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## Zoonoses and Other Human Health Hazards

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I. INTRODUCTION

Zoonoses is derived from the Greek words zoon (meaning animals), and noses (meaning disease), and refers to the infectious diseases and infestations that are transmissible directly from an animal host to humans. The biomedical literature contains numerous reports of zoonotic diseases and parasitic infestations from laboratory mice and their wild counterparts. The extended maintenance of the laboratory mouse over a number of generations under controlled and increasingly sophisticated laboratory animal housing conditions with veterinary oversight and effective infection control measures has markedly reduced the likelihood that zoonotic agents would be encountered in a modern animal care and use environment. However, when these essential animal program quality measures fail or are not incorporated into the animal facility operations, zoonotic pathogens may be unwittingly introduced and perpetuated, placing personnel at increased risk of exposure. Wild caught mice that are maintained in naturalistic housing environments in the laboratory, laboratory mice that have contact with wild or feral mice, and mice kept as pets in the home environment are examples of animal management conditions that would be conducive to the expression and transmission of zoonotic diseases and other mouse-associated hazards. In addition to the zoonoses, mice are capable of inflicting bites on inadequately trained personnel and are a rich source of allergens for a substantial number of persons predisposed to develop mouse-associated allergic sensitivities. This chapter discusses the mouse-associated zoonotic diseases and other health hazards and explains the strategies that are helpful for reducing or eliminating the risk of personnel exposure to these conditions.

II. VIREAL DISEASES

A. Lymphocytic Choriomeningitis Virus (LCMV)

Lymphocytic choriomeningitis virus (LCMV) is an enveloped single-stranded RNA virus in the Old World serocomplex group of the family Arenaviridae. It is the only representative of the group of Old World arenaviruses that is present in the United States and survives in the house mouse, Mus musculus, as its principal host through which it has achieved a worldwide distribution (Buchmeier et al. 2001) (see also Chapter 7 of this volume). The arenaviruses have a predilection for rodent reservoirs, and several with zoonotic
implications in the New World serocomplex group are present among the wild rodents endemic to the United States such as *Neotoma* spp. and *Peromyscus* spp. (2000; Buchmeier et al. 2001; Fulhorst et al. 2002). Research animal programs that import wild rodents for laboratory studies should stay abreast of the developments on the identification and host-range characteristics of the New World arenaviruses of emerging importance. This section will focus only on lymphocytic choriomeningitis (LCM), a naturally occurring viral zoonosis of the laboratory mouse.

1. Reservoir and Incidence

Many published reports of human LCM infection are associated with laboratory animal and pet contact, particularly mice and hamsters, and these studies now span many decades (Armstrong and Lillie 1934; Bowen et al. 1975; Dykewicz et al. 1992; Jahrling and Peters 1992; Lehmann-Grube et al. 1979; Rousseau et al. 1997). There seems to be a resurgent awareness among physicians that LCM should be sought as an etiology in human neurological disease and in pediatric congenital brain disorders (Barton and Hyndman 2000; Barton et al. 1995, 2002; Romero and Newland 2003). LCMV is widely distributed among the wild mouse population throughout most of the world presenting a zoonotic hazard (Childs et al. 1992; Childs and Peters 1993; Morita et al. 1996; Smith et al. 1993). Surveys conducted within the urban environment of Baltimore, Maryland, reported that 9% of house mice and 4.7% of persons tested had measurable LCMV antibody titers (Childs et al. 1991, 1992). A similar serological survey conducted in Spain across urban and rural ecological settings also found a 9% prevalence in mice and a 1.7% prevalence among persons by immunofluorescence assay (Lledo et al. 2003). The recent serological detection of LCMV in five mice on the treeless, sub-Antarctic, Macquarie Island of Australia, indicates the extent of distribution of this agent to the remotest areas of our planet (Moro et al. 2003).

The apparent ease with which LCMV is transmitted to humans also occurs in a variety of other laboratory animal species; hamsters, guinea pigs, swine, dogs, and nonhuman primates, especially callitrichids, which readily sustain natural infections. In the case of the callitrichids, there have been numerous reports of epizootic infectious hepatitis (callitrichid hepatitis) due to LCMV, with a high mortality rate in zoological parks in both the United States and England over the past two decades (Lucke and Bennett 1982; Montali et al. 1989; Stephens et al. 1990, 1991, 1995). Rodent (mouse) infestations of these zoos and/or the supplementation of the diets of tamarins and marmosets with suckling mice, a common practice (Richter et al. 1984), are potentially rich sources for LCMV.

In the research animal facility environment, the laboratory mouse continues to merit attention as the species of primary concern as a reservoir for cases of human LCM (Dykewicz et al. 1992). In the laboratory mouse, and to a lesser degree the hamster, breeding colonies can become endemically infected when the virus is transmitted to pups in utero or early in the neonatal period, producing a tolerant subclinical infection characterized by chronic viremia and viruria. When infected, athymic and other immunodeficient mouse strains may be predisposed to harboring silent, persistent infections and present a higher risk to personnel (Dykewicz et al. 1992). Under some circumstances LCMV also produces a pantropic infection and may be copiously present in blood, cerebrospinal fluid, urine, nasopharyngeal secretions, feces, and tissues of infected natural hosts and possibly humans. Bedding material and other fomites contaminated by LCMV-infected animals can also be important sources of infection for humans, as demonstrated in a recent outbreak among laboratory animal technicians and on many previous occasions (Biggar et al. 1975; Dykewicz et al. 1992).

The experimental passage of tumors and cell lines contaminated with LCMV has long been recognized (Haas and Stewart 1956) and represents one of the biggest threats for the introduction of LCMV into animal facilities at the present time (Bhatt et al. 1986; Dykewicz et al. 1992; Nicklas et al. 1993). Reported that 17 of 63 rodent transplantable tumors screened were positive for LCMV and identified contamination in 4 of 14 hamster tumors and 2 of 81 mouse tumors that had been propagated in animals (Nicklas et al. 1993).

The growth of LCMV in insect cell lines has also been demonstrated (Rahacek 1965), and the article by Hotchin summarized the work of others indicating that numerous experimentally infected, bloodsucking ectoparasites are capable of transmitting the disease to laboratory rodents (Hotchin 1971). LCM virus also has been recovered from cockroaches (Armstrong and Lillie 1934).

2. Mode of Transmission

The diagnosis and control of LCMV infection in mouse colonies has been reviewed in Chapter 7 of this volume. Tumor and cell-line screening before animal passage, the control of wild rodent infestations in areas where animals are housed or used, and the early detection of colony infections through sound colony health surveillance practices are of critical importance to the prevention of infection in mouse colonies. Once established in mouse breeding colonies, the high viral load characteristically shed by mice infected congenitally or neonatally represents a very serious hazard to personnel.

Most of the cases of human infection, whether involving exposure in the home, agricultural, or laboratory setting, have involved contact with live mice and their excreta or mouse carcasses (Dykewicz et al. 1992; Havens 1948; *Morbidity and Mortality Weekly Report* 1984). Several authors have emphasized the association between the actual handling of infected mice and the contraction of the disease by humans (Dykewicz et al. 1992; Havens 1948; Smithard and Macrae 1951). Several cases of human infection have suggested the possibility that infected rodent tissues can serve as a source of infection for laboratory personnel (Baum et al. 1966; Dykewicz et al. 1992; Tobin 1968). Humans may be infected by inhalation or by the contamination of mucous membranes or broken skin with infectious tissues or fluids from infected animals. The transmission.
3. Clinical Signs, Susceptibility, and Resistance in Humans

Following an incubation period of 1 to 3 weeks, humans may experience asymptomatic or a mild febrile disease ranging to a serious flu-like illness characterized by anorexia, malaise, diffuse myalgia and arthralgia, fever, chills, vomiting, headache, stiff neck, and photophobia. Some patients enter a second stage of the disease several days after the resolution of early mild symptoms, developing meningoencephalitis and exhibiting additional signs such as drowsiness, confusion, sensory disturbances, and motor abnormalities. Patients can also develop more serious nonneurological manifestations of the disease such as maculopapular rash, lymphadenopathy, parotitis, orchitis, arthritis, and epicarditis (Peters 1997). Central nervous system involvement has resulted in death in several cases. Infections during pregnancy pose a risk of infection for the human fetus (Wright et al., 1997). Wright et al. reported 26 cases in human infants, with LCMV confirmed serologically over a two-year period in a major U.S. medical center (Wright et al. 1997). These infants presented with ocular abnormalities, macrocephaly, and hydrocephalus with microcephaly. Fifty percent of the mothers reported having had illnesses compatible with LCMV infection, and over half reported exposures to rodents during their pregnancies.

4. Diagnosis, Treatment, and Control

The diagnosis of LCM infection in humans is currently made by serological testing using either the immunofluorescent antibody (IFA) test or the enzyme-linked immunosorbent assay (ELISA) (Barton et al. 2002). Both of these tests are available through the Centers for Disease Control and Prevention and are superior to the complement fixation test that is widely available commercially. Although there are no proven effective antiviral therapies for LCM infection, intravenous ribavirin therapy reduces mortality in patients infected with Lassa fever virus (a member of the Old World Arenavirus serocomplex) and may be of some benefit in patients with severe LCMV infections (Andrei and De Clercq 1993; McCormick et al. 1986).

This disease can be prevented in the laboratory through periodic serological surveillance using ELISA and IFA tests of newly introduced animals with inadequate disease profiles and of resident animal colonies at risk. Thorough screening of all tumors and cell lines intended for animal passage using the highly sensitive mouse antibody production assay or newer PCR-based laboratory tests for the presence of LCMV is another crucial element in the program to prevent the introduction of LCMV into established animal colonies (Besselsen et al. 2003 and Chapter 7 of this volume).

Sound animal facility sanitation practices and the use of microbarrier caging systems with proper infection-control techniques should prevent or suppress the spread of LCMV if present in the environment. The elimination of wild rodent infestations in animal facilities is very important to prevent the introduction of LCMV into the animal facility environment. Also, facilities with wild rodent infestations may encounter the relatively common, free-living, bloodsucking mite of the rodent, Ornithonyssus bacoti, in abundance (personal communication). Although the natural LCMV transmission to humans from bloodsucking ectoparasites is unproven, the control of potential ectoparasitic vectors of this type would be a prudent measure.

B. Rabies

Rabies is an acute, almost invariably fatal disease that occurs worldwide with the exception of a few countries, generally island nations, and other regions that have excluded the disease through animal importation and control programs and the aid of geographic barriers. Neither the laboratory mouse nor other small wild rodent hosts appear to be important as reservoirs of natural rabies infection. Hence, the principal reason for our discussion of rabies as a zoonotic disease of the laboratory mouse is to provide information that should quickly allay the fears of uninformed research and animal facility staff who suffer the bite of a mouse. On the other hand, the experimental use of mice in the study and characterization of rabies virus and in rabies vaccine development is an important component of some animal care and use programs that deserves special attention by the institution during all phases of research planning and implementation.

