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Natural Pathogens of Laboratory Mice, Rats, and Rabbits and Their Effects on Research

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INTRODUCTION

Historical Perspective

Weisbroth (714), in an excellent review of the historical struggle against pathogens of laboratory rodents, divides the last 100 years of research involving laboratory animals roughly into three periods. The first, from 1880 to 1950, was the period of domestication, during which many rodent species became much-used research subjects. Many of these original stocks harbored a variety of natural, or indigenous, pathogens. However, during this period, many improvements were made in sanitation, nutrition, environmental control, and other aspects of animal husbandry. The result was a great reduction in the range and prevalence of pathogens found in laboratory animals. The second period, from 1960 to 1985, was the period of gnotobiotic derivation, when cesarean rederivation was exploited as a means of replacing infected stock with uninfected offspring. In this procedure, full-term fetuses are removed from an infected dam and transferred to a germ-free environment and foster care. This procedure was very successful in eliminating pathogens not transmitted in utero. Weisbroth has described the third period, from 1980 to 1996, as the period of eradication of the indigenous murine viruses. In this period, additional pathogens dropped from the scene or were found less and less often. These reductions were accomplished through serologic testing of animals for antibodies to specific pathogens and subsequent elimination or cesarean rederivation of antibody-positive colonies, in addition to continued advances in animal husbandry methods. Pathogen prevalence studies have been (475) and continue to be (234) conducted. Examination of several of these reports from past decades as well as the present one will confirm the steady decline in the range and extent of microbiological contamination in laboratory colonies.

To put things another way, someone has summarized the advances in laboratory animal disease control in the following way: At the turn of the century, an investigator might have said, "I can't do my experiment today because my rats are all dead"; at the midpoint of the current century, an investigator might have said, "I can't do my experiment today because my rats are all sick"; while today, an investigator might say, "I can't do my experiment today because my rats are antibody positive." Surely there has been a steady increase in the awareness of the varied and generally unwanted effects of natural pathogens in laboratory animals and there have been ever-greater efforts to exclude pathogens from research animals. Only when laboratory animals are free of pathogens which alter host physiology can valid experimental data be generated and interpreted.

Infection versus Disease

In interpreting the microbiologic status of laboratory animals, it must be understood that infection is not synonymous with disease (475). Infection simply indicates the presence of microbes, which may be pathogens, opportunists, or commensals, of which the last two are most numerous (475). Few agents found in laboratory animals today cause overt, clinical disease. It is hoped that investigators will appreciate that overt disease need not be present for microorganisms to affect their research. Animals that appear normal and healthy may be unsuitable as research subjects due to the unobservable but significant local or systemic effects of viruses, bacteria, and parasites with which they may be infected. Microbiology and serology reports should be interpreted with the assistance of a veterinarian trained in laboratory animal medicine. Such a professional can assist the investigator in determining the significance of organisms reported.

As accrediting and funding bodies increase their scrutiny of pathogen status and, by inference, the experimental suitability of the animals used in sponsored research, investigators will also want to work with a laboratory animal veterinarian or animal facility manager to ensure that laboratory animals are obtained from reputable, pathogen-free sources and are maintained under conditions that preclude, as much as possible, the introduction of pathogens. It is far better to prevent the introduction of pathogens than to have to account for their presence when interpreting experimental results. At this point, it is appropriate to mention another valid reason for preventing pathogen entry into an animal facility: in some cases, the drugs used to clear pathogens will themselves alter the host physiology and interfere with research. For example, parasiticides with proven immune system-modulating activity include ivermectin (53), levamisole (82), and thiabendazole (676). Additionally, chlorpyrifos, an organophosphate occasionally used to treat mite infestations, has been reported to decrease brain acetylcholinesterase activity in mice (515).

Scope of the Review

This review is intended to inform clinical and other research scientists, laboratory animal veterinarians, and students of laboratory animal medicine of the known or potential effects of natural pathogens of laboratory mice, rats, and rabbits, on host physiology and subsequently on research efforts involving those laboratory animal species. I have tried to include what I consider the most important infectious agents currently found in laboratory animals. The review is not intended to include pathogens that were historically prevalent and important but are no longer so or are only very rarely found in modern animal facilities. Additionally, efforts have been made to include as much information as possible from natural outbreaks of disease. However, a considerable amount of information has also been included from experimental infections when the conditions of infection, e.g., the route and dose, were compatible with those of natural infections. Some information from in vitro studies has been included when that information seemed relevant. Information from infections induced by abnormal routes has been, for the most part, excluded.

This review is intended to add current information to the excellent body of literature previously published by others, for example Lussier (409) and, more recently, the National Research Council (475). In this regard, special recognition is due the many authors who contributed to the latter publication; it is an outstanding reference on the subject of infectious diseases of mice and rats. I have drawn heavily from that resource and wish to acknowledge this fact. The interested reader is directed there for additional information about the history, biology, and pathophysiology of specific pathogens, as well as for specific references pertaining to the effects of pathogens on mice and rats.

The reader may notice that considerably more information is presented on the effects of natural pathogens of mice and rats than on those of rabbits. This reflects the disparity between what is known about the pathogens of these species. Mice and rats have achieved a level of use in biomedical research unparalleled by other species, including rabbits. Consequently, far greater efforts have been made to identify the effects of pathogens in mice and rats. In addition, many of these infections serve as useful models of human infections or disease mechanisms and have therefore been more extensively studied than those of rabbits.

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The review is organized first by the host species, then by the body system affected, and lastly by the pathogen. This organization of material best facilitates the finding of information concerning the pathogens that affect specific body systems, as well as information on specific pathogens.

MICE AND RATS

Respiratory System

Viruses. (i) Pneumonia virus of mice. Pneumonia virus of mice is a single-stranded RNA (ssRNA) virus of the family *Paramyxoviridae*, genus *Pneumovirus*. Transmission is via aerosol and contact exposure to the respiratory tract (450). Active infections are short-lived and generally without clinical signs in euthymic mice and rats, and there is no carrier state (61, 475). In contrast, athymic (*nu*/*nu*) mice develop chronic pneumonia and wasting and die (550). Pathologic lesions have not been reported in naturally infected mice or rats. Experimental intranasal infections of mice have resulted in mild rhinitis and interstitial pneumonia (91). The susceptibility of mice and rats may be increased by a variety of local and systemic stressors (475), and immune responsiveness is strain dependent (584). Experimentally infected athymic mice develop persistent interstitial pneumonia (92). While natural infections appear to be of little consequence in immunocompetent rodents, pneumonia virus of mice infection could alter the pulmonary architecture and interfere with immunological studies (409). Natural infection of athymic mice results in death and would therefore confound studies with such animals.

(ii) Sendai virus. Sendai virus (SV) is one of the most important pathogens of mice and rats (475). Hamsters may also be infected, although their infection is asymptomatic. SV is an ssRNA virus of the family *Paramyxoviridae*, genus *Paramyxovirus*, and species parainfluenza 1. Multiple strains have been described (565). SV is extremely contagious, and transmission is via contact and aerosol infection of the respiratory tract (302, 475). Natural infection of rats with SV is generally asymptomatic, with only minor effects on reproduction and growth of pups (415). Natural infections of mice present as enzootic or epizootic infections. Enzootic infections are those endemic to a colony, where the constant supply of susceptible animals maintains the infection. Mice are infected shortly after weaning as maternal antibody levels wane, and they show few clinical signs. Since there is no carrier state, cessation of breeding eventually results in elimination of the infection, although antibody titers remain in previously infected animals. Epizootic infections occur upon first introduction of the virus to a colony. Clinical signs may include teeth chattering, dyspnea, prolonged gestation, poor growth, and death of young mice (475). Where breeding is occurring, the enzootic pattern eventually takes over.

SV contains HN protein, with hemagglutinating and neuraminidase activities, and F glycoprotein, with cell fusion, cell entry, and hemolytic activities (475, 641). Conversion of the F glycoprotein to the active form is dependent on host proteases and is inhibited by pulmonary surfactant (643). However, there are considerable differences in susceptibility to SV among both rat and mouse strains. Among rat strains, LEW and Brown Norway (BN) rats are more susceptible than F344 rats (400, 606). Among mouse strains, 129/J and DBA strains are among the most susceptible and SJL/J and C57BL/6J are among the most resistant (322, 452, 453, 475). Because of these strain differences in susceptibility, pathologic lesions vary in severity. The hallmark of SV infection is transient hypertrophy, necrosis, and repair of airway epithelium as the virus descends the respiratory tract. Repair of airway epithelium results in epithelial hyperplasia, squamous metaplasia, and syncytial cell formation (475). Upon reaching the lungs, focal interstitial pneumonia occurs, with inflammatory and hyperplastic changes being most severe around terminal bronchioles, in contrast to infection with *Mycoplasma pulmonis*, which affects more proximal airways. The lungs appear focally reddened. Viral replication occurs in the respiratory tract for only about 1 week postinfection, so lesions resolve quickly and eventually consist only of loose peribronchiolar and perivascular lymphocyte cuffing. Lesions are more severe and varied when additional pathogens such as *M. pulmonis* are present. Aged (329) and immunodeficient mice and rats infected with SV develop a severe form of pneumonia, with delayed viral clearance (475, 516).

There is a considerable volume of literature on immune responses to SV (113, 194, 223, 238, 304–308, 310, 313, 452, 453, 492, 516, 657, 658). Immunity to SV is both cell and antibody mediated. Natural infection with SV could profoundly interfere with a wide variety of research efforts involving mice and rats, since SV has been shown to affect rodents in many ways. Reported effects include interference with early embryonic development and fetal growth (390); alterations of macrophage, natural killer (NK) cell, and T- and B-cell function (77, 108, 205, 223, 227, 332, 333, 347, 552); cytokine and chemokine production (123, 310); bronchiolar mast cell populations (606); pulmonary hypersensitivity (122, 607); isograft rejection (625); airway physiology (566, 737, 743); response to transplantable tumors (427) and lung allografts (728); neoplastic response to carcinogens (513); apoptosis rates (658); and wound healing (348). Recently, SV has been used experimentally as a gene vector (654, 741). Natural infection would, of course, interfere with such studies.

Bacteria. (i) CAR bacillus. Cilia-associated respiratory (CAR) bacillus is a relatively recently identified pathogen of wild (73) and laboratory rats and, to a lesser extent, mice and rabbits; it has been used in experimental infections of guinea pigs and hamsters (598). CAR bacillus is a gram-negative, filamentous rod of uncertain classification. Analyses of small-subunit rRNA sequences indicate that rat-origin CAR bacillus may be closely related to *Flavobacterium ferrugineum* and *Flexibacter sancti* (711). Recent studies suggest that CAR bacillus isolates of rat and rabbit origins may be distinct strains and suggest that, in mice, isolates of rat origin may be more virulent than those of rabbit origin (136). Transmission is probably via contact exposure to the respiratory system (323, 426). Current information suggests that CAR bacillus is usually a copathogen (135), most prominently of *M. pulmonis* in rats, and that it exacerbates lesions of murine respiratory mycoplasmosis (MRM) (254). However, primary infection of rats with CAR bacillus has been recently reported (439). The clinical signs following natural CAR bacillus infection that have been reported for rats are similar to those of severe murine respiratory mycoplasmosis (see the discussion of *M. pulmonis*, below) and include hunched posture, lethargy, rough coat, and periocular porphyrin staining (425, 475). Lesions of CAR bacillus infection are similar to those of MRM, and the reader is referred to that section for a full description. In addition, CAR bacillus infection produces severe bronchiolectasis, pulmonary abscesses, and atelectasis of entire lung lobes (425, 475). These lesions are due mainly to accumulation of pus in the airways. Large numbers of CAR bacilli can be observed between cilia on respiratory epithelial surfaces and cause the ciliated border to appear dense. Lesions may also be found on epithelial surfaces in nasal passages, larynx, trachea, and middle ears (475). Lesions have been observed in mice of the ICR strain

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experimentally infected with CAR bacillus (598), and lesions compatible with CAR bacillus infection have been reported in C57BL/6J-*ob*/*ob* mice, although these latter mice may have also been infected with SV and/or PVM (254). Information is lacking concerning effects of natural CAR bacillus infection on rats and mice. However, one might expect that CAR bacillus infection could contribute to the morbidity and mortality associated with MRM and could compromise studies of the respiratory system.

(ii) *Klebsiella pneumoniae.* *Klebsiella pneumoniae* is a gram-negative bacterium normally inhabiting the intestinal tract of rats, mice, and numerous other animals. Reports of clinical disease in immunocompetent rodents are rare (208, 275, 325, 579), and *K. pneumoniae* is therefore considered an opportunistic pathogen (475). The prevalence in rodent colonies is high and may increase with antibiotic treatment which eliminates other bacteria (272). Transmission is primarily fecal-oral; aerosol transmission is effective (58). Clinical signs in mice most commonly include dyspnea, sneezing, cervical lymphadenopathy, inappetance, hunched posture, and rough coat (208, 579), and those in rats include cervical and inguinal abscesses (275, 325). Following hematogenous spread, focal abscess formation can occur in any organ. In the lungs of mice, this results in granulomatous pneumonia. Clinical signs in immunocompromised rodents are generally more severe.

The majority of clinical *K. pneumoniae* isolates produce a high-molecular-weight capsular polysaccharide, which is one of the dominant virulence factors (289). Immunity is age related (708); is directed against lipopolysaccharide (LPS) and related antigens (542); involves interleukin-1 (IL-1) (693), IL-8 (692), IL-12 (250), leukotrienes (19), chemokines (613), tumor necrosis factor (TNF) (381), TNF-α-mediated mast cell chemoattraction (417) (which may be influenced by macrophage inflammatory protein type 2 [252]), neutrophil activity (315), and production of defensins (357); and may be inhibited by IL-10 (251). Rats and/or mice infected with or exposed to products from *K. pneumoniae* serve as models of pneumonia (106, 290), endotoxemia (480, 686), sepsis (163, 293), cystitis and pyelonephritis (87), antibiotic pharmacokinetics (174, 265), host resistance (418), riboflavin metabolism (72, 537), and human phacoantigenic uveitis (738). In addition, infection has been shown to lower thyroxine levels in plasma (72). Natural primary or opportunistic infection of laboratory mice and rats would interfere with such studies.

(iii) *Mycoplasma pulmonis.* *M. pulmonis* is, without question, one of the most important pathogens infecting laboratory rats and mice, and is the cause of MRM. *M. pulmonis* lacks a cell wall and has membrane-associated hemolytic activity (447). Prevalence rates can be high within animal facilities. Transmission is primarily intrauterine and by aerosol (302, 475, 618). The organism readily establishes infection by colonizing the nasopharynx and middle ears (145). Infection is usually asymptomatic, causing some researchers to consider *M. pulmonis* a commensal under ideal conditions (475). Its pathologic effects vary, depending on a variety of host, organismal, and environmental factors (314, 475, 580), including concurrent infection with copathogens (582). Levels of susceptibility differ according to host stock and strain (94, 96, 198, 380, 433). In this regard, the most resistant mouse strains include C57BR/cdJ, C57BL/6NCr, C57BL/10ScNCr, and C57BL/6J (93). Clinical signs typically follow chronic infection and include "snuffling" in rats and "chattering" in mice, dyspnea, weight loss, hunched posture, lethargy, and, in rats, periocular and perinasal porphyrin staining (475). Mice may be asymptomatic. *M. pulmonis* preferentially colonizes the luminal surfaces of respiratory epithelium lining the proximal airways. This characteristic gave rise to the earlier designation of "proximal airway disease" (475).

Grossly, the lungs appear focally consolidated and airways contain a highly viscous exudate. Microscopically, the spectrum of pathologic changes may include rhinitis, otitis media, laryngitis, tracheitis, suppurative bronchitis, bronchiectasis, pulmonary abscesses, and alveolitis (475, 517). *M. pulmonis* is a mitogen for rat lymphocytes and induces the hyperplasia of bronchus-associated lymphoid tissue (472, 473) which is a histologic hallmark of MRM in rats. The severity of airway disease may be influenced by profiles of cytokine production (199), by interactions with sensory nerve fibers (68), and by alveolar macrophage viability (147). Immunodeficient mice are equally susceptible to pneumonia and death compared to immunocompetent mice and may develop severe arthritis following infection with *M. pulmonis* (96, 192). Genital mycoplasmosis also occurs, particularly in LEW rats (85, 96). A recent study demonstrated that the time of infection plays a major role in determination of pregnancy outcome and spread of infection from the genital tract to the respiratory tract (75).

