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Chapter 22

Zoonoses and Other Human Health Hazards

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THE MOUSE IN BIOMEDICAL RESEARCH, VOL. II

ISBN 0-12-262502-1

I. INTRODUCTION

Derived from the Greek words *zoon*, meaning animals, and *noses*, meaning disease, *zoonoses* literally refers to diseases transmitted directly to man by animals. This chapter reviews known or potential zoonotic agents and the disease manifestations produced in man by exposure to infected mice. We discuss other health hazards that may be encountered when working with mice, such as bites and allergies. Selected transmission of human infectious agents to mice is also briefly mentioned.

Although the mouse, either feral, laboratory, or pet, is not commonly considered a reservoir for human pathogens, a review of the literature contests that notion. It should also be noted that many of the zoonotic diseases affecting mice also occur in rats (Geller, 1979). However, with the advent of modern laboratory animal production and management, zoonotic diseases are being curtailed and are nonexistent in many laboratories.

II. VIRAL DISEASES

A. Lymphocytic Choriomeningitis Virus (LCM)

Of the many latent viruses present in the mouse, only LCM naturally infects man. A review of the literature attests to the ease with which LCM can be transmitted from animals to man (Lehmann-Grube, 1971; see also Chapter 12, this volume).

1. Reservoir and Incidence

The natural association of LCM virus and the mouse provides for mutual survival in a symbiotic relationship. Neither the virus nor the host significantly suppresses the other, though each can do so. LCM exists in the wild mouse population throughout the United States, Europe, Asia, Africa, and probably the world (although it has not been isolated from mice in Australia). Wild mice are the ultimate reservoir of infection for laboratory mice and other susceptible hosts (Maurer, 1964). Mice, and hamsters to a lesser extent, are the only species in which a long-term, asymptomatic infection is known to exist (Hotchin, 1971; Parker *et al.*, 1976). In an early study, 21.5% of mice surveyed in the Washington, D.C., area were infected (Armstrong *et al.*, 1940). In a more recent survey (1967-1970) in the United States, LCM infection was detected in only 2 of 22 production or research colonies (Poiley, 1970). It was present at a low-level incidence for at least 2 years in one colony. However, this survey was conducted only in retired breeding stock, and the monitoring technique detected only nontolerant infections. LCM has also been reported in other mouse colonies used for research in the United States. (Soave and Van Allen, 1958). Early investigations in the United Kingdom demonstrated infection in 1 of 18 mouse-breeding colonies (Findlay *et al.*, 1936) and in "many strains" surveyed at a later date (MacCallum, 1949). LCM still existed in colonies in selected institutions in England in 1970 (Skinner and Knight, 1971) and undoubtedly persists in some colonies maintained in the United States. Infection has been eradicated in almost all colonies, however, by surgical derivation, routine serological monitoring, culling, and prevention of entry of wild mice into laboratory colonies.

Another source of infection for man is the presence of LCM virus in experimental tumors induced in mice. This source was first recognized in a much used, transplantable leukemia of C58 mice, line I, in which inoculation of the tumor produced mild clinical illness in mice. It had been assumed that the sickness was due to a toxic substance produced by the leukemia cells; it was discovered, however, that the etiologic agent was LCM virus (Lindorfer and Syverton, 1953; Taylor and MacDowell, 1949). Subsequently, LCM virus has been found in other commonly used tumor lines (Collins and Parker, 1972; Stewart and Haas, 1956). LCM virus has also been found as a contaminant of mycoplasma and murine poliovirus (Findlay *et al.*, 1938; Wenner, 1948).

2. Mode of Transmission

Diagnosis and control of this infection in mouse colonies has been described in Chapter 12. Mice that are congenitally infected are born normal and appear normal for most of their life span, even though they are persistently viremic and viruric. Virtually all cells can be infected with the virus. Most human laboratory infections have been associated with improper handling of infected murine tissues (Baum *et al.*, 1966; Tobin, 1968). Before manipulative procedures begin, all murine tumor lines should be screened for this virus. Man can also be infected with LCM virus either directly from feces or urine of mice or indirectly by inhaling the dried excreta carried on aerosolized dust originating from the animal cage or room. The wild house mouse plays an important role in the incidence of human disease from LCM virus (Dalldorf *et al.*, 1946; MacCallum, 1949). The original description of human infection with LCM was associated with a reservoir of the virus in the form of persistent latent infections in the wild house mice, *Mus musculus* (Armstrong and Lillie, 1934). Although LCM infection can cause death in man, none of these cases was fatal, nor was there evidence of transmission by human contact. Several authors have emphasized that acutal handling of LCM-infected mice appeared to be important in causing the disease in humans (Havens, 1948; Smithard and Macrae, 1951). The bite of an

infected mouse can also cause human infection (Scheid *et al.*, 1964).

