaminated serum. Seroconversion is likely when contaminated materials are inoculated into competent mice, and can occur after experimental administration of Vaccinia virus to competent mice. However many animals inoculated with biological materials are immunodeficient, and do not seroconvert reliably, and dirty bedding sentinels also may not be sufficiently 'inoculated' to seroconvert reliably. Recent out breaks associated with contaminated biological materials have used combinations of ELISA and PCR testing, and pathology findings to detect and characterize the disease. PCR testing of biological materials is a primary means of protection from this agent.

9. Papovaviridae

Papovaviruses are enveloped double stranded (DS) DNA viruses. Important papovaviruses of mice have been the polyomaviruses, Murine Polyomavirus, and Murine Pneumotropic Virus. Natural infections are not likely in contemporary laboratory mouse colonies.

a. Mouse Papillomavirus [162] [163]

A mouse papillomavirus was identified recently in proliferative skin lesions and papillomas in nude mice.

b. K virus, murine pneumotropic virus, mouse pneumotropic virus [164]

Natural infections by Mouse pneumotropic virus,also known as K virus, is unlikely in contemporary colonies. This agent was discovered originally as a contaminant of transplantable mouse tumors. Natural infection tends to be subclinical and persistent. Experimentally infected neonates or athymic nude mice may die with edema and hemorrhage in the lungs.

c. Murine Polyomavirus, Mouse Polyomavirus [164]

Natural infections by Mouse Polyomavirus also are unlikely in contemporary colonies, and are subclinical in immunocompetent adult mice. Experimental infections of neonates or athymic nude mice can lead to tumors in multiple tissues (poly + oma, meaning many tumors). Nude mice may develop multifocal necrosis and inflammation with intranuclear inclusion bodies, possibly paralysis due to vertebral tumors, or demyelination. The characteristic tumor resulting from experimental infections of neonates is a pleomorphic salivary gland tumor, called a myoepithelioma, with concurrent inflammation that is unusual in spontaneous salivary gland tumors. Tumors also can be induced in other tissues, especially in susceptible strains. K virus, adenoviruses and MCMV are other possible causes of intranuclear viral inclusion bodies in mouse tissues. TMEV is another possible cause of paralysis and demyelinating central nervous system disease in nude mice.

10. Paramyxoviridae [101] [165] [166] [167] [168]

Paramyxoviruses are enveloped single stranded (SS) RNA viruses. Sendai virus and Murine pneumonia virus are the significant species in mice. Their prevalence in laboratory mice has diminished significantly in the last 2 decades.

a. Murine pneumonia virus (also called Pneumonia Virus of Mice, PVM) [101] [165] [166]

PVM is a paramyxovirus that has been prevalent in laboratory mice, rats, and hamsters. It is closely related to human and bovine respiratory syncytial viruses and has been used to model human RSV infection and ARDS is susceptible mouse strains. Natural infection usually is subclinical in immunocompetent mice; but nude mice may develop chronic wasting disease with progressive interstitial pneumonia.

b. Sendai virus (Sen) [101] [167] [168]

Sendai virus is a Paramyxovirus similar to human parainfluenza virus type 1. It has been an important viral cause of morbidity and mortality in laboratory mice. Since the advent of effective isolator caging it has become uncommon. Some mouse strains such as 129 and DBA, are very susceptible, develop clinical respiratory disease and may die. C57BL/6 and SJL/J are more resistant to disease development. Epithelial necrosis in competent mice is largely T cell mediated. In T cell deficient mice such as nude or scid mice, primary changes reflect direct effects of the virus, resulting in epithelial syncytia, intranuclear inclusion bodies and epithelial proliferation. Progressive proliferative lesions in nude and scid mice, and in some chronically infected competent mice can become nodular and tumor-like.

Clinical signs: Dyspnea, chattering (respiratory noise), and high mortality in susceptible mice; chronic respiratory disease and wasting in immunodeficient mice.

Gross findings: Consolidation and or discoloration of lungs

Histopathology: In competent mice, there can be necrotizing rhinitis, tracheitis, and bronchiolitis as well as interstitial pneumonia. During recovery, epithelial proliferation can progress to cuboidal metaplasia in alveoli and squamous metaplasia in the bronchioles, sometimes with fibrosis. In nude

and SCID mice, proliferative changes predominate, and can progress to tumor like lesions. Intracytoplasmic inclusion bodies, and epithelial syncytia, may be prominent or inconspicuous.

Detection: Serology testing using multiplex or ELISA technologies, with confirmation by IFA are common test techniques. Necrotizing or proliferative respiratory tract lesions with syncytia or cytoplasmic inclusion bodies, are highly suggestive of Sendai virus and should lead to further testing to assess for this agent. Although Sendai virus is considered to be highly contagious via aerosol, sentinel mice exposed to dirty bedding from infected animals do not reliably seroconvert. In addition, some outbred stocks of mice do not seroconvert consistently.

Control: These enveloped RNA viruses are susceptible to routine environmental sanitation by detergents and disinfectants. Primary strategies to eliminate viruses from mice include: 1) Test, cull and decontaminate, 2) Rederivation or fostering into virus free barriers.

11. Parvoviridae; Parvoviruses Minute Mouse Virus (MMV), Mouse parvovirus (MPV) [169] [170]

Parvoviruses are tiny, non enveloped single stranded (SS) DNA viruses. They infect and lyse proliferating cells, specifically cells in S phase, such that, depending on the tissue tropism, or preference, of the parvovirus type, proliferating immunopoietic or hematopoietic cells, embryonic cells, or cancer cells, are infected, and damaged or destroyed. Parvoviruses remain quite common in contemporary mouse colonies. Minute Mice Virus (MMV) and of Mouse Parvovirus (MPV) are parvoviruses of mice. Natural infections are asymptomatic, although there is immune modulation. Experimental MMV infections in neonatal and immunocompromised mice can be lethal, or can cause abnormalities such as runting, cerebellar hypoplasia, renal infarcts, and anemia. Parvoviruses including MMV have been identified as contaminants of hybridomas and other transplantable tumors and cell lines. Various parvoviruses, including MMV, have been investigated as potentially therapeutic oncolytic (tumor lysing or tumor killing) agents.

Clinical signs: usually subclinical

Gross findings: usually none

Histopathology: usually none

Detection: Serology testing can be frustrated by slow or weak seroconversion, and strain variations in seroconversion. PCR of mesenteric lymph nodes or feces may be useful in active infections with shedding.

Control: These small non enveloped viruses persist in the environment, resist many decontaminants, and are highly infectious. Biological materials, wild mice, and contaminated food, bedding and other fomites are potential sources. Primary strategies to eliminate parvoviruses include: 1) Test, cull and decontaminate, 2) rederivation or fostering into parvovirus free barriers.

12. Picornaviridae; Cardioviruses [143] [171] [172]

a. Encephalomyocarditis virus (EMCV) [171] [172]

Picornaviridae are small, non enveloped single-stranded (SS) RNA viruses. Encephalomyocarditis virus (EMCV) is a cardiovirus in this group. EMCV is unlikely in contemporary colonies and is not routinely included in surveillance testing. EMCV is an important cause of myocarditis in piglets and abortion in pregnant sows, and of 'outbreaks of myocarditis and sudden death in zoo animals. Small rodents, including mice, have been suspected to be reservoir hosts. Certain strains of EMCV (e.g. EMCV-D) has been used to model diabetes mellitus in susceptible mice.

b. Theiler's mouse encephalomyelitis virus(es) (TMEV, GDVII) [143]

TMEV represents a group of several cardioviruses that infect mice. GDVII is one of several strains of TMEV that can infect mice and cause disease. Natural infection usually is subclinical, but may cause posterior flaccid paralysis, and chronic infections may contribute to hyperglobulinemia, immunoglobulin deposition in kidneys, and glomerulonephritis. SJL/J mice are especially susceptible to demyelination

and paralysis from experimental infections. Various susceptible and resistant strains have been used to study mechanisms of virus induced and immune mediated demyelination.

13. Reoviridae [173] [174] [175] [176] [177]

Reoviridae are non enveloped, double-stranded (DS) RNA viruses. Natural infections with mouse rotavirus also known as the EDIM virus, and Reovirus 3 can cause disease in mice, but are not common in contemporary mouse colonies.

a. Mouse rotavirus (MRV, EDIM) [173] [174] [175] [176] [177]

MRV or EDIM are mouse specific, group A rotaviruses in the family Reoviridae. Similar to Group A rotaviruses of other species, MRV causes diarrhea in young animals and has been used to model human rotavirus diarrhea. Multiple strains of MRV (EDIM) have been isolated and identified as causes of pup diarrhea and runting. Even immunocompromised mice are only susceptible to disease up to about 15 days of age. Older mice can be infected but do not develop disease It is much less common in contemporary colonies. However, it should be considered when there is neonatal diarrhea, runting, high morbidity, low mortality, and no clinical disease in older mice.