1. Reservoir and Incidence

There are no known cases of human rabies from rodents in the United States (2002). The incidence in larger wild rodent species within the United States has increased in recent years, however. During the interval 1971–1984, a total of 97 cases of rabies in rodents were recorded, but from 1995 to 2000 approximately 52 cases were reported in large rodents annually (2002). The rodents involved were woodchucks and beavers, both species presumably large enough to survive the chance encounter and attack by a wild rabid carnivore such as the raccoon, skunk, fox, or feral cat. Earlier literature on the Federal Republic of Germany summarized findings from 1961 to 1967, which indicated that three mice, one rat (species not given), nine Norway rats, and three muskrats were infected with rabies and had bitten humans (Scholz and Weinhold 1969). Despite rare reports of this nature, rodents are not a proven source of rabies transmission to humans (Johnson 1989).
2. Clinical Signs

All mammals are generally regarded as susceptible to rabies. In humans, the course of the disease proceeds through several phases: incubation, prodromal, acute neurological, coma, and rarely, recovery (Johnson 1989). The incubation period varies from 9 days to over 8 months. During the prodromal stage lasting 2 to 4 days, patients experience a period of apprehension and develop headache, malaise, and fever. An abnormal, indefinite sensation at the site of a prior animal bite wound is the first specific symptom. Patients also may develop intermittent periods of excitation, nervousness, or anxiety interspersed with quiet periods when the mental state appears normal. Further progression of the disease involves paresis or paralysis, inability to swallow, and the related hydrophobia, delirium, convulsions, and coma. Rabies produces an almost invariably fatal acute viral encephalomyelitis, with death due to respiratory paralysis.

Adult mice used experimentally in rabies studies usually exhibit clinical signs between 5 and 15 days following inoculation and die within 5 days of the onset of clinical signs coinciding with the period of viral shedding. Clinical signs in the mouse consist of muscular tremors, incoordination, excitation, or paralysis. Certain rabies virus isolates from skunks produce a spastic paralysis in adult mice followed by recovery in a high percentage of infected mice. Also, infant mice inoculated with certain strains of street rabies virus are capable of full recovery (Johnson 1989).

3. Diagnosis, Treatment, and Control

Personnel working with mice experimentally infected with rabies virus should adhere to the well-established and detailed procedures that have been described in other sources for animal inoculation, husbandry, and tissue harvest procedures (Johnson 1989). Vaccination of personnel involved in rabies studies with adult mice used experimentally in rabies studies usually exhibit clinical signs between 5 and 15 days following inoculation and die within 5 days of the onset of clinical signs coinciding with the period of viral shedding. Clinical signs in the mouse consist of muscular tremors, incoordination, excitation, or paralysis. Certain rabies virus isolates from skunks produce a spastic paralysis in adult mice followed by recovery in a high percentage of infected mice. Also, infant mice inoculated with certain strains of street rabies virus are capable of full recovery (Johnson 1989).

C. Other Viruses

Four other viruses that produce natural infections in the mouse have been implicated previously or are known to be infectious for humans. These include hantavirus, Sendai virus, Reovirus 3, and mouse hepatitis virus. For none of these viral agents is there documented evidence of zoonotic transmission of the agent from naturally infected laboratory mice to personnel in the laboratory. Hantaviruses are zoonotic viruses comprising at least 22 species that are maintained among natural rodent reservoirs, despite the presence of neutralizing antibody in the rodent host (Elliott et al. 2000; Meyer and Schmaljohn 2000). Approximately half of the hantaviruses are known human pathogens producing virus-specific patterns of disease that include hantavirus pulmonary syndrome, hemorrhagic fever with renal syndrome, and its benign form, nephropathia endemica (Mills and Childs 1998). Although Mus musculus can exhibit the pattern of persistent hantavirus infection in the presence of neutralizing antibody when induced experimentally (Araki et al. 2003), this does not occur in natural infections of the mouse (Meyer and Schmaljohn 2000). This is the likely reason that the wild mouse apparently is not important as a natural reservoir for the hantaviruses. This interpretation is supported by serological studies of wild Mus musculus that detected either no or a very low incidence of serological evidence to hantavirus exposure even when other wild rodent species in the vicinity had a high level of endemic infection (Kantakamalakul et al. 2003; Meyer and Schmaljohn 2000; Pacsa et al. 2002; Zuo et al. 2004). Mus musculus is used in the laboratory as an animal model to study various aspects of hantavirus infection ranging from vaccine development (Choi et al. 2003), viral pathogenicity (Ebihara et al. 2000; Kim and McKee 1985), and immunological aspects of persistence (Araki et al. 2003), and it is primarily in this context that hantavirus deserves mention as a zoonotic infection in the mouse. The control of wild rodent infestations in animal facilities, quarantine and testing of wild caught rodent species during importation, and proper observance of animal biosafety guidelines for hantavirus-infected animals would be expected to virtually eliminate the risk of this zoonosis in laboratory maintained mice.

Mouse hepatitis virus (MHV) remains a prevalent infection in many mouse colonies where it potentially impacts colony health and disrupts experimental studies (see Chapter 6). Earlier studies have demonstrated that human sera contained complement-fixing and neutralizing antibodies to MHV (Hartley et al. 1964). Later studies suggested that this was most likely due to cross-reactive antibodies from human cold virus infections (Bradburne 1970; McIntosh et al. 1967). Mouse hepatitis virus and the two prototype human cold viruses (OC43 and 229E) are members of the antigenic group 2 coronaviruses, and it is now known that members of this group share four, and in some cases five, structural genes that could account for this cross-reactivity (Navas-Martin and Weiss 2003). The coronaviruses have a very narrow host range and generally replicate only in the cells of the host species (Navas-Martin and Weiss 2003). However, under unique laboratory conditions involving persistent cell culture infection, the use of mixed cell cultures of murine and of a nonpermissive species, or the use of cells possessing modified receptors, MHV has been adapted to grow in human, nonhuman primate, and hamster cells. Also, the many strains of MHV in combination with use of targeted RNA recombinant system have also been very useful for experimental study of the molecular basis of coronavirus pathogenicity (Masters 1999). Application of the targeted RNA recombinant system to MHV for exploring of emerging coronavirus infections such as SARS may delineate the molecular basis for expanding of host range. These studies may warrant the reader’s future attention, but at the present, MHV can be reasonably dismissed as a zoonotic infection.
Sendai virus was once a prevalent agent in mouse colonies but has become a rarity in most institutions. This is due to its ease of eradication through the use of temporary cessation of breeding to eliminate a naïve population that is susceptible to infection and through the use of caging systems that prevent transmission (see Chapter 11). Sendai virus was originally isolated and described in the 1950s during the investigation of cases of human respiratory illness (Gerngoss 1957; Kuroya et al. 1953a, 1953b; Sano et al. 1953; Zhandoff et al. 1957). In the original report involving the isolation of Sendai virus from Japanese newborn human infants suffering from fatal pneumonitis, lung suspensions from the newborns were inoculated intranasally into mice, producing lung consolidation and death in several cases (Kuroya et al. 1953b). In later studies, Sendai virus isolates were reported to produce disease in human volunteers (Kuroya et al. 1953a; Yamada 1956), and reports from many countries indicated that serological evidence of Sendai virus infection was associated with outbreaks of human respiratory illness (Demetio and Walker 1958; Gardner 1957; Jensen et al. 1955). Tennant et al. demonstrated that personnel working with laboratory animals had antibody titers to Sendai virus, but personnel with no known exposure to laboratory animals also had significant titers to the agent (Tennant et al. 1967). Recombinant Sendai virus is widely used for gene transfer experiments, and these vectors can readily infect human airway epithelium and a variety of other human tissues under experimental conditions (Nagai 1999; Pinkenburg et al. 2004). Although these recent studies have clearly demonstrated that Sendai virus is capable of infecting human tissues, the initial evidence for its role as a human pathogen remains doubtful. The mice used for the early isolations of the agent may have already been endemically infected with Sendai and served as the source, or it may be that other serologically cross-reactive parainfluenza viruses, which were not characterized during this era, were responsible for producing false positive reactions to Sendai virus (Ishida and Homma 1978).

Reoviruses are generally regarded as the cause of childhood infections producing asymptomatic or very mild disease, and there are few reports linking these infections with a particular disease (Tsai 2000). Reovirus 3 was originally isolated from the feces of a clinically ill child (Stanley et al. 1953), and it continues to receive attention as a possible etiology for neonatal hepatitis and extrahepatic biliary atresia in infants (Richardson et al. 1994; Steele et al. 1995). Reovirus 3 is highly infectious for infant laboratory mice and still receives some attention in the health-screening programs for the mouse and laboratory rodent species. Jacoby and Lindsey (1997) reported that mouse colonies in the United States continue to have a 5 to 20% prevalence of reovirus 3 infection. Although there are no confirmed reports of reovirus 3 transmission from mice (or other laboratory animal species) to humans, the laboratory mouse should be considered a possible source for this infectious agent for humans and other susceptible species.

### III. RICKETTSIAL DISEASE

#### A. Rickettsialpox

The Rickettsiales are fastidious, small pleomorphic cocobacillary organisms maintained in nature in a cycle of infection involving mammalian hosts and arthropod vectors as reservoirs (Saah 2000). In most rickettsial infections, humans serve only as an incidental host and do not contribute to the propagation of the organism in nature. Such is the case for rickettsialpox, a nonfatal, self-limiting zoonotic disease caused by *Rickettsia akari*, which is perpetuated in a cycle of infection involving *Mus musculus* as the primary host and a mite vector (*Liponyssoides sanguineus*). Isolation of the organisms from rats (*Rattus*) and voles (*Microtus*) has also been reported. The first cases of human rickettsialpox were described in patients in New York City (Huebner et al. 1946a, 1946b), and outbreaks of the disease have generally remained clustered within large urban areas of the United States and in rural North Carolina, Utah, South Africa, Korea, and the former Soviet Union (Koss et al. 2003). According to Koss et al. approximately 800 cases of rickettsialpox have been reported in the literature, with nearly 500 of these within the three years following the original description of the disease (Koss et al. 2003). Prior to the report by Koss et al. the largest case study included 13 patients accumulated over a 10-year period. The recent report by Koss et al., however, included 18 patients in New York City reporting over only a 20-month period in the wake of the September 11, 2001 attacks, suggesting that perhaps the heightened sensitivities to possible bioterrorism events stimulated an upsurge in the reporting of cases as a byproduct of increased patient concerns (Koss et al. 2003). Authors have commented on a variety of other social and demographic factors that may also be contributing to the noticeable increase in the incidence of rickettsialpox and murine typhus in the urban environment (Comer et al. 1999; Paddock et al. 2003).

There are no reported cases of rickettsialpox in personnel related to exposure to naturally infected laboratory mice. The mite vector *L. sanguineus* has not been reported in laboratory mouse colonies either historically or contemporarily. However, the tropical rat mite (*Ornithonyssus bacoti*) can be experimentally infected with *R. akari* but has not been shown to play a role in the natural cycle of infection. In the authors’ experience of *Ornithonyssus bacoti* infestations of laboratory mouse or rat colonies are still seen with some frequency in facilities that have resident wild or feral mouse populations and should be addressed in the institution’s pest control and infection control programs.