In general terms, control of LCM is related directly to sanitary conditions in homes and laboratories; infestation of the premises with LCM-infected mice may increase the likelihood of LCM infection (Armstrong and Sweet, 1939). Careful washing of hands or using disposable gloves reduces the chance of infection in man.

LCM can be considered an arthropod-borne virus, having been transmitted experimentally by various bloodsucking insects, including mosquitoes (*Aedes aegypti*), Rocky Mountain wood ticks (*Dermacentor andersoni*), and fleas; all of these organisms could conceivably gain entrance into a laboratory animal facility (Hotchin and Benson, 1973). LCM virus can also occur spontaneously in cockroaches (Armstrong, 1963).

3. Clinical Signs, Susceptibility, and Resistance in Man

Although its expression can vary greatly, LCM virus infection appears most frequently as a mild influenza-like syndrome, with or without apparent involvement of the central nervous system (Duncan *et al.*, 1951).

In one epidemic of nonmeningitic LCM virus infection, caused by exposure to infected hamsters, an influenza-like illness was described with typical symptoms of retro-orbital headache, severe myalgia, malaise, anorexia, and aching pain in the chest (Baum *et al.*, 1966). Fever was a consistent symptom. The author compared this illness to the disease in two other meningitic human cases in his laboratory, caused by contact with infected mice. Sequelae to the initial infection can consist of arthritis, orchitis, parotitis, and a mild generalized alopecia of the scalp (Baum *et al.*, 1966; Lewis and Utz, 1961).

B. Rabies

Rabies virus, a rhabdovirus, has been recognized since ancient times in Europe and Asia. This virus probably produces fatal disease, by inoculation, in all warm-blooded animals; mice must therefore be considered a potential source of rabies virus. In fact, laboratory diagnosis of rabies can be aided by intracerebral inoculation of mice with test suspensions.

1. Reservoir and Incidence

Rabies occurs on all continents of the world except Australia; islands such as New Zealand, Hawaii, and Great Britain are also free of the disease. It has been successfully excluded by rigid quarantine requirements. Rabies is uncommon in man, and its natural reservoirs are wild carnivora, bats, and rarely certain rodents, such as squirrels (Benenson, 1975).

The incidence of rabies varies within select populations and geographic locations. No cases of human rabies in the United States have been associated with the bite of rabid mice or rats. However, in the Federal Republic of Germany, from 1961 to 1967, three mice, one rat (species unspecified), nine Norway rats, and eight muskrats were reportedly infected with rabies and had bitten humans (Scholz and Weinhold, 1969).

Rabies is transmitted via virus-laden saliva and is inoculated by a bite of a rabid animal or contamination of a wound with saliva. Most rabid animals transmit virus 3–5 days before the appearance of clinical signs and during the course of clinical disease.

2. Clinical Signs

Rabies appears nearly the same in man and animals, with both furious and paralytic signs being presented. The incubation period can range from 12 days to 6 months or more.

In experimentally inoculated mice, paralysis of the hindlimbs occurs as early as the seventh day or as late as the twenty-fifth day; death follows paralysis within 24 hr. Convulsions may be observed just before paralysis begins (Bruner and Gillespie, 1973). Extreme caution should be used when working with experimentally infected mice, as with other infectious agents.

Other than in experimental settings involving rabies research, routine antirabies prophylaxis is not practiced for individuals bitten by laboratory-reared mice. Though the likelihood of rabid wild mice biting man is slim, the possibility does exist (Scholz and Weinhold, 1969).