Clinical signs: diarrhea in neonatal mice, hence the name: epizootic diarrhea of infant mice (originally Epidemic Diarrhea of Infant Mice, or EDIM). Pups continue to nurse and have milk in their stomachs, evident though their thin skin. Pups usually survive but may be runted. Infection in older mice is subclinical.

Gross findings: Yellow diarrhea in nursing neonates with milk in their stomachs.

Histopathology: Vacuolation of apical villus epithelium in small intestine is transient, and may be difficult to distinguish from normally lipid laden villus epithelium in nursing neonates. Cytoplasmic inclusion bodies in enterocytes have been described, special stains may be required to visualize them.

Detection: Serology testing using multiplex or ELISA technologies, with confirmation by IFA are common test techniques. RT PCR of feces may be useful in shedding animals.

Control: These DS RNA viruses are not enveloped and fairly resistant to sanitation by detergents and disinfectants. Primary strategies to eliminate MRV include: 1) Test, cull and decontaminate, 2) rederivation or fostering into virus free barriers. Cessation of breeding to break the cycle of continuous fecal oral transmission in breeding situations, has been reported to be effective.[174]

b. Reovirus 3 (REO3) [173]

Reoviruses are not as host specific as rotaviruses are. Of the four mammalian Reovirus serotypes (1-4), only Reovirus 3 (REO3) is associated with disease in mice. It also can infect mice, rats, hamsters, and guinea pigs. Natural infections are not expected in contemporary mouse colonies. Clinical disease is unusual in natural infections, but stunted growth, diarrhea, jaundice, and oily hair coat, sometimes called OHE (oily hair effect), have been associated with infection in susceptible young mice.

14. Retroviridae, Murine retroviruses [23] [178] [179]

Retroviruses exist as either exogenous viruses or endogenous viruses. Exogenous retroviruses (RNA viruses) outside the genome are transmitted horizontally like many other viruses. Exogenous retrovirus is duplicated in an infected cell using its own reverse transcriptase enzyme to produce DNA from its RNA genome, the DNA inserts into the host genome and replicates as part of the host cell's DNA. Examples of exogenous retroviruses in humans include Human Immunodeficiency virus (HIV) and Human T Lymphotropic Virus (HTLV). Endogenous viruses (also called proviruses) are DNA of complete or nearly complete viruses that is integrated into the mouse genome, and inherited in a Mendelian pattern like

other genes. Many endogenous retroviruses or proviruses are defective, incomplete and unable to replicate, but lurk in the genome and can be identified by characteristic sequences. Under certain conditions some proviruses can be induced to synthesize complementary RNA sequences, package themselves into virions, enter the bloodstream, participate in tumorigenesis, and be shed in milk, saliva, semen, urine, or feces. Retroelements refer to retroviruses and pieces of them that are scattered throughout the genome. Retrotransposons, intracisternal A particle (IAP's), VK30's, and long interspersed nuclear elements (LINEs) are examples of retroelements. Retroelement insertions into the genome (insertional mutagenesis) can disrupt or modify expression of functional genes, contributing to mutations like the *hr* mutation in the *Hr* locus (hairless Hr^{hr}); *d* (dilute) mutation in *Myo5a* ($Myo5a^{d}$); *lpr* (lymphoproliferation) mutation in the *Fas* locus (Fas^{lpr}); *nu* (nude) mutation in *Foxn1* locus ($Foxn1^{nu}$); *ob* (obese) mutation in the *Lep* (leptin) locus (Lep^{ob}). Taken together endogenous retroviruses and retroelements may comprise more than 30% of mouse genome. Because of their ubiquity, testing for these agents is not included in routine surveillance. Despite their incriminating names, murine mammary tumor viruses (MMTV) and murine leukemia viruses (MuLV) frequently do not participate in tumorigenesis, and do not necessarily lead to the type of tumor for which they are named.

a. Murine mammary tumor viruses (MMTV) [23]

MMTV exist as exogenous and endogenous viruses. Exogenous MMTV (Bittner agent) is transmitted vertically to nursing pups via milk, and is also shed and can be transmitted by saliva and semen. Exogenous MMTV has been eliminated from most strains by cross-fostering and rederivation, but wild mice carry exogenous MMTV. 100% of female C3H mice that received exogenous MMTV (Bittner agent) from their dam's milk develop mammary tumors by 9 months of age. All mouse strains have endogenous MMTV. Many of these have become named genes with the gene symbol Mtv followed by a number (e.g., Mtv1, Mtv2 etc) on various chromosomes. Expression of MTV 29 leads to development of B cell lymphoma in SJL/J mice. Expression of MTV1 leads to mammary tumors in C3H and DBA mice. Expression of MTV2 leads to mammary tumors in GR or GRS mice. Mammary tumors attributed the endogenous viruses occur later than tumors caused by the exogenous virus.

b. Murine leukemia viruses (MuLV) [178]

Exogenous MuLV also have been eliminated from most laboratory mice by fostering or cesarian rederivation, but exist in wild mice, and occasionally are transmitted from biological material.[180] All common strains of laboratory mice have endogenous MuLV, with gene symbols such as Emv1, Emv2 etc. (for Ecotropic MuLV genes), Pmv1, Pmv2 etc, (for Polytropic MuLV genes), and Xmv1, Xmv2 etc. (for Xenotropic MuLV genes). Endogenous viruses are considered to be ecotropic, polytropic, or xenotropic depending on whether their virions are infectious in vitro to mouse cells only (ecotropic), to mouse and non mouse cells (polytropic), or to non mouse cells only (xenotropic). Many endogenous MuLV are incomplete or "defective," and require another virus or virus component, or inducer genes in order to be expressed and produce virions.

Several hematopoietic neoplasms in mice are associated with expression of combinations of endogenous MuLVs in thymus or other hematopoietic tissues. AKR, C58, NODscid and related strains develop early onset of thymic lymphomas, while BALB/c and A/J mice often develop later onset lymphomas. Both of these lymphomas result from combined coexpression of several Emv's with ensuing transformation of specific lymphocyte types. Although these agents are called leukemia viruses, and all hematopoietic neoplasms in mice were commonly called "leukemias," most spontaneous hematopoietic neoplasms in mice are malignant solid lymphoid tumors that are more correctly referred to as lymphoma. True myelogenous (granulocytic) or erythroid leukemias have been attributed to MuLV and can be induced experimentally.

V. Infectious agents, Bacteria

Table II above, lists bacteria by their likely sites of infection or types of disease. The spectrum of disease varies with the strain and immune competence of the mice.

Table V summarizes bacteria, test methods and percent positive results from submissions to a major diagnostic laboratory for over several years prior to 2009. [80] Also included are the approximate percent of positive institutions (%Pos institutions) as determined by a 2006 survey of large NIH funded institutions in the US,[82] and some of the recommended specimens for PCR testing. The agents listed represent bacteria that are likely to be tested for in surveillance or quarantine programs or in diagnostic submissions, and also included in the 2002 FELASA recommendations for the health monitoring of rodent colonies in breeding and experimental units.[136] A few additional agents are included in the discussion below.

1. *Bordetella species, B. avium, B. bronchiseptica, B. hinzi* [98]

A gram negative small rod, Bordetella species in mice usually are opportunist agents. There are recent reports of respiratory disease associated with B hinzii, which shares many features with B avium. B. bronchiseptica is not an expected problem in mice, but can be highly pathogenic in Guinea pigs, and is a common agent in rabbits, which may be in close proximity to laboratory mice.

2. Cilia-Associated Respiratory Bacillus. (CAR Bacillus; CARB) [107]

A gram negative small filamentous rod, CARbacillus is an unclassified bacterium, related to Flavobacterium or Flexibacter species. In mice and rats it has been an important copathogen with Mycoplasma pulmonis, but it can cause pneumonia in the absence of M. pulmonis. Histopathology findings include bronchopneumonia, with abnormally clumped cilia in respiratory epithelium. Warthin Starry silver stain can reveal silver staining filamentous bacteria among the unstained cilia. CARbacillus is unlikely in contemporary mouse colonies. It cannot be cultivated on cell free media, but antibodies can be detected by ELISA, and it can be detected by PCR.