#### 1. Clinical Signs

Rickettsialpox has an incubation period of 7 to 21 days following the bite of the infected mite (Saah 2000). The disease is
mild to severe with an abrupt onset, and it typically presents with a classic triad of an eschar, fever, and a papulovesicular rash. The papule develops at the site of the bite and later ulcerates and progresses to an eschar, 0.5 to 3 cm in diameter, as *R. akari* proliferates locally in the skin and vasculitis develops (Koss et al. 2003; Saah 2000). The rash begins with firm, generally nonpruritic, erythematos papules, 2 to 10 mm in diameter, that develop into vesicles and heal by crusting. In addition to fever, patients may experience chills and headache, and less commonly, backache, myalgia, and photophobia. The disease is mild and self-limiting within 6 to 10 days, and serious complications or death have rarely been reported (Saah 2000). Patients typically respond quickly after the initiation of antirickettsial therapy with tetracycline, doxycycline, or other appropriate agent (Koss et al. 2003; Saah 2000). However, following resolution of the infection, headache and lassitude can persist for 1 to 2 weeks. The reader should refer to Koss et al. for information on other rash-producing or eschar-related diseases that should be considered in the differential diagnosis to rickettsialpox (Koss et al. 2003).

*Rickettsia akari* are diagnosed by complement fixation tests or the more sensitive indirect immunofluorescent antibody test. Serum antibody to *R. akari* generally takes 2 weeks to develop, and paired sera are needed to confirm a four-fold rise in antibody titer (Saah 2000). During the acute phase of the infection, immunohistochemistry or PCR analysis can be used for a rapid diagnosis on biopsy material obtained from the papulovesicular rash or eschar (Koss et al. 2003; Paddock et al. 2003).

Laboratory mice infected with *R. akari* develop fatal pneumonia with intranasal inoculation and severe illness and death with intraperitoneal inoculation. Mice develop anorexia, depression, and dyspnea. Peritonitis, splenomegaly, and lymphadenitis are found upon necropsy examination. Subcutaneous inoculation produces an active infection for 1 month, with organisms being recovered from the spleen but not the feces or urine (Bell 1970).

The control and eradication of *R. akari* infections depend on the prevention of wild mice and the mite vector from entering laboratory animal facilities and human dwellings.

**B. Murine Typhus**

Murine typhus is a rickettsial disease caused by *Rickettsia typhi* (previously *R. mooseri*) that occurs worldwide with epidemics or with high prevalence in particular geographic areas (Dumler and Walker 2000). In the United States, most human cases of the disease are concentrated in Texas and Southern California. The disease is now predominantly associated with the rat as the primary host species for the Oriental rat flea (*Xenopsylla cheopis*), which serves as the principal ectoparasitic vector transmitting the disease to humans. However, the mouse can also serve as a host for this flea, as well as for the northern rat flea (*Nasopsyllus fasciatus*) and the mouse flea (*Leptosylla segnis*), which also bite man and can be involved in the transmission of *R. typhi* (Flynn 1973; Pratt and Wiseman 1962; Yunker 1964). An early report in the literature indicated that *X. cheopis* was easily established in an animal facility inhabiting rooms used for housing laboratory mice (Yunker 1964). It is now also known that the cat and opossum and the cat flea (*Ctenocephalides felis*) can be involved in sustaining the cycle in some geographic localities (Azad et al. 1997). Clark and Will (1994) reported on use of the laboratory mouse as an experimental host for rearing *X. cheopis*, but there have been no reports of natural infestations of mouse colonies with any of the flea vectors of *R. typhi* for several decades. Also, *R. typhi* has not been isolated from natural infections in laboratory mice. Murine typhus is a more serious disease than rickettsialpox and presents with fever, headache, chills, nausea, and vomiting. Splenomegaly, hepatomegaly, central nervous system involvement, and multiorgan failure can occur as severe and potentially fatal complications. A skin rash, which is typically maculopapular in the case of murine typhus, occurs much less commonly than in rickettsialpox, and its absence should not dissuade the clinician from making a diagnosis of murine typhus and from promptly instituting therapy due to the potential severity of the disease (Dumler and Walker 2000). The methods used for the laboratory diagnosis and treatment of the disease in humans and the principles of preventing the introduction of *R. typhi* into laboratory animal colonies are similar to those for *R. akari*.

**IV. BACTERIAL DISEASES**

**A. Leptospirosis**

Leptospirosis microorganisms were discovered in 1914 when they were isolated from jaundiced patients (Inada et al. 1916); after further study they were named in 1917 (Noguchi 1918). Leptospirosis is solely a zoonotic disease of livestock, pet and stray dogs, and wildlife, including wild rodents. Rodent reservoir hosts of leptospirosis include, in addition to rats, mice, field moles, hedgehogs, gerbils, squirrels, rabbits, and hamsters (Fox and Lipman 1991; Torten 1979). Human to human transmission is extremely rare. *Leptospira interrogans* (comprising more than 200 serovars) have been isolated worldwide (Tapper et al. 2000).

*L. interrogans* contains 23 serogroups with strains pathogenic for amphibians, reptiles, and mammals including humans. Serovars *australis*, *ballum*, *bataviae*, *hardjo*, *grippotyphosa*, *icterohemorrhagiae*, *javanica*, and *pomona* are associated with rodent infections. Leptospira serovars, including *L. australis*, *bataviae*, *grippotyphosa*, *hebdomoidis*, *icterohaemorrhagiae*, *pomona*, and *pyrogenes*, are found in the house mouse (Torten 1979). *Leptospira ballum* has also been reported from mice and is
most commonly associated with zoonotic outbreaks (Borst et al. 1948; Friedmann et al. 1973; Stoenner and Maclean 1958). Although particular serovars usually have distinct host species, most serovars can be carried by several hosts. Leptospira are well adapted to a variety of mammals, particularly wild animals and rodents.

1. Reservoir and Incidence

In the chronic form, the organism chronically infects the host and is shed in the urine inconspicuously for long periods of time. Rodents are the only major animal species that can shed leptospires throughout their lifespan without clinical manifestations (Fox and Lipman 1991; Torten 1979). Active shedding of leptospires by rodents can go unrecognized until personnel handling the animals become clinically infected or are infected by exposure to water or food contaminated by urine.

Rats and mice are common animal hosts for serotype, \textit{L. ballum}, although it has been found in other wildlife as well. Water can often be contaminated with infected rodent urine. The infection can persist unnoticed in laboratory rodents, though their carrier rates for laboratory-maintained rodents in the United States are unknown, but it is probably low. The organism is not routinely screened on health surveillance protocols for pathogenic strains (Fox and Lipman 1991; Stoenner and Maclean 1958). In one study, 8 of 58 employees handling the infected laboratory mice (80% of breeding females were excreting \textit{L. ballum} in their urine) contracted leptospirosis in 1984 in a research colony of mice in the United States being housed in a large research institution (Alexander 1984).

2. Mode of Transmission

Because leptospirosis in humans is often difficult to diagnose, the low incidence of reported infection in humans may be misleading. From 1974 to 1979, only 498 cases were reported, for an incidence of 0.05 per 100,000 people per year (Sanger and Thiermann 1988). Leptospirosis was removed from the reportable disease category in the United States in 1995 because of the small number of cases reported. Outbreaks have been documented in the United States from personnel working with laboratory mice (Barkin et al. 1974; Stoenner and Maclean 1958). In one study, 8 of 58 employees handling the infected laboratory mice (80% of breeding females were excreting \textit{L. ballum} in their urine) contracted leptospirosis (Stoenner and Maclean 1958).

Infection with leptospirosis most frequently results from handling infected animals (contaminating the hands with urine) or from aerosol exposure during cage cleaning (Barkin et al. 1974; Friedmann et al. 1973; Stoenner and Maclean 1958). Skin abrasions or exposure to mucous membranes may serve as the portal of entry. All secretions and excretions from infected animals should be considered infective. In one instance, a father apparently was infected after his daughter used his toothbrush to clean a contaminated pet mouse cage (Boak et al. 1960). Rodent bites can also transmit the disease (Looke 1986).

In Detroit, children from the inner city had a significantly higher \textit{L. icterohaemorrhagiae} antibody when compared to children living in the Detroit suburbs. Therefore, children living in rodent-infested tenements may be at increased risk of infection (Demers et al. 1983). In Europe and more recently in North America, rodents including house mice have provided a source of leptospirosis for swine and by extension could also infect personnel working in swine production units (Galton 1966; Smith et al. 1992). \textit{Leptospira interrogans} serovar \textit{bratislava} is commonly reported in these mice.

3. Clinical Signs

The disease may vary from unapparent infection to severe infection and death. A self-limited systemic illness is seen in approximately 90% of infected humans. The incubation period is usually 5 to 14 days. Individuals infected with leptospirosis experience a biphasic disease (Faine 1991; Sanger and Thiermann 1988; Stoenner and Maclean 1958). They become suddenly ill with weakness, headache, myalgia, malaise, chills, and fever and usually exhibit leukocytosis. During the second phase of the disease, conjunctival suffusion and a rash may occur. Upon examination, renal, hepatic, pulmonary, and gastrointestinal findings may be abnormal. Intravenous penicillin is the drug of choice in treating early-onset and late-stage leptospirosis infection (Faine 1991; Taber and Feigin 1979; Watt et al. 1988). Ampicillin and doxycycline also have been effective in treating people with mild to moderate forms of leptospirosis.

4. Diagnosis

Because of the variability in clinical symptoms and the lack of pathognomonic pathologic findings in humans and animals, serologic diagnosis or actual isolation of leptospires is imperative (Faine 1991). As an aid to diagnosis, leptospires can sometimes be observed by examination or direct staining of body fluids or fresh tissue suspensions (Sulzer et al. 1968). The definitive diagnosis in humans or animals is made by culturing the organisms from tissue or fluid samples, or by animal inoculation (particularly in 3- to 4-week-old hamsters) and subsequent culture and isolation. Culture media with long-chain fatty acids with 1% bovine serum albumin are routinely used as a detoxicant (Faine 1991). Serologic assessment is accomplished by indirect hemagglutination, agglutination analysis, complement fixation, microscopic agglutination, and fluorescent antibody techniques (Faine 1991). The serologic test most frequently used is the modified microtiter agglutination test. Titers of 1:100 or greater are considered significant. Molecular techniques including PCR and randomly amplified polymorphic DNA fingerprinting are used for identification of serovars (Tappero et al. 2000).

5. Epidemiology and Control

In mouse colonies infected with \textit{L. ballum}, antibodies against \textit{L. ballum} were detected in sera of mice of all ages, but
leptospires could be recovered only from mature mice. Progeny of seropositive females had detectable serum antibodies at 51 days of age but not at 65 days. It was also reported that progeny of seropositive female mice, which possessed antibody at birth and acquired additional antibody from colostrums, remained free of leptospires if isolated from their mothers at 21 days of age, despite exposure during the nursing period (Stoenner 1957).

Studies in mice experimentally infected with *L. grippotyphosa* demonstrated that maternal antibodies, whether passed through milk or placental transfer, conferred protection of long duration against the carrier state and shedding of leptospires. Thus, serologically positive immune mothers do not transmit the disease to their offspring. However, mice born to nonimmune mothers, if infected at 1 day postpartum, become carriers with no trace of antibodies. Thus a population of carrier pregnant mice without antibody could serve as a precipitator in outbreaks among susceptible mouse populations (Birnbaum et al. 1972). Field surveys have supported this data in a significant percentage of carrier mice do not have antibodies. This led to the diagnostic approach, which specifies that both serologic and isolation methods must be utilized to determine the rate of leptospirosis in rodents (Galton et al. 1962).