C. Other Viruses

Three other viruses commonly associated with disease in mice have been implicated as being infective to man. Complement-fixing and neutralizing antibody titers to mouse hepatitis virus, a coronavirus, have been found in human sera (Hartley *et al.*, 1964). The titer's presence is most likely due to cross-reactivity with antibody from infections with human coronaviruses, such as OC 38–OC 43 (McIntosh *et al.*, 1967, 1969) and HCV 229B (Bradburne, 1970), rather than to indicators of zoonotic disease.

Another prevalent agent in mouse colonies, Sendai virus (parainfluenza virus), was originally isolated during an epidemic of fatal pneumonitis is Japanese children (Kuroya *et al.*, 1953a; Sano *et al.*, 1953). Lung suspensions from fatal cases were inoculated intranasally into laboratory mice, and Sendai virus was isolated from diseased lungs of the mice. A year later, another investigator demonstrated the indigenous nature of the virus in mice (Fukumi *et al.*, 1954). Rising antibody titers were demonstrated in patients, and the virus

was supposedly capable of producing disease in human volunteers (see Parker and Richter, Chapter 8, this volume, for a review). Others have also reported isolating the virus from cases of human respiratory illness (Gerngross, 1957; Kuroya *et al.*, 1953b; Zhdanoff *et al.*, 1957). In a survey to detect the presence of antibody to murine viruses, antibody to Sendai virus was noted in personnel working with laboratory animals; significant titers were also present in personnel with no laboratory animal exposure (Tennant *et al.*, 1967). Though a definitive answer to the question remains debatable, the antibody titer is probably due to cross reactions with antigenically related parainfluenzea viruses (Heath *et al.*, 1962; see also Chapter 8, this volume).

Reovirus 3, a prevalent virus in mouse colonies, was first isolated in 1953 from the feces of a clinically ill child (Stanley *et al.*, 1953). Since then, the presence of antibody to reovirus 3 in human sera has been reported, although no human clinical syndrome has been well defined. The occurrence of reovirus 3 in mice and humans suggests possible natural transmission between these species and others that harbor these viruses. Such transmission has yet to be demonstrated, but it may occur occasionally (Rosen, 1968).

III. RICKETTSIAL DISEASES

A. Rickettsialpox

1. Reservoir and Incidence

A variety of rodent hosts are included in the transmission cycle of rickettsial disease in nature. The house mouse is the natural host of *Rickettsia akari,* the causative agent of rickettsialpox and a member of the spotted fever group of rickettsiae. The organism has also been isolated from rats (*Rattus*) and voles (*Microtus*). Rickettsialpox in humans was first described by two physicians in New York City. The causative agent was isolated from the patient, the mite vector *Liponyssoides* (*Allodermanyssus*) *sanguineus,* and the wild house mouse (Huebner *et al.*, 1946a,b, 1947). Subsequent clinical cases in New York City have been reported, principally among residents of buildings where mice, mites, and rickettsia maintain a cyclic infection (Nichols *et al.*, 1953). Other cases in eastern United States cities, Korea, and the USSR have been reported. In man, the disease has not been associated with naturally infected laboratory mice. The mite vector *L. sanguineus* occurs in many parts of the world but has not been reported in conventional rodent colonies. This may be due to confusion with other species of mites, such as *Ornithonyssus,* which can appear in laboratory mice and rats, or *Dermanyssus,* which may infest rats (Flynn, 1973). The tropical rat mite *Ornithonyssus* (*Liponyssus*) *bacoti,* which also infests mice, has been infected experimentally but is not known to be involved in the natural cycle of rickettsialpox.

2. Clinical Signs

Rickettsialpox is initially characterized by skin papules, chills, fever, and a rash; the clinical manifestations range from mild to severe. Headache and general malaise, with muscular pain, are frequent. Clinical diagnosis is confirmed serologically by a positive complement fixation test between the second and third week of the illness (Benenson, 1975). Because many rickettsial infections mimic each other and occur in varying frequencies, rickettsialpox is difficult to diagnose either clinically or anatomically. Also, other bacterial and viral diseases, such as typhoid fever, chickenpox, or measles, can produce similar febrile reactions with an accompanying rash (Robbins, 1974). Specific serologic tests (complement fixation and agglutination) are extremely important in making proper diagnoses. Skin biopsies may be helpful for early specific diagnosis (Dolgopol, 1948). The blood of febrile patients can also be inoculated into mice and the organism recovered.