3. *Citrobacter rodentium* [110] [181] [182]

A gram negative small rod, formerly called *C. freundii* biotype 4280, C. rodentium is the etiologic agent of transmissible murine colonic hyperplasia. Natural infection is unlikely in contemporary colonies. Diarrhea, rectal prolapse and grossly thickened large bowel were expected clinical and gross findings when the agent was more prevalent. Suckling mice and C3H strain mice are especially susceptible. Competent mice clear the agent rapidly so it can be difficult to detect, even in affected tissues. Helicobacters are more commonly identified and implicated in inflammatory and proliferative bowel disease in contemporary colonies. *C. rodentium* is an attaching effacing pathogen, with mechanistic similarities to enteropathogenic *Escherichia coli* (EPEC), enterohemorrhagic *E. coli* (EHEC) disease in humans and other species, so it is used to model EPEC, EHEC disease.

4. Chlamydiae [183]

Chlamydiae are intracellular gram negative bacteria, with atypical bacterial morphology. They form intracytoplasmic inclusion bodies called elementary and reticulate bodies, composed of RNA and DNA. C muridarum is a parasite of mice and hamsters. It is found in wild mice, and can cause pneumonia in laboratory mice, but is unlikely in contemporary mouse colonies. C. *muridarum* has been studied as a model for human chlamydial respiratory disease and chlamydial genital tract infections. Mice can be infected experimentally with C. trachomatis, C. psittaci, and C. pneumoniae.

5. *Clostridium* species [112] [184] [185] [186]

Most *Clostridium* species are large Gram positive rods with low oxygen tolerance that reside in the lower intestine, or other sites with low oxygen tension. Most clostridium species are not problematic in mice. Some *Clostridium* species are normal and possibly beneficial residents of the mouse distal intestine. *Clostridium* species are included in 'recipes' of altered Schaedler's flora used to populate the gut of gnotobiotic mice with defined flora. *Cl. piliforme* (formerly *Bacillus piliformi*s) is a recent addition to the genus *Clostridium*. In contrast to many other clostridia, it is gram negative, with long slender morphology, and it is an obligate intracellular parasite. It has seen a significant pathogen especially in immunodeficient mice, but is no longer common in laboratory rodent colonies.

a. ***Cl. perfringens, Cl. difficile* and other species.** Clostridial enterotoxemias, or morbidity or mortality due to clostridial toxins, are rarely proven in mice, but are suspected with findings of gas and hemorrhage in the intestine, sometimes with apparent overgrowth of clostridial bacteria. Cl. perfringens and its toxins, have been implicated in death with necrotizing enterocolitis in mice, and lactating mice may be especially vulnerable. Mice are used to model various clostridial enterotoxemias. [185]
b. ***Cl. piliforme*** is a gram negative, filamentous, obligate intracellular parasite, recently classified into the genus Clostridium. Cl. piliforme is the agent of Tyzzer's disease. Infections can be subclinical, with disease severity influenced by host strain, bacterial isolate or subtype, and environmental stressors. C. piliforme has been an important cause of mortality in susceptible mice, including DBA/2, and various immunodeficient mice. Clinical signs can include watery diarrhea, lethargy, ruffled hair coat, and sudden death. Important differential diagnoses for diarrhea in young mice include EDIM and MHV infection. The most consistent gross finding in mice is multiple pale foci of necrosis in the liver (multifocal necrosis). Histopathology findings of hepatic necrosis with characteristic stacks of filamentous bacteria in cells at edges of necrotic lesions, are diagnostic. Typhlocolitis and cardiac necrosis with the intracellular bacteria occur in some cases. Warthin Starry silver stain, PAS or Giemsa stains make the agents more conspicuous. Cl. piliforme is an obligate intracellular parasite, requiring special techniques to cultivate, but it is readily identified by PCR. [186]

6. Corynebacterium species [93] [187] [188]

Corynebacteria are gram-positive, small, pleomorphic rods. Important species in mice include *C bovis* and *C. kutscheri*. *C bovis* can be especially problematic in immunodeficient or hairless mice. *C kutscheri* is no longer very common in rodent colonies. Other *Corynebacterium* species (similar to *C bovis*?) are sometimes identified in abscesses or skin lesions in mice.

a. *Corynebacterium bovis* (hyperkeratosis associated coryneform bacteria) [93] [187]
C. bovis causes outbreaks of flakey skin, especially in nude mice, and other immunodeficient or hairless mice. This infection can be associated with pup mortality in breeding colonies of immunodeficient mice. Histopathology findings of acanthosis, hyperkeratosis, with intracorneal and intrafollicular colonies of small pleomorphic, gram positive bacteria are characteristic. PCR from skin swabs or flakes can be useful for rapid detection.

b. *Corynebacterium kutscheri* [93]
C. kutscheri was known for causing the disease called pseudotuberculosis in mice and rats, characterized by caseating granulomas or abscesses in various tissues, including lungs and liver. Conspicuous cervical lymphadenomegaly is due to a robust immune response and reactive hyperplasia in immune competent mice, not to abscessation. This agent is not expected in contemporary colonies.

7. *Helicobacter* species [189] [190] [191] [189]

Gram negative, curved or spiral bacteria, the Helicobacter species that naturally infect mice include *H hepaticus, H bilis, H mastomyrinus, H muridarum, H rodentium and H typhlonius,* among others. The prevalence of Helicobacter spp. in research colonies is quite high. Some *Helicobacter* spp. have been identified as causes of hepatitis and typhlocolitis in susceptible mice, as a contributor to liver tumors in susceptible strains, and to other tumors in some models. Some species seem to have minimal or no pathogenic significance. *H. hepaticus or H mastomyrinus* may be the most pathogenic of the genus. Helicobacters should be considered as causes of or contributors to inflammatory hepatic or enteric disease phenotypes even in immune sufficient mice. Primary diagnostic considerations for necrotizing hepatitis in mice should include MHV and *Cl. piliforme*. Diagnostic considerations for rectal prolapse also can include *Citrobacter rodentium* and pinworms. Diagnosis of Helicobacter by fecal PCR is the most common and practical test method. Helicobacters and many other bacteria stain with silver stains such as Modified Steiner's or Warthin Starry, however sensitivity and specificity of silver staining is low compared to PCR.

8. *Klebsiella* species

***Klebsiella* spp bacteria are Gram negative rods grouped in the enterobacteriaciae.** They are ubiquitous in the environment, and are considered to be opportunistic pathogens. Most of these bacteria have a mucopolysaccaride capsule that contributes to their virulence, and can be evident as a clear halo on histology.

a. ***K. oxytoca*** [96] [99] [110] can be isolated from the intestinal tracts of clinically normal mice. In immunodeficient mice, there may be morbidity, and mortality due to bacteremia with necrosis in kidneys and other tissues, with scant or suppurative inflammation, and gram negative bacteria. C3H/HeJ mice that lack Tlr4 are susceptible to K oxytoca infections and otitis.
b. ***K. pneumoniae*** [110] K pneumoniae also is an opportunist that can be isolated from the intestinal tracts of clinically normal mice. In immunodeficient mice, there may be significant morbidity, mortality, pneumonia, empyema (pus in the thoracic cavity), and abscesses in any organ.

9. *Lactobacillus* species [184] [184]

These aerotolerant short gram positive rods usually are normal and beneficial residents of the upper gastrointestinal tract (oropharynx, esophagus, stomach) of mice. *Lactobacillus* species are included in Schaedler's flora 'recipes' of used to populate the gut of gnotobiotic mice with defined flora.

10. Leptospirosis, *L. interrogans*

Leptospires are spirochaetes, transmitted in the urine of rodents primarily. Leptospirosis is not expected in laboratory mice. Wild rodents and other animals are important reservoirs of these zoonotic agents that can cause disease in humans and animals. L interrogans can infect Mus musculus. It is found in wild Mus species, and has been used to model kidney and liver disease in susceptible mice.

11. *Mycobacterium* sp [192] [193]

Mycobacteria are variably gram staining, acid fast, intracellular bacteria. Mycobacteriosis is an unlikely natural infection in contemporary colonies. Natural infections of mice with *Mycobacterium avium intracellulare*, or *M lepraemurium* have been rare. *M. lepraemurium* is the agent of rodent leprosy. Although genetically similar to *Mycobacterium avium* complex (MAC) organisms, it is not typically considered part of the MAC. Mice have been used to model tuberculosis, leprosy and other mycobacterial infections. Their responses vary with the type of mycobacteria, dose and route of infection, as well as with the strain and sex of the mice. Effective inflammatory responses that control mycobacterial growth usually are characterized by histiocytic, granulomatous, sometimes nodular

(tubercle- like), inflammatory lesions and intrahistiocytic acid fast bacteria. Failure to control mycobacterial growth usually is characterized by fulminant bacterial growth, dissemination, sometimes necrotizing lesions, and high mortality. Sclc1 (formerly Nramp1) polymorphisms are implicated in susceptibility or resistance to some mycobacterial agents, also Salmonellosis and leishmaniasis.