In mice, humoral responses contribute to but do not guarantee protection from systemic infection (94) while in rats, cellular immunity is more important (96). Immune system responsiveness is age related (617). *M. pulmonis* may disseminate widely throughout the host and therefore may alter the experimental results in numerous ways. The effects thus far reported include alteration of (i) pulmonary carcinogen and immune responses, ciliary function, and cell kinetics; (ii) reproductive efficiency; (iii) adjuvant- and collagen-induced arthritis; and (iv) systemic immune responses (199, 475, 557). *M. pulmonis* infection in mice is an invaluable model for the study of host defenses against respiratory mycoplasmas in vivo, including those of *M. pneumoniae*, an important worldwide cause of human death and disability (94, 146). Natural infection of laboratory rats and mice could seriously impair research efforts investigating a variety of body systems, primarily the respiratory, reproductive, and immune systems.

(iv) *Streptococcus pneumoniae.* *Streptococcus pneumoniae* is a gram-positive diplococcus commonly found in laboratory rodent colonies. More than 80 strains, grouped by capsular type, have been reported. Transmission is primarily via aerosol from infected humans. The organism is considered a commensal under most conditions, although host strain susceptibility differences have been reported (638). Typically, a carrier state is established in the nasal passages and middle ears. Clinical signs are uncommon, although natural outbreaks of disease have been reported (475). When present, clinical signs are nonspecific and may include dyspnea, weight loss, hunched posture, and snuffling (475). Virulence is related to several bacterial components, most prominently pneumolysin, a multifunctional toxin with distinct cytolytic and complement-activating activities (156, 561, 709). Infection begins in a bronchopulmonary segment and spreads centrifugally (475). The infection spreads from the lung to the pleura, pericardium, and, via septicemic spread, to the rest of the body. The affected lung is first edematous, then becomes consolidated and eventually is cleared of cellular debris (733). There may be suppurative or fibrinous lesions throughout the respiratory tract and adjacent structures. These most commonly include suppurative rhinitis and otitis media (475) but may also include similar changes in and around the deeper tissues of the respiratory tract. Septicemia may result in suppurative lesion establishment in virtually any organ, with death being a common sequela. Athymic mice are not more susceptible to disease (727). Host immunity is primarily humoral (16, 563, 677), with considerable help from the complement and mononuclear phagocytic systems (475), C-re-

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active protein (633, 634), TNF-α (637), and pulmonary surfactant (651). IL-10 production is induced following *S. pneumoniae* infection and attenuates the proinflammatory cytokine response within the lungs, hampers effective clearance of the infection, and shortens survival (678). Rats and mice experimentally infected with *S. pneumoniae* serve as models of respiratory tract infection (638), peritonitis (220), meningitis (624), otitis media (410), and the effects of exercise on the course of bacterial infections (318). Natural infections of laboratory rats and mice with *S. pneumoniae* have been shown to alter hepatic metabolism, levels of biochemicals in serum, blood pH and electrolytes, thyroid function, and respiratory parameters (475) and could be expected to interfere with a variety of studies depending on the bacterial distribution following septicemic spread. The cost of eliminating the organism from colonies must be evaluated in light of the intended use of the animals.

Fungi. (i) *Pneumocystis carinii*. *Pneumocystis carinii*, recently classified as a fungus (626), inhabits the respiratory tracts of laboratory mice and rats. It is a pathogen only under conditions of induced or inherent immunodeficiency. Transmission is via inhalation of infective cysts (608). Placental transmission does not occur (321). Recent studies have demonstrated differences in host specificity (38, 589, 712) and susceptibility (366). Clinical signs are absent in immunocompetent animals. Infection has been detected and clinical signs have been induced following several weeks of corticosteroid administration (629). Clinical signs in immunosuppressed or immunodeficient mice and rats include wasting, rough coat, dyspnea, cyanosis, and death (475). The lungs are enlarged, dark, and rubbery. Microscopic changes include alveolar septal thickening and alveolar filling with foamy, eosinophilic material consisting of organisms, dead host cells, serum protein, and pulmonary surfactant (104, 150, 186, 446). Pneumonia may be exacerbated by the presence of coinfecting pneumotropic pathogens (29, 559). The attachment of *P. carinii* to lung cells may play a role in the pathophysiology of *P. carinii* pneumonia (5) and may be enhanced by surfactant-associated protein A (725).

Immunity is age related (229) and occurs via both humoral and cell-mediated mechanisms, with macrophages and neutrophils playing major roles in killing organisms (41, 249, 270, 361, 388, 420). Glycoprotein A is the immunodominant antigen of *P. carinii* (232). *P. carinii* has been demonstrated to alter alveolar capillary membrane permeability (740) and uptake of tracheally administered compounds (455) and to elevate TNF (361), IL-1 (103), IL-6 (102), arachidonic acid metabolite (97), and surfactant-associated protein A (524) levels. Mice and rats have been used as models of opportunistic human *P. carinii* pneumonia (15, 373, 531, 536). Infected mice and rats are likely to develop severe pneumocystosis following immunosuppression and will be rendered unsuitable for most experimental purposes.

Digestive System

Viruses. (i) Cytomegalovirus. Cytomegaloviruses (CMVs) are dsDNA viruses of the family *Herpesviridae*, subfamily *Betaherpesvirinae*. Mouse cytomegalovirus (MCMV) is commonly found in wild mice, principally in the submandibular salivary glands (475). Its prevalence in laboratory colonies is thought to be much lower, although survey results are affected by the screening method. Because the salivary glands are persistently infected, transmission is via contact with infectious saliva. Vertical transmission may also occur (662). Aside from the salivary glands, latent infections can occur in the kidneys, prostate, pancreas, testicles, heart, liver, lungs, spleen, neurons of the cerebral cortex and hippocampus, and cells of the myeloid lineage and are directly correlated with the extent of viral replication during acute infection (117, 448, 502, 532, 662). Natural infections of immunocompetent mice with MCMV are subclinical. Pathologic changes are limited to finding intranuclear inclusions in enlarged (cytomegalic) salivary gland cells (502). In addition, experimental infection results in adrenalitis without compromise of adrenal function (538). The effects of experimental infection are dependent on a variety of host factors, with newborn and immunocompromised mice being more susceptible than adult immunocompetent mice (176, 475). Lathbury et al. (387) reported that BALB/c and A/J mice are more susceptible to infection than are C57BL/10 and CBA/CaH mouse strains, whereas Dangler et al. (141) reported that C57BL/6 mice infected with MCMV develop inflammatory lesions affecting the ascending aorta and pulmonary artery more readily than do BALB/c mice. In addition, multiple natural and experimental strains of MCMV differing in virulence have been reported (63, 224). Immunity is primarily cell mediated, with $CD8^+$ T cells and NK cells playing critical roles in controlling MCMV replication (387, 500). Monoclonal antibodies against MCMV antigens have been shown to cross-react with host proteins, suggesting a potential autoimmune component to immunity analogous to that described in humans (391). CMVs have recently been recognized as having superantigen activity (312). Natural MCMV infection has not been shown to interfere with research results. However, experimental infection may alter a variety of host physiologic functions, including depression of antibody and interferon production, major histocompatibility complex (MHC) class I-restricted antigen presentation, $CD4^+$ lymphocyte numbers in bronchoalveolar lavage fluid, lymphocyte proliferation, cytotoxic lymphocyte responses, and allogeneic skin graft rejection; decreased fecundity; thrombocytopenia; exacerbation of normal cardiac calcification in BALB/c mice; formation of anticardiac autoantibodies; increased susceptibility to opportunistic infections; and induced reactivation of dormant *Toxoplasma gondii* infection (241, 475, 491, 534, 644).

Natural cases of rat cytomegalovirus (RCMV) have been reported in wild but not laboratory rats (81, 475). The biology and pathophysiology of experimental RCMV infection is similar to that of MCMV infection, and the reader is referred to the above description of MCMV for that information. Experimental RCMV infection has been reported to alter macrophage function, the response to sheep erythrocytes, and peripheral lymphocyte subsets; exacerbate the development of collagen-induced arthritis; induce vascular wall inflammation; enhance smooth muscle cell proliferation and intimal thickening of rat aortic allografts; and induce interstitial lung disease in allogeneic bone marrow transplant recipient rats independent of acute graft-versus-host response (255, 256, 364, 397, 475, 610, 612). Mice and rats are commonly used as models of human CMV infection (228, 349, 454, 593, 661), and CMV particles and promoters have recently been used in gene vector research (271, 595). Natural infection of these and other laboratory mice and rats could confound research through alteration of a variety of immunological and other functions.

(ii) Mouse parvovirus type 1. Mouse parvovirus type 1 (MPV-1), formerly known as orphan parvovirus, is a recently recognized and very important pathogen of laboratory mice. The prevalence of infection appears to be high within and among rodent facilities, although many colonies have yet to be screened. Three isolates (MPV-1a, MPV-1b, and MPV-1c) of one serotype have been reported (328). MPV-1 is an ssDNA virus of the family *Parvoviridae*. Like other parvoviruses, MPV-1 requires actively dividing or differentiating cells for survival. The virus is shed via urinary, fecal, and perhaps re-

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spiratory routes (605). Transmission is therefore most probably primarily direct, although extensive transmission studies have yet to be conducted (605). Transmission may also occur following experimental exposure to selected, infected T-cell lines (434). Natural infections of mice are generally asymptomatic and apathogenic, even for neonatal and immunocompromised mice (605). In immunocompetent mice, viral replication occurs in the pancreas, small intestine, lymphoid organs, and liver and may persist for several weeks (331, 605). Viral replication is more widespread in immunodeficient mice (605). MPV-1 has some antigenic cross-reactivity with minute virus of mice, another rodent parvovirus, due to two highly conserved nonstructural proteins (23, 49, 328). MPV-1 affects processes linked to cell proliferation. Reported effects include direct modulation and dysfunction of T lymphocytes and altered patterns of rejection of tumor and skin allografts (435). It is anticipated that additional effects will be reported as more studies are conducted on this important virus. Recently, a new parvovirus of rats, designated RPV-1, has been identified (327). To date, little is known about the virus. However, RPV-1 may suppress the development of lymphoid tumors (327).

(iii) Mouse rotavirus. The disease caused by mouse rotavirus, formerly known as epizootic diarrhea of infant mice, is commonly diagnosed in young laboratory mice with diarrhea. Rotaviruses are dsRNA viruses of the family *Reoviridae*. Mouse rotavirus is a member of the group A rotaviruses, which are known to infect a variety of vertebrate hosts, including humans. Multiple strains of mouse rotavirus have been identified (84, 316). Infection is highly contagious and is acquired through exposure to contaminated airborne dust and bedding and through contact with infected mice. There is no evidence of transplacental transmission (475). Mice are most susceptible from birth to about 2 weeks of age, possibly due to transient features of intestinal enterocytes (475). Virus is shed in the feces for up to about 10 days postinfection. It remains uncertain whether a carrier state, with persistent, low-level fecal virus shedding exists.

Clinical signs generally are seen only in mice infected within the first 2 weeks of life and include watery, mustard-colored stool; lethargy; and distended abdomen. Infection and pathologic changes progress from the proximal to distal intestine. Apical villous enterocytes are primarily affected, while crypt cells are largely spared (404). Affected enterocytes may be vacuolated and contain pyknotic nuclei. Malabsorption and osmotic diarrhea with overgrowth of *Escherichia coli* may contribute to the clinicopathologic pattern (517). Athymic (*nu*/*nu*) mice are no more susceptible to rotavirus disease than are normal mice (183). In contrast, mice with severe combined immunodeficiency (*scid*/*scid* mice) are more severely affected (551). Rotavirus may bind to mouse intestinal cells via a subset of sialylated glycoconjugates, i.e., glycoproteins containing O-linked sialic acid moieties (726). This conclusion is consistent with the observation that intestinal mucins inhibit rotavirus infection and may represent a barrier to infection (101).

Immunity to rotavirus infection in mice occurs through the activities of several effector components, including antibodies, antigen-presenting cells, and T lymphocytes (80, 84, 436, 438, 707). Protection may be related to the intestinal replication properties of the virus rather than to specific immunogenic properties of specific viral proteins (437). Rotavirus alters host physiology in many ways and may therefore confound research. Infected mice are more susceptible to the pathologic effects of copathogens (481) and have alterations in intestinal physiology (116, 317). In addition, rotavirus infection may alter results of dietary and nutritional studies (463, 488, 564). The rotavirus-infected mouse serves as a model of human rotavirus diarrhea, which is responsible for the deaths of approximately 800,000 children per year (217). Natural infection of laboratory mice with rotavirus would confound such research efforts and may interfere with other studies involving the gastrointestinal system.

(iv) Rat rotavirus-like agent. Rat rotavirus-like agent (RVLA), like mouse rotavirus, is a dsRNA virus in the family *Reoviridae*. Unlike mouse rotavirus, however, RVLA has been tentatively classified as a group B rotavirus (696). The natural hosts of RVLA include rats and humans. It has yet to be grown in culture. Transmission is probably via direct contact with contaminated feces, fomite transmission, human contact, and possibly airborne spread of contaminated dust and bedding (475). Clinical signs are seen in rats 1 to 11 days of age and consist of poor growth, diarrhea, and perianal dermatitis (695). These signs led to the designation "infectious diarrhea of infant rats." Pathologic changes include watery, discolored proximal small-intestinal contents; villous atrophy and epithelial necrosis; increased crypt depth; and syncytial cell formation (569, 695). RVLA infection results in a net secretory state for water and in impaired sodium absorption (568, 569). Relatively little is known about immune mechanisms in RVLA infection, but it is likely that there are similarities to immunity to mouse rotavirus infection. In addition to acquired immunity, intestinal mucins may inhibit rotavirus replication and may be dependent on specific mucin-virus interactions (739). Natural infection of rats with RVLA would probably confound studies involving the intestinal system.

(v) Mouse thymic virus. Relatively little is known of mouse thymic virus (MTV) due to the inability to culture the virus in vitro. MTV is considered a member of the *Herpesviridae*, which are dsDNA viruses. Transmission appears to be via direct contact (623) and possibly via transmammary passage (464). Natural infections are subclinical. Pathologic changes are limited to transient lymphoid necrosis of the thymus, lymph nodes, and spleen of neonatal mice, followed by a diffuse granulomatous response with giant cells, which eventually resolves (732). The thymus is most severely affected, especially lymphocytes, epithelial reticular cells, macrophages, and lymphoepithelial cell complexes (thymic nurse cells). $CD4^+$ $CD8^+$ and $CD4^+$ $CD8^-$ lymphocytes are selectively lysed by MTV (17). Both T-helper and T-cytotoxic lymphocytes may be involved (112). The virus also infects and persists in salivary glands. MTV infection has been shown to reduce T-cell responsiveness to concanavalin A and phytohemagglutinin and to reduce the graft-versus-host response (132). Natural infection of laboratory mice might therefore temporarily interfere with immune competence.

(vi) Reovirus type 3. Mammalian reoviruses are grouped into serotypes 1, 2, and 3. Reovirus type 3 is the most pathogenic reovirus of laboratory rodents (36). The primary importance of reovirus type 3 is as a contaminant of transplantable tumors and cell lines (475, 484). Reovirus type 3 is a dsRNA virus in the family *Reoviridae*. Transmission is thought to be primarily via direct contact. However, Barthold et al. (36) demonstrated that transmission of virus to cagemates or mothers of infected infants did not occur, indicating low contagiousness. The preponderance of the literature on the effects of reovirus type 3 reports on experimental infections. The effects of natural infections as well as relevant findings from experimental infections are reviewed here. Natural infection with reovirus-3 is nearly always asymptomatic. Cook (120) reported the following clinical signs in first litters of mice infected with reovirus type 3: stunting, diarrhea, oily coats, abdominal alopecia, and jaundice. Pathologic changes consisted of enlarged, black gallbladders; hepatic necrosis; and yellow kidneys (120).

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Experimentally inoculated mice have a wider scope of organ involvement (36, 475, 507).