Laboratory mice are susceptible to *R. akari;* intranasal inoculation causes fatal pneumonia, and intraperitoneal injection of the organism produces severe illness and death in most animals. Anorexia, depression, and dypsnea are marked. Necropsy findings include peritonitis, splenomegaly, and lymphadenitis. Subcutaneous inoculation of *R. akari* causes active infection for 1 month, with organisms being recovered from the spleen but not from urine or feces. The nature of the natural infection in the mouse is not known (Bell, 1970).

Control and eradication of the disease depend on preventing wild mice and the mite vector from entering animal research facilities and human dwellings.

B. Murine Typhus

Another rickettsial disease, murine typhus or endemic typhus, is transmitted to man by rat fleas (*Xenopsylla cheopis* and *Nasopsyllus fasciatus*); rats and mice are its natural reservoirs. *Rickettsia mooseri,* the causative agent, has not been isolated from natural infections in laboratory mice. Clinical signs, diagnosis, and control in man are similar to those described for rickettsialpox. A total of 18 laboratory workers were infected with *R. mooseri* while performing intranasal inoculations with this agent and while handling infected mice (Loffler and Mooser, 1942; Van den Ende *et al.*, 1943).

IV. BACTERIAL DISEASES

A. Leptospirosis

Leptospira microorganisms were discovered in 1914, when isolated from jaundiced patients (Inada *et al.*, 1916), and after further study were named in 1917 (Noguchi, 1918).

1. Reservoir and Incidence

Reservoir hosts of leptospirosis include rats, mice, field moles, hedgehogs, gerbils, squirrels, rabbits, hamsters, other mammals, and reptiles. A particular species of animal will usually act as the primary host of a particular serotype, but most serotypes can be carried by several hosts. Leptospira are well adapted to a variety of mammals, particularly wild animals and rodents; clinical manifestations in the chronic form are inconspicuous, with the organism being carried and shed in the urine for long periods of time. Rodents and perhaps hedgehogs are the only animal species that can shed leptospires throughout their life span without clinical manifestations (Babudieri, 1958; Faine, 1963). Active shedding of leptospires by laboratory mice can go unrecognized until personnel handling the animals become clinically affected. Many leptospira prototypes, including *L. australis, bataviae, grippotyphosa, hebdomidis 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).

Rats and mice are common animal hosts for *L. ballum,* although it has been found in other wildlife, including skunks, rabbits, oppossums, and wild cats (Mailloux, 1975). The infection in mice is inapparent and can persist for the animal's lifetime (Torten, 1979). Although earlier reports indicated that several colonies of laboratory mice harbor the organism (Wolf *et al.*, 1949; Yager *et al.*, 1953), no current estimates of the carrier rate among laboratory rodents in the United States are available. In several European laboratories, transmission of leptospires from laboratory rats to laboratory personnel has been reported (Geller, 1979). In a study of leptospiral infections in feral rodents, 2673 rodents of 10 species were collected in Georgia. Of the 933 tested for leptospires (by kidney culture), *L. ballum* was the only serotype cultured. It was isolated from 22% of the house mice and 0.8% of the old-field mice *Peromyscus polionotus* (Brown and Gorman, 1960).

Since leptospirosis in humans is often difficult to diagnose, the low incidence of reported *L. ballum* infection in man may be misleading. Between 1947 and 1973, only 17 cases of *L. ballum* infection in man were recorded in the United States (Boak *et al.*, 1960; CDC, 1965, 1966; Friedmann *et al.*, 1973; Stoenner and Maclean, 1958). Outbreaks in personnel working with laboratory mice in the United States have been documented (Barkin *et al.*, 1974; Boak *et al.*, 1960; Stoenner and Maclean, 1958. In one study, 8 of 58 employees handling the infected laboratory mice (80% of breeding females were excreting *L. ballum* in their urine) experienced leptospirosis. Humans have also contracted leptospiral infection by handling infected pet mice (Friedmann *et al.*, 1973).