12. *Mycoplasma* sp [107]

Mycoplasmas are the smallest and simplest bacteria. They lack a rigid cell wall, so are pleomorphic. They are gram negative, but stain poorly. M pulmonis, the agent of murine respiratory mycoplasmosis, has been one of the most important pathogens of rats and mice, but is largely eliminated from contemporary research colonies. Some serology tests for M pulmonis may cross react with some non M pulmonis agents. Natural infections by *M arthritidis, M collis, M neurolyticum* and other *Mycoplasma* species are not expected to cause disease in mice. Inoculation of contaminated biological material, or experimental infections with some of these agent can cause disease, such as arthritis (M arthritidis), or 'rolling disease' due to neurotoxin of *M neurolyticum*. The genus *Mycoplasma* recently was expanded by the addition of a group of intraerythrocytic bacteria, now called haemotrophic mycoplasmas.

a. ***Mycoplasma coccoides (Eperythrozoon coccoides); M haemomuris (H muris)*** [107] [194] [195]
Haemotrophic mycoplasmas or haemoplasmas include the agents formerly known as Eperythrozoon coccoides and Haeomobartonella muris, now called M. coccoides and M. haemomuris. Neither of these arthropod transmitted blood parasites is expected in contemporary mouse colonies. They are obligate parasite of erythrocytes, causing erythrocyte deformity and hemolysis. P. serrata (the blood sucking 'mouse louse') was an important vector for M. coccoides, when these agents were more prevalent. Clinical signs included regenerative anemia and icterus. Typical gross findings were icterus and splenomegaly. Histopathology confirmed exuberant hematopoiesis in enlarged spleens, increased macrophages and phagocytosis of red cells and cell debris. Diagnosis can be made from examination of blood films, and identification of small (1-3u) annular organisms, red-purple with Giemsa stain, on the erythrocyte surface, in a context of reduced red cells, with relatively increased large pale immature erythrocytes, consistent with hypochromic, macrocytic, regenerative anemia. The small agents can be confused with Howell Jolly bodies or inclusions of reticulocytes and artifacts in red cells. Free (extraerythrocytic) organisms are common and can be confused platelet fragments,. M. haemomuris is primarily a parasite of rats.

b. ***M pulmonis*** [107] is primarily a pathogen of the respiratory tract, but also can cause disease in the reproductive tract (genital mycoplasmosis) and arthritis. Clinical signs in susceptible, chronically infected animals include "chattering," dyspnea, weight loss, hunched posture, and lethargy. Immunodeficient mice are particularly susceptible to pneumonia and death, and may develop severe arthritis following infection. Disseminated infections that involve the reproductive tract may reduce breeding performance. Susceptibility varies with mouse strain, with resistant strains including C57BL/6, and susceptible strains including C3H. Typical gross lesions include lung consolidation, and dilated airways (bronchiectasis), filled with thick exudate (pus). Histopathology findings can include upper respiratory infection, including suppurative rhinitis, otitis media, tracheitis, as well as pneumonia, bronchiectasis, lung abscesses, and prominent perivascular and peribronchiolar lymphoid infiltrates, attributed to lymphocyte mitogenic effect of this agent. Coinfections with CARbacillus were likely when these agents were prevalent.

13. *Pasteurella* spp.: *P. pneumotropica* [94] [196]

Gram negative small pleomorphic rods, Pasteurella species bacteria can be commensal agents or pathogens in diverse host species. *P. pneumotropica* is a common bacterial isolate from mice in contemporary colonies. The Jawetz and Heyl biotypes may represent several species of *P. pneumotropica. P. pneumotropica* can be isolated from the oropharynx, intestinal tract, and reproductive tract of clinically normal mice. It has been implicated in various clinical syndromes, including conjunctivitis, infections of the respiratory and reproductive tract, otitis, and subcutaneous abscesses, especially in immunodeficient mice. Clinical findings may include subfertility (associated with reproductive tract infections), periocular swelling (from keratoconjunctivitis), inguinal swelling (involvement of preputial or clitoral glands), possibly dyspnea (from bronchopneumonia). Eye lesions and vaginal swabs may be especially high yield sites for detection. Histopathology findings can include intense inflammation +/- necrosis, without obvious bacteria, even when a high yield or only *P. pneumotropica* is isolated. *S aureus* is a primary differential for inflammatory swellings or abscesses, but usually that agent is cultivated easily, and colonies are seen easily with H&E or gram stain. Other *Pasteurella* species, including *P multocida*, which is a significant pathogen in laboratory rabbits, seem to be uncommon pathogens in laboratory mice.

14. *Proteus mirabilis* [110]

A gram negative rod grouped in the enterobacteriaciae, *P mirabilis* is a common resident of the intestinal tract of healthy mice, grows rapidly in aerobic cultures, and can easily overgrow more fastidious agents. Usually in immunodeficient mice, P mirabilis has been associated with bacteremia, septicemia or peritonitis.

15. P*seudomonas aeruginosa* [110]

A gram negative rod grouped in the enterobacteriaciae, *P. aeruginosa* is common in the environment and is a common resident of the nasal cavity, throat, and lower digestive tract of healthy mice, rats, humans, and other vertebrates. Immunodeficient animals can harbor *P aeruginosa* subclinically, until stressed or made neutropenic, e.g. by irradiation. 'Outbreaks' in immunosuppressed animals manifested as high mortality. Septicemia can be confirmed by culture of the organism from blood. Otitis and abscesses sometimes with green pus from the pigment pyoverdin, also are possible. Pseudomonas and Aeromonas species are common in tap water. Acidification, hyperchlorination, or other treatments are applied to animal facility water systems to largely to eliminate these agents.

16. Segmented filamentous bacteria of the distal small intestine of mammals and birds (SFB) [184] [197] [198] [199]

Gram positive spore forming filamentous bacteria, SFB are not pathogenic, and are important in development of mucosal immunity and Th17 responses. SFB cannot be cultured in vitro, and do not yet have a traditional (binomial) taxonomic name, but are currently grouped in the Clostridiales. They are found in the distal small intestine, often near mucosal lymphoid tissue (Peyer's patches). They attach or anchor to villus enterocytes' apical surface by a hold fast structure. They can be conspicuous in young or immunodeficient animals, and should not be confused with pathogens. Variation in Th17 and intestinal immune responses among mice from different source has been attributed to the presence of SFB (e.g. C57BL/6 mice from Taconic and Charles River) or absence of SFB (e.g. C57BL/6 mice from Jackson).

*17. Salmonella enteritidis (***serotype *typhimurium)*** [110]

Gram negative rod grouped in the enterobacteriaciae, *S. enteritidis* includes approximately 1500 serotypes, of which *typhimurium* is the most common in laboratory rodents. *S typhimurium* is potentially zoonotic. Natural infections in contemporary mouse colonies are unlikely, but this agent has been implicated in important epizootics. Infections can be subclinical, or non specific with or without high mortality. There may be no gross lesions, or in chronic disease, there can be splenomegaly and lymphadenomegaly, and pale foci of necrosis or granulomas in the liver. Histopathology findings can include necrosis and pyogranulomatous inflammation in mesenteric lymph nodes, spleen, liver, and ileum and cecum. C57BL/6 and other strains that carry a susceptibility mutation (s) in Sclc1 (formerly Nramp1) are more susceptible to significant disease from this agent.

18. Staphylococcus species (S aureus; S hominins, S xylosus etc.) [93] [200]

Gram positive plump cocci, Staphylococci are commonly isolated from healthy animals, but also are capable of causing disease, especially via contaminated wounds or in compromised individuals. S aureus is one of only a few coagulase positive species of this genus. Coagulase negative species are generally far less pathogenic, and more commonly isolated from healthy mice (and humans). *S xylosus* and *S sciurei* may be especially common on skin of healthy mice. These and other species can be isolated from skin wounds or abscesses, especially in immunodeficient mice. Staphylococcal toxins or virulence factors vary with the bacterial species and strain or isolate, and include coagulase, hemolysins, dermatonecrotoxin, leukotoxins, gelatinase, hyaluronidase.

***S. aureus* is a fairly common resident of the skin of many animals,** including mice. Disease may be precipitated by stress or immunosuppression. Entry of the organism into the body is via breaks in normal barriers (e.g. wounds), or ulcerative dermatitis. Botryomycosis refers to nodular pyogranulomatous lesions, in which histology reveals grapelike colonies of bacteria (*S. aureus* and other species), surrounded by eosinophilic protein material, within abscesses or granulomas. Furunculosis refers to abscesses or granulomas originating from hair follicles. Mice with abnormal hair growth and follicles, such as nude or hairless mice, may be especially susceptible. It often occurs on the muzzle, and *S. aureus* is a common isolate. Clinical signs of *S. aureus* in mice include soft tissue swellings due to furunculosis or facial abscesses, or preputial and clitoral gland abscesses, or sepsis and death in susceptible mice. Pus in the abscesses is usually white or creamy. Several genes are implicated in strain related susceptibility to disease. Characteristic plump gram positive cocci usually are evident in histopathology. In chronic MUD lesions *Staphylococcus* spp as well as other organisms may be isolated and evident on histopathology.