Immunity to reovirus type 3 infection is primarily humoral (26, 133, 665) but also involves T lymphocytes (133, 134, 689). Protective antibodies may act at least partially by inhibiting internalization and intracellular proteolytic uncoating of the virion (688). Athymic (*nu*/*nu*) mice are no more susceptible to disease than are immunocompetent mice (594). The reported effects of natural infection with reovirus type 3 are limited to lysis of transplantable ascites tumors (46, 479). Experimentally, reovirus type 3 has also been shown to reduce the pulmonary clearance of *Staphylococcus aureus* (354); suppress pulmonary carcinogenesis (645); inhibit cellular DNA synthesis and induce apoptosis (296); cause pulmonary neutrophil influx, increased levels of chemokine mRNA expression (196), and acute myocarditis (597); induce murine NK cell cytotoxicity (7) and TNF-α levels (197); synergize with chemotherapeutic agents to cause the rejection of various murine tumors (615); and enhance tumor-specific immunity (360, 570). Mice and, to a lesser extent, rats infected with reovirus type 3 are commonly used as models of human acute and chronic hepatitis, chronic biliary obstruction, extrahepatic biliary atresia, pancreatitis, lymphoma, and pneumonia (459, 614). Natural infection of laboratory rodents could alter intestinal studies and multiple immune response functions.

Bacteria. (i) *Helicobacter* spp. The genus *Helicobacter* contains an ever-increasing number of recently identified, gram-negative, spiral, microaerophilic, gastrointestinal system pathogens that are known to infect mammals (127, 212). Species naturally infecting mice and/or rats include *H. hepaticus*, *H. bilis*, *H. muridarum*, *H. trogontum*, *H. rodentium*, and "*Flexispira rappini*," a *Helicobacter* sp. based on 16S rRNA analysis (212). Among these, *H. hepaticus*, a pathogen of mice, is most prominent. The prevalence of *H. hepaticus* is currently unknown but may be quite high (591). Rats, guinea pigs, and hamsters are not susceptible to infection (706). Transmission is via direct fecal-oral contact or fomites. Clinical signs are absent in immunocompetent mice but include rectal prolapse in immunodeficient mice (704). *H. hepaticus* selectively and persistently colonizes the bile canaliculi and cecal and colonic mucosae (211, 706). Pathologic changes include chronic, active hepatitis, possibly of autoimmune etiology (705); occasional enterocolitis; and hepatocellular neoplasms induced by as yet undelineated nongenotoxic mechanisms (88, 213, 706). Other, lesser known *Helicobacter* spp. include *H. bilis*, associated with multifocal chronic hepatitis and isolated from the liver, bile, and lower intestine of aged, inbred mice (214); *H. muridarum*, from the intestinal mucosa of rats and mice (394); *H. rodentium* and *F. rappini*, from the colons and ceca of mice (212, 576); and, lastly, *H. trogontum*, recently isolated from the colonic mucosa of Wistar and Holtzman rats (440). *H. hepaticus* has been associated with hepatic carcinomas and elevated levels of alanine aminotransferase in serum (215, 706). *H. hepaticus* serves as a model for *H. pylori*-induced chronic gastritis, gastric ulcers, and gastric adenocarcinoma (213). Natural infection of laboratory mice with *H. hepaticus*, and possibly other *Helicobacter* spp., could confound carcinogenicity research and research involving the gastrointestinal system. It is certain that much additional information concerning these and yet unknown murine *Helicobacter* pathogens will be published in the scientific literature in the near future.

(ii) *Citrobacter rodentium*. *Citrobacter rodentium* (577), formerly *Citrobacter freundii* biotype 4280, is the etiologic agent of transmissible murine colonic hyperplasia (31). *C. rodentium* is a gram-negative, facultatively anaerobic rod. Rats are not susceptible to infection (37). Transmission is via direct contact (71) or via contaminated food or bedding. *C. rodentium* is generally considered an opportunistic pathogen. For example, the use of antibiotics effective primarily against gram-negative rods may allow an overgrowth of *C. rodentium* in the mouse intestine (681). Clinical signs, when present, are nonspecific and may include ruffled coat, weight loss, depression, stunting, perianal fecal staining, and rectal prolapse (475). Nursing mice are most susceptible. Strain differences in susceptibility exist, with C3H/HeJ mice more susceptible than DBA/2J, NIHS (Swiss), or C57BL/6J mice (37). Infection is transient, and there is no carrier state. The hallmark pathologic lesion of *C. rodentium* infection is colonic hyperplasia. Generally, the descending colon is most affected. However, the entire colon and cecum may be involved, with crypt elongation, variable mucosal inflammation, crypt abscesses, occasional erosions and ulcers, and, with healing, goblet cell hyperplasia (32, 475). Transient colonization of the mouse small intestinal mucosa, followed by colonization of the large bowel, is dependent on the presence of the chromosomal *eae* gene (575). Once colonization has occurred, *C. rodentium* causes the formation of attaching and effacing (A/E) lesions. Outer membrane proteins, known as intimins, are required for formation of the A/E lesions (218). Immunity appears to be humoral and may be directed at least partially toward intimin antigens (218). Reported effects on research are few, but they include acceleration of carcinogenesis by 1,2-dimethylhydrazine (34). *C. rodentium* is used as a model of A/E lesions in vivo and in intestinal disease of humans. Natural infection of laboratory mice might severely, if only transiently, alter intestinal cytokinetics.

(iii) *Clostridium piliforme*. *Clostridium piliforme* (177), formerly *Bacillus piliformis*, is the causative agent of Tyzzer's disease. *C. piliforme* is a gram-negative, filamentous, endospore-forming bacterium. Prevalence remains high in laboratory rodent colonies (475). Possible explanations for this include the moderately contagious nature of the organism (61) and the wide range of susceptible and naturally infected host species (475). However, concerning the latter, Franklin et al. (219) have suggested that both cross-infective isolates and more host-specific isolates may exist. With this in mind, transmission is thought to be via ingestion of infectious endospores in contaminated food or bedding. Inadequate sterilization of feed or bedding components may facilitate the entry of the pathogen into an otherwise well-managed rodent colony.

Most infections are subclinical. Various host and environmental stressors may precipitate clinical disease. Clinical signs occur most commonly in suckling and weanling rodents and include sudden death, watery diarrhea, lethargy, and ruffled fur (475). Pathologic changes involve three main phases. These include the establishment of infection in the ileum and cecum, the ascension of the pathogen to the liver via the portal circulation, and hematogenous spread to other tissues such as the myocardium (475). This triad of organ involvement is the hallmark of Tyzzer's disease. In mice, the affected intestine is thickened, edematous, and hyperemic. Necrotic foci develop in the affected intestine, liver, and myocardium. Lesions are similar in rats, except that megaloileitis is a common finding (273). Waggie et al. (697) demonstrated that B-cell- but not T-cell-deficient mice were more susceptible and concluded that immunity to *C. piliforme* was therefore primarily humoral. More recently, others have demonstrated increased susceptibility to a toxigenic isolate of *C. piliforme* in nude mice and have concluded that T cells may also play a role in immunity to Tyzzer's disease (405). Those authors acknowledge that the cytotoxin produced by the isolate may have contributed to the severity of clinical disease and lesions. Athymic (*nu*/*nu*) rats have also been shown to be highly susceptible (650). Effects on research

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include increased mortality, alteration of the pharmacokinetics of warfarin and trimethoprim, and alteration of the activity of hepatic transaminases (475). In addition, experimental manipulations have been reported to provoke or exacerbate clinical disease caused by *C. piliforme* (475). Natural infection of laboratory mice and rats could severely alter the findings of studies involving the gastrointestinal and cardiopulmonary systems.

(iv) *Pseudomonas aeruginosa*. *Pseudomonas aeruginosa* is a gram-negative rod that normally inhabits the nasopharynx, oropharynx, and lower digestive tract of many vertebrate species. The primary importance of *P. aeruginosa* is as an opportunistic pathogen (475). *P. aeruginosa* is commonly found in soil and organic waste and as a normal skin inhabitant, and it is frequently cultured from facility water systems. Active exclusion of the organism from the animal facility is achievable but costly. Transmission is via contact with contaminated water, feed, bedding, and infected rodents and humans (670).

Clinical signs are generally not observed in immunocompetent hosts, although the host response to *P. aeruginosa* infection varies among inbred mouse strains. For example, mice of the BALB/c strain are resistant to *P. aeruginosa* lung infection whereas mice of the DBA/2 strain are susceptible (460). Some immunocompromised mice and rats may develop hunched posture, apathy, dullness, shortness of breath, ruffled coat, emaciation, circling movements around their longitudinal axis, and oblique head posture, and some of them will die (167, 335, 475). Clinical disease is due to invasion of deep tissues, resulting in hematogenous spread of the bacteria to multiple organs. Entry into the vascular system may be facilitated by pseudomonal proteases and bradykinin generated in infectious foci (567). Pathologic lesions are found in affected tissues and consist of multifocal necrosis, abscess formation, and suppuration (517). Lesions are often most severe in the lungs (517). Vegetative lesions may be found on heart valves of animals with infected indwelling vascular catheters (517).

Much of what is known of the cell biology of *P. aeruginosa* infections comes from experimentally induced infections. Studies of immune responses to *P. aeruginosa* present evidence of both humoral (525) and cellular (178, 621) contributions to immunity, which is enhanced by vitamin B_2 (13) and IL-1 (691). Type 1 T-helper (Th1) cells may participate in part by triggering TNF-α-mediated hypersensitivity to *P. aeruginosa* (221). Macrophages and neutrophils are important effector cells (471), with neutrophil accumulation mediated through CD11 and CD18 cells (539). Also, inbred mouse strains differ in susceptibility (461). Susceptible mice have been shown to have a defect in TNF-α production (245, 460). In addition, strains of *P. aeruginosa* differ widely in virulence (225). Bacterial flagella (412), pyoverdin (which may compete directly with transferrin for iron [443]), pyocyanin (596), elastase (640), and potent exotoxins (263, 294, 490, 642) play major roles in determining virulence. Most prominent among the exotoxins is exotoxin A, a superantigen (451, 528).

Numerous publications have reported on the effects of *P. aeruginosa* on research involving immunocompromised mice and rats. Most reports are from experimental infections. Effects include early death following exposure to radiation, cyclophosphamide treatment, CMV infection, or cold stress; increased severity of infection following airway trauma; depressed contact sensitivity to oxazolone; stimulation of T-cell proliferation within splenocytes of nude mice; induction of thymic atrophy via apoptosis; inhibition of wound healing; inactivation of cytokines by bacterial proteases; possible T-cell-dependent immune system suppression mediated by the polysaccharide fraction of LPS; altered fluid transport across the lung epithelium; suppression of delayed hypersensitivity responsiveness; increase in cardiac excitability and enhanced vulnerability to hypoxic insults; inhibition of macrophage function by bacterial rhamnolipids; and altered behavioral and clinical pathologic parameters following experimental infection of surgical wounds (69, 173, 277, 287, 376, 423, 433, 475, 508, 528, 701, 736). In addition, rodents with streptozotocin-induced diabetes mellitus are more susceptible to *P. aeruginosa* infection (353). Rodent-*P. aeruginosa* systems have been developed as models for numerous human diseases and conditions, including indwelling-catheter infections (350), pyelonephritis (659), burn trauma (478, 620), chronic mucosal colonization (526), immunization strategies (131), and infection accompanying cystic fibrosis (336, 411). From these reports, it is apparent that natural infection of immunocompromised mice and rats could affect a variety of research projects, depending upon the organ systems affected.

(v) *Salmonella enteritidis*. *Salmonella enteritidis* and the roughly 1,500 serotypes of that species are gram-negative, nonendospore-forming bacteria that colonize the intestinal tracts of a wide variety of animal hosts. The primary importance of *Salmonella* spp. is as zoonotic agents and as pathogens in immunocompromised mice and rats. *S. enteritidis* serotype *typhimurium* is the most common serotype infecting laboratory rodents, although the prevalence of asymptomatic carriers is unknown but probably low. Transmission is via ingestion of contaminated feed ingredients and water and by contact with contaminated bedding and animal facility personnel (475). Reports of natural outbreaks of disease are rare in the literature (475), probably because most infections are asymptomatic in normal hosts. When clinical effects are observed, reproduction is most prominently affected, while other signs are nonspecific (398). Diarrhea is an uncommon finding (475). Many host, pathogen, and environmental factors determine the pathologic findings and severity of infection, including host age and genotype; makeup of the intestinal flora; nutritional state; immune status; presence of concurrent infections; bacterial serotype; and environmental stressors such as food and water deprivation, temperature, iron deficiency, and experimental manipulations (475). Inbred mouse strains have a wide range of susceptibility to *S. enteritidis*. Susceptible strains include DBA/1, BALB/c, C57BL/6, and C3H/HeJ. Relatively resistant strains include C3H/HeN, A/J, and DBA/2 (475). Susceptibility is determined by three distinct genetic loci (475).

Following ingestion, the mucosa and Peyer's patches in the distal ileum are initial sites of invasion. From those sites the organism reaches the mesenteric lymph nodes and gains access to the vascular system, to be distributed throughout the body. Lesion development depends upon the distribution of the pathogen. The organs most commonly infected include the terminal small intestine and the large intestine, lymph nodes, liver, and spleen. Hallmarks of the infection include local hyperemia, focal necrosis, and pyogranulomatous inflammation, consistent with septicemic disease; they also include crypt epithelial hyperplasia in the intestine (475, 517). Immunodeficient rodents are more severely affected. Numerous virulence factors have been identified, each of which contributes to the pathogenic potential of various *S. enteritidis* isolates (622, 630, 646).

A combination of humoral and cellular immune mechanisms control infection with *S. enteritidis*, while gamma interferon (IFN-γ) may contribute to pathology in septic shock (288). Cellular mechanisms participating in immunity include $L3T4^+$ and Lyt-2^+ T cells (535, 571) and T lymphocytes that express a γ/δ T-cell antigen receptor (449). Reported interference of *Salmonella* spp. with research includes induced resistance or increased mortality to copathogens, suppression of growth of

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transplantable tumors, reduced glucose levels and hepatic enzyme levels in blood, reduced intestinal enzyme levels (475), and increased rates of crypt cell proliferation, resulting in substantial growth of the small intestine (476). In addition to the changes observed with infection, there is a large body of literature concerning the effects of *Salmonella* LPS on mouse and/or rat systems under experimental and often in vitro conditions. These effects include mitogenic activity (631); stimulation of cytokine production (111); lung damage and decreased circulating leukocyte counts (556); recruitment of neutrophils to the lung, probably due to the chemoattractant properties of macrophage inflammatory protein type 2 (262); induction of vasodilation of isolated rat skeletal muscle arterioles (236); decreased amino acid incorporation into proteins (298); altered guanine nucleotide regulatory (G) protein function (414); activation of the nuclear transcription factor kappa B and expression of E-selectin mRNA in hepatocytes, Kupffer cells, and endothelial cells (189); mortality in neonates and stimulation of adherent splenic cell thromboxane B2, IL-6, and nitrite production (110); altered development of the hypothalamic-pituitary-adrenal axis with long-term effects on stress responses (592); altered glucose metabolism (248); increased expression of Mac-1 (CD11b/CD18) adhesion glycoproteins on neutrophils (730); increased calcitonin gene-related peptide and neuropeptide Y levels in plasma (702); and altered liver levels of 1,2-diacylglycerol and ceramide (664). It remains to be discerned which of these observations extend to the mouse or rat infected with *S. enteritidis*. Mice and/or rats infected with *S. enteritidis* serve as models of enteritis (477), typhoid fever, and other septicemic diseases (231).

Parasites. (i) *Giardia muris*. *Giardia muris* is a flagellated intestinal protozoan. Infections are occasionally detected in laboratory rodent colonies. Strains of *G. muris*-infected mice and rats may be host specific (372). The life cycle is direct. Environmentally resistant and infectious cysts are passed in the feces. Excystation occurs following ingestion. The minimum infectious dose for a mouse is approximately 10 cysts (611). Shortly after excystment, trophozoites divide longitudinally and colonize the mucosal surface of the proximal small intestine, adhering to columnar cells near the bases of intestinal villi and moving within the mucus layer on the mucosa (475). Most infections are asymptomatic. When apparent, clinical signs are nonspecific and include weight loss, stunted growth, rough coat, and enlarged abdomen. In athymic or otherwise immunocompromised hosts, clinical signs may be more severe and may include diarrhea and death; and cyst shedding may be prolonged (60, 555). Pathologic changes include villous blunting; increased numbers of intraepithelial lymphocytes, goblet cells, and mast cells; and alterations in intestinal disaccharidase content (685).