*Leptospira ballum* is frequently found in the common house mouse (*M. musculus*) (Brown and Gorman 1960; Yager et al. 1953). Therefore, eradication of infected colonies, use of surgically derived and barrier-maintained mice or of conventional laboratory mice free of leptospirosis infection, coupled with the prevention of ingress of wild rodents, should effectively preclude introducing the organism into research and commercial laboratories (Loosli 1967). *Leptospira ballum* has been eliminated from a mouse colony by administration of feed containing 1000 gm chlorotetacycline hydrochloride per ton for 10 days. After 7 days of antibiotic therapy, mice were transferred to clean containers and administered clean water, both having been sterilized by steam. Mouse traps and rodenticides were used to destroy escaped mice and to prevent reintroduction of *L. ballum* by the common house mouse (Stoenner et al. 1958). Commercial animal colonies maintained in research vivarium today are not routinely screened for leptospiriosis, assuming that the organism has been effectively eliminated from commercial and research-maintained mice.

B. Rat Bite Fever

1. Reservoir and Incidence

Rat bite fever can be caused by either of two microorganisms: *Streptobacillus moniliformis* or *Spirillum minus*. *Streptobacillus moniliformis* causes the diseases designated as streptobacillary fever, streptobacillar rat bite fever, or streptobacillosis. Haverhill fever and epidemic arthritic erythemia are diseases associated with ingestion of water, food, or raw milk contaminated with *Str. moniliformis*. Sodoka, derived from the Japanese words for rat (so) and poison (doku), spirillosis, and spirillary rat bite fever are caused by another bacterium, *Spirillum minus*. The bite of an infected rat is the usual source of infection. In some cases, other animal bites, including mice, gerbils, squirrels, weasels, ferrets, dogs, and cats, or rare traumatic injuries unassociated with animal contact, cause the infection. In a retrospective analysis covering three decades (1970–1998) of 45 *S. moniliformis* isolates (91% from humans) from the Department of Public Health in Berkeley, California, 50% of the isolates were from children ≤ 9 years of age (Graves and Janda 2001). In 75% of the human infections where a diagnosis was made, rat bite fever (RBF) was suspected; 83% of those suspected cases involved either known rat bite or exposure to rodents. Two cases of RBF were attributed to exposure—in one case a squirrel, and in the second a mouse (Graves and Janda 2001).

2. Mode of Transmission

Interestingly, ≥ 9% of the cases could not be attributed to a rat bite or scratch, indicating that close contact with infected rodents can be sufficient to become infected (Graves and Janda 2001). Other reports have indicated that the disease can occur in individuals who have no history of rat bites, but reside or work in rat-infested areas or have pet rats with whom they have close contact (Fordham et al. 1992; Holroyd et al. 1988; Rumley et al. 1987). Rat scratches can also be the source of the organism (Edwards and Finch 1986; Shanson et al. 1985). Exposure to cats and dogs that prey on wild rodents may also be the source of the organisms.

These organisms are present in the oral cavity and upper respiratory passages of asymptomatic rodents, usually rats (Wilkins et al. 1988). Mice can be infected with resulting morbidity and mortality due to arthritis and pneumonia. In one study, *Streptobacillus moniliformis* was isolated as the predominant microorganism from the upper trachea of laboratory rats (Paegle et al. 1976). Presumably the incidence of *Str. moniliformis* is now lower in high-quality, commercially reared specific pathogen-free rats. Surveys in wild mice indicate 0 to 25% infection with *Spirillum minus* (Hull 1955).

3. Clinical Signs

Rat bite fever is not a reportable disease, which makes it difficult to assess its prevalence, geographic location, racial data, and source of infection in humans. The disease, though uncommon in humans, has nonetheless appeared among researchers or students working with laboratory rodents, particularly rats (Anderson et al. 1983). Historically, wild rat bites and subsequent illness (usually small children) relate to poor sanitation and overcrowding (Hull 1955). Acute febrile diseases, especially if associated with animal bites, are routinely treated with penicillin or other antibiotics. Therefore, accurate data regarding prevalence is usually not provided.
Streptobacillus moniliformis incubation varies from a few hours to 2 to 10 days, whereas Spirillum minus incubation ranges from 1 to 6 weeks (Table 26-1). Fever is present in either form. Inflammation associated with the bite and lymphadenopathy are frequently accompanied by headache, general malaise, myalgia, and chills (Arkless 1970; Cole et al. 1969; Gilbert et al. 1971; McGill et al. 1966). The discrete macular rash that often appears on the extremities may generalize into pustular or petechial sequelae. Arthritis occurs in 50% of all cases of S. moniliformis but is less common in Spirillum minus. Streptobacillus moniliformis may be cultured from serous to purulent effusion, which is recovered from affected larger joints.

A total of 18 cases of endocarditis due to S. moniliformis were reported from 1915 to 2000 (Shvartsblat et al. 2004). Death has occurred in cases of S. moniliformis involving preexistent valvular disease or as a result of endocarditis in a previously healthy individual. Infants can also die of the infection (Sens et al. 1989).

If antibiotic treatment—usually penicillin at doses of 400,000 to 600,000 daily for 7 days—is not instituted early, complications such as pneumonia, hepatitis, pyelonephritis, enteritis, and endocarditis may develop (Richter 1954). If endocarditis is present, the penicillin should be given parenterally at doses of 15 to 20 million units daily for 4 to 6 weeks. Streptomycin and tetracyclines are also effective antibiotics for those individuals with penicillin-associated allergies. Addition of streptomycin to standard therapy is also advised in cases where isolates of Str. moniliformis are cell wall deficient (Rupp 1992).

C. Salmonella

1. Reservoir and Incidence

The genus Salmonella are gram-negative bacteria with approximately 2000 serotypes. Nontyphoidal salmonellosis is caused by any of these serotypes. Other than Salmonella typhi, the causative agent of typhoid fever, salmonellosis occurs worldwide and is important in humans and animals. S. typhi and Salmonella choleraesuis have only one serotype, whereas the remaining 2000 serotypes are within the species Salmonella enteritidis. References to the Salmonella enteritidis serotypes are abbreviated such that “enteritis” is dropped; for example, S. enteritidis serotype typhimurium is called Salmonella typhimurium. Salmonella typhimurium is the serotype most commonly associated with disease in both animals and humans. Other serotypes most commonly reported from humans and animals are Salmonella heidelberg, Salmonella agona, Salmonella montevideo, and Salmonella newport. Salmonellae are pathogenic to a variety of animals.

2. Mode of Transmission

Salmonella are ubiquitous in nature and are routinely found in water or food contaminated with animal or human excreta. Fecal-oral transmission is the primary mode for spreading infection from animal to animal or to humans. Transmission is enhanced by crowding and poor sanitation.

During the early 1900s, rodenticides containing live cultures of S. enteritidis were distributed on a large-scale basis by commercial and public health organizations in an attempt to eliminate feral rats. These cultures were known as “rat viruses” and were widely used in Europe, England, and the United States as “rat poisons” (Weisbroth 1979). However, enthusiasm for their use waned when it was discovered that the spread of the organisms couldn’t be limited; predictably, the baiting program was implicated in several epidemics among exposed human populations (Weisbroth 1979). Surprisingly, as late as the 1950s in England, S. enteritidis (serovar danzy) was isolated from adults living four miles apart. The source of infection was traced to contaminated cakes from a local bakery. Mice that had acquired the artificial media but only in the presence of 15% blood and sera, usually 10% to 20% rabbit or horse serum incubated at reduced partial pressures of oxygen. Sodium polyanethol sulfonate sometimes found in blood-based media because of its properties as a bacterial growth promoter should not be used due to its inhibitory effects on Str. moniliformis (Lambe et al. 1973; Shanson et al. 1985). Growth on agar consists of 1 to 2 mm gray, glistening colonies. The API ZYM diagnostic system can be used for rapid biochemical analysis and diagnosis. A PCR-based assay has also been described to diagnose Str. moniliformis (Berger et al. 2001).
infection from living *S. danzy* cultures in rodenticide baits had infected food in the bakery (Brown and Parker 1957).

As with other fecal-oral transmitted diseases, control depends on eliminating contact with feces, food, or water contaminated with Salmonella or animal reservoirs excreting the organism. Salmonella survive for months in feces and are readily cultured from sediments in ponds and streams previously contaminated with sewage or animal feces. Fat and moisture in food promote survival of salmonella. Pasteurization of milk and proper cooking of food (56°C for 10 to 20 minutes) effectively destroys salmonella. Municipal water supplies should be routinely monitored for coliform contamination (Pavia and Tauxe 1991).

### 3. Clinical Signs

Clinical signs of salmonellosis in humans include acute sudden gastroenteritis, abdominal pain, diarrhea, nausea, and fever. Diarrhea and anorexia may persist for several days. Organisms invading the intestine may create septicemia without severe intestinal involvement; most clinical signs are attributed to hematogenous spread of the organisms. As with other microbial infections, the severity of the disease relates to the organism's serotype, the number of bacteria ingested, and the host's susceptibility. In experimental studies with volunteers, several serovars induced a spectrum of clinical disease ranging from brief enteritis to serious debilitation. Incubation varied from 7 to 72 hours. Cases of asymptomatic carriers, persisting for several weeks, were common (Hull 1955).

Salmonella are flagellated, nonsporulating, aerobic gram-negative bacilli that can be readily isolated from feces on selective media designed to suppress bacterial growth of other enteric bacteria. Salmonella serotyping requires antigenic analysis (Fox 1991).

Salmonella gastroenteritis is usually mild and self-limiting. With careful management of fluid and electrolyte balance, antimicrobial therapy is not necessary. In humans, antimicrobial therapy may prolong rather than shorten the period that salmonella are shed in the feces (Nelson *et al.* 1980; Pavia and Tauxe 1991). In one double-blind placebo study of infants, oral antibiotics did not significantly affect the duration of salmonella carriage. Bacteriologic relapse after antibiotic treatment occurred in 53% of the patients, and 33% of these suffered a recurrence of diarrhea, whereas none of the placebo group relapsed (Nelson *et al.* 1980).

### D. Other Potential Bacterial Diseases

1. *Borrelia* Species (Tick borne Relapsing Fever)

   Tick-borne relapsing fever occurs primarily in foci in the western part of the United States, as well as other parts of the world. The disease is caused by at least 15 *Borrelia* species and is transmitted to humans from a variety of rodents (chipmunks, squirrels, rats, mice, prairie dogs, hedgehogs) via soft ticks of the genus *Ornithodorus*.

2. Helicobacteriosis

   Of recent interest are the increasingly recognized enterohepatic *Helicobacter* spp., which cause both hepatic and intestinal disease in mice (Whary and Fox 2004). One of these, *H. bilis*, isolated routinely from mice, has been found using PCR-based assays in bile and gallbladder of Chilean patients with chronic cholecystitis and in biliary cancers in Japanese patients (Fox *et al.* 1998; Matsukura *et al.* 2002). Whether these new helicobacters will be linked to zoonotic transmission from wild or laboratory rodents will require further studies.