19. Streptobacillus moniliformis [110] [201] [202]

A gram negative pleomorphic rod shaped bacterium with filamentous or beaded morphology, *S. moniliformis* is the (in)famous cause of rat bite fever (also called Haverhill fever) in humans. The disease in humans is usually transmitted via rat bites and is characterized by fever, myalgia, vomiting, headache and rash. *S moniliformis* is unlikely in contemporary mouse colonies. Infections in laboratory mice have been associated with exposure to wild rats, which can carry it in their upper respiratory tract. Historical epizootics in mice featured high mortality due to septicemia, and polyarthritis in survivors. Gross lesions can include serosal hemorrhages and necrosis in spleen, liver, and other tissues, splenomegaly and lymphadenomegaly, dermatitis, and swollen joints due to arthritis. Histopathology findings can include gram negative bacterial emboli, necrosis or abscesses in liver, spleen, kidneys, and lymph nodes, and reactive lymphadenomegaly. C57BL/6 mice have been highly susceptible to disease and death.

20. Streptococcus (and Enterococcus) species [93] [203]

Gram positive aerobic cocci frequently in pairs (diplo-) or chains (strepto-), streptococci have been grouped by their characteristic hemolytic properties, then further sub grouped by other properties or serotypes. Beta hemolytic Group A streptococci (GAS) are pathogenic in many species, but many streptococci are capable opportunists, and cause significant morbidity and mortality in susceptible or compromised animals. Streptococci can be isolated from the oral cavity or pharynx of healthy mice. Characteristic colonies of gram positive cocci, frequently in pairs or chains, are likely to be found in histopathology of relevant lesions.

Alpha hemolytic streptococci include *S pneumoniae* (also known as *Diplococcus*) and streptococci of the *viridians* group. *S pneumoniae* is an important cause of human bacterial pneumonia, otitis media, sinusitis, and meningitis. Natural infections in mice usually seem to be inapparent. Experimental infections in susceptible strains or GEM are used to model human disease. [204] [205]

Beta hemolytic streptococci, most of these are subclassified into 5 Lancefield groups (A, B, C, D, E). Many species are not usually pathogenic. Groups A, B and C are most well known and include some of the most pathogenic species, although reports of natural disease in mice are limited.

Group A streptococci (GAS) *S. pyogenes* is the primary agent in human GAS infections, including "strep throat", acute rheumatic fever, scarlet fever, acute glomerulonephritis and necrotizing fasciitis. GAS infections in laboratory mice are unusual but have been reported to cause abscess in lymph nodes and other tissues.

Group B (GBS) [203] GBS such as *S. agalactiae*, can cause human pneumonia and meningitis usually in neonates and the elderly. GBS in immune deficient mice has been reported to cause pyelonephritis and bacteremia in DBA mice, or meningoencephalitis and ventriculitis in immune deficient mice

Group C streptococci include *S. equi*, which causes strangles in horses, and *S. zooepidemicus* which causes 'lumps' in Guinea pigs. Group C streptococci have caused abscesses in mice

Non hemolytic (or gamma hemolytic) streptococci include a number of former *Streptococcus* species that have been reclassified as *Enterococcus* species. *Enterococcus* sp. can be isolated from the intestinal tract of healthy mice. Species such as *E faecalis* and *E durans* been identified as opportunistic pathogens in immunodeficient mice, sometimes causing bacteremia with bacterial emboli, abscesses, necrotizing lesions, or otitis with gram positive bacterial colonies. [105] [108] [206]

VI. Eukaryotes: Fungi, Protozoa, Metazoa.

Table VI summarizes eukaryotes, detection methods and results (expressed as % positive results) from Pritchett-Corning, Cosentino, Clifford (2009).[80] Also included are the approximate percent of positive institutions (%Pos institutions) as determined by a 2006 survey of large NIH funded institutions in the US, [82] and recommended specimens for commercial PCR testing. The agents listed represent eukaryotes commonly tested in surveillance or quarantine programs, and agents included in the 2002 FELASA recommendations for the health monitoring of rodent colonies in breeding and experimental units.[136] A few additional agents are included in the discussion below.

VI. Eukaryotes:

1. Fungi [103]

Other than *Pneumocystis murina* in immunodeficient mice, significant fungal disease is not expected in contemporary mouse colonies. Microsporidia (including *E cuniculi)* are currently included in the kingdom Fungi, but are not likely causes of natural disease in mice. Dermatophytes are not common in mice any more. Non pathogenic gastric yeasts are occasionally identified in rodents and other species. Opportunistic fungi can cause disease in compromised or immunodeficient mice.

a. **Dermatophytes (Ringworm)** ***Trichophyton mentagrophytes (T quinckeanum)*** [103] [207] [208]

Dermatophytosis or dermatomycosis ("ringworm") is unlikely in contemporary mouse colonies. Trichophyton mentagrophytes (formerly *T quinckeanum)* was the most common agent reported in subclinical and overt ringworm in mice, and caused the disease '**Favus'** in mice, with BALB/c mice being especially susceptible. Hamsters, Guinea pigs, humans and other species are susceptible to ringworm caused by this agent. Other *Trichophyton* spp. and *Microsporum* spp. are possible isolates from mouse ringworm. Clinical signs of favus are alopecia and yellow crusts on the skin of the head and body. Histopathology reveals a mat of fungal elements (mycelium) comprising the crust (called a scutulum in this disease), a zone of neutrophil infiltration, and underlying epidermal hyperplasia, with mononuclear inflammation, with hairs in follicles surrounded, but not invaded by fungal elements. Microscopic but conspicuous fungal elements in skin crusts in this condition are easily identified and distinguished from scurfy hyperkeratotic lesions of C. bovis. Dermatophytes are cultivated readily on dermatophyte test media (DTM). Treatment of mice has not been described recently. Especially in immunodeficient mice, rederivation into cleaner barrier conditions may be necessary.

b. ***Encephalitozoon cuniculi*** [209]

E cuniculi is a microsporidian parasite (now classified as a fungus) that can infect a wide range of hosts, including mice and rats. It is still quite common in pet rabbits, but is unexpected in contemporary laboratory mouse colonies. Infection is usually asymptomatic in immunocompetent rodents. Immunodeficient mice can experience high mortality. *E cuniculi* infects and elicits granulomas in kidneys and brain, and is shed in the urine. Gross findings are inconspicuous, although severely affected kidneys may be pitted. Histopathology findings of granulomas in kidney or brain, with approximately 4u diameter, gram positive, slightly birefringent spores are characteristic. The spores also should stain well with Gram or Giemsa stains. Serology (ELISA) is used primarily in surveillance for this agent.

c. Gastric yeasts; Kazachstania (Candida spp, Torulopsis spp) [210] [211]

Kazachstania (formerly *Torulopsis*) species yeast forms can be found in the stomach of rodents, cattle and other species. Taxonomically related and morphologically similar to *Candida* species, the yeast forms can be found on the mucosal surface of the glandular stomach. They may colonize other sites after treatment with antimicrobials. They are considered to be commensal, and should not be confused with the protozoan *Cryptosporidium muris*, which are a similar size, but usually located in gastric glands in/under the cell membrane. The yeasts are 6-8u diam oval or egg shaped, and stain well with PAS or GMS.

d. Opportunistic fungi: *Aspergillus sp. Candida spp., Cryptococcus spp, Paecilomyces, Rhizopus*, etc. [103] [105]

Spontaneous disease due to opportunistic fungi is unlikely in competent mice. Classically immunodeficient mice (nude, scid etc), and genetically engineered immunodeficient mice can develop significant and devastating disease from these fungi, and from other agents in the environment. Competent mice treated with various combinations of antibiotics, corticosteroids, chemotherapeutic agents, or irradiation, can be made susceptible to fungal opportunists. Tissues affected are likely to depend largely on the route of infection, e.g. respiratory disease from inhalation; gastrointestinal disease from ingestion; urogenital infection ascending from traumatized genitalia. Angiocentric fungal lesions (fungal elements and inflammation in and around blood vessels) in multiple tissues are consistent with vascular dissemination.

e. Pneumocystis murina [212]

P murina is now classified as a fungus, although it has many protozoan characteristics. Several species of Pneumocystis with different host specificities have been identified. Several Pneumocystis species inhabit the respiratory tracts of many species, including laboratory mice and rats. It is pathogenic only under conditions of induced or inherent immunodeficiency. P murina is the species that infects mice. In immunosuppressed or immunodeficient mice, clinical signs of pneumonia can include wasting, rough hair coat, dyspnea, cyanosis, and death. Gross findings of usually pale lung consolidation in immunodeficient mice are highly suggestive. Direct smears stained with Gomori's Methenamine Silver (GMS) or Periodic Acid Schiff (PAS) stain may reveal cysts or organisms. Histopathology findings of airways filled by foamy eosinophilic extracellular material (trophozoites and cysts) in airways, are characteristic, although cysts are sparse in some infections or stages of disease. Inflammation may not be conspicuous in immunodeficient hosts. Pneumocystis pneumonia may be concurrent with bronchopneumonia related to other agents, or concurrent with acidophilic macrophage pneumonia in susceptible mice. PCR of lung (dead mice), or of oropharyngeal swabs (live mice), is a practical diagnostic test. Several antibiotics have been used to control infection in immunodeficient mice, but do not eliminate the agent, and disease can be expected to recur after treatment is withdrawn.