Strain differences in susceptibility have been observed. Resistant mouse strains include DBA/2, B10.A, C57BL/6, and SJL/2; the relatively more susceptible strains include BALB/c, C3H/He, A/J, and Crl:ICR (475, 684, 685). The bases for these differences are unknown, although both MHC and non-MHC genes appear to influence the outcome of primary *G. muris* infections (683). In addition, male mice shed cysts in their feces longer than females do and trophozoites are present in their intestines for a longer period than in females (143).

Protective immunity is dependent upon both cellular and humoral mechanisms (291, 522, 553), with IFN-γ somehow playing a role in clearance of trophozoites (685). The mechanisms responsible for elimination of a primary infection may not be identical to those required to resist a secondary challenge infection (600). Reported effects of *G. muris* include alterations in intestinal disaccharidase levels (142, 144) and mucosal immune responses (406), transient reduction in immunoresponsiveness to sheep erythrocytes (43), and increased severity of concurrent infections in athymic (*nu*/*nu*) mice (60). Natural infection of laboratory mice and rats with *G. muris* could interfere with studies involving the gastrointestinal and immune systems.

(ii) *Spironucleus muris*. *Spironucleus muris* (formerly *Hexamita muris*) is a second flagellated protozoan commonly infecting laboratory mice and rats. Host-specific strains of *S. muris* have been identified (574). The biology of *S. muris* appears to be much like that of *G. muris*; however, due to the inability to culture *S. muris*, considerably less is known about this organism. Infectious cysts are passed in the feces. The minimum infective dose for a mouse is 1 cyst (611). Following ingestion, excystation occurs and trophozoites colonize the crypts of Lieberkühn in the small intestine. Infections with *S. muris* are asymptomatic in immunocompetent, adult mice and rats. However, weanling and immunodeficient mice may develop clinical disease. It has been reported by several investigators that young mice may develop diarrhea, dehydration, weight loss, rough coat, lethargy, abdominal distension, and hunched posture and may die (475, 720), although in none of the reported cases were other potential causes of the clinical signs excluded. In athymic (*nu*/*nu*) and lethally irradiated mice, *S. muris* causes severe chronic enteritis and weight loss (371, 441). In severe infections, the intestine is reddened and filled with fluid and gas. The crypts are hyperplastic and may be distended with trophozoites, microvilli and villi may be shortened, and enterocyte turnover is increased; inflammation is minimal (475, 720). *S. muris* has been shown to interfere with research in several ways, including increasing the severity of copathogen infection; increasing the mortality associated with cadmium treatment; and altering macrophage function and lymphocyte responsiveness to sheep erythrocytes, mitogens, and tetanus toxoid (475).

(iii) Oxyuriasis (pinworms). Pinworms commonly infecting laboratory rodents include the rat pinworm *Syphacia muris* and, in mice, *Syphacia obvelata* and *Aspicularis tetraptera*. *S. obvelata* has also been reported to infect humans (475). Life cycles are direct, with adult worms inhabiting the cecum and colon. Eggs are deposited in the perianal region of the host (*Syphacia* spp.) or are excreted with the feces (*A. tetraptera*). The eggs are very light and will aerosolize, resulting in widespread environmental contamination. Embryonated eggs are infective to another rodent and can survive for extended periods at room temperature. The prevalence of infection remains high (475, 527), even in well-managed animal colonies. Pinworm burden in an infected rodent population is a function of age, sex, and host immune status. In enzootically infected colonies, weanling animals develop the greatest parasite loads, males are more heavily parasitized than females, and pinworm numbers diminish with increasing age of the host. While infections are usually subclinical, rectal prolapse, intussusception, fecal impaction, poor weight gain, and rough coat have been reported in heavily infected rodents, although generally without adequate exclusion of other pathogens (475). Very heavy parasite loads may lead to catarrhal enteritis, liver granulomas, and perianal irritation. Athymic (*nu*/*nu*) mice are reportedly more susceptible to infection (326). Immunity is probably mostly humoral, as for many other helminthiases. In this regard, *Syphacia*-specific antibodies have been demonstrated in pinworm-infected mice (573). There are a few reports documenting the effects of pinworms on research. Pinworm infection resulted in significantly higher antibody production to sheep erythrocytes (573), reduced the occurrence of adjuvant-induced arthritis (512), and impaired intestinal electrolyte transport (408). While many consider pinworm infection irrel-

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evant in laboratory rodents, specific research goals may justify the eradication of pinworms from an animal colony.

Dermal System

Viruses. (i) Mouse mammary tumor virus. Mouse mammary tumor virus (MMTV) is a ssRNA type B retrovirus of the family *Retroviridae*. At least four major variants of the virus have been identified in laboratory mice, including MMTV-S ("standard"), MMTV-L ("low oncogenic"), MMTV-P ("pregnancy"), and MMTV-O ("overlooked") (428, 475). More recently, additional variants, including MMTV-SW and MMTV-C4, have been described (590). Mechanisms of transmission differ among the major variants. MMTV-O is endogenous to the genome of most mice, MMTV-S is transmitted via milk, MMTV-L is transmitted via germ cells, and MMTV-P is transmitted through both milk and germ cells (475). T cells are needed for transmission of milk-borne MMTV from the gut to the mammary gland (734). The variants also differ in oncogenicity, with MMTV-S and MMTV-P being highly oncogenic and MMTV-L and MMTV-O being less so (475). Depending upon the mouse strain and virus variant, MMTV may be expressed in mammary and many other tissues (698), including lymphoid tissues (345, 468, 663), or may exist as a provirus in the DNA of the host (680). Clinical signs of infection are generally limited to mammary tumors, which may arise several months after infection, although distant metastases can also occur with subsequent organ compromise. Most virus-induced tumors are adenocarcinomas (475). While the mechanism of tumor induction is unknown, it is thought that MMTV induces hyperplastic nodules which eventually become neoplastic (475). MMTV may integrate into and disrupt the *Tpl-2/cot* proto-oncogene (188). Various hormones (57), carcinogens (475), diet (204), and transforming growth factor α (467) may accelerate the development of tumors. Mouse strains differ in their susceptibility to MMTV to the point that mouse strain selection can be used as a control measure (475). Immunity involves both cellular and humoral components (47, 428). B cells are the primary targets of infection for MMTV. However, for productive retroviral infection, T-cell stimulation through the virally encoded superantigen (SAg) is necessary. SAg is expressed on lymphocytes (735); binds MHC class II molecules; stimulates T cells via interaction with the Vβ domain of the T-cell receptor (3); activates B cells, leading to cell division and differentiation (99, 290); is involved in the transmission of milk-borne MMTV from virus-infected milk in the gut to the target mammary gland tissue (735); may initiate or aggravate graft-versus-host disease (444); and has the ability to destroy a large portion of $CD4^+$ T cells (744). In addition, MMTV affects T-cell (392, 744) and B-cell (99) responses, activates NK cells through superantigen-dependent and -independent pathways (233), and lowers the amount of prolactin required to elicit α-lactalbumin production from mammary epithelial cells (56). MMTV is used as a model for viral carcinogenesis. Natural infection of laboratory mice with MMTV will interfere with carcinogenesis studies and result in a shortened life span.

Bacteria. (i) *Pasteurella pneumotropica*. *P. pneumotropica* is a gram-negative, nonhemolytic bacterium. Multiple biotypes have been reported (62). While most species of rodents may harbor the organism (445, 475), reports of natural outbreaks are rare and are generally limited to rats and immunocompromised mice (61). McGinn et al. (432) reported otitis media in CBA/J mice used in hearing research. *P. pneumotropica* was isolated from infected otic bullae. However, in that report the primary pathogen was not clearly established. *P. pneumotropica* is frequently isolated from several sites on and within healthy rats and mice and is therefore considered an opportunistic pathogen (475). Transmission is probably via direct contact and fomites (475). Clinical disease, when apparent, is generally limited to lesions of the skin and adnexal structures, although ophthalmitis, conjunctivitis, and mastitis have also been reported (475). Lesions are characterized by suppurative inflammation (475). Natural infection of rats with *P. pneumotropica* could compromise research involving the skin.

(ii) *Staphylococcus aureus*. *Staphylococcus aureus* is a gram-positive, coagulase-positive coccus that commonly inhabits the skin, upper respiratory tract, and lower digestive tract of many animals, including laboratory rodents, in which it occasionally causes disease. Transmission is direct, and entry into the body is via breaks in normal barriers. Disease frequently occurs following physiologic changes in the host (e.g., stress and immunosuppression). A variety of clinical presentations have been reported in rats and mice. These include tail lesions, ulcerative dermatitis, and traumatic pododermatitis in rats; and facial abscesses, ulcerative dermatitis, preputial gland abscesses, and penile self-mutilation in mice (475). Lesions are more severe in immunocompromised hosts. In addition, rats inapparently infected during nonsterile surgical procedures are less active in open-field testing. Infected rats have alterations in the fibrinogen level in plasma, the glucose level in serum, total leukocyte counts, and wound histology scores (69). The hallmark of *S. aureus* infection is suppurative inflammation, with abscess formation in virtually any organ. Most commonly, infection occurs in the skin and subcutaneous tissues, but it may also be found in the upper airways, lungs, conjunctiva, and other tissues.

Immunity to *S. aureus* is primarily via complement-mediated killing by neutrophils (475). Cell-mediated immunity may also be important and may secondarily contribute to the pathogenesis of some lesions (475). Nitric oxide, IFN-γ, TNF, and IL-6 are induced during infection (210, 470). *S. aureus* produces several biologically active products, including hemolysins, leukocidins, nuclease, coagulase, lipase, hyaluronidase, exotoxins, fibronectin- and collagen-binding proteins, protein A, and enterotoxins (334, 545, 560). Many of these may be degraded by phagocytic cells into other active products (206). The effects of these products are numerous and include cell lysis (292); increases in pulmonary microvascular permeability (585); contractile dysfunction (50); shock and multiple-organ failure (151); epidermolysis (18); and induction of excess sleep, fever, TNF, cytokine, IL-1, and IL-1 receptor antagonist (206). Staphylococcal enterotoxins have been termed superantigens based on their ability to stimulate polyclonal proliferative responses of murine and human T lymphocytes (230). In addition, infection with *S. aureus* has been shown to alter immune responses (45). Colonization of conventionally housed rodents is unavoidable. Natural infection of immunodeficient rodents can be prevented, but at great expense, by barrier facility housing. However, this may be necessary to prevent infection and to ensure accomplishment of specific research objectives. Natural infection of immunodeficient mice and rats could compromise a variety of studies involving these animals.

(iii) *Corynebacterium* spp. in athymic mice. Corynebacteria are gram-positive, diphtheroid bacilli. Reports of hyperkeratosis in nude mice naturally infected with *Corynebacterium* spp. have occasionally appeared in the literature (549). In the report by Richter et al. (549), the pathogen isolated was similar to *Corynebacterium pseudodiphtheriticum*, while in a more recent report, the pathogen was most like *Corynebacterium bovis* based on biochemical profiles (109). The authors of the latter report thoroughly described several aspects of an outbreak of hyperkeratosis in athymic nude (homozygous and heterozy-

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gous) mice, with hairlessness being a contributing characteristic. Those authors found that transmission was accomplished via direct contact and via contaminated bedding and gloves (109). Clinical signs included flaking of the skin, primarily along the dorsum, and, in some animals, pruritus. Pathologic changes were characterized as orthokeratotic hyperkeratosis and follicular keratosis; marked acanthosis; and mild neutrophilic, macrophage, and mast cell infiltration (109). While reports of natural infection of mice with this *Corynebacterium* sp. have been rare, this condition may appear with greater frequency in the future. Nude mice naturally infected with this pathogen would be unsuitable for dermatologic and possibly other research projects.

Parasites. (i) Acariasis (mite infestation). While many species of mites infest wild rodents, only three species of nonburrowing mites are commonly found on laboratory mice and rats. *Myobia musculi* and *Myocoptes musculinus* infest mice, while *Radfordia affinis* infests rats (475). Mice are much more commonly infested than are rats. The life cycles of all three mites are direct, with all stages (egg, nymph, and adult) present on the host. Consequently, hairless mice are not susceptible. Life cycles require roughly 3 weeks for completion. Transmission is via direct contact. Once a facility is infested, eradication of the parasites is achievable but labor-intensive. Clinical signs vary in severity depending upon host factors and mite species. C57BL and related strains are most susceptible to severe disease, due to overexuberant type 1 hypersensitivity reactions (475). *M. musculi* is considered the most pathogenic of the three common species because it alone feeds on skin secretions and interstitial fluid (but not on blood) while *M. musculinus* and *R. affinis* feed more superficially (517). Infestation may be asymptomatic or may cause wasting; scruffiness; pruritus; patchy alopecia, which may be extensive; accumulation of fine bran-like material, mostly over affected areas; self-trauma to the point of excoriation or amputation; and secondary pyoderma (20, 340, 475). Lesions are most common on the dorsum, primarily on the back of the neck and interscapular region. Pathologic changes include hyperkeratosis, erythema, mast cell infiltration, ulcerative dermatitis, splenic lymphoid and lymph node hyperplasia, and eventual secondary amyloidosis (339, 340, 475). Mite infestation has reportedly caused secondarily amyloidosis; altered behavior (475); selective increases in immunoglobulin G1 (IgG1), IgE, and IgA levels and depletion of IgM and IgG3 levels in serum; lymphocytopenia; granulocytosis; increased production of IL-4; and decreased production of IL-2 (339, 340). These immunologic changes are consistent with a Th2-type response, with marked systemic consequences (339).

Hematopoietic System

Viruses. (i) Lymphocytic choriomeningitis virus. Lymphocytic choriomeningitis virus (LCMV) is a noncytopathic ssRNA virus of the family *Arenaviridae*. The primary importance of LCMV is as a zoonosis and as a contaminant of transplantable tumors and cultured cell lines (180, 413, 475, 484). Natural infections of mice with LCMV are uncommon, and only mice and hamsters are known to transmit the infection, although rats and many other mammals (and chickens) are also susceptible (475, 511). Along with implantation of infected tumors, transmission is via exposure of mucous membranes and broken skin to infectious urine, saliva, and milk (475) and possibly via ingestion (540). In addition, both transovarian and transuterine transmission occur in mice (475).

Patterns of infection differ depending on host and pathogen factors, including mouse strain and age, inoculum dose, route of inoculation, and virus strain (465, 475, 652). Typical clinical patterns include the persistent tolerant infection, which follows in utero or neonatal infection. Persistent infection of T-helper lymphocytes, viremia, and lifelong viral shedding occur (475). Clinical signs include initial growth retardation and eventual immune complex glomerulonephritis accompanied by emaciation, ruffled fur, hunched posture, ascites, and, occasionally, death (475). Pathologic features of this pattern, including ICG, stem from unabated B-cell activity, including production of pathologic amounts of anti-LCMV antibodies, lymphoid hyperplasia, and perivascular lymphocyte accumulation (475). In contrast, T-cell activity is diminished. Eventually, immune tolerance breaks down, resulting in chronic illness with widespread lymphocytic infiltration and vasculitis (517). A second clinical pattern is that of the nontolerant infection (475). This pattern occurs with acute infection of postneonatal mice. Viremia occurs without viral shedding. Infected mice either die or eliminate the virus, frequently without showing signs of disease (475). Pathologic features of this pattern include necrotizing hepatitis (246) and generalized lymphoid depletion (517). Lymphocytic choriomeningitis is generally seen only following experimental intracerebral inoculation and is not a feature of natural infection (517).

Eventual clearance of the infection primarily involves cytotoxic (Lyt-2^+) T cells (341), NK cells (718), IL-2 (125), IL-12 (501), and IFN-γ (671) and involves perforin-dependent mechanisms (342). Intestinal intraepithelial lymphocytes are also activated (632). Virus-specific antibody is also induced (601). Several investigators have reported effects of LCMV on research; however nearly all of this information comes from experimental infections (475). LCMV has been shown to alter synaptic plasticity and cognitive functions (153); abolish experimental hepatitis B infections (261); increase levels and/or expression of ICAM-1 and other endothelial adhesion molecules in serum (107, 422); cause hepatitis (246) and hemolytic anemia (619); alter behavior (242); alter immune system reactivities (65); alter cytokine gene expression (115); inhibit tumor induction by polyomavirus; delay the rejection of skin and tumor allografts; increase susceptibility to other pathogens, bacterial endotoxin, and radiation; and alter the time course of naturally occurring diabetes (475). Natural infection of laboratory mice would jeopardize human health and interfere with a variety of research endeavors, especially those involving the immune system and central nervous system (CNS).