3. *Staphylococcus aureus*

   Pathogenic *Staphylococcus aureus* of human phage type can cause clinical disease in mice and rats. This organism has been

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**TABLE 26-2**

| Probable Source of Infection | Number of Persons Infected | Lesions Appearing On Infected Mice Or Rats | References |
|------------------------------|-----------------------------|------------------------------------------|------------|
| Pet white mice; inbred albino laboratory mice (VSBS, A2G) | 7 children; 2 lab technicians | 2 or 104, diffuse alopecia | (Mackenzie 1961) |
| Laboratory mice | 6 lab technicians | 0 f 96 (222 cultured), survey of commercial stock | (Alteras 1965) |
| Laboratory mice | 2 lab technicians | <1% of all mice, carrier rate 90% | (Davies and Shewell 1964) |
| BALB/c C3H/Bl mice | 6 lab technicians | % not determined, alopecia, increased scaling on head and back, 10 mice | (Booth 1952) |
| White mice | 1 lab worker | 60 of 400, crusted or crustless plaques, circular with prominent periphery; general alopecia; mortality in some mice | (Cetin *et al.* 1965) |
| White mice | 1 bacteriologist | 20% colony with alopecia and scaly skin | (Dolan *et al.* 1958) |
| Wistar rats | 1 technician | Alopeia with crusting an erythema | (Povar 1965) |
| Rats | 1 technician | | |
introduced into SPF barrier-maintained mouse colonies and SPF rats and guinea pigs; the same phage type was isolated from their animal caretakers (Davey 1962; Shults et al. 1973). Colonization by normal *S. aureus* strains in the nasopharyngeal area of humans presumably minimizes the zoonotic potential of animal-originated *S. aureus*.

V. DERMATOPHYTOSIS (RINGWORM)

As reviewed comprehensively in Blank, reports of ringworm (fauw) in the mouse began to appear in the European literature in the mid-nineteenth century and in the North American literature during the early twentieth century (Blank 1957). Several of the early authors noted the similarities between the lesions of favus in the mouse and in humans. Quincke, who is generally credited with isolating the causative agent which he named θ-Pilz (now *Trichophyton mentagrophytes*), suggested that the infection in the mouse was also a source of infection of the cat, and thereby, of humans. Earlier reports of murine ringworm referred to the causative agent as *T. quinckeanaum*, but the successful crossing of *T. quinckeanaum* with the perfect state of *T. mentagrophytes*, *Arthroderma behamiae*, indicates that *T. quinckeanaum* is not a distinct species (Ajello et al. 1968). A later study of the two varieties, *T. mentagrophytes* var. *mentagrophytes* and *T. m. var. quinckeanaum*, noted that the conidia from both produced two morphological variants on cultivation (granular and fluffy), and these variants were *A. behamiae* type + and pathogenic (Hejtmanek and Hejtmanekova 1989). In addition to *T. mentagrophytes*, *Epidermophyton floccosum*, *Microsporum gallinae*, *M. gypseum*, *M. canis*, *T. erinacei*, *T. schoenleinii*, and *T. (keratinomyces) ajello* have been reported as zoophilic dermatophytes that can infect mice and cause ringworm in humans (Dvorak 1964; Kreml-Lamprecht and Bosse 1964; Marples 1967; Papini et al. 1997; Refai and Ali 1970).

1. Reservoir and Incidence

The dermatophytes are distributed worldwide and can involve a variety of small animal host species in addition to the mouse. Chmel et al. (1975) conducted field studies in a wooded farm setting in Czechoslovakia and detected an overall prevalence rate of 4.4% (57 positive of 1288) for *T. mentagrophytes* infection in 6 of 13 species sampled; the prevalence in *Mus musculus* was 3.4%, with mice comprising 15.8% of the infections detected. Of the species that harbored the infection, all frequented the barn or granary area; the seasonal incidence was highest during the winter months when the rodent carriers were more likely to seek harborage indoors. Chmel et al. (1975) also analyzed patient data and demonstrated that *T. mentagrophytes* was the predominant isolate from those who did agricultural work, while *T. verrucosum* was the main isolate from individuals who worked with farm animals. Also, human *T. mentagrophytes* infections were most common on the hands, wrist, forearm, face, and neck, unprotected skin sites readily contaminated by fodder, litter, or other materials while working in the barns. Ringworm infections associated with the handling of bags of grain in which mice had been living have also been reported (Alteras 1965; Blank 1957).

Ringworm infection in laboratory mice is often asymptomatic, remaining unrecognized until laboratory personnel become infected. Early reports in the literature indicated that the prevalence of *T. mentagrophytes* was 80 to 90% among some laboratory mouse stocks (Davies and Shewell 1964; Dolan et al. 1958). However, these reports predated the era of modern laboratory animal colony management marked by the commercial availability of cesarean-derived, barrier-maintained rodents. Moreover, the modern production practices that have been universally adopted by the industry for decades and the use of microbarrier cages with appropriate technique have further reduced the opportunity for ringworm to become a significant problem in contemporary colonies. In recognition of this fact, none of the major commercial vendors in the United States survey their colonies for dermatophyte infections as part of routine health monitoring. Sporadic cases of ringworm infections in rodents have been reported in the past three decades (Hironaga et al. 1981; Mizoguchi et al. 1986; Papini et al. 1997). Programs involved in importing mice from sources that fail to meet contemporary rodent production and husbandry practices should consider screening mice for dermatophytes during the quarantine period.

2. Mode of Transmission

The ease of transmission of dermatophytes from animals to humans is well known and is a significant health hazard. Laboratory mice, as well as other laboratory animal species, can harbor dermatophyte infection, with few or no visible skin lesions transmitting the infection to unsuspecting personnel (Dolan et al. 1958). Transmission can occur through direct contact with the infected animal or through indirect contact with animal bedding or other materials in the environment of the contaminated animal room. Rigorous facility and equipment sanitation has long been recognized as an essential element of an effective control program and should be undertaken in conjunction with efforts to treat valuable animals or to repopulate previously contaminated areas of a facility (Davies and Shewell 1964; Dolan et al. 1958; Mizoguchi et al. 1986). The importance of barrier protections by donning appropriate clothing, using gloves and other personal protective equipment, and modifying work practices to minimize skin exposure to dermatophytes has also been acknowledged for the prevention of transmission (Dolan et al. 1958). When prevention methods fail, allowing the introduction of dermatophyte infection into a mouse colony, and when transmission to humans occurs, clinical cases of dermatophytosis routinely respond well either to topical or systemic antifungal therapy.
TABLE 26-3
SELECTED ECTOPARASITES OF RODENTS WITH ZOONOTIC POTENTIAL*

| Species                    | Disease in humans                                      | Host                                                      | Agent transmitted                                                      |
|----------------------------|--------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------------------|
| Mites                      |                                                        |                                                           |                                                                       |
| Obligate skin mites        |                                                        |                                                           |                                                                       |
| *Sarcoptes scabiei*        |                                                        |                                                           |                                                                       |
| subspecies                 |                                                        |                                                           |                                                                       |
| Nest-inhabiting parasites  |                                                        |                                                           |                                                                       |
| *Ornthonyssus bacoti*      | Dermatitis, murine typhus, rickettsialpox              | Rodents and other vertebrates                             | Coxsackie, WEE, SLE virus, *Rickettsia typhi*, *Rickettsia akari*, *Francisella tularensis* |
| *Liponyssoides sanguineus* | Dermatitis, rickettsialpox                             | Rodents, particularly *Mus musculus*                     | *Rickettsia akari*                                                    |
| *Haemogamasus pontiger*    | Dermatitis                                             | Rodents, insectivores, straw bedding                     |                                                                       |
| *Ixodids (ticks)*          |                                                        |                                                           |                                                                       |
| *Dermacentor variabilis*   | Irritation, RMSF, tick paralysis, other diseases       | Wild rodents, cottontail rabbits, dogs from endemic areas | *Rickettsia rickettsia, F. tularensis*                                |
| *Amblyomma americanum*     | Irritation, RMSF, tick paralysis                       | Wild rodents, dogs                                       |                                                                       |
| *Ixodes scapularis*        | Irritation, possible tularemia                         | Dogs, wild rodents                                       |                                                                       |
| *Ixodes dammini*           | Human babesiosis, Lyme disease                         | Wild rodents, especially *Peromyscus* sp.                |                                                                       |
| *Fleas*                    |                                                        |                                                           |                                                                       |
| *Xenopsylla cheopis*       | Dermatitis, plague, murine typhus, *R. nana*, *R. diminuta* | Rat, mouse, wild rodents                                | Rodent tapeworms, *Yersinia pestis*, *Rickettsia typhi*               |
| *Nasopsyllus fasciatus*    | Dermatitis, plague, *R. nana*, *R. diminuta*, murine typhus | Rat, mouse, wild rodents                                | Rodent tapeworms, *Yersinia pestis*, *Rickettsia typhi*               |
| *Leptopsylla segnis*       | *R. diminuta*, *R. nana*, murine typhus               | Rat                                                       | Rodent tapeworms, harbors salmonella, *Rickettsia typhi*              |

*Found in laboratory animals that cause allergic dermatitis or from which zoonotic agents have been recovered in nature (see Yunker 1964).
**WEE, western equine encephalitis.
*SLE, St. Louis equine encephalitis.
**RMSF, Rocky Mountain spotted fever.

3. Clinical Signs

Dermatophytosis or ringworm in humans can be asymptomatic and minor, often self-limiting and drawing little attention from the affected individual. The infection usually causes an expanding, scaly and erythematous inflammatory plaque on the skin that occasionally contains fissures or vesicles when severely eczematous. On the trunk and extremities, the lesion may consist of one or more circular lesions with a central clearing and sharply defined margins, forming a ring, and hence the name “ringworm” (Fig. 26-1) (Merlin et al. 1994). Other dermatophytes are named according to the sites of involvement on the body (e.g., tinea pedis for foot infections, tinea capitis for scalp infections). The dermatophyte infections of humans associated with direct or indirect contact from mice usually involve the body or extremities, especially the arms and hands. Zoophilic *T. mentagrophytes* infection usually produces a highly inflammatory lesion and often undergoes rapid resolution. However, it can also produce furunculosis—deep infection of the hair follicles or widespread tinea corporis—which is also seen in infections of *E. floccosum*. In a laboratory-acquired infection with *T. (keratinomyces) ajelloi*, mice were the source of infection for a laboratory technician who developed small, grayish-white, scaly lesions on both hands. Hand lesions yielded the organism, as did 2 of 250 apparently healthy mice (Refai and Ali 1970).
VI. HELMINTH DISEASES

A. Tapeworms

1. Hymenolepis diminuta, the Rat Tapeworm

A. RESERVOIR AND INCIDENCE Although this parasite occurs in the mouse intestine, it is more commonly associated with rats and is especially common in wild Norway (Rattus norvegicus) and black (Rattus rattus) rats throughout the world (Faust and Russell 1970; Stone and Manwell 1966; Wardle and McLeod 1952). It has been reported in humans worldwide, including several areas in the United States.