VI. Eukaryotes

2. Agents Protozoal

Protozoa other than flagellates or entamoebae in the large intestine are uncommon in contemporary colonies, but may be fairly common in wild mice or pet store mice. Enteric protozoa usually are identified by direct examination of contents of the gut region where they reside. Protozoal cyst forms or oocysts can be identified by direct examination of fecal contents in heavy infections, or by the fecal flotation method that floats and concentrates helminth eggs, and much smaller protozoal cysts. Histopathology of relevant tissues is diagnostic, although agents such as enteric flagellates are not reliably speciated by histology alone. PCR of feces is becoming more widely used for diagnosis of these agents. Natural infections in competent mice are usually subclinical. Antiprotozoal treatments such Metronidazole or Fenbendazole are not effective for some of these agents, so Cesarean rederivation may be the most effective strategy to eliminate them.

Table VIa summarizes some of the protozoal agents in mice, and the anatomic sites where they are usually found.

a. ***Chilomastix* sp. - see Enteric flagellate protozoa in large intestine**

b. ***Cryptosporidium* species; *C. muris* and *C. parvum* [213]** [214] [215] [216] [217] [218]

Cryptosporidia are coccidian parasites, not expected in contemporary laboratory mouse colonies, but found in wild mice. Most stages of their life cycles are intracellular but extracytoplasmic, just under the apical cell membranes of affected mucosa, such that they are evident on histology as small nodular structures, 4-8u diameter, in mucosal surfaces. They may elicit proliferative and inflammatory responses in infected regions. Acid fast staining combined with fluorescent microscopy can improve sensitivity of fecal evaluations. PCR methods are highly sensitive and commercially available.

C muris infects the mouse glandular stomach. Resistance to infection normally develops shortly after weaning in competent mice. Histology findings of dilated gastric glands with small, spherical to ovoid, basophilic endogenous stages in the microvilli of/in the luminal surface of gastric gland epithelium are characteristic. Glands can be prominently distended by free and embedded parasites and degenerate epithelial cells. Especially in immunodeficient mice the parasite load can be impressive, in the absence of clinical signs, and inflammation is usually absent or mild. Gastric yeasts are about the same size but normally lie on the mucosal surface or in the lumen, not in glands. Oocysts in feces are 5-8 u diameter, slightly larger than *C parvum*

C. parvum is slightly smaller than *C. muris* and normally inhabits the ileum. It is an important cause of diarrhea in young livestock, and humans, especially veterinary students. Competent mice should clear the infection with no clinical signs. Immunodeficient mice may develop persistent infections with wasting, icterus, and death, with histology findings of cholangitis, periportal hepatitis, and cholecystitis. Oocysts are 3-6u diameter, significantly smaller than most other protozoal pathogens.

c. ***Eimeria* species** [219] [220]

Eimeriae are enteric coccidia. Multiple *Eimeria* species infect mice. Only a few are pathogenic, associated with typhlocolitis and runting in young mice. Infections are rare in laboratory mice and mostly associated with wild or pet mice. Histology findings of different developmental stages in mucosal epithelial cytoplasm are diagnostic. Schizonts, gamonts and gametocytes are the larger forms that are more conspicuous in enterocytes. Typical *Eimeria* oocysts in feces have 4 sporocysts, each containing 2 sporozoites. Coccidian oocysts can be identified by direct examination of fecal contents in heavy infections, or by the fecal flotation method that floats and concentrates helminth eggs, and much smaller coccidian oocysts. They may exhibit autofluorescence when examined under UV light (i.e. with fluorescent microscope).

d. Entamoeba muris

Entamoebae are classified in the amoebozoa, amoeboid protozoa. *E muris* is common in laboratory mice. It is considered to a commensal resident of the mouse large intestine, not associated with disease. Like commensal flagellates in the large intestine, their primary significance may be as an indicator of less stringent or exclusionary barrier conditions. The amoeboid trophozoite and spherical cyst forms are 8-30u diameter. They can be identified in histology specimens, or by microscopic examination of wet mounts or smears of cecum or colon contents, or feces. Mature spherical cysts have 8 nuclei.

e. **Enteric flagellate protozoa in large intestine** oxymonads (e.g. *Monocercomonoides* sp); retortomonads (e.g. *Chilomastix* sp., *Retortomonas* sp); Trichomonads (e.g. *Hexamastix* sp., *Trichomitus* sp., *Trichomonas* sp., *Tritrichomonas* sp.); *Octomitus* sp

Flagellate protozoa in the lumen of the mouse large intestine are considered to be commensal, not associated with disease. Trichomonads and Chilomastix sp probably are the most common in laboratory mice. Their primary significance probably is as an indicator of less stringent or exclusionary barrier conditions. Most are pyriform, slender or plump, 3-8u diameter, up to 20u long including their flagella, which may not be obvious on histology. Flagellates can be impressively abundant, apparently filling the large intestine lumen. They are readily identified as flagellates but not so easily speciated by histology alone. Variable protozoal morphology in a specimen may indicate infection by multiple species or genera. *Octomitus* is a diplomonad, related to *Giardia* and *Spironucleus*.[221] Coinfections of multiple flagellate species, or of flagellates with *Entamoeba muris* are not uncommon. Characteristic motility in direct smears or wet mounts may aid in identification of genera. http://dora.missouri.edu/mouse/

f. Chilomastix bettencorti common, rounded uninucleate 10-15u, 6-9u cyst, see Enteric flagellate protozoa in large intestine

g. Giardia muris

Giardia sp. are flagellate protozoa in the duodenum of various animal hosts. *G. muris* infects mice, hamsters and rats, and wild rodents. Giardiasis is not expected in contemporary mouse colonies, but may be common in wild mouse species, e.g. *Peromyscus* sp, and in pet and laboratory hamsters. Competent mice clear infection, and may develop mild inflammation. Immunodeficient mice can develop persistent infection. Clinical signs or inflammatory changes usually are not obvious. Histopathology findings of 4-8u diameter 'flying saucer'-shaped binucleate flagellate, on or near villi in the duodenum, are characteristic. Histology, scrapings or direct smears of pylorus and duodenum, are useful diagnostic specimens.

h. *Hexamastix* sp , see Enteric flagellate protozoa in large intestine

i. Klossiella muris

K. muris is a coccidian parasite of the mouse kidney. Once common in laboratory mice, it can be found in wild *Mus musculus* but is unlikely in contemporary laboratory mouse colonies. All developmental stages of *K. muris* in the kidney, in glomeruli and renal tubules, and oocysts are shed in the urine.

j. ***Monocercomonoides* sp**, see Enteric flagellate protozoa in large intestine

k. ***Octomitus spp (O intestinalis)*** – binucleate diplomonad, plump 10-15udiam**,** see Enteric flagellate protozoa in large intestine

l. ***Retortomonas* sp,** see Enteric flagellate protozoa in large intestine

m. Sarcocystis muris

Sarcocysts may be found in histology of muscle of wild mice. Cats are the definitive host of S muris. Mice are intermediate hosts. Mouse infection requires ingestion of oocysts in cat feces, so is unlikely in contemporary mouse colonies.

n. Toxoplasma gondii

Cats are the definitive hosts of *T. gondii.* Mice are intermediate hosts. Histology findings of tissue cysts, sometimes associated with granulomatous inflammation, can occur in almost any tissue, especially brain, lung, muscle, kidney. Mouse infection usually requires ingestion of oocysts in cat feces, so natural infection is unlikely in contemporary mouse colonies. Transplacental transmission from infected dam to offspring can occur. Mice are used to study toxoplasmosis, and to propagate *T gondii* for research purposes.

o. *Spironucleus muris* (formerly *Hexamita muris*)