(ii) Lactate dehydrogenase-elevating virus. Lactate dehydrogenase-elevating virus (LDEV) is a ssRNA virus of the family *Togaviridae*. Multiple strains exist (475). Mice and mouse cell cultures are the only hosts (475). Rats are not susceptible. The major importance of LDEV is as a contaminant of transplantable tumors and of inocula of other infectious agents serially passaged in mice (475, 484, 494). Transmission is via transplantation of contaminated tumors, cells, or serum but may also occur via direct contact, bite wounds, and transplacental or transmammary passage; however, given the short period when viral shedding occurs, the latter routes are less important (475, 517). Clinical signs are limited to neurologic disorder in selected mouse strains that have been immunosuppressed (475). Generally, however, there are no clinical signs of infection (475).

Pathologic changes have not been described in natural infections (517) and are mainly in lymphoid organs in experimental infections. Virus replication occurs for one cell cycle only in a small population of macrophages. The virus is therefore concentrated in organs with high macrophage populations (475). Transient thymic necrosis, splenomegaly, and lymphocytopenia occur early in the infection (517). LDEV causes

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persistent viremia, which induces antiviral antibodies and, eventually, circulating antigen-antibody complexes (282), which may result in a mild membranous glomerulonephritis (475). The diagnostic hallmark of LDEV infection is elevation of lactate dehydrogenase (LD) levels in serum, which occurs due to reduced clearing of one LD isozyme (475). Levels of other enzymes in serum are also elevated although not to the same extent.

LDEV alters several bodily functions, including those of affected macrophages; it causes transient increases in cytokine and cell receptor activities; transient depression of cellular immunity; increased (or suppressed) tumor growth (both spontaneous and transplanted); prolonged survival of allografts; altered immunity to copathogens; increases in the levels of several enzymes and gamma globulins in serum; altered humoral immunity (475); decreased binding of asparaginase to monocytes (458); suppressed streptozotocin-induced insulinitis (278), neutrophil migration (279), development of antinuclear antibodies, and glomerulonephritis (281); altered superoxide anion production by macrophages (283, 284); inhibited contact sensitivity to 2,4-dinitrofluorobenzene (280); and abrogated increases in ICAM-1 and LFA-1 expression associated with the development of glomerulonephritis seen in (NZB $\times$ NZW)F_1 mice (343). Clearly, infection of laboratory mice with LDEV could seriously alter research results, especially where immune system function is involved, without any outward evidence of infection.

Central Nervous System

Viruses. (i) Theiler's murine encephalomyelitis virus. Theiler's murine encephalomyelitis virus (TMEV) is a ssRNA virus of the family *Picornaviridae*. TMEV has been found infrequently in laboratory mice and even less often in rats (475). Its primary importance is as a model of poliomyelitis, multiple sclerosis, and virus-induced demyelinating disease (475, 660). Multiple strains exist and are classified according to virulence. Because the virus naturally infects the intestinal mucosa, transmission is primarily fecal-oral, although the infection is not highly contagious. Viral shedding occurs for roughly 2 months (475). In addition, transplacental transmission has been documented (2), and mouse and rat cell cultures may be infected.

Generally, no clinical signs of infection are observed. However, viremia may disseminate virus from the intestine to many tissues, including the liver, spleen, and CNS, where spread via direct extension occasionally results in unilateral or bilateral flaccid paralysis of the hind limbs and, rarely, other neurologic signs (267, 475). Following dissemination of the virus, which is rare but occurs most often around 6 to 10 weeks of age (475), pathologic changes may be seen in the spinal cord and brain; they consist of poliomyelitis with necrosis, nonsuppurative meningitis, microgliosis, perivasculitis, neuronophagia of ventral horn cells (517), and demyelination, possibly mediated by $CD4^+$ T lymphocytes (356), TNF-α (320), and IL-1 (562). Mouse strains differ in their susceptibility to demyelinating disease (483, 497), which is usually induced via experimental inoculation. In addition, intraperitoneal inoculation results in acute myositis that progresses to a chronic inflammatory muscle disease which may be immune system mediated (243). Clearing of the virus depends on the involvement of virus-specific cytotoxic T lymphocytes and IL-2 (386, 496). Natural infection of mice has reportedly interfered with the study of other viral infections (475). In addition, TMEV slows the conduction of spinal motor and somatosensory evoked potentials (324) and could compromise studies involving the CNS.

Multiple and Miscellaneous Systems

Viruses. (i) Adenoviruses. Mouse adenoviruses are dsDNA viruses of the family *Adenoviridae*. Two strains have been reported, the FL-1 (currently MAd-1) and K87 (MAd-2) strains, which are probably distinct species (269). Infections in the mouse, the principal host, have been reported only rarely. Infection of rats has been suspected based on serologic and morphologic studies (475). Transmission of both strains is by contact. MAd-1 has a systemic distribution pattern and may be shed in the urine for up to 2 years (679). This ability of MAd-1 to persist cannot be explained by the model of reduced class I MHC-associated antigen presentation proposed for human adenoviruses (370). Clinical signs have never been observed during natural infection with either strain. However, clinical signs and/or pathologic changes in mice have been observed in a stock- or strain-dependent manner following experimental infection with MAd-1 (235, 260, 369, 679). MAd-1 infection has a striking tropism for the CNS and causes a fatal illness in adult C57BL/6 mice but not in adult BALB/c mice (260). Susceptible mice show symptoms of acute CNS disease, including tremors, seizures, ataxia, and paralysis. Light microscopic examination of CNS tissue revealed petechial hemorrhages, edema, neovascularization, and mild inflammation in the brain and spinal cord (260). In other studies, pathologic lesions were most prominent in the kidneys, heart, spleen, adrenal glands, pancreas, liver, and intestines (52, 235, 274, 286, 421).

MAd-2 may be shed in the feces for 3 weeks in immunocompetent mice (276) and for at least 6 months in athymic mice (669). In contrast to MAd-1, infection with MAd-2 is localized to the intestine, causes no clinical signs, and results in pathologic changes that are limited to intranuclear inclusions in crypt and villous cells of the small intestine (639). Immunity to adenoviruses is primarily humoral. Einarsson et al. (185) found slightly increased IL-11 elaboration in airway stromal cells. Mouse adenovirus infection, while uncommon, may interfere with a variety of studies, particularly those involving the CNS, renal, and gastrointestinal systems.

(ii) Ectromelia virus. Ectromelia virus is the causative agent of mousepox. It is a dsDNA virus in the family *Poxviridae*. Mice are the natural hosts. Rats may be transiently infected only experimentally (475). Reports of natural infection in laboratory mice have become rare in the United States but continue to be common in Europe. However, clinical mousepox was recently reported in mice at a U.S. government facility. The mice had been injected with contaminated, commercially produced pooled mouse serum (162). Serologic surveys conducted in the United States occasionally reveal seropositive mice, further confirming that the agent is present. Importation of animals and/or tissues from Europe represent additional opportunities for introduction into U.S. animal facilities. Transmission is primarily via direct contact and fomites, with skin abrasions serving as portals of entry. Resistance to mousepox varies among mouse strains and is dependent upon multiple genes (76, 499). The C57BL/6 and C57BL/10 strains are highly resistant and generally do not show signs of infection (475). In contrast, C3H, BALB/c, and DBA/2 are among the strains most commonly showing signs of disease. In these mice, clinical signs are evident in nearly all members of the colony and consist of foot swelling, pocks, lethargy, depression, and sudden death (475). Following entry via broken skin, the virus replicates locally in skin and lymph nodes and then causes mild, primary viremia and spreads to the liver and spleen. Massive replication in the macrophages of these organs results in a greater secondary viremia. The virus then localizes in many tissues but most prominently in the skin, conjunctiva, and

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lymph nodes (475). Pathologic changes include massive splenic, lymph node, thymic, and hepatic necrosis; small intestinal mucosal erosions; and cytoplasmic inclusions in the skin and liver. Distal portions of the tail and limbs may necrose and slough, giving rise to the name ectromelia (475). While virus persists for several months in the spleens of infected mice, it is shed in the feces for only about 3 weeks (475). Multiple strains of ectromelia virus exist, with the Moscow strain being most virulent. Virulence appears to be dependent upon the presence of a poxvirus protein with a CHC_4 (RING) zinc finger motif (407, 588). Immune system clearance of the virus is absolutely dependent upon the effector functions of $CD8^+$ T cells, while NK cells, $CD4^+$ T cells, and macrophages are necessary for the generation of an optimal response (152, 346, 485, 653). Like many other poxviruses, ectromelia virus expresses a soluble IFN-γ receptor homolog capable of inhibiting the antiviral activities of IFN-γ (466). Natural infection of laboratory mice with ectromelia virus would severely compromise most research efforts involving mice.

(iii) H-1 virus. H-1 virus (Toolan's H-1 virus) is an ssDNA virus of the family *Parvoviridae*. Relatively little is known of the natural biology of H-1 virus, and its significance is low in rats, the natural host, since natural infection does not cause clinical disease and effects on research are few (475). The primary importance of H-1 virus is as a model for experimentally produced malformations in the CNS and skeletal system of rats (475). Transmission is via exposure to infectious urine, feces, nasal secretions, and milk (475). Natural infection with H-1 virus does not cause disease. However, pathologic changes observed in experimental H-1 virus infection derive from the need for parvoviruses to infect replicating cells, wherein they are lytic (475). Reports of H-1 virus affecting research are limited to hepatocellular necrosis in rats exposed to pathogens or chemicals causing liver injury (475) and possibly to a reduction of the incidence of *Yersinia*-associated arthritis (257, 258), although in the latter studies other copathogens may also have been present. In spite of the paucity of data incriminating H-1 virus as a confounder of research, natural infection of laboratory rats could alter studies of fetal development.

(iv) Kilham rat virus. Kilham rat virus (KRV) is another ssDNA virus of the family *Parvoviridae*. More is known of the natural biology of KRV than of H-1 virus. As with H-1 virus, rats are the natural host of KRV. Transmission is via direct contact with infectious urine, feces, nasal secretions, and milk or by contact with contaminated fomites. The latter is probably more important than for many other rodent viruses, since parvoviruses are highly resistant to environmental extremes and are highly contagious. In addition, transplantable tumors and cell cultures may be infected (475, 484). Rats may remain persistently infected for variable times depending upon their age at infection. Clinical signs of infection are rarely observed but have been reported in rats at day 13 of gestation (351). Rats in that outbreak had reproductive anomalies, including increased fetal resorptions, as well as runting, ataxia, cerebellar hypoplasia, and jaundice of many offspring. In another report, scrotal cyanosis, abdominal swelling, dehydration, and death occurred in young rats exposed to serologically positive adults (114).

Like other parvoviruses, KRV infects actively replicating cells and results in cell lysis and tissue destruction. Therefore, KRV causes lesions primarily during fetal development and neonatal life. Infection may persist for variable times depending upon the age of the rat at infection, but it generally does not last beyond about 3 to 4 months (475). Lesions may occur in multiple organs, including the CNS and gastrointestinal and reproductive systems (475); they consist of focal necrosis, frequently in the liver; hemorrhage; and hypoplasia (475). Infection of laboratory rats has been reported to result in teratogenesis, suppression of leukemia development due to Moloney murine leukemia virus, alteration of lymphocyte responses, induction of IFN production (475), induction of acute type I diabetes in diabetes-resistant BB/Wor rats (74), and alteration of lipid metabolism following in vitro infection (583). Lastly, KRV may alter leukocyte adhesion to rat aortic endothelium (226) and may reduce the incidence of *Yersinia*-associated arthritis (257, 258), although in those three studies other copathogens may also have been present. KRV could profoundly interfere with research involving a variety of body systems, especially if infection occurred during fetal development.

(v) Minute virus of mice. Minute virus of mice (MVM) is an ssDNA virus of the family *Parvoviridae* and therefore shares many biological features with other murine parvoviruses such as mouse parvovirus-1, H-1 virus, and Kilham rat virus. Like other parvoviruses, MVM is extremely contagious. Transmission is primarily via exposure to infectious feces and urine but may also be via fomites and via exposure to nasal secretions. In addition, MVM is commonly found as a contaminant of transplantable tumors and mouse leukemia virus stocks (475, 484). Multiple strains have been described. Probably the best studied are MVM(p), the prototype strain, and MVM(I), an immunosuppressive strain (475). MVM(I) grows lytically in mouse T lymphocytes, whereas MVM(p) infects fibroblasts (475). Mouse strains differ in their susceptibility to MVM (78, 79, 344); however, there are usually no clinical signs with MVM infection, and natural infections cause no pathologic changes. Experimental infection will, however, cause damage to multiple organs if infection occurs during fetal development or shortly after birth (78, 475, 541). While direct evidence of interference with research is limited to a report of myelosuppression (586), it can be surmised that MVM may interfere with research involving the immune system, since MVM(I) infection results in T-lymphocyte lysis and altered B- and T-lymphocyte activities and MVM(p) suppresses the growth of ascites tumors (475).

(vi) Mouse hepatitis virus. Mouse hepatitis virus (MHV) is probably the most important pathogen of laboratory mice. Rats may also become infected but only as sucklings and only under experimental conditions (635). MHV is an ssRNA virus of the family *Coronaviridae*. It is extremely contagious and is transmitted primarily via aerosol, direct contact, fomites, and, experimentally, via transplantable tumors and transplacental passage (302, 475, 484).

Susceptibility, tissue tropism, clinical signs, and pathologic lesions are dependent on several host, environmental, and pathogen factors (30, 70, 475, 703). Approximately 25 strains or isolates of MHV have been described (475) and have been classified as either respiratory or enterotropic. Recently, an outbreak of a highly hepatotropic strain of MHV was reported from a breeding colony of nude mice in Taiwan (399). The presence or absence of the MHV receptor, a glycoprotein in the carcinoembryonic antigen family of the Ig superfamily, may determine tissue tropism (240). Respiratory (polytropic) strains establish in the nasal mucosa, descend to the lungs, and disseminate hematogenously throughout the body or ascend along neurons to the CNS (35, 378, 475, 521). Intestinal involvement is usually absent. Polytropic strains include MHV-1, MHV-2, MHV-3, A59, S, and JHM (475). Enterotropic strains may also become established in the nasal mucosa or in the intestinal tract and disseminate only locally to the liver, abdominal lymph nodes, and, in some cases, the CNS (475, 523). Pulmonary involvement is uncommon. Enterotropic strains include LIVIM, MHV-D, and MHV-Y (475). While polytropic

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strains have historically been considered more common, this situation is thought to have reversed (95, 301). Lesions are present for only 7 to 10 days following infection, are dependent upon strain of virus, and are characterized by multifocal necrosis. Additionally, multinucleate syncytial giant cell formation occurs and may be associated with fragmentation and rearrangement of the Golgi apparatus (389). Lesions due to polytropic strains may be observed in the olfactory mucosa, brain, lungs, and liver, while lesions due to enterotropic strains are generally, though not always, confined to the intestinal tract. Lesions caused by either strain tend to be more severe and widespread in immunocompromised mice (475).

Most infections follow one of three clinical patterns (475). Enzootic (subclinical) infection, commonly seen in breeding colonies, occurs when infection is endemic in the colony and is maintained only by the continual arrival of susceptible animals (newborns). No carrier state exists, although in a recent study viral RNA was detected in the liver up to 60 days after infection (362). Adults are asymptomatic, and their young become asymptomatically infected by the time passively transferred maternal immunity wanes at weaning. Epizootic (clinical) infection occurs less commonly when the pathogen is introduced to a naive colony. Adult infections are again usually asymptomatic. Clinical signs depend upon the virus and mouse strains and are most evident in infant mice; typically, they include diarrhea, poor growth, and death. As the infection becomes established in the colony, the epizootic pattern is replaced with the enzootic pattern. Immunodeficient mice, such as athymic (*nu/nu*) mice, develop a wasting syndrome characterized by severe generalized disease and eventual death (666). Immunity to MHV is primarily but not entirely cell mediated; is partially protective between closely related virus strains; and is known to involve T lymphocytes, macrophages, IFN, and NK cells (299, 300, 377, 378, 578, 723).