2. Mode of Transmission

Infection with *L. ballum* most frequently results from handling the infected mice (contaminating the hands with urine) or from aerosol exposure during cage cleaning. Skin abrasions may serve as the portal of entry, since *L. ballum* presumably does not penetrate intact skin. In one instance, it was speculated that a father was infected after his daughter, because of an argument, used his toothbrush to clean the contaminated pet mouse cage (Friedmann *et al.*, 1973). Also, laboratory or wild mice that are to be used for primary kidney tissue cultures should be ascertained to be free of leptospires (Turner, 1970).

3. Clinical Signs, Susceptibility, and Resistance in Man

Infected individuals experience a biphasic disease (Heath and Alexander, 1970). They become suddenly ill with weakness, headache, myalgia, malaise, chills, and fever. Leukocytosis, usually associated with leptospirosis, is found inconsistently with *L. ballum* infection. During the second phase of the disease, a common finding is painful orchitis. Unlike the orchitis associated with mumps, leptospirosis caused enlarged testes in only one patient (Friedmann *et al.*, 1973). Two infected personnel in a laboratory mice-associated outbreak required more than a month for recovery (Stoenner and Maclean, 1958). Renal, liver, pulmonary, gastrointestinal, and conjunctival findings may be abnormal (Barkin *et al.*, 1974).

4. Diagnosis

Because of variability in the clinical symptoms and lack of pathognomonic pathological findings in man and animals, it is essential that serologic diagnosis or actual isolation of leptospires be undertaken to establish a correct diagnosis (Torten, 1979). As an aid to diagnosis, leptospires can sometimes be observed by examination or direct staining of body fluids or fresh tissue suspensions. A definitive diagnosis in man or mouse 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. Serologic assessment of host infection is accomplished by indirect hemagglutination, agglutination/analysis, complement fixation, microscopic and macroscopic agglutination, and fluorescent antibody techniques (Stoenner, 1954; Torten, 1979).

In a survey of trapped wild urban rats, diagnosis of leptospirosis was more accurate by urine or kidney culture, rather than by either indirect fluorescent antibody or macroscopic slide agglutination (Sulzer *et al.*, 1968). Another survey of wild rats confirmed that culture techniques identified more positive rats than did macroscopic slide agglutination (Higa and Fujinaka, 1976).

5. Epidemiology and Control

In mouse colonies infected with *L. ballum,* antibodies against *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 colostrum, 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 leptospirae. 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 that the percentage of carrier mice that do not have antibodies is significant. This led to the diagnostic approach, which specifies that both serologic and isolation methods must be utilized to determine the rate of leptospiral infection in rodents (Galton *et al.*, 1962).

Leptospira ballum is found frequently 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 leptospira infection, coupled with the prevention of ingress of wild rodents, should effectively preclude introduction of the organism into research and commercial laboratories (Loosli, 1967). *Leptospira ballum* has been elminated from a mouse colony by administration of feed containing 1000 gm chlorotetracycline 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 DDT were used to destroy escaped mice and to prevent reintroduction of *L. ballum* by the common house mouse (Stoenner *et al.*, 1958).

B. Pasteurellosis

Pasteurella pneumotropica, P. multocida, and *Yersini pseudotuberculosis,* causes of infection in man, have also been recovered from mice. Although *Y. (Pasteurella) pestis,* usually transmitted to man by a flea bite, occurs endemically in wild rodent populations (Hudson *et al.*, 1964), it should not be found in established mouse colonies if these mice have no contact with wild rodents.

1. Incidence and Reservoir

Pasteurella pneumotropica, first identified and studied in 1948 (Jawetz, 1948, 1950 (and rarely *P. multocida* or *Y. pseudotuberculosis*), usually occur as latent infections, though they can be a primary pathogen in laboratory mice (Brennan *et al.*, 1965, 1969; Hoag *et al.*, 1962). However, these organisms are rarely associated with human disease. Although direct transmission of *P. pneumotropica* from mice to man has not been reported, this organism has been transmitted via the bites of other animals (Miller, 1966; Olson and Meadows, 1969; Winton and Mair, 1969). Because mice harbor this organism in the upper respiratory system and pharynx, exposure could result from mouse bites.