S. *muris* are flagellate protozoa in the duodenum of mice, hamsters, rats and some wild rodents. *S. muris* infection is not expected in contemporary mouse colonies, but may be common in wild rodent species, e.g. *Peromyscus* sp, and in pet and laboratory hamsters. Competent mice clear infection, and may develop mild inflammation. Immunodeficient mice can develop persistent infection. Clinical signs or inflammatory changes usually are not obvious. Histopathology findings of slender, torpedo shaped, flagellate approximately 12 u long, < 4 u diameter, in crypts of the duodenum, are charactreristic. Egg-shaped cysts 4–7 u diam can be found in the large intestine and feces.

p. ***Trichomonas* sp, *Tritrichomonas* sp (**e.g. *Tritrichomonas muris, T diminuta, T wenyoni*) trichmonad morphology, ~3-25u depending on species, pyriform-rounded, 1 anterior nucleus, 3-4 anterior flagella, undulating membrane see Enteric flagellate protozoa in large intestine

VI. Eukaryotes

3. Metazoa: Arthropods and Helminths

A. Arthropods
   1. Lice
   2. Mites
      - Follicle mites
      - Fur mites
      - Mesostigmatid mites

B. Helminths
   a. Nematodes
      i. Pinworms
   b. Cestodes
      i. Cysticercus fasciolaris
      ii. Hymenolepis diminuta
      iii. Rodentolepis microstoma
      iv. Rodentolepis nana

A. Arthropods [124] [125] [127] [128] [130]

Fur mites and mesostigmatid mites are less prevalent than in recent decades but continue to be annoying and expensive problems in contemporary mouse colonies. Follicle dwelling mites and lice are not expected in contemporary mouse colonies and may indicate exposure to wild rodents or to pet store rodents. Non parasitic arthropods in the mouse environment, such as Psocoptera, are pests that should be distinguished from parasites.

1. Lice *Polyplax serrata*

P serrata is the mouse louse, a blood sucking louse that can be found in wild mice but is unlikely in contemporary laboratory mouse colonies. P. serrata is the primary vector of the haemotrophic mycoplasma, M coccoides. Infestation with lice is referred to as pediculosis. Bites can be pruritic, resulting in scratching and dermatitis, similar to mite infestations. Severe infestations or infections by P serrata can cause anemia and debilitation. Moving white adults (1-1.5mm), and their eggs ("nits") attached to the bases of hair shafts may be seen without magnification in heavy infestations. Direct examination of the skin and pelage at low magnification (10x) with a dissecting microscope is recommended for diagnosis. Alternatively, allowing a fresh cadaver to cool on a dark background, the motile white lice can be lifted off with cellophane tape for identification under a dissecting microscope. Adult lice with 6 legs attached to thoracic segment should be easily distinguished from smaller adult mites with 8 legs. Evaluation of skin scrapings is not recommended for diagnosis of pediculosis. Pyrethroids or ivermectin may be effective in eradication of lice, but may have toxic effects in some mice, or may affect some experimental results.

2. Lice *Psocoptera, Psocid lice –* non parasitic lice in the environment

Psocid lice are not parasites but are fairly common in the environment. They feed on cellulose, such as bedding and paper products in the laboratory mouse environment. When humidity rises, populations can expand dramatically, and the lice attract the attention of care takers, scientists, visitors, and inspectors. Like other non parasitic arthropods, they can be allergenic, but are primarily pests, without reported effects on laboratory mice.

3. Mites - Follicle mites *Demodex musculi* [222]

Demodex mites in mice have not been reported recently in laboratory mice, but these arthropods can be found in follicles in wild mice, and have been found in immunodeficient genetically engineered mice. Demodex mites can be diagnosed by histopathology, by microscopic examination of plucked hairs or deep skin scrapes, or by pelt digestion.

4. Mites - Follicle mites *Psorergates simplex*

Psorergates mites inhabit hair follicles, but seem not to have been reported in laboratory mice since the 1950's. Plump round adult mites (approximately 100u diameter) with eggs and larvae, expand follicles and elicit a granulomatous and eosinophilic inflammatory response, resulting in nodular skin lesions extending to the deep dermis. The nodules can be seen in the subcutis side of the skin when the pelt is removed from a dead mouse. Microscopic examination of nodule contents should confirm the presence of mites.

5. Mites - Fur mites (*Myobia musculi*, *Myocoptes musculinus, Radfordia affinis, Trichoecious romboutsi)* [127] [128] [223] [224]

Fur mites remain prevalent (persistent) in laboratory mouse colonies. The term acariasis refers to mite infestation in any host species. Mouse fur mites are smaller than lice, less than 500u diameter, and like other arachnids they have 8 legs. Mite eggs (200-250u) also are smaller than louse eggs. Nymphs and larval mites are smaller may have only 6 legs. Fur mites can cause overt disease (pruritus, alopecia,

dermatitis) in some strains of mice, alter immune responses, and interfere with reproduction and colony maintenance because of wounds and secondary infections, or infections(infestations may be subclinical. ***Myobia musculi*** (Figure 4.5) and ***Myocoptes musculinus*** (Figure 4.6) are the most commonly identified and studied fur mites of mice. *Radfordia affinis* (formerly *Myobia affinis*) resembles *M musculi*, and *T romboutsi* (formerly *Myocoptes romboutsi*) resembles *M musculinus*. *M. musculi* is considered to be the most irritating and pathogenic because it feeds on skin secretions and interstitial fluid (but not on blood), while M. musculinus feeds more superficially. *Radfordia affinis* seems to be less irritating or pathogenic, and reports of T romboutsi are uncommon. Mixed infestations are common. Their life cycles are direct, with all stages (egg, nymph, and adult) attached to hairs on the host. Consequently, hairless mice are not susceptible.

Clinical signs of fur mites can include pruritus, alopecia, self excoriation, possibly leading to ulcerative dermatitis. The spectrum of clinical signs and pathology varies with the mouse strain and the mite species. Secondary changes and sequela in chronic infections with ulcerative dermatitis can include leukocytosis, lymphadenomegaly, splenomegaly and systemic amyloidosis. Direct microscopic examination of skin scrapings from the dorsum and ventrum are reported to be highly sensitive detection method.[128] Histopathology can reveal arthropods or eggs often attached to hairs, but they may be sparse. PCR of pelt swabs is commercially available, and may prove to be a cost effective detection strategy especially for quarantine and 'outbreak' testing, when rapid or high volume testing is needed. Additional histopathology changes can include dermatitis (usually with eosinophils), epidermal hyperplasia and hyperkeratosis. C bovis should be considered when there is acanthosis, hyperkeratosis and intracorneal bacterial colonies. **Table VIb** summarizes some of the features of mouse fur mites. Mixed infections are common, and species identification likely will not have much impact on treatment. Avermectins, Permethrins and other agents have been used to treat fur mites, with variable long term success.

Mites – Mesostigmatid mites (*Laelaps echidnina, Ornithonyssus bacoti*) [225]

Mesostigmatid mites feed on blood. In the absence of preferred hosts, they will feed from less preferred hosts, including humans, especially in environments where their preferred hosts have been eradicated, e.g. after successful extermination of rodents from a laboratory, dormitory or other premises. Itching and rash on wrists or belt areas of personnel is a suggestive history. These mites feed and leave, so detection on their victims is challenging. Engorged mites are about 1mm diam, larger and darker than unengorged (hungry) mites. They may be detected as moving dark spots on filter tops, and leave a blood spot when squished. Blood sucking parasites pose a risk for transmission of blood borne diseases, and should be eradicated. Eradication requires elimination of the mites as well as of feral hosts that harbor them in the environment. Treatment with pyrethrins has been successful. Non insecticidal preventive methods, such as environmental application of insect growth regulators or silica-based sprays, may be useful in some situations.

Wild rodents can host several species of Laelaps, *Liponyssoides*, or *Ornithonyssus*. *Ornithonyssus bacoti* (tropical rat mite), has the widest host range , including mammals and birds. It is also the most commonly reported mesostigmatid mite in laboratory rodent colonies, and in cases of human parasitism by rat mites. *Laelaps echidnina* (spiny rat mite) also is reported in mouse colonies. Mesostigmatid mites are dorsoventrally flattened with all four pairs of jointed legs attached to the anterior half of the body. *Laelaps*, *Liponyssoides*, or *Ornithonyssus* are about 1mm diam when engorged. Compared to *O. bacoti*, *L echidnina* is slightly rounder, with more prominent setae (spiney hairs). Other species also are possible mesostigmatid intruders in rodent facilities.

B. Helminths[124] [126] [129]

Helminth parasites in mice include cestodes and nematodes. Of these only pinworms remain common in contemporary mouse colonies.