Numerous reports document effects of natural or experimental infection with MHV on host physiology and research. In immunocompromised mice, these effects include necrotic changes in several organs, including the liver, lungs, spleen, intestine, brain, lymph nodes, and bone marrow; differentiation of cells bearing T-lymphocyte markers; altered enzyme activities, bilirubin concentration, and antibody responses to sheep erythrocytes in serum; enhanced phagocytic activity of macrophages; rejection of xenograft tumors; impaired liver regeneration; and hepatosplenic myelopoiesis (311, 475). In immunocompetent mice, reported effects include transient immunostimulation followed by immunodepression; thymic involution; depletion of LDEV-permissive macrophages; microcytic anemia and changes in ferrokinetics; decreases in lymphocyte proliferative responses, antibody secretion, phagocytic activity, liver regeneration, blood cell production, number of hepatic sinusoidal endothelial cell fenestrae, incidence of diabetes mellitus in nonobese diabetic mice, and IFN production during SV infection; apoptotic changes in the thymus; increased tumoricidal activity of peritoneal macrophages, hepatic uptake of injected iron, susceptibility or resistance to copathogens, and IFN and IL-12 production; altered hepatic enzyme activity, behavior of ascites myelomas, and expression of cell surface markers on splenic T lymphocytes; molecular mimicry of the host Fc gamma receptor; nerve demyelination; impaired bone marrow pre-B and B cells; induced production of α-fetoprotein and antiretinal autoantibodies in serum; and induced macrophage procoagulant activity (126, 129, 160, 191, 195, 239, 303, 309, 337, 377, 382, 384, 395, 475, 495, 616, 636, 674, 724). Clearly, natural MHV infection of laboratory mice with MHV may affect a plethora of scientific studies and seriously compromise the value of these animals as research subjects.

(vii) Sialodacryoadenitis virus. Sialodacryoadenitis virus (SDAV) is a common, important, and highly contagious pathogen of laboratory rats. SDAV is an ssRNA virus of the family *Coronaviridae*. Transmission is via direct contact and fomites (385). Infant mice, but not adult immunocompetent or *scid* mice, are susceptible to experimental infection (33, 385, 520). Natural infection of mice has not been reported (475). SDAV infections follow patterns similar to those of MHV, another coronavirus. Enzootic infection occurs in breeding colonies and is sustained only by the continual introduction of susceptible hosts (newborns). Suckling rats develop transient conjunctivitis. Weanlings and adults are asymptomatic (330). Epizootic infection occurs when the agent is introduced to a fully susceptible population. Clinical signs are again transient, may vary in severity, and include cervical edema, sneezing, photophobia, conjunctivitis, nasal and ocular discharge, porphyrin staining, and corneal ulceration and keratoconus (330, 475).

Multiple strains of SDAV exist (358), and tissue tropisms differ somewhat among strains (475). SDAV has a tissue tropism for tubuloalveolar glands of the serous or mixed serous-mucous types (475). Therefore, inflammatory changes consisting primarily of diffuse necrosis are seen in the lacrimal (including the Harderian) glands and submandibular and orbital salivary glands. Secondary damage may occur to structures of the eye. Cervical lymph nodes and the thymus may also be mildly necrotic. Some strains of SDAV affect the respiratory tract, where pathologic changes may include patchy necrotizing rhinitis, tracheitis, bronchitis, and bronchiolitis, with multifocal pneumonitis (51, 400, 722). SDAV causes more severe respiratory tract lesions in LEW rats than in F344 rats (400). Virus is present in tissues for only about 1 week. There is no carrier state, so clinical signs and pathologic changes are transient. In athymic rats, infection is more severe, is persistent, and may be fatal (266). SDAV has been shown to alter estrous cycles, increase embryonic and postnatal mortality (673), cause depletion of epidermal growth factor in submaxillary salivary glands (518), cause anorexia and weight loss (489, 672), and reduce IL-1 production by alveolar macrophages (66). In addition, SDAV potentiates lesions caused by *M. pulmonis* (580, 582), though not by altering pulmonary clearance or intrapulmonary killing (482). Natural infections of laboratory rats with SDAV would be expected to interfere with studies involving the lacrimal, salivary, respiratory, ocular, olfactory, reproductive, and immune systems and to interfere with growth of infected newborns.

Bacteria. (i) *Corynebacterium kutscheri*. *Corynebacterium kutscheri* is a gram-positive bacillus that infects both mice and rats. Transmission is fecal-oral. The oral cavity and large intestine most commonly serve as reservoir sites for a latent carrier stage (8, 9). Natural infections are usually subclinical (8, 9) and are revealed only by the immunosuppressive effects of certain drugs, experimental manipulations, or other infectious agents (475). Clinical signs in rats, when present, usually include dyspnea with abnormal lung sounds, weight loss, humped posture, and anorexia. Hematogenous spread occurs in both species and accounts for abscess formation in various organs. In rats, abscesses commonly develop in the lungs and extend to the pleura, while in mice, abscesses occur more often in the kidneys and liver (713, 715). Strain differences in colonization sites (9) and susceptibility have been reported. C57BL/6 and B10.BR/SgSn mice are among the more resistant strains, while Swiss, BALB/cCr, and A/J are among the more susceptible strains (10, 295). Strain susceptibility may reflect differences in

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the efficiency of mononuclear phagocytes (296) or cytokine responses (352). Experimental procedures that cause immunosuppression of rats or mice may result in the unwanted development of active *C. kutscheri* infection, which could compromise a variety of studies, including those of the respiratory system.

Parasites. (i) *Encephalitozoon cuniculi.* *Encephalitozoon cuniculi* is a microsporidian protozoan parasite infecting a wide range of hosts, including laboratory mice and rats. At least three strains have been identified based on host specificity and other criteria (166). The prevalence remains high in many rabbitries, and rabbits may serve as a source of infection for mice and rats (475). In contrast, the prevalence is low in modern rodent facilities. The primary significance of *E. cuniculi* in laboratory rodents is as a contaminant of transplantable tumors (475). In addition to infected tumors, transmission is via exposure to infectious urine. Following ingestion, sporoplasm from infectious spores gains entrance to host intestinal epithelium, where multiplication occurs. Continued multiplication results in eventual host cell rupture, with dissemination to other organs, including the brain, kidneys, liver, and lungs (475).

Infection is usually asymptomatic in immunocompetent rodents. Lesions are most commonly found in the kidneys and brain. In the kidneys, lesions consist of intracellular parasites in the renal tubular epithelium and inflammatory changes, with eventual focal destruction of tubules and replacement by fibrous connective tissue, resulting in pitting of the renal surface (475). In the brain, lesions consist of meningoencephalitis. In rats, but not in mice, there is also multifocal granulomatous inflammation (475). Mouse strains differ in their susceptibility to infection, with C57BL/6, DBA/1, and 129J being highly susceptible; C57BL/10, DBA/2, and AKR being of intermediate susceptibility; and BALB/c, A/J, and SJL being relatively resistant (475). In contrast to immunocompetent mice, athymic (*nu/nu*) mice experience high mortality with infection (165, 475). Macrophage microbicidal activity may involve nitrite (NO_2) (164). Infection with *E. cuniculi* transiently increases NK cell activity, causes hepatosplenomegaly with ascites, alters brain and kidney architecture, alters host responses to transplanted tumors, and reduces cellular and humoral responses to a variety of immunogens (475). *E. cuniculi* infection of mice is used as a model of human microsporidiosis (164, 365). Natural infection of laboratory mice and rats would compromise studies involving the gastrointestinal, renal, and central nervous system and possibly others.

RABBITS

Respiratory System

Bacteria. (i) *Bordetella bronchiseptica.* *Bordetella bronchiseptica* is a gram-negative rod commonly found inhabiting the respiratory tracts of rabbits. Transmission is via aerosol, fomites, and contact and occurs early in life. There is a high prevalence of seropositivity in laboratory rabbits (519). Most infections are asymptomatic and become problematic only in association with *Pasteurella multocida* infection (148). In those cases, clinical signs include oculonasal discharge ("snuffles"), lethargy, anorexia, dyspnea, and occasionally death. I have also treated cases of rabbit bordetellosis in which no other pathogens could be identified or where a primary infection with *P. multocida* was cleared with antibiotics, only to have clinical signs resume with overgrowth of *B. bronchiseptica*. Rabbits also occasionally develop *B. bronchiseptica* abscesses. Typical pathologic changes of the lower respiratory tract are those of suppurative bronchopneumonia and interstitial pneumonitis (517). Microscopically, there may be prominent peribronchial lymphocyte cuffing (517). *B. bronchiseptica* causes ciliostasis in canine tracheal outgrowth cultures (44). Similar effects in rabbits could facilitate infection and clinical disease caused by copathogens such as *P. multocida* (517). It has been reported that rabbits with *B. bronchiseptica* infection have defective alveolar macrophage function (746), which supports the hypothesis that infection with *B. bronchiseptica* facilitates infection with other pathologic agents. Clinical bordetellosis would compromise the usefulness of laboratory rabbits used in respiratory studies. However, given the high prevalence of latent *B. bronchiseptica* infection, it is unlikely that a laboratory rabbit colony can become or remain free of infection without resorting to expensive barrier housing. Clinically affected rabbits should be treated immediately or, preferably, culled.

(ii) CAR bacillus. As described above, CAR bacillus is a gram-negative, filamentous, rod-shaped, gliding bacterium. Analyses of 16S rRNA gene sequences from rabbit-origin CAR bacillus suggest close relationship to members of the genus *Helicobacter* (137). Infection of laboratory rabbits has been reported in the United States (136) and Japan (375). Clinical disease in rabbits has not been demonstrated or induced. Kurisu et al. (375) reported that organisms were primarily found colonizing the apices of cells lining the larynx, trachea, and bronchi. Lesions consisted of slight hypertrophy and hyperplasia of ciliated upper respiratory epithelium, with occasional loss of cilia and mild inflammation of the lamina propria. Others have reported seroconversion without the development of either lesions or clinical disease following experimental infection of rabbits with CAR bacillus of rat (426) or mouse (598) origin. Natural infection of rabbits may confound studies in which upper airway architecture is evaluated histologically.

(iii) *Pasteurella multocida.* *P. multocida*, a gram-negative, bipolarly staining rod, is the most common pathogen of laboratory rabbits. Infection is nearly ubiquitous among rabbit colonies; within a colony, infection is also common, frequently occurs at birth, and increases with age. Transmission is by direct contact and, to a lesser extent, fomite, aerosol, and sexual exposure. Disease susceptibility depends upon host, environmental, and bacterial factors. Differences in susceptibility have been reported among rabbit strains (172). Environmental factors such as shipping, experimentation, wide temperature fluctuations, and high ammonia levels increase susceptibility (154). Lastly, bacterial strains differ in many aspects including growth characteristics (169) and colonization site. The colonization site may indirectly affect virulence, probably due to production of specific adhesion molecules (59, 155, 237). Bacterial strains also differ in endotoxin and exotoxin production and in their ability to resist phagocytosis and killing by neutrophils. However, these factors have not been absolutely correlated with virulence (154, 170, 627). Bacterial strains have been grouped based on an indirect hemagglutination assay or gel diffusion precipitin test.

The majority of rabbits infected with *P. multocida* are asymptomatic carriers. Transition from asymptomatic to symptomatic infection is related to factors discussed above. When present, clinical signs can occur in nearly any organ, probably due to hematogenous spread of the organism. The most common presentations, in descending order of occurrence, are rhinitis (snuffles), conjunctivitis, pneumonia, otitis media, otitis interna, abscesses, genital tract infections, and septicemia (154). Physiologic alterations may also occur (656). Colonization often occurs initially in the pharynx. The infection quickly spreads to the nasal cavity, from which it disseminates via

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direct or hematogenous spread to the lungs, middle ear, conjunctival sac, subcutaneous tissues, and visceral organs (154). Regardless of the organ system affected, the hallmark of *P. multocida* infection is suppurative inflammation. The accompanying exudate is most often purulent. Microscopically, affected tissues may be edematous, hyperemic, congested, and necrotic (517). As alluded to above, the factors responsible for tissue damage are incompletely known but may include the production of toxins, antiphagocytic substances, or adhesions (154). Large amounts of thick pus may also place direct pressure on adjacent tissues, such as in the lungs, and may further compromise organ function. *P. multocida* infection has been shown to increase the expression of vascular cell adhesion molecule 1 by aortic endothelium (548) and to alter host physiology (656). Eventual natural infection of laboratory rabbits with *P. multocida* is nearly unavoidable without the use of expensive barrier housing. While latent nasal colonization will probably have no effect on experimental studies, clinical pasteurellosis could invalidate several types of studies, particularly those involving the respiratory tract.

Digestive System

Viruses. (i) Adenovirus. Adenoviruses are dsDNA viruses that have been recovered from many animal species. However, adenovirus infections are uncommon in rabbits and have been reported only in Europe. Bodon and coworkers (54, 55) reported isolating an adenovirus from the spleen, kidney, lungs, and intestines of 6- to 8-week-old rabbits with diarrhea. The virus agglutinated rabbit erythrocytes. Little information is available on the mechanisms and consequences of adenovirus infection in rabbits. Therefore, much of what is known about adenovirus infection of rabbit tissues comes from studies with rabbit models and adenoviruses from other species. Reddick and Lefkowitz (543) observed persistent viral infection of lymphoid tissues following experimental infection of rabbits with human adenovirus type 5. Lippe et al. (403) demonstrated binding of the E3/19K protein component of adenovirus type 2 to newly synthesized human cell line MHC class I molecules, with inhibition of MHC molecule phosphorylation and trafficking to the cell surface.

Recombinant adenoviruses have successfully infected rabbit hepatocytes (367), autologous rabbit vascular interposition grafts (374), and cultured rabbit corneal epithelial cells (12). Others have used an in vivo rabbit model system to test the efficacy of novel antiviral drugs against human adenovirus type 5 infections (244). These studies illustrate the utility of rabbit-adenovirus model systems. It is likely that endogenous infections with rabbit adenovirus would interfere with such studies as well as with research on rabbit intestinal physiology or with adenovirus vaccine studies conducted in rabbits (742).

(ii) Rabbit enteric coronavirus. Two distinct forms of coronavirus infection have been reported in rabbits. These include rabbit enteric coronavirus and pleural effusion disease/cardiomyopathy virus, which is discussed in the section on multiple systems, below. The inability to culture these viruses in vitro has limited experimental study of them.

Rabbit enteric coronavirus, an ssRNA virus, has been detected in the feces of young rabbits with diarrhea in Canada and Europe (181, 383, 503, 514). Serologic surveys have extended knowledge of the range of infected rabbitries to the United States (149). However, only one natural outbreak of disease has been reported, in Germany (181). In that outbreak, clinical signs in 3- to 8-week old rabbits included lethargy, diarrhea, abdominal distension, and 100% mortality. The cecum was distended with watery fluid, and diffuse inflammation and mucosal edema were found throughout the intestinal tract. In experimental infections, clinical signs are limited to variable fecal water content without mortality (158, 503). In one study, the small intestines were congested, with transient evidence of villus tip and M cell necrosis, atrophy, and crypt hyperplasia. The cecal contents were watery (158). The virus hemagglutinates rabbit erythrocytes but has not been shown to be cytopathic for a variety of cell lines (159, 383).

There is a high level of serologic cross-reactivity between rabbit enteric coronavirus and other mammalian group 1 viruses (604). Therefore, natural infection of laboratory rabbits would not only interfere with research involving the intestinal tract but would also confound research with polyclonal antimammalian coronavirus serum produced in infected antibody-producing rabbits.

(iii) Lapine parvovirus. Lapine parvovirus is an ssDNA virus. Infection has been identified serologically in commercial rabbitries in the United States, Europe, and Japan (442). Like other parvoviruses, transmission is fecal-oral. Clinical signs in neonatal rabbits consist of anorexia and listlessness. Pathologic changes consist of catarrhal enteritis with hyperemia of the small intestine, hypersecretion of intestinal mucus, and exfoliation of small intestinal epithelial cells. Virus can be detected in most visceral organs (424). Natural infection of laboratory rabbits could interfere with research in which rabbit cell cultures or in vitro immunologic assays are used and in research in which architectural changes in visceral organs would be confounding.