B. MODE OF TRANSMISSION Like other tapeworms, H. diminuta requires an intermediate host, usually a flour beetle (Tribolium sp.), moth, or flea (Voge and Heyneman 1957). Larval development in Tribolium sp. at 30°C requires 8 days. Therefore, humans become infected only through ingestion of infected insects, such as flour beetles, which may contaminate rodent food or cereal marketed for human consumption.

C. CLINICAL SIGNS The infection in humans is usually asymptomatic, but in moderate to heavy infections it may cause headaches, dizziness, abdominal discomfort, and diarrhea. The greatest length of an adult parasite removed from a patient was 1 meter. Usually, adult parasites are 20 to 50 cm long and as much as 4 mm wide (Markell et al. 1999).

2. Rodentolepsis nana (formerly Hymenolepis) the Dwarf Tapeworm of Humans

A. RESERVOIR AND INCIDENCE The dwarf tapeworm is a common parasite of both the wild house mouse and the laboratory mouse. As indicated earlier in the text, in most well-managed mouse colonies, R. nana incidence is low compared to earlier reports of its high incidence in rodent colonies (Wescott 1982).

The estimate that 20 million humans in the world are infected was made many years ago but probably is an underestimate (Markell et al. 1999). Surveys conducted in Central Europe report that this tapeworm in humans is more prevalent in warm than in temperate regions. An incidence of 10% has been noted in some South American countries (Jelliffe and Stanfield 1978). It is most commonly diagnosed in children. Diagnosis is made by observing characteristic eggs in the feces.

B. MODE OF TRANSMISSION R. nana is unique among tapeworms in that the adult worm develops after the egg is ingested. The hooked oncosphere then invades the intestinal mucosa and develops into a cysticercoid larva. Rodentolepsis nana eggs can contaminate hands, be trapped on particulate matter, or be aerosolized, and then accidentally ingested. Since no intermediate host is required, the eggs are readily infective for the reciprocal hosts (Faust and Russell 1970). Precautions against infection include strict personal hygiene, appropriate laboratory uniforms, and use of disposable gloves and face masks when handling contaminated bedding and feces.

C. CLINICAL SIGNS The clinical picture of R. nana infection is quite cosmopolitan. In well-nourished persons, essentially no symptoms occur; the infection is noted when the proglottids or ova are seen in the stool. In other persons, the symptoms include headaches, dizziness, anorexia, inanition, pruritis of the nose and anus, periodic diarrhea, and abdominal distress. A tapeworm identified as R. nana was found in a tumor removed from the chest wall (Jelliffe and Stanfield 1978). The diagnosis is based on identification of the characteristic eggs or proglottids in the stool.

D. TREATMENT Praziquantel, given orally in a single dose of 25 mg/kg body weight is the drug of choice. Alternatively, niclosamide is given daily for 5 days because of the tissue phase of the parasite. The dose is 2 gm for adults and 1.5 gm for children > 34 kg, and 1.0 gm for children between 11 and 34 kg (Markell et al. 1999).

3. Rodentolepsis (formerly Hymenolepis) microstoma

Recently, a parasite known to naturally colonize mice, R. microstoma, has been identified in the feces of humans living in the northwest of Western Australia (Macnish et al. 2003). Although R. nana was the most common enteric parasite based on microscopic examination of feces, R. microstoma was identified as a mixed infection in 4 of 11 individuals by using a molecular-based assay consisting of restriction fragment length polymorphism of tapeworm DNA as well as a sequencing of the PCR product of the internal transcribed spacer 1 region of ribosomal DNA (Macnish et al. 2002). Given that R. microstoma requires an intermediate host, Tribolium confusum for its life cycle, it is understandable why it was not as common as R. nana in this study. However, given the morphological similarities of the eggs of R. nana and R. microstoma, the true prevalence of R. microstoma in humans won’t be known until molecular techniques to differentiate the two species are utilized in future studies.

B. Roundworms (Syphacia obvelata)

1. Reservoir and Incidence

Syphacia obvelata is an ubiquitous parasite in both wild and laboratory mice. Although parasitology texts report that Syphacia is infectious to humans, this citation originates from a publication in 1919, in which two S. obvelata adult worms and eggs reportedly were found in the formalin preserved feces of a Filipino child whose entire family of five was infected with
H. nana (Riley 1919). No mention is made of the method of collecting the feces, nor is it known whether the feces could have been contaminated with murine feces or with the parasite and/or eggs. The only other report is an unpublished finding of *S. muris* eggs in the feces of two children and two rhesus monkeys, cited in a personal letter from Dr. E. E. Faust of Tulane University, dated January 6, 1965 (Stone and Manwell 1966). Both of these cases may therefore be examples of spurious parasitism, but definitive information for that conclusion is lacking. Regardless, no published information indicates that laboratory personnel have been infected by working with *Syphacia*-infected mice.

2. Mode of Transmission

Contamination of food or utensils or accidental ingestion of *Syphacia* ova (e.g., via contaminated hands) could result in infection of humans. People working with infected mice probably ingest ova occasionally, but there is no evidence that this exposure results in active infection.

3. Clinical Signs

Because *Syphacia* infection in humans has not been described, clinical signs have not been noted.

4. Diagnosis

There are striking differences in size between specimens of female *S. obvelata* and those of *Enterobius vermicularis*, the pinworm, in humans (Markell and Voge 1965). *Syphacia* is 3.5 to 5.8 mm long, whereas the *Enterobius* sp. female reaches a length of 8 to 13 mm. The male *Syphacia* sp. measures 1.1 to 1.5 mm compared to 2.5 mm for *Enterobius*. The size difference between the eggs of the two species is also marked: *Syphacia* eggs are more than twice as long (125 μm versus 52 μm as those of *Enterobius*). It is unlikely therefore that *Syphacia* sp. would be misdiagnosed as *Enterobius* sp., assuming, of course, that the observer was aware of the size difference and measured the eggs.

VII. ARTHROPOD INFESTATIONS

A. Mites

Although many species of mites are found on laboratory mice, only *Ornithonyssus bacoti*, the tropical rat mite, and *Liponyssoides sanguineus*, the house mouse mite, are vectors of human disease. *Ornithonyssus bacoti* is seen in laboratory mice (Fox 1982); *L. sanguineus* has been identified only on wild mice. Bites from these mites, as well as from another mouse mite, *Haemalaelaps casalis*, are responsible for allergic dermatitis, or local inflammation, in humans.

1. *Ornithonyssus bacoti*—Tropical Rat Mite

*Ornithonyssus bacoti* can be found on many rodents; the brown Norway rat and the black roof rat are probably the primary host species (Beaver and Jung 1985). Since the time of the first report of human *Ornithonyssus bacoti*—associated dermatitis in Australia in 1913, and a 1923 report in humans in the United States, many other cases have continued to be described throughout the world (see Table 26-4) (Charlesworth and Clegern 1977; Chung et al. 1998; Dove and Shelmire 1931; Dowlati and Maguire 1970; Engel et al. 1998; Fox 1982; Haggard 1955; Hetherington et al. 1971; Riley 1940; Theis et al. 1981; Wainschel 1971; Weber 1940).

*Ornithonyssus bacoti* is an obligate bloodsucking parasite, usually tan but red when engorged with blood. Both the male and female feed on a rodent as their preferred host. The female is 700 μm to 1 mm in length; the male is smaller (Fig. 26-2). Eggs are laid in bedding or wall crevices by the female, which survives for about 70 days and feeds about every two days during this period. The mite has five developmental stages: adult, egg, nonfeeding larva, bloodsucking protonymph, and nonfeeding deutonymph. After feeding, the adults and protonymphs leave their host and seek refuge in cracks and crevices. The life cycle from adult to egg requires 7 to 16 days at room temperature. Unfed protonymphs have survived for 43 days (Brettman et al. 1981).

The mite often gains access to the premises on wild rodents and lives in crevices. If wild rodents are not readily available or are captured, the mite will seek blood elsewhere, either from the wild or laboratory rodent (if in an animal research facility) and/or humans. In some infestations, the rodent shows no clinical signs. However, in more chronic cases, dermatitis and anemia may develop. Historically, this mite has been a troublesome parasite in certain laboratory animals, especially rats, mice, and hamsters (Fox 1982; Keefe et al. 1964).

a. Clinical Signs Tropical rat mites produce painful, pruritic lesions in humans. Examination of patients often discloses popular lesions on the wrists, arms, abdomen, and chest. Raised erythematous papules and nodules several millimeters to greater than 1 cm in size occur singly or in linear configuration (Fig. 26-3). Epidemiologically, cases usually occur in clusters that involve a common source of exposure to the mite. Experimentally, cases have been shown to be a vector of pathogens. In the laboratory, mite transmission of various rickettsial species, *Pasteurella tularensis*, and Coxackie virus between different laboratory animals has been shown (Hopla 1951; Petrov 1971; Philip and Hughes 1948; Schwab et al. 1952).

Affected individuals may be treated with topical lindane or treated symptomatically, given that the mite does not reside on humans for any extended periods. Papular dermatitis will regress after a period of 7 to 10 days post-therapy. Recurrence of *Ornithonyssus bacoti* infestations is common unless the
### TABLE 26-4

**REPORTS OF *ORNITHONYSSUS BACOTTI*-INDUCED DERMATITIS IN HUMANS: UNITED STATES, 1931–1998**

| Host     | Person(s) afflicted | Environment                  | Lesions                                                                 | Anatomical location                           | References                                      |
|----------|---------------------|------------------------------|-------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------|
| Rat      | 200 adults and children | Residence, theater        | Adults: urticarial wheals, papules                                        | Adults: ankles, trunk, back, neck              | (Dove and Shelmire 1931)                        |
|          |                     |                              | Children: papules, urticarial wheals, vesicles                           | Children: beltline, upper part of shoulders   |                                                 |
| Rat      | 4 women, 1 man      | Department store            | Wheals, papules, few wheals with central puncture                       | Women: arms, forearms                         | (Weber 1940)                                   |
| Rat      | Employees           | Department store            | Macular skin eruptions                                                  | —                                             | (Riley 1940)                                   |
| Mice     | Infants, adult      | Foundling home              | Papular urticaria, grouping of bites                                     | —                                             | (Haggard 1955)                                 |
|          | occupants           |                              |                                                                         |                                                 |                                                 |
| Rat      | 8-yr.-old boy; 5 siblings, and both parents affected with milder symptoms | Residence                  | Excoriated urticarial papules                                           | Trunk, upper part of arms, buttocks             | (Dowlati and Maguire 1970)                     |
| Norway rat | 60 yr. old         | Residence                   | 1- to 4-mm papules, excoriated macules                                  | Neck, shoulders, back, scalp, forearm, arms, abdomen | (Hetherington et al. 1971)                     |
| Rat      | 56-yr.-old father and 2 sons; 73-yr.-old woman | Residence (apartment over food store) | “Insect bites,” papular excoriated dermatitis                        | Thorax, extremities, buttocks, genitalia, entire body | (Wainschel 1971)                                |
| Rat      | 69-yr.-old woman    | Residence                   | Papules with erythema                                                   | Breast, shoulders, arm                        | (Charlesworth and Clegern 1977)                 |
| Rat      | 3 female adults, 3 children | Residence                  | Papular urticaria, erythematous                                          | Neck, shoulders, arms, legs, abdomen, back    | (Theis et al. 1981)                            |
| Mice     | 5 research personnel, 2 animal care technicians | Animal research laboratory | Several millimeters to >1 cm raises erythematous papules and nodules    | Wrists, arm, abdomen, chest                   | (Fox 1982)                                     |
| Rodents  | 10 medical students | Library                     | Erythematous papules                                                    | Neck axilla, abdomen, both extremities        | (Chung et al. 1998)                            |
|          | (9 males, 1 female) |                              |                                                                         | Legs, arms, waist, laterally on the trunk     | (Engel et al. 1998)                            |
| Rodents  | 6 medical students  | Residence in centuries old house | Red papules and seropapules                                             |                                                |                                                 |

*Fig. 26-2  Left, Adult *Ornithonyssus* recovered from mouse cage (×10). Right, Enlarged view of mite mouth parts (×100).*
Fig. 26-3 A circular ringworm lesion on the arm of a man; contracted from a rodent infected with *Trichophyton mentagrophytes*. (Courtesy of Dr. William Kaplan.)

premises have been treated with an appropriate insecticide, and any feral rodents eradicated (Engel et al. 1998).