2. Mode of Transmission

Reported cases in man are usually attributed to animal bites or exposure to ill animals. Also, *P. pneumotropica* was reportedly introduced into a barrier-maintained, specific pathogen-free (SPF) rat and mouse colony by personnel working in the area, who carried this organism in their upper respiratory system (Wheater, 1967). *Pasteurella pneumotropica* with similar biochemical characteristics was isolated from sputum and sinus infections from humans (Henriksen and Jyssum, 1961; Henriksen, 1962). An organism closely related to *P. pneumotropica* was recovered from 1% of sputum samples obtained during an 8-month period at a public health laboratory in England (Jones, 1962). It is suspected, however, that transmission of pasteurella infection from man to mice is rare, and despite the lack of confirmatory literature, transmission of pasteurella organisms from mouse to man probably is also rare.

3. Clinical Signs, Susceptibility, and Resistance in Man

Pasteurellosis is seldom reported in man, possibly because *Pasteurella* is usually an opportunistic pathogen with low pathogenicity for man or because the organism may be confused with *Hemophilus influenzae* or *Acinetobacter* sp. (e.g., *Mima polymorpha*) (Freigang and Elliott, 1963; Schipper, 1947). Deaths from *P. pneumotropica* infection have been recorded: One 51-year-old man died 48 hr after being bitten by a dog (Miller, 1966). Local inflammation, purulent discharge, pyrexia, and pain have been caused by bite wounds from which *P. pneumotropica* has been isolated (Olson and Meadows, 1969). Similarly, *P. multocida* was isolated from a wound after a bite from a laboratory rat, although the organism was not found in subsequent cultures from the rat (Bergogne-Berezin *et al.*, 1972). Septicemia and meningitis due to pasteurella have also been reported (Cooper *et al.*, 1973; Rogers *et al.*, 1973). Hubbert and Rosen (1970) listed 316 cases of *P. multocida* in man, usually associated with animal exposure. *Yersinia pseudotuberculosis* in man is reported rarely, but man can develop severe systemic infections from it.

C. Rat-bite Fever

Rat-bite fever can be caused by either of two microorganisms: *Streptobacillus moniliformis* (*Actinomyces muris*) or *Spirillum minus* (*Spirillum minor*) (*Spirillum morsus muris*); synonym (sodoku).

1. Reservoir and Incidence

These organisms are present in the oral cavity and upper respiratory passages of asymptomatic rodents. Reported incidences of mice as asymptomatic carriers of *S. moniliformis* or *Sp. minus* were not found. Nearly 50% of the asymptomatic laboratory rats cultured in an early study harbored *S. moniliformis* as normal oral flora (Strangeways, 1933). In a more recent study in laboratory Sprague-Dawley rats, *S. moniliformis* was the predominant microorganism isolated from the upper trachea of control animals (Paegle *et al.*, 1976). The lack of reported carrier rates in mice is attributed partly to the usual asymptomatic carrier state and partly to the difficulty in isolating the organisms. *Spirillum minus* cannot be cultured *in vitro* and requires inoculation of culture specimens into laboratory animals and subsequent identification of the organism by dark field microscopy. *Streptobacillus moniliformis* grows slowly on artificial media, but only in the presence of sera, usually 10–20% rabbit or horse serum incubated at reduced partial pressures of oxygen (Holmgren and Tunevall, 1970; Rogosa, 1974).

Arkless (1970) and Gilbert *et al.* (1971) described infection caused by the bite of a laboratory mouse and a pet mouse, respectively. The disease is not commonly reported in man but has been reported in personnel engaged in research involving laboratory rodents, particularly rats (Cole *et al.*, 1969; Gilbert *et al.*, 1971; Holden and MacKay, 1964). Historically, however, wild rat bites and subsequent illness have been associated with social conditions of poor sanitation and overcrowding, and almost 50% of all cases have involved children under the age of 12 (Brown and Nunemaker, 1942; Raffin and Freemark, 1979; Richter, 1945; Roughgarden, 1965).

Rat-bite fever is not a reportable disease; thus, its incidence, geographic location, racial data, or source of infection in humans is difficult to assess. Acute febrile diseases, especially if associated with animal bites, are routinely treated with penicillin or other antibiotics without prior culturing of the bite wound. This therapeutic approach, though successful in aborting cases of potential rat-bite fever, does not allow accurate recording of the disease in humans. One would suspect, therefore, because of the high number of rodent bites suffered by humans, that the incidence of rat-bite fever is low.