1. Cestodes – tapeworms *Hymenolepis diminuta, Rodentolepis nana, Cysticercus fasciolaris* (*Strobilocercus fasciolaris, Taenia taeniaeformis*) [226] [227]

Most cestodes require multiple hosts to complete their life cycles, so tapeworms are not expected in contemporary mouse colonies, but can be found in wild mice with access to necessary primary or intermediate hosts. *Cysticercus (Strobilocercus) fasciolaris* are larval tapeworms, for which mice are only intermediate hosts. Treatment of affected colonies is futile unless the source of fecal contamination by the primary hosts is eliminated. Rodents are important primary hosts for *Hymenolepis diminuta, Rodentolepis microstosma*, and *R. nana*, which also can infect primates, including humans. These tapeworms normally require arthropod intermediate hosts, such as beetles or cockroaches. Primary hosts (rodent or primate) must ingest larvae (cysticercoids) usually within intermediate hosts, in order to develop productive infection and complete the life cycle. Control of wild mice reservoirs and arthropod intermediate hosts is essential to control these cestodes. Natural infections in rodents are usually subclinical.

a) Cysticercus fasciolaris (Strobilocercus fasciolaris, Taenia taeniaeformis)

C. fasciolaris is the larval form of *T. taeniaeformis.* A carnivore, often a cat, is the definitive host of the adult form (*Taenia taeniaeformis*). Eggs shed in feces (often in stored bedding or feed) are ingested by rodents. Larvae migrate to the liver and form cysts. Gross findings of larval cysts usually in the liver, white, about 5mm diameter, are characteristic. The encysted larval form found in rodents is called a strobilocercus and consists of scolex, neck and segmented strobila, (body) and bladder. Larval forms do not shed segments or eggs into feces so diagnosis is normally by identification of cysts at necropsy.

b) ***H. diminuta*** **is called the rat tapeworm,** but it infects other rodents, and primates. It requires an arthropod intermediate host, such as a beetle. Adults 3 - 4 mm wide can be up to 60 mm long, and the scolex lacks hooks. Natural infections in wild mice usually are subclinical, diagnosed by finding adult tapeworms in the upper small intestine, although they may migrate up the pancreatic and biliary ducts in heavy infections. Gravid segments and eggs are shed in the feces. The cysticercoid larvae develop in the arthropod intermediate host and cannot develop in the definitive host.

c) ***R. microstoma*** **is the mouse bile duct tapeworm,** but it infects other rodents, and primates**.** Its life cycle normally requires a beetle intermediate host, but it can complete a direct life cycle in nude mice. Natural infections in wild mice usually are subclinical, diagnosed by finding adult tapeworms, < 2mm wide by 80-35mm long in bile ducts or nearby intestine, or by finding segments or round eggs in feces. Like R nana, the mouth parts (scolex and rostellum) are armed with a ring of hooklets (23-28) that can be identified by microscopy or histology. Although infections are usually subclinical, there is local inflammation the bile duct.

d) ***R. nana*** is the dwarf tapeworm of mice. Mice, rats, hamsters, other rodents, humans, and nonhuman primates are potential hosts. Human and rodent infections are common in some parts of the world. *R nana* has a direct life cycle, requiring no intermediate host, although it can use an arthropod intermediate host (flea or beetle). Heavy infections with *R. nana* can cause weight loss and growth retardation, catarrhal enteritis, and granulomatous inflammation associated with attached adults, or with larvae in tissues. Diagnosis is by detection of eggs through fecal flotation, by direct exam of the small intestine, or by histopathology. In feces, embryonated eggs are oval, 30 to 60 u diameter, and have three distinctive hooks. In the small intestine, threadlike adult tapeworms are less than 1 mm in diameter and up to 40 mm long. Its mouth parts (scolex and rostellum) have 4 suckers and a ring of 20-27 hooklets. Histopathology findings can include adult tapeworms in intestine lumen, or because *R nana* does not require an intermediate host, cysticercoid larvae in the lamina propria of intestinal villi, occasionally in lymph nodes or liver, with associated granulomatous inflammation. Adult and larval forms have armed mouthparts, with microscopic hooklets.

2. **Nematodes, pinworms**[89] [90] [126] [228] [229]

Helminths other than pinworms in mice likely indicate exposure to wild animals, or pet animals, or experimental infection. *Calodium hepaticus, Gongylonema species, Nippostrongylus brasiliensis* and *Trichuris muris* are examples of nematodes that are encountered in wild rodents, and may be studied in experimental infections.

- *Calodium hepaticus* (formerly *Capillaria hepaticus*) causes hepatic capillariasis especially in (wild/feral) rats, but can infect mice. Adults, and eggs with characteristic bipolar plugs, are found in the liver, usually in biliary tree, with associated granulomatous and esosinophilic inflammation. The life cycle in rodents is completed by ingestion of eggs in (other rodents') liver.
- *Gongylonema* species nematodes can be found in the squamous mucosa of the forestomach.
- *Nippostrongylus brasiliensis* are hookworms found primarily in (wild/feral) rats, and used experimentally in mice. Larvae migrate through the lung and can cause inflammation, adults are found in the small intestine.
- *Trichuris muris* are whipworms found in the cecum and colon in wild rodents, and used in mice to model human Trichuris infections. Like other whipworms, their anterior end burrows into the mucosa, and the posterior end remains free in the lumen. Eggs with bipolar plugs are shed into feces.

a. Pinworms, Oxyuriasis: *Aspiculuris tetraptera, Syphacia muris, S obvelata* [126] [228] [229]

Oxyuriasis refers to infections by oxyurid nematodes (pinworms). Ingestion of infectious embryonated eggs in the environment is the primary route of infection. Aspiculuris tetraptera, Syphacia muris, S obvelata have direct life cycles, so do not require other host species. Oxyuriasis is frequently subclinical, although heavy infestations can contribute to poor condition, rough hair coat, runting, and rectal prolapse. The prevalence of pinworms in an infested colony depends on host age, sex, and immune status. In enzootically infected colonies, young weanlings have the greatest parasite loads. Syphacia numbers tend to diminish with increasing age of the host, and males may be more heavily parasitized than females. Young or immunodeficient mice can develop impressive parasite burdens, sometimes associated with rectal prolapse and failure to thrive. In the absence of helicobacters or other intestinal infections, histologic changes are usually mild, characterized by infiltrates of eosinophils, mast cells, and mononuclear inflammatory cells in the lamina propria of the large intestine. Direct microscopic examination of cecum and colon for adults is the most sensitive diagnostic test for

pinworms. PCR of feces is now commercially available, also very sensitive, and does not kill the mouse. Perineal tape test is effective for diagnosing Syphacia sp., which shed more eggs in a single accessible site than do Aspiculuris species. Fecal flotation is used to detect Aspiculuris eggs in feces. Difficulty in infecting immune competent adult mice contributes to the difficulty in detecting pinworms using dirty bedding sentinels. Pinworm eggs are very light and can aerosolize, resulting in widespread environmental contamination. The eggs survive for variable periods in the environment, resist dessication, and common disinfectants, but are susceptible to high temperatures. Various treatment regimens involving Ivermectin (and other avermectins) or fenbendazole been used with variable long term success. Ivermectin can be delivered in the drinking water, via gavage, formulated in feed, or it can be administered topically. Fenbendazole diets are commercially available. Consideration should be given to possible effects of anthelmintics on experimental parameters.[230] [231]

Syphacia muris is a parasite primarily of rats, but can also infest mice, hamsters, gerbils, and wild rodents**.** ***Syphacia obvelata*** is a parasite of mice, and is more common than *S muris* in mice (*S muris* is more commmon in rats). *S. obvelata* also can infest rats, hamsters, gerbils, and wild rodents. S obvelata eggs are larger (~ 120-150 x 30-50µm) more asymmetric and curved, and more fragile than *S muris* eggs (~90 x 40 µm). For practical purposes of detection and elimination, these agents are very similar. They have similar life cycles and both deposit large numbers ofasymmetric eggs around the anus of the host mouse. *Syphacia* spp. eggs may embryonate (develop into embryos or larvae) on the host and retroinfect the animal by migrating back into the colon.

Aspiculuris tetraptera is a parasite primarily of mice, but it can also infect wild rodents and rarely rats. Adults are found primarily in the colon where females lay eggs. Unembryonated eggs leave the host on fecal pellets. The eggs become infectious after 6 to 7 days at room temperature. *A. tetraptera* eggs are ellipsoid and symmetrical, more symmetric and plumper than *Syphacia* eggs. Longer prepatent period (time from ingestion of infectious eggs, to production of eggs by adult), less frequent shedding of fewer eggs, compared to *Syphacia* spp, contribute to the 'sneakiness' and difficulty in detecting the agent, especially with low levels of infection.

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