**B. Fleas**

Fleas are seldom found in laboratory mice but are common parasites of feral rodents. The Oriental rat flea, *Xenopsylla cheopis*, and another flea, *Nasopsyllus fasciatus*, both naturally infest mice and rats; they are vectors for murine typhus. Apparently, *X. cheopis* is easily established in animal facilities. At a midwestern U.S. university, it inhabited a room housing laboratory mice where, on two separate occasions, the flea caused distress by biting students (Yunker 1964). *Leptopsylla segnis*, the mouse flea, bites humans and is a vector for plague and typhus, serious diseases in humans. Also, *L. segnis* can serve as an intermediate host for the rodent tapeworms *R. nana* and *R. diminuta*, which can infect people. The flea’s bite can also be irritating and cause allergic dermatitis.

**VIII. BITES**

Authoritative information on the incidence and impact of animal bites in the general population over the past several decades is scant, and reliable data on the incidence of mouse bites among personnel who work in laboratory animal facilities or among the general populace is lacking. There have been occasional studies on the occurrence and clinical characteristics of rat bites within urban populations, including a recent investigation of 622 bites over the period 1974–1996 that associated this phenomenon with urban blight, poverty, and unemployed populations (Hirschhorn and Hodge 1999). Traditionally, animal bites have received attention from the clinical perspective of wound management and complications and from the epidemiological perspective on the transmission of infectious diseases, principally rabies. The bite of the rat is far more powerful and more likely to be disfiguring than that of the mouse, and rat bites are known to be associated with the transmission of bacterial zoonoses such as rat bite fever and leptospirosis (see elsewhere in this chapter). One should assume that the mouse is also capable of transmitting these agents via bite. Rabies transmission from small rodents in the wild occurs but is exceedingly rare (Gdalevich et al. 2000); therefore, rabies is of concern only if experimental studies with the virus are being conducted in mice. Mice can also transmit hantavirus infection and lymphocytic choriomeningitis virus infection via bites.

Anecdotally, most animal care and use programs report that rodent bites among personnel are a reasonably common occurrence that often are unreported to an institution’s occupational medical service, despite the fact that bites inflict pain, produce anxiety, and may have significant health consequences. In addition to the hazard of zoonotic disease or local wound infection with pyogenic or toxin producing bacteria such as *Clostridium tetani*, *Staphylococcus* spp., *Streptococcus* spp., *Escherichia coli*, and *Bacillus subtilis*, rodent bites, including those of the mouse, can induce a severe local allergic reaction or anaphylaxis in individuals previously sensitized to allergen (Hesford et al. 1995; Teasdale et al. 1983; Thewes et al. 1999). Thus, bite wounds from mice should be immediately cleaned thoroughly and reported to the institutional occupational medical service to permit evaluation of the person’s tetanus immunization status and need for additional local wound or other medical care. The need for additional training of bitten persons in animal handling may also be indicated.

**IX. ALLERGIC SENSITIVITIES—LABORATORY ANIMAL–ASSOCIATED ALLERGY (LAA)**

**A. Incidence and Clinical Signs**

Allergic skin and respiratory reactions to laboratory mice are very common in laboratory animal caretakers and technicians who work with these animals. A survey by Lutsky (1987) demonstrated that three-fourths of all institutions with laboratory animals had animal care personnel with allergic symptoms. The prevalence of symptoms of laboratory animal–associated allergy (LAA) among personnel working with laboratory animals has been estimated as between 10 and 46% in numerous recent studies, and among these individuals, approximately 10% are estimated to eventually proceed to the development of asthma (Chan-Yeung and Malo 1994; Eggleston and Wood 1992; Hollander et al. 1996; Hunskaar and Fosse 1990; Knysak 1989; Renstrom et al. 1994). Furthermore, other sources have suggested that among atopic individuals with preexisting allergic disease, up to 73% of persons exposed to lab animal allergens
may eventually develop LAA (Committee on Occupational Health and Safety in Research Animal Facilities/National Research Council Allergens 1997). The population at risk for work-related exposure to rodents was estimated at 90,000 (Newill et al. 1986); this population has likely grown in the intervening years to the expanding populations of genetically modified mice that are used in contemporary biomedical research programs and require care. Moreover, a recent study would seem to suggest that the risk of exposure to mouse allergens is not confined to those working in the laboratory animal facility environment. Data analyzed from the first National Survey of Lead and Allergens in Housing in the United States demonstrated that 82% of homes of diverse types and income levels across geographic locations had evidence of mouse allergen; 57% had detectable levels on the kitchen floors specifically; and 22% had allergen concentrations greater than 1.6 μg/g of dust collected, a level previously correlated with the significantly increased rate of sensitization to mouse allergen (Cohn et al. 2004). The large number of staff at risk of exposure in the workplace or already presensitized, in combination with the substantial added costs to employers for the medical management, operational disruptions, and retraining efforts related to employees who develop LAA and later proceed to asthma, should provide the impetus for many institutions to pay greater attention to this element of the occupational health and safety program (Schweitzer et al. 2003).

The major allergen of the laboratory mouse is the Mus m 1 protein, a member of the mouse major urinary proteins encoded by a multigene family consisting of approximately 35 genes (Clark et al. 1984a, 1984b). The earlier literature on the subject of mouse allergy referred to the mouse urinary proteins (MUPs), whereas recent literature cites the specific protein (Mus m 1) that is now known to be the primary offending allergen in the MUP multigene family. The Mus m 1 protein is in the lipocalin family of proteins that are produced in the saliva and liver and are excreted in the urine at levels 100 times higher than are present in mouse serum. Lipocalins serve to bind small hydrophobic molecules and function biologically to transport vitamins, small volatile odorants, and pheromones conferring the characteristic odor to mouse urine (Cavaggioni et al. 1999; Flower et al. 1993; Konieczny et al. 1997; Santa et al. 1998; Virtanen et al. 1999). Several studies have indicated that production of Mus m 1 is under hormonal control and that the urine of male mice contains four-fold higher levels than the urine of female mice (Hastie et al. 1979; Lorusso et al. 1986; Price and Longbottom 1987). In addition to being present in the saliva and urine, Mus m 1 in the serum becomes incorporated into the pelt, conferring the allergenic property to mouse dander. The main allergens of many furred animals are structurally similar proteins within the lipocalin family, including those of the cow (Bos d 2), horse (Equ c 1), dog (Can f 1), and rat (Rat n 1) (Virtanen et al. 1999). The Mus m 1 and Rat n 1 lipocalin allergens, to which 90% of mouse and rat allergic individuals react, respectively, are closely related, sharing a 66% homology (Clark et al. 1984a).

Some have proposed that personnel exposed to laboratory animal allergens can be categorized into four basic risk groups based on their history of allergic disease and sensitization to animal proteins (Committee on Occupational Health and Safety in Research Animal Facilities/National Research Council Allergens 1997). These risk groups are (1) normal individuals, (2) atopic individuals with preexisting allergic disease, (3) asymptomatic individuals with IgE antibodies to allergic animal proteins, and (4) symptomatic individuals with clinical symptoms upon exposure to animal allergens. Individuals in the normal risk group do not have a history of allergic disease, and 90% will never develop symptoms of LAA. If LAA develops in individuals in the normal risk group, it usually appears during the first three years of exposure. However, infrequently individuals in this risk group who have remained free of LAA for 10 or more years of exposure have developed a delayed onset of the condition (Department of Health and Human Services, National Institute of Occupational Safety and Health 1997).

Atopic individuals have a genetic predisposition for an exaggerated tendency to mount IgE responses to common environmental allergens. Atopic individuals have higher total levels of IgE in the circulation and higher blood eosinophil counts compared to normal individuals, possibly as a result of the activation of cytokines involved in IgE isotype switching, eosinophil survival, and mast cell proliferation (Janeway et al. 2001). Among atopic individuals, up to 73% of those exposed to allergenic animal proteins eventually develop symptoms (Agrup et al. 1986).

In asymptomatic individuals with elevated circulating IgE antibodies to animal allergens, up to 100% are at risk of developing allergic symptoms. Of the individuals in risk groups that are already symptomatic for LAA, approximately 33% will develop chest symptoms and 10% are likely to develop occupational asthma and face the prospect that continued exposure will result in permanent impairment.

Allergic rhinitis, allergic conjunctivitis, and contact urticaria are the most common disorders seen in LAA (Committee on Occupational Health and Safety in Research Animal Facilities/National Research Council Allergens 1997). Clinically, allergic rhinitis and conjunctivitis present with the symptoms of sneezing, clear nasal discharge, nasal congestion, itchiness, and watery eyes. Contact urticaria presenting as raised, circumscripted, erythematous lesions may also be present in LAA patients who report an intense itchiness to the skin in the area of contact with the allergen. Figs. 26-4 and 26-5 (Fox and Brayton 1982) illustrate the typical wheal and flare reaction on the skin provoked in an individual who had developed hypersensitivity to mouse urine over a period of several years and who was exposed by having a mouse with urine-contaminated feet walk over his arm (Ohman 1978).

One large survey of laboratory animal workers summarized in the NIOSH Alert (Department of Health and Human Services, National Institute of Occupational Safety and Health 1997) reported that of 5641 animal workers from 137 animal
facilities, 23% developed allergic symptoms related to laboratory animals. Of the workers reporting symptoms, 82% had nasal or eye symptoms, 46% had skin complaints, and 33% had asthma. Patients who develop asthma as a more serious complication of LAA manifest symptoms of wheezing, intermittent dyspnea or shortness of breath, cough, often nocturnal or in the early morning, and tightness of the chest. The key clinical sign in these patients is wheezing on auscultation, and physiological abnormalities include airflow obstruction, which may vary over time, bronchodilator responsiveness, and increased airway responsiveness (airway hyperreactivity) (Tang et al. 2003).