2. Mode of Transmission

The bite of an infected rodent, usually a wild rat but occasionally a laboratory rat or mouse, is the usual source of infection. In some reported cases, infection was attributed to dog, cat, or other animal bites and rarely to traumatic injuries unassociated with animal contact (Richter, 1945; Roughgarden, 1965). Outbreaks of febrile illness in humans have been associated with *Streptobacillus*-contaminated milk or food. The disease gained the synonym *Haverhill fever* after a 1926 outbreak in Haverhill, Massachusetts, attributed to contaminated milk (Place and Sutton, 1934).

3. Clinical Signs, Susceptibility, and Resistance in Man

Incubation varies from a few hours to 1–3 days in infection with *S. moniliformis* and may range from 1 to 6 weeks with *Sp. minus*. Fever is almost always present during the illness, whether it is caused by *Sp. minus* or *S. moniliformis*. In *Sp. minus* infection, inflammation at the site of the bite wound, as well as regional lymphadenopathy, often occurs; both these signs may coincide with the onset of fever. Inflammation and lymphadenopathy are infrequently documented with *S. moniliformis* infection. The fever and local signs may be accompanied by headache, general malaise, myalgia, and chills (Gilbert *et al.*, 1971; Raffin and Freemark, 1979). In most cases, a discrete macular rash appears on the extremities, frequently involving the palms and soles; it may become generalized, with pustular or petechial sequelae.

Arthritis reported in 50% of the cases of *S. moniliformis* infection usually affects larger joints; it also occurs in *Sp. minus* infection, but less commonly. Prolonged and recurrent joint involvement is noted in untreated patients. Serous to purulent effusion can be recovered from affected joints, with *S. moniliformis* being cultured from the fluid. Complications of the primary infection can result if antibiotic treatment is not instituted early. Pneumonia, heptatitis, pyelonephritis, enteritis, and endocarditis have been reported (McGill *et al.*, 1966). Deaths from *S. moniliformis* endocarditis have occurred, usually in cases with preexisting valvular disease.

D. *Salmonella*

Although there are 1600 recognized serotypes, *Salmonella typhimurium* and *S. enteritidis* have been associated most commonly with infections in laboratory mouse colonies (Haberman and Williams, 1958; Hoag and Rogers, 1961). Other serotypes have also been reported in mice (Ganaway, Chapter 1, this volume). From 1974 to 1978, the most frequently isolated serotype in the United States was *S. typhimurium* (CDC, 1976; MMWR, 1980). Other frequently isolated serotypes were *S. newport, S. enteritidis,* and *S. heidelberg*.

1. Reservoir and Incidence

Salmonella infection in man and animals, including mice, occurs worldwide. The organism is an enteric bacterium inhabiting the intestinal tract of many animals. Salmonella are routinely associated with food-borne disease outbreaks, are contaminants of sewage, and are found in many environmental water sources.

Although the reported incidence of salmonella in laboratory mice has decreased in the last several years because of management practices, environmental contamination with salmonella continues to be a potential source of infection for laboratory animals and, secondarily, for personnel handling these animals. Animal feed containing animal by-products continues to be a source of salmonella, especially if diets consist of raw meal and have not undergone a pelleting process (Hoag *et al.*, 1964; Stott *et al.*, 1975; Williams *et al.*, 1969). Until rodent feeds in the United States and Europe are salmonella-free, laboratory rodent-associated cases of salmonellosis will remain a distinct possibility.

Salmonella infections in rodents have also caused food-borne outbreaks of salmonellosis. In an interesting epidemiological study performed in England, *S. enteritidis* var. *danyz* was isolated from two adults living 4 miles apart. The source of infection was contaminated cakes from a local bakery. Mice from the bakery were trapped and cultured; they had acquired the infection from living *S. danyz* cultures in rodenticide baits and had infected food in the bakery (Brown and Parker, 1957). In another study, salmonella serotypes were isolated from 17% of 170 wild house mice. The authors concluded that house mice are a reservoir of infection and play an important role in human and animal salmonellosis (Shimi *et al.*, 1979). Undoubtedly, rodent excreta is the source of other food-forne outbreaks.