(iv) Rabbit oral papillomavirus. Rabbit oral papillomavirus is a dsDNA virus of the family *Papovaviridae*. The prevalence of infection is low in laboratory rabbit colonies. Transmission is via direct contact. Development of lesions may be facilitated by damage to the oral mucosa (716). When present, lesions are usually found on the ventral surface of the tongue but may also be found on the mucosal surface of the buccal cavity (517); they consist of small whitish growths which may eventually ulcerate (171) before disappearing (509). Histologically, the lesions appear as papillomas (716). Natural infection of laboratory rabbits with rabbit oral papillomavirus could interfere with feeding and studies in which feed intake and/or weight gain is measured.

(v) Rotavirus. Rotaviruses are dsRNA viruses of the family *Reoviridae*. Rotaviruses are classified into groups and subgroups (171). The isolate infecting rabbits, group A serotype 3, also infects humans and other animals. Infection is common in both wild and laboratory rabbits. The virus is extremely contagious, and transmission is fecal-oral. Clinical signs vary depending on host age, exposure history, and the presence of other synergistic organisms (171). In endemically infected colonies, outbreaks are most common in recently weaned rabbits, probably due to waning of passively transferred maternal antibodies. Disease is most severe in preweanlings from naive colonies. Clinical signs include severe diarrhea, anorexia, dehydration, and high mortality (171). Pathologic changes include marked congestion, distension, and petechiation of the colon (572); small intestinal distension with mucosal hemorrhages; and a fluid-filled cecum (98). It should be borne in mind, however, that in most reports of outbreaks, attempts to demonstrate the presence of other pathogens have not been made. It is generally thought that pure rotavirus infections are mild and that lesions are limited to a fluid-filled cecum, swollen mesenteric lymph nodes, small intestinal villous atrophy most pronounced in the ileum, increased crypt depth, and lymphocytic infiltrates in the lamina propria, without involvement of the large intestine (171, 396, 514, 648). In this regard, Thouless et al. (647) reported a synergistic effect between rotavirus and

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Escherichia coli, whereby weanling rabbits developed more severe diarrheal disease than that resulting from either pathogen alone. Infection is self-limiting, and immunity is long-lasting (118, 171, 268). Therefore, natural infection of laboratory rabbits with rotavirus would have at least temporary adverse effects on research involving intestinal physiology.

Bacteria (i) *Clostridium piliforme.* As discussed in the section on pathogens of mice and rats, *C. piliforme* is a gram-negative, filamentous bacteria infecting a wide range of animals, including rabbits, and is the causative agent of Tyzzer's disease. The prevalence of infection remains high in domestic rabbits supplied for research (247). Transmission is via ingestion of infectious endospores. Young rabbits are most susceptible, although rabbits of all ages may develop clinical signs. Both epizootic and enzootic infections occur (154). Clinical signs include profuse, watery diarrhea; lethargy; anorexia; dehydration; and death. Surviving rabbits may become chronically affected and serve as a source of infection for other rabbits. Enzootic infections may be revealed following immunosuppression or other stressors (6). Lesions of Tyzzer's disease consist primarily of necrotic foci in the cecum and adjacent intestinal segments, the liver, and, rarely, the myocardium. There are petechial and ecchymotic hemorrhages on the serosal surface of the cecum and adjacent intestine. Intestinal stenosis may follow fibrotic healing of necrotic foci (6, 154). Natural infection of rabbits used in research would compromise studies involving the gastrointestinal and cardiac system even if no deaths occurred.

(ii) *Clostridium spiroforme.* Enteric diseases in general and specifically enterotoxemic conditions are common in laboratory rabbits. *Clostridium spiroforme*, a gram-positive, endospore-forming anaerobe, is the predominant causative agent of rabbit enterotoxemia. Occasionally, other clostridial species such as *C. perfringens* and *C. difficile* are involved (154). Rabbits do not normally harbor *C. spiroforme*, and transmission is fecal-oral. Recently weaned rabbits are most susceptible to enterotoxemia, probably due to opportunistic overgrowth of their immature gastrointestinal flora by *C. spiroforme*. Overgrowth is facilitated by, but does not require, some local or systemic stress such as weaning, antibiotic administration, or change of feed to a high-energy, low-fiber diet (154). Disease also occurs in adults following disruption of the normal flora by antibiotics; copathogens; or other stressors, including lactation or dietary changes (154). The hallmark of enterotoxemia is acute onset of watery diarrhea accompanied by anorexia and lethargy, which may end in death. Peracute cases with no premonitory signs, and chronic cases presenting as anorexia and weight loss, also occur. Pathologic findings include petechial and ecchymotic hemorrhaging on the serosal surface of the cecum and, occasionally, other segments of the large intestine. The cecum is usually filled with fluid and gas (154). Mucosal lesions consist of inflammation, focal necrosis, and formation of erosions and ulcers. All rabbit isolates of *C. spiroforme* produce a cytotoxin similar to *C. perfringens* type E iota toxin. Natural infection of laboratory rabbits would interfere with many types of studies, most notably those involving the gastrointestinal system.

Parasites. (i) *Cryptosporidium parvum.* Rabbits, like other mammals, may become infected with *Cryptosporidium parvum*, an intracellular, extracytoplasmic parasitic protozoan inhabiting the epithelial lining of the ileum and jejunum. The prevalence of infection is assumed to be low in laboratory rabbits. The life cycle is direct, and sporulated infectious oocysts are released in the feces. Unlike in other mammals, in which infection often results in severe disease and clinicopathologic changes (140), both natural and experimental infections of rabbits are usually asymptomatic (319, 544). Despite the lack of clinical signs, histologic examination of the intestines of infected rabbits reveals alterations in villus architecture, including a decrease in the villus-to-crypt ratio, disruption of microvilli, mild edema of the lamina propria, and dilation of intestinal lacteals (319, 544).

Rabbits are used in a variety of ways in cryptosporidiosis research. Near-term fetal rabbit small intestinal xenografts are suitable for studies of early events of cryptosporidial infection (649). Laboratory rabbits are used to produce polyclonal anti-cryptosporidial antiserum (487, 546). Natural infection of antibody-producing rabbits with *C. parvum* might skew the seroreactivity profiles of such rabbits. Also, natural infection may complicate the interpretation of histologic changes in the intestines of rabbits in studies in which the intestinal mucosal architecture is evaluated.

(ii) *Eimeria stiedae.* *Eimeria stiedae* , an Apicomplexan parasite, is the causative agent of hepatic coccidiosis in rabbits. While infection may be common in some commercial rabbitries (533, 700), modern laboratory animal husbandry methods and effective chemotherapeutics have considerably reduced the prevalence of infection in laboratory rabbits. The life cycle is direct, with unsporulated oocysts released in the bile and exiting the rabbit with the feces. Sporulation to the infective stage occurs in less than 3 days under optimal conditions (609). Sanitation of cages removes infectious oocysts. Sporozoites penetrate the small intestinal mucosa and arrive in the liver. The exact means of transport from the intestine to the liver is uncertain, although evidence exists for both hematogenous and lymphatic migration (506). Once in the liver, sporozoites invade the bile duct epithelium and undergo asexual replication (schizogony) followed by the production of sexual stages (gametogony), which unite to form oocysts. Revets et al. (547) reported finding virus-like RNA particles in sporozoites of all isolates of *E. stiedae* examined. The significance of such particles is unknown.

Mild infections are frequently asymptomatic. When present, severe infections usually occur in young rabbits (27, 700) and proceed through four pathophysiologic events: (i) hepatic damage during schizogony, (ii) cholestasis, (iii) metabolic dysfunction, and (iv) "immunodepression" (28). When present, clinical signs are referable to hepatic dysfunction and biliary blockage and include anorexia, icterus, diarrhea or constipation, and, rarely, death. Gross necropsy findings include hepatomegaly with dilated bile ducts appearing as yellowish lesions throughout the liver. The gallbladder may also be enlarged and contain exudate. Microscopically, there is destruction and regeneration of the bile duct epithelium resulting in bile duct hyperplasia, reduplication, fibrosis, distension, and lymphoplasmacytic infiltration. Rupture of enlarged bile ducts results in a severe granulomatous response, while compression of adjacent liver tissue results in ischemic hepatic necrosis (506). Clinicopathologic changes in natural and/or experimental infections include increases in β- and γ-globulin, β-lipoprotein, succinate dehydrogenase (which later declines), bilirubin, alanine transaminase, and aspartate transaminase levels in serum. Decreases in α-lipoprotein, glucose, and protein levels in serum and in alkaline phosphatase activity in the liver have also been noted (1, 27, 28, 506). In addition, pharmacokinetics, hepatic biotransformation, and biliary and urinary excretion of conjugated bromosulfophthalein are markedly altered following experimental infection (190).

Mildly infected rabbits mount both cellular and humoral immune responses (355, 506). In contrast, Barriga and Arnoni (28) reported that the final pathophysiologic event of overwhelming hepatic coccidiosis is "immunodepression," so called because young rabbits were unable to control the production of

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sexual stages of the parasite. However, caution is warranted in using the term "immunodepression," since no immune function tests were conducted to evaluate immune system status. Rabbits may have been unable to control the infection due to immunosuppression, clonal exhaustion, anergy, clinicopathologic changes, etc. Further studies are needed to explain the apparent unresponsiveness in terminal hepatic coccidiosis.

E. stiedae has been used to establish a model of liver disease mimicking biliary cirrhosis (190). Natural infection of laboratory rabbits with *E. stiedae* would interfere with such studies and may confound other studies involving the hepatobiliary system and/or evaluation of enzyme profiles in serum.

(iii) Intestinal coccidiosis. Coccidia of several species of the genus *Eimeria* are known to infect laboratory rabbits. The most pathogenic species are *E. intestinalis* and *E. flavescens*, followed by *E. magna*, *E. irresidua*, *E. piriformis*, *E. perforans*, *E. neoleporis* (*E. coecicola*), and *E. media* (682, 690). Both mixed- and single-species infections are common, although the prevalence has declined with improvements in facility management. The life cycles of intestinal coccidia are similar to that of *E. stiedae*, except that all stages occur in the intestine (401), with the exact location depending upon the species of *Eimeria*. Drouet-Viard et al. (175) have suggested that sporozoites invade the duodenal epithelium and migrate to the ileum by an as yet unknown nonluminal tissue route. Asexual stages have also been reported to develop in intestinal lymphoid tissue (505). Clinical signs are variable and are usually present only in young animals; they include weight loss, diarrhea with or without blood, intussuception, and death (506). The cecum and colon contain dark, watery, foul-smelling fluid. Histopathologic changes in infected intestinal segments include epithelial necrosis; mucosal ulceration, congestion, edema, and, occasionally, hemorrhages; villous atrophy; and leukocytic exudate. Clinicopathologic changes reported in cases of experimental coccidiosis included hemodilution and hypokalemia (517). Unlike for avian coccidia, where considerable information is available on physiologic effects of *Eimeria* spp., such as on TNF production (747), little similar information is available on intestinal coccidiosis of rabbits. As with *E. stiedae*, mild infections result in the development of protective immunity (124, 486). However, immunity is not cross-protective among intestinal coccidia. Natural infection of laboratory rabbits with intestinal coccidia may confound studies of intestinal physiology and/or architecture.

(iv) *Passalurus ambiguus*. *Passalurus ambiguus*, the rabbit pinworm, is common in lagomorphs in many parts of the world. The life cycle is direct, with adult worms found principally in the anterior cecum and large intestine and larval stages found in the mucosa of the small intestine and cecum. Infection is established following ingestion of infective eggs (297). Many consider rabbit pinworms harmless, while others have reported declines in the general condition and breeding performance of rabbits coinfected with *P. ambiguus* and *Obeliscoides cuniculi*, a helminth parasite uncommonly found in the stomachs of rabbits (179). As is the case with rodent pinworm infections, more sophisticated studies may reveal subtle effects of these parasites on rabbit health and suitability as research subjects.

Dermal System

Viruses. (i) Cottontail rabbit (Shope) papillomavirus. Cottontail rabbit papillomavirus is a dsDNA virus of the family *Papovaviridae*. Infection is common in wild rabbits of the midwestern and western United States but uncommon in laboratory rabbits. Transmission to domestic rabbits most probably occurs only from infected wild rabbits, since virus is rarely detected in lesions of domestic rabbits but is common in lesions of wild rabbits. Transmission is via arthropod vectors such as mosquitoes and, historically, ticks (171). In domestic rabbits, wartlike growths (papillomas) occur most commonly on the eyelids and ears (264) and frequently progress to squamous cell carcinomas that commonly metastasize to regional lymph nodes and lungs (368). Amyloid deposition in the kidneys, liver, and spleen is also common (171). Cottontail rabbit papillomavirus was the first oncogenic mammalian virus recognized. It has been extensively studied as a model of oncogenesis (402, 558). Natural infection of laboratory rabbits would compromise several types of studies, most obviously long-term carcinogenicity studies.

Bacteria. (i) *Staphylococcus aureus*. The reader is referred to the section on mice and rats for a discussion of the biology of *S. aureus*. Multiple strains of *S. aureus* have been isolated from rabbits (161). In addition to entry via breaks in normal barriers, transmission may occur following ingestion of mastitic milk. Infection occurs most commonly in the skin and subcutaneous tissues but may also be found in the upper airways, lungs, conjunctiva, middle ear, feet, and mammary glands. Occasionally, staphylococcal septicemia occurs, initiating disseminated abscess formation (154). Suppurative inflammation consists primarily of neutrophils and necrotic cellular debris and may be accompanied by edema, hemorrhage, and fibrin deposition (154). As discussed in the section on *S. aureus* infection of mice and rats, biologically active products of *S. aureus* (86, 105, 130, 154, 206, 334, 498, 545, 560) have profound effects on the host (50, 206, 292, 585). In addition, specific effects in rabbits include vasoconstriction (699), inhibition of myocardial function (498), changes in the activity of hepatic enzymes (363), and decreased neutrophil function (24).

Rabbits are highly susceptible to staphylococcal infections and are therefore used extensively in *S. aureus* research (11, 25, 39, 88, 90, 105, 121, 187, 431). While asymptomatic colonization is of no concern and, indeed, is unavoidable outside of strict barrier containment, active infection would interfere with many studies involving rabbits.

(ii) *Treponema cuniculi*. *Treponema cuniculi* is a gram-negative spirochete and is the causative agent of rabbit syphilis. Infection is common in wild hares from many parts of the world and occasionally occurs in rabbits produced for research facilities. Transmission is primarily sexual via penetration of mucous membranes but may also occur by other routes (154). Susceptibility is rabbit age and strain dependent (139). The course of the disease is relatively lengthy. Lesions develop 3 to 6 weeks following exposure and are most apparent on and around mucocutaneous junctions of the face and genitalia. Lesions begin as areas of erythema and edema, with or without vesicles, and progress to ulcers and crusts. The lesions generally resolve after several weeks (138). Histologically, advanced lesions consist of epidermal ulceration, hyperkeratosis, hyperplasia, and acanthosis overlain by crusts (154). Dermal inflammation consists primarily of macrophages and plasma cells. Serologic responses are also slow to develop, requiring 2 to 3 months from the time of infection (139). In unmedicated rabbits, in contrast to rabbits treated with antibiotics, antibodies may remain positive (168), suggesting a carrier state, possibly in regional lymph nodes (154).

Because most treponemes cannot be grown in vitro and because *T. pallidum*, the causative agent of human syphilis, is known to infect rabbits, the laboratory rabbit has been extensively used as a model of human syphilis (22, 83, 474, 530, 587). Consequently, a considerable body of information has been gathered on *T. pallidum* infections of rabbits, and cautious extrapolation to *T. cuniculi* is possible. By using the rabbit-*T.*

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pallidum model, it has been demonstrated that the development of immunity is extremely complex and involves a composite of both stimulation and down-regulation (207). Mononuclear cells from rabbits chronically infected with *T. pallidum* may lose the ability to produce or bind IL-2 (530). Spleen cells of rabbits infected with *T. pallidum* produce antitreponemal lymphotoxins. This ability was disturbed when circulating immune complexes and autolymphocytotoxins were present, suggesting that the impairment of the ability of the cells to produce antitreponemal lymphotoxins may facilitate the survival of treponemes in the host despite the presence of immunologically competent cells (529). Defensins produced by rabbit alveolar macrophages and neutrophils may contribute to the control of local *T. pallidum* infection, suggesting a role for acute inflammatory processes in the resolution of early experimental syphilis (64). Natural infection of laboratory rabbits would interfere with several types of studies, such as those involving the dermal and immune systems.