Though quite rare, generalized anaphylactic reactions that are potentially life threatening can occur in individuals highly sensitized to animal allergens. Anaphylaxis may manifest as diffuse itching, hives, and swelling of the face, lips, and tongue. In some individuals, breathing becomes difficult owing to laryngeal edema, and others develop asthma and wheezing. In the most severe cases, the cascading events of angioedema, stridor, respiratory obstruction, hypotension, and shock can be life threatening (Committee on Occupational Health and Safety in Research Animal Facilities/National Research Council Allergens 1997).

B. Pathogenesis

Laboratory animal-associated allergy is an example of the Type I, IgE antibody-mediated, immune reaction, and the reader should refer to other sources for a detailed discussion of the molecular mechanisms involved in developing this reaction (Janeway et al. 2001). In the case of animal allergens, the usual route of initial exposure is airborne, although bite exposures (saliva) and direct contact with the skin can also become important in later clinical symptoms. In the Type I reaction, upon exposure to antigen, which is often a protein or glycoprotein, the allergen is taken up and processed by cells of the innate and adaptive immune systems and by dendritic cells located in the mucosal-associated lymphoid cells, gut-associated lymphoid cells, and/or the dermis. The cytokine profiles of these cells favor the development of naïve CD4 T cells into Th2 cells that induce B cells to produce IgE specific for the allergen. Once the IgE response is initiated, it can be further enhanced by basophils, mast cells, and eosinophils that also drive allergen-specific IgE production (Janeway et al. 2001).

IgE is normally found only in low levels in the circulation because it binds to tissue mast cells and circulating basophils. In the sensitized individual, restimulation with the sensitizing allergen results in allergen binding to IgE and the release of histamine and other chemical mediators from the mast cells and basophils. These mediators produce the array of clinical signs and symptoms that are characteristic of the allergy: itchiness, nasal congestion, sneezing, nasal and ocular drainage, coughing, wheezing, and shortness of breath.

C. Diagnosis

To establish the diagnosis of LAA related to mouse exposure, the physician should begin by considering the strength of the history, physical examination findings, the temporal relationship between the patient symptoms and the environmental exposure to mice, and possibilities of alternative explanations for the patient’s problems such as exposure to other potential allergens in the workplace or allergens of a nonoccupational nature. The development of clinical symptoms concomitant with or following exposure to an environment containing mice or Mus m 1 laden mouse products should help in narrowing the number of allergens tested. The patient’s family history of allergy is also very important to consider because atopy is a proven risk factor in developing LAA (Botham et al. 1995; Meijer et al. 2002; Venables et al. 1988).
Physical examination of the patient and clinical monitoring for the progression of allergic disease incorporate a number of approaches. Pulmonary function tests such as bronchial hyper-responsiveness (in response to pharmacologic challenge with methacholine and not the specific allergen) and the forced expiratory volume in one second (FEV₁) are commonly used to evaluate the degree of airway impairment and the response to bronchodilators, glucocorticoids, and other therapeutic agents. Radiographs may also be useful in patients with pulmonary involvement. Routine laboratory tests may also aid in the characterization and management of the patient’s condition, such as complete blood count and nasal smears for eosinophilia which is common in allergic individuals but also can be seen in those with perennial nonallergic rhinitis (Dykewicz et al. 1998).

Measurement of total serum IgE has little value to the physician as an aid in distinguishing whether a particular patient has allergic disease, but it may offer some potential for the identifying of populations at risk for developing of LAA as indicated in both prospective and cross-sectional studies of laboratory animal workers (Hollander et al. 1996; Renstrom et al. 1995). Use of the radioallergosorbent test (RAST) for the detection of human IgE antibodies of defined allergen specificity is also available for patient evaluation. However, the quality of the laboratory performing the in vitro RAST assays, the specificity of the allergens used, and the potential for cross-reactivity are important considerations in adopting the RAST as a diagnostic tool (Hamilton 2003). Even when properly conducted, in vitro tests usually fail to detect a modest number of skin test-positive individuals, and on a per-test basis, skin tests have lower time and reagent costs (Hamilton 2003).

Clinicians agree that when properly performed, prick-puncture skin tests are generally considered the most convenient and least expensive screening method for detecting allergic reactions in most patients (Demoly et al. 2003). The valid interpretation of these tests relies on standardized allergens and methods, and negative prick-puncture tests may be confirmed by more sensitive in vitro techniques. Even after false-positive and false-negative tests have been eliminated, the proper interpretation of results requires thorough knowledge of the patient’s history and physical findings. A positive skin test alone does not confirm a definite clinical sensitivity to an allergen in the asymptomatic patient but possibly predicts the onset of allergic symptoms. A positive skin test in conjunction with a history suggestive of clinical sensitivity strongly indicates the allergen as the cause of the disease (Horak 1985). Strong positive skin tests along with a suggestive clinical history also correlate well with results of bronchial or nasal challenges with the antigen.

D. Treatment and Prevention

The animal facility conditions and practices that contribute to mouse-associated LAA as a serious and prevalent workplace hazard have received considerable study over the past several decades, enabling effective strategies for achieving control of exposures in most research animal care and use settings. In summary, these strategies involve exposure reduction through source reduction, containment of hazard through the use of modern equipment and engineering controls, and barrier protection with personal protective equipment. The Mus m 1 allergen load in the environment is markedly increased when male mice are used in studies due to the fact that they excrete 4-fold higher levels of allergen in the urine than do female mice (Lorusso et al. 1986). Therefore, sources have recommended, that whenever scientifically possible, use of only female mice would be a means of reducing allergen load in the environment and minimizing the exposure of personnel (Department of Health and Human Services, National Institute of Occupational Safety and Health 1997; Renstrom et al. 2001). Furthermore Renstrom et al. (2001) reported a three-fold higher rate of allergic sensitization in technicians who worked with male rodents. Although this approach may be useful in a few studies, this method of source reduction would appear to have only very limited applicability across the broad scope of contemporary studies using mouse models. Source reduction of mouse allergen is also achieved through reduction of animal density within an animal room (the number of animals per room volume) and through use of frequent, effective facility sanitation practices (Department of Health and Human Services, National Institute of Occupational Safety and Health 1997).

The risk of exposure to mouse allergen varies by the type of animal-related activities conducted by personnel and by the type of animal housing systems and equipment containment devices employed in the use and maintenance of laboratory mice (Gordon et al. 1997, 2001; Schweitzer et al. 2003; Thulin et al. 2002). Many studies have examined the different caging systems used for mouse housing, and the ability of each cage system design to reduce environmental allergen is well known (Gordon et al. 2001; Schweitzer et al. 2003). The application of just a simple filter sheet top or fitted filter bonnet to an open cage is effective in reducing ambient allergen levels (Reeb-Whitaker et al. 1999). However, studies indicate the clear superiority of individually ventilated caging (IVC) systems run under negative pressure for the purpose of controlling room allergen levels (Gordon et al. 2001; Reeb-Whitaker et al. 1999; Schweitzer et al. 2003). Gordon et al. (2001) suggested that the use of efficient negative IVC in combination with other engineering controls for allergen containment during procedures and waste processing would potentially produce a virtually allergen-free work environment. When negative pressure IVC housing is not available, the placement of cages in a HEPA-filtered, ventilated cabinet is effective at reducing room allergen loads (Thulin et al. 2002).

Gordon et al. (1997) reported that individuals who have direct contact with mice (animal technicians) have the highest exposure, followed by those who have intermittent contact with
anesthetized animals or mouse tissues (scientists and necropsy technicians), followed by those with indirect contact (office workers or histology technicians). The specific animal husbandry activities that are known to result in high exposure of personnel to mouse allergen are cage-changing activities, including animal transfer, stacking dirty cages, and manual emptying of cages; handling animals directly (particularly males); and room sweeping (Gordon et al. 1997). For each of these activities, use of improved containment equipment and changes in equipment handling procedures are effective in the controlling the allergen hazard and should be encouraged. For example, use of ventilated cabinets or biological safety cabinets during cage changing and animal handling is effective in conjunction with the use of microisolation cages (Gordon et al. 2001; Schweitzer et al. 2003; Thulin et al. 2002). Containment equipment has also been designed for the capture of airborne allergens generated when the bottom of one dirty cage is placed into the opening of another to stack the cages for transport to the cage wash area or when dirty bedding is removed prior to cage washing (Gordon et al. 1997; Kacergis et al. 1996). Room cleaning with a vacuum equipped with HEPA filtration followed by mopping with a damp mop also aids in reducing the environmental allergen load and personnel exposure (Kacergis et al. 1996).

Use of personal protective equipment and dedicated work clothing for personnel involved in high-exposure activities is an important asset in reducing allergen exposure. It is important for the work clothing to remain at work, as evidenced by the finding that children of laboratory animal workers had a higher incidence of clinical signs during provocative testing, positive skin tests, and IgE specific to laboratory rodents than did the children of parents who worked in other occupations (Krakowiak et al. 1999). Full sleeve protection and gloves should be worn to prevent the urticarial reactions in persons who are highly sensitive to the Mus m 1 allergen. Personnel should also be provided with respiratory protection and eye or face protection when warranted. Either filtering facepiece particulate respirators (N95 equivalent) or powered air purified respirators are effective in reducing airborne exposure and alleviating clinical symptoms (Schweitzer et al. 2003; Thulin et al. 2002). Special attention must be paid to the selection and fitting of N95 filtering facepiece particulate respirators to ensure proper function (Morbidity and Mortality Weekly Report 1998).

When the elimination of mouse allergen exposure in the workplace is not achieved through the use of engineering controls, work practices, and personal protective equipment, allergic reactions in persons sensitive to Mus m 1 can be managed with pharmacological agents that have a long history of use for this condition. These include antihistamines, topical α-adrenergic agents (bronchodilators), cromolyn sodium as a nasal spray, and intranasal potent glucocorticoids (Austen 2004). Prophylaxis in patients with mild symptoms is often provided with topical cromolyn sodium on a continuous basis, supplemented with the intermittent use of antihistamines often at bedtime. The selection of the antihistamine has been an area of considerable discussion, and the reader should refer to Casale et al. (2003) for further insights into this matter. In more serious cases, potent topical glucocorticoids may be necessary for alleviating clinical signs. Immunotherapy, or hyposensitization, is typically reserved for patients who are unable or unwilling to escape the allergen provoking the response. Although allergy to the dog or the cat can be ameliorated by immunotherapy (Norman 1998, 2004), the infrequent reports in the literature of immunotherapy for allergy to mice and other small laboratory animals have failed to establish the usefulness of this approach for the control of allergy to these species (Sorrell and Gottesman 1957; Wahn and Siraganian 1980).

X. CONCLUSION

The progress made in the past two decades in the evolution of health care systems responsible for the monitoring, control, and elimination of infectious diseases in laboratory mice as well as the advancements in the facilities, equipment, and techniques used to maintain mice in contemporary animal care and use programs, has vastly reduced the likelihood that personnel will encounter zoonotic diseases or other health hazards in the laboratory under most circumstances. Continued program success in the control of mouse-associated hazards relies on the use of well-designed and maintained animal facilities, exclusion of wild rodents and other vermin, and quality control in animal care and veterinary care practices. In unique experimental situations that place personnel at a high risk of exposure to mouse-associated hazards, institutional review should ensure that procedures are carefully planned and conducted using personal protective equipment for worker safety.

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