Parasites. (i) *Cheyletiella parasitivorax.* *Cheyletiella parasitivorax* is a nonburrowing mite with widespread distribution (297). The entire life cycle is completed on the rabbit host. Mites attach to the host, primarily in the interscapular region, and obtain tissue fluids. When present, histopathologic changes include subacute dermatitis with mild hyperkeratosis, accompanied by an inflammatory exudate. Affected areas may be partially alopecic, with a finely granular material (dried exudate) covering the skin. The lesions are nonpruritic (216, 675). While infested rabbits appear largely unaffected by the parasite, histopathologic changes in the skin could compromise dermal studies conducted in affected rabbits.

(ii) *Psoroptes cuniculi.* *Psoroptes cuniculi* is an obligate, nonburrowing parasite causing otoacariasis in domestic rabbits. The prevalence of infestation is high, and infestation has been found worldwide. Mites are found almost exclusively on the inner surface of the pinnae. The entire life cycle is completed on the rabbit. Clinical signs include intense pruritus (itching), scratching, and head shaking with subsequent serum exudation and crusting on the pinnae, which are painful. Self-excoriation may lead to secondary bacterial infections. The mites initially feed on skin detritus and later feed on serum exudates. Gross observations include inflammation and serum crusting of the inner surfaces of the pinnae. Histologically, the pinnae become chronically inflamed with hypertrophy of the malpighian layer, parakeratosis of the horny layer, and epithelial sloughing (297). As in other animal species with psoroptic mange, the clinical signs and histopathology of infested rabbits are suggestive of an IgE-mediated type 1 hypersensitivity response. Lymphocyte responsiveness and antibody production are suppressed in heavily infested rabbits (667), and immunogenic parasite glycoprotein antigens have been identified (668). While very mild infestations may not alter immune responsiveness (667), heavy infestations could alter the immune function of laboratory rabbits. Additionally, behavioral changes in pruritic rabbits could alter a variety of studies, including those dependent upon adequate feed intake. Laboratory rabbits are routinely treated prophylactically with ivermectin to prevent clinical infestations.

(iii) *Sarcoptes scabiei.* *Sarcoptes scabiei* is an obligate, burrowing parasite that rarely infests domestic rabbits. Infestations usually begin on the muzzle and extend to the remainder of the head. The entire life cycle is completed on the rabbit. Female mites tunnel burrows into the epidermis and are found within these burrows, along with eggs and young larvae, while older larvae, nymphs, and adult males are found on the surface (297). Mites feed on epithelial cells and serum exudates. Pruritus associated with scabies is considered among the most intense known in veterinary or human medicine. Animals will forego feeding in favor of scratching in an attempt to obtain some relief. Self-excoriation often leads to secondary bacterial infections. In addition to pruritus, clinical signs may include general debility, emaciation, and death (297). Pathologic findings include dermatitis with serum exudation. Heavy infestations may result in anemia, leukopenia, and changes in biochemical levels in serum (14). It is possible that rabbits proceed through stages of cutaneous hypersensitivity and show immune response patterns similar to those described for swine with sarcoptic mange (21); however, this has not been explored. Serum antibody profiles of infested rabbits have been reported (456). Natural infestation would probably render laboratory rabbits unusable for nearly any purposes, pending treatment with ivermectin or other acaricides.

Fungi. (i) Dermatophytes. Dermatophytes, most commonly *Trichophyton mentagrophytes* but also *Microsporum gypseum* and *M. canis*, are common in rabbitries in many parts of the world (119, 457, 599, 655). Similar species of dermatophytes infect laboratory rabbits (48, 694), although the incidences of infection and clinical disease (dermatophytosis, ringworm, favus) are low in well-managed animal facilities. Young or immunocompromised rabbits are thought to be most susceptible (48). Dermatophytes infect the epidermis and adnexal structures, including hair follicles and shafts, usually on or around the head, and cause pruritus, patchy alopecia, erythema, and crusting. Histopathologic changes in the underlying skin include neutrophilic and lymphoplasmacytic dermatitis, hyperkeratosis, folliculitis, and acanthosis. Abscess formation in hair follicles may occur secondarily (48, 517). Natural infection of laboratory rabbits may result in histopathologic changes which could confound studies involving the skin.

Genitourinary System

Viruses. (i) Rabbit hemorrhagic disease virus. Rabbit hemorrhagic disease virus is an ssRNA virus, most probably of the family *Caliciviridae* (493); it is closely related to European brown hare syndrome virus (729) and the newly named rabbit calicivirus (89). On the basis of both outbreaks and serologic studies, distribution appears to be worldwide (171). Transmission is horizontal. Sudden death may preclude the observation of additional clinical signs. When observed, the clinical signs may be referable to nearly any body system, since the underlying pathology is one of viremia followed by disseminated intravascular coagulation and multiple organ system failure. Pathologic changes are most prominent in the lungs and consist of congestion, hemorrhage, and thrombosis. Acute hepatic necrosis is also usually evident. Virtually any other organ may have pathologic changes due to microinfarction (419). Hematologic alterations include lymphopenia, thrombocytopenia, and prolongation of clotting times (171). The effects of natural rabbit hemorrhagic disease virus infection on research could vary from mild to catastrophic, depending on the virulence of the infecting strain. Strains exist for which clinical signs have not been readily observed (554) and for which mortality is high (687).

Parasites. (i) *Encephalitozoon cuniculi.* *E. cuniculi* is a microsporidian protozoan parasite capable of infecting a range of hosts, including rabbits and humans (157). The prevalence remains high in some rabbitries (253, 719), ensuring that at least some laboratory rabbits are infected. The life cycle is incompletely known. Transmission is thought to be horizontal, primarily via the urine. Following ingestion, sporoplasm from infectious spores gains entrance to the host intestinal epithelium, where multiplication occurs. Continued multiplication

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results in eventual host cell rupture, with dissemination to other organs, including the liver, lungs, brain, and kidneys (128).

Infection is usually asymptomatic. When clinical signs do appear, they are generally referable to the nervous system and include torticollis, convulsions, tremors, paresis, and coma (510). Infection of dwarf rabbits has also been implicated in phacoclastic uveitis (731). Lesions are most commonly found in the kidneys and brain. Multiple, pinpoint lesions may be observed on the surface of the kidneys. Microscopically, these represent areas of granulomatous nephritis or lymphoplasmacytic infiltration, with fibrosis, tubular degeneration, and eventual focal and segmental hyalinosis and sclerosis (209, 504). Organisms may be observed, following special staining, within renal tubule cells. In the brain, the lesions consist of randomly distributed, multifocal granulomas (granulomatous encephalitis), characterized by areas of necrosis, often containing organisms, and usually surrounded by mixed leukocytes. Lesions are often perivascular and periventricular. Lymphoplasmacytic perivascular cuffing and nonsuppurative meningitis may also be present (506). Though less common, cardiac, pulmonary, and/or hepatic lesions have also been reported (222, 359, 721).

E. cuniculi infection of mice is used as a model of human microsporidiosis, and it may be possible to cautiously extrapolate pathophysiologic and/or immune mechanisms observed in the mouse model to the rabbit. For example, Didier (164) demonstrated that reactive nitrogen intermediates contribute to the killing of *E. cuniculi* by LPS plus IFN-γ-activated murine peritoneal macrophages in vitro.

Natural infection of laboratory rabbits used directly in microsporidial (721), renal, or brain research would probably compromise such efforts. In addition, infection of rabbits used in the production of antimicrosporidial antibodies may compromise the usefulness of these antisera, since antibodies to *E. cuniculi* cross-react with antigens of several microsporidia, including *E. bieneusi* (717).

Multiple Systems

Viruses. (i) Coronavirus (pleural effusion disease/infectious cardiomyopathy virus). During the 1960s in Scandinavia, and subsequently elsewhere in the world, a coronavirus was found contaminating stocks of *T. pallidum* used experimentally in rabbits (201, 259, 338). It remains uncertain whether the agent is a natural pathogen of rabbits. A lack of any reports of natural infections suggests that the virus may be from another species (171). Clinical signs of infection depend on the strain and passage of the agent (171) but may include fever, anorexia, weight loss, atony, muscular weakness, tachypnea, iridocyclitis, circulatory insufficiency, and death. Likewise, pathologic findings depend on the phase of the disease and may include pulmonary edema, pleural effusion, and right ventricular dilation in the acute phase. Rabbits dying after the first week may have ascites and subepicardial and subendocardial hemorrhages. Other pathologic findings include myocarditis with myocardial degeneration and necrosis; hepatosplenomegaly with reduction of splenic white pulp; focal hepatic necrosis; congestion and focal degeneration of lymph nodes followed by proliferation; focal degenerative changes of the thymus; mild proliferative changes of renal glomeruli; and mild nonsuppurative, nongranulomatous anterior uveitis (171). The major target organ is the heart (182, 203, 338). In one report, infectious sera produced cytopathic effects in primary rabbit kidney and newborn human intestine cells (603). Clinical pathologic changes include transient lymphopenia, heterophilia, transient hypoalbuminemia, increased potassium and lactate dehydrogenase levels in serum and elevated serum γ-globulin levels (200, 202, 203). Manifestations of pleural effusion disease/infectious cardiomyopathy (PED/IC) virus infection are multisystemic, and are similar to those observed in cats with feline infectious peritonitis, another systemic coronavirus infection (193). In addition, antisera to the PED/IC virus cross-react with other members of the mammalian group I viruses, including feline infectious peritonitis virus, canine coronavirus, porcine transmissible gastroenteritis virus, and human coronavirus (604).

PED/IC virus infection of rabbits is currently used as a model of cardiomyopathy (4). Infection of laboratory rabbits with PED/IC virus would result in undesirable changes in multiple body systems, including the lymphoid, hematologic, pulmonary, cardiovascular, ophthalmic, and renal systems, and would result in profound alterations of research results.

(ii) Myxoma virus. Myxoma virus is a dsDNA virus of the family *Poxviridae* with nearly worldwide distribution in wild rabbit populations. Infection is uncommon in laboratory rabbits but can occur via arthropod vectors, primarily mosquitoes and fleas. Clinical signs of infection (myxomatosis) vary greatly depending on the strains of both virus and host. Virulent strains, such as that found in California, frequently cause sudden death, often with conjunctivitis and edema and inflammation of the eyelids and around the nasal, anal, genital, and oral orifices. Skin nodules, while characteristic of the disease caused by strains elsewhere in the world, are not observed. Due to the generalized nature of the infection, pathologic changes, which are again virus strain dependent, may be observed in many organs. When present, localized skin tumors consist of masses of stellate mesenchymal cells ("myxoma cells") and occasional inflammatory cells, interspersed within a matrix of mucin-like material. Other pathologic changes include cutaneous edema and hemorrhaging of the skin, heart, and gastrointestinal subserosa. In addition, proliferative and/or hemorrhagic lesions, followed by degeneration and necrosis, may be observed in the lungs, liver, spleen, vasculature, kidneys, lymph nodes, and testes (171).

Recent studies have shown that myxoma virus, like other leporipoxviruses (285), may be immunosuppressive through down regulation of class I-mediated presentation of viral antigen (67) and through inhibition of TNF activity (581). Also, myxoma virus produces a serine proteinase inhibitor which ameliorates chronic inflammation in an antigen-induced arthritis model of chronic inflammation (416). Experimental rabbit-myxoma virus models are therefore used to study the biology of poxviruses and are used in arthritis research. Given the generalized nature of infection, natural infection of laboratory rabbits would compromise these and many other fields of research involving rabbits.

Bacteria. (i) *Listeria monocytogenes*. *Listeria monocytogenes* is a gram-positive, rod-shaped, intracellular bacterium which uncommonly causes disease in rabbits. Infection is acquired with contaminated feed. Clinical signs are generally absent or may be nonspecific, including anorexia, ascites, depression, weight loss, and sudden death. Pregnant does may abort and are more susceptible to infection, either because of physiological stress or because of a uterine microenvironment more conducive to survival of the organism (154). Pathologic findings are most prominent in the liver and consist of multifocal hepatic necrosis. Similar microabscesses may be seen in the spleen and adrenal glands. Septicemic spread is facilitated by phagocytosis and transport by macrophages. Pregnant does may develop acute necrotizing suppurative metritis. Pathogenesis is dependent on hemolysin production (40, 710). Abortion may also be related to the ability of pathogenic strains of *L. monocytogenes*

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to cause myometrial contraction (393). Hematologic changes include a marked monocytic reaction (429). While protection is primarily cell mediated (469), serologic responses also develop and are greater in rabbits infected orally rather than intragastrically (42). Laboratory rabbits are frequently used to produce anti-*Listeria* antiserum, and a rabbit-*L. monocytogenes* model has been used to study human keratitis (745). Natural infection of laboratory rabbits could interfere with these studies or with other studies in which the cellular architecture of a variety of visceral organs is studied.

(ii) *Francisella tularensis.* *Francisella tularensis* is a gram-negative coccobacillus that causes acute septicemic disease (tularemia) in a wide range of mammalian hosts, including humans. Infection is common in wild rabbits but rare in laboratory rabbits. Two biovars infect rabbits, with *F. tularensis* bv. tularensis (found only in North America) being the more pathogenic (462). Virulence appears to be associated with catalase activity, cytochrome b_1 levels (184), and the presence of a newly recognized "envelope antigen C" (628). Transmission is via multiple routes, most commonly arthropod vectors and direct contact. Clinical signs, when present, may consist of anorexia, depression, and ataxia, or sudden death without premonitory signs. Pathologic changes include focal coagulative necrosis and congestion of the liver, spleen, and bone marrow (154). Natural infection of laboratory rabbits not only could be fatal, but also could alter the results of research involving the liver, spleen, and bone marrow.

ANIMAL HOUSING FOR PATHOGEN EXCLUSION OR CONTAINMENT

Several excellent publications describe animal housing for pathogen exclusion or containment (475). Animal housing ranges from "conventional" housing in open cages with little pathogen protection to rigid "barrier" housing designed to exclude all pathogens. The laboratory animal professional can advise the investigator on the level of protection that is appropriate to meet the research needs.

HEALTH-MONITORING PROGRAMS

Most modern animal facilities incorporate some form of health monitoring into their animal care program. While health monitoring is costly, it is sure to result in significant long-term savings in time, effort, and money. Through these programs, the animal facility director and/or manager can monitor the health status of the colony, inform the investigator of the pathogen status of the colony, prevent the entry of most pathogens into the facility, and promptly detect and deal with pathogens that do manage to enter the colony. It is far more cost effective to prevent the entry of pathogens into a facility or to detect and eliminate them early than to throw out months of research data because undetected infection rendered laboratory animals unfit for research and hence rendered the data unreliable. The interested reader is referred to other publications for more detailed information on health-monitoring programs (100, 379, 475, 602).

FUTURE TRENDS

What does the future hold regarding the natural pathogens of laboratory mice, rats, and rabbits? Several events can be anticipated. First, the decline in the prevalence of natural pathogens will continue as housing and husbandry methods improve even more. This continued "cleansing" of animal colonies will be driven by the efforts of animal facility personnel to facilitate meaningful research, by accrediting and funding bodies, by the public, intent on seeing only valid animal-based research conducted, and by investigators increasingly aware of the impact of pathogens on research results. It is unreasonable to expect that all infectious agents will be eradicated from all animal colonies. After all, they are natural pathogens and therefore exist in feral animal populations. Breaks in the physical integrity of an animal facility or failure to adhere to standard operating procedures for pathogen exclusion will continue to allow pathogens occasional access. Second, additional effects of currently known pathogens will be reported as new research uses are found for traditional laboratory animals, new questions are asked, and new technologies are applied to those questions. Third, new pathogens will continue to be discovered and reported. Most of these previously unknown agents will not result in clinical disease, but many may affect experimental results. According to Weisbroth (714), many of these "emerging" pathogens may even be acquired from humans. While the range and magnitude of infections has decreased in laboratory mice, rats, and rabbits, continued diligence and additional study are required to ensure the wellbeing of animals used in biomedical research.

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