Both man and animals are carriers and periodic shedders of salmonella; they may have mild, unrecognized cases or they may be completely asymptomatic. Asymptomatic animals that shed salmonella are particularly important in biomedical research because they are a potential source of infection for other animals, animal technicians, and investigators (Fox and Beaucage, 1979). The incidence of carrier mice in the colony may vary from 1% to 20% (Haberman and Williams, 1958); indeed, one investigator suggested that clinically apparent salmonellosis is rare in infected mice (Margard *et al.*, 1963). In a survey of 19,137 nonhuman-origin salmonella isolations from pet-type animals, conducted in the United States from 1962 to 1965, a total of 227 isolates were recovered from rodents (Kaufman, 1966). The incidence of salmonellosis in man acquired from mice or vice versa is unknown; however, a treatise on diseases of laboratory mice (Hoag and Meier, 1966) states, "Occasional paratyphoid carriers are found among mouse handlers, but are not important sources of animal infection" (p. 594). No further expansion of this statement was provided.

2. Clinical Signs

The most common clinical sign of salmonellosis in man is acute gastroenteritis with sudden onset, abdominal pain, diarrhea, nausea, and fever. Loose bowels and anorexia may persist for several days. When organisms invade the bowel wall, some cases can lead to febrile septicemia without severe intestinal involvement; in these cases, most clinical signs are attributed to hematogenous spread of the organisms (Robbins, 1974). As with other microbial infections, severity of this disease is related to the organism's serotype, the number of bacteria ingested, and host susceptibility. Inapparent infections are encountered frequently; laboratories maintaining mice should consider screening animal technicians for subclinical salmonella infections.

E. Other Potential Bacterial Diseases

1. Erysipelas

Erysipelas, caused by *Erysipelothrix rhusiopathiae,* which affects a variety of fishes and mammals, including man, was first recognized when Koch discovered an organism he called

bacillus of mouse septicemia. The disease in man, called *erysipeloid* (not human erysipelas), was recognized by Rosenbach in 1887. The first report of natural infection in wild mammals appears to be an epizootic among migrating meadow mice and house mice in California (Wayson, 1927). Although the laboratory mouse is susceptible to experimental infection, neither natural disease nor human infection from handling diseased mice has been reported.

2. *Pseudomonas*

Pseudomonas aeruginosa, a virulent pathogen in immunosuppressed mice and a potential pathogen in conventional or SPF mice, may be acquired from human carriers. Van der Waaij *et al.* (1963) documented two outbreaks of pseudomonas infection spreading within the colony from infected animal caretakers. Infection was curtailed by transferring infected personnel who served as reservoirs and by instituting rigid sanitation and hygienic precautions.

3. *Staphylococcus*

Staphylococcal organisms are ubiquitous; there is abundant evidence that humans can carry phage types of *Staphylococcus aureus* that can cause clinical disease in mice. Pathogenic *S. aureus* of the human phage type have been introduced into SPF barrier-maintained mouse colonies where they had previously been absent; the same phage type was isolated from animal caretakers working in the area (Blackmore and Francis, 1970; Davey, 1962; Shults *et al.,* 1973). The lack of indigenous strains of staphylococci in SPF barrier-maintained animals may account for colonization of and resulting disease produced by human phage-type staphylococci (Blackmore and Francis, 1970). A similar phenomenon has been demonstrated in humans where the nasopharynx resists colonization by virulent strains of staphylococci due to the presence of avirulent *S. aureus* strains (Eichenwald, 1965). Pathogenic *S. aureus* of various human phage types have also been isolated from other laboratory animal species (Fox *et al.,* 1977; Renquist and Soave, 1969; Rountree *et al.,* 1956). Animals, including mice, therefore conceivably could serve as sources of potentially pathogenic staphylococci for humans.

4. *Streptococcus*

Streptococci of Lancefield groups A, B, C, and D have been isolated from disease outbreaks in mice (Besch and Williford, Chapter 4, this volume). Groups A, B, C, and D streptococci have also been isolated from man; group D streptococci are routinely isolated as common bacteria of human and animal intestinal flora. Group A streptococci (the most common species causing disease in man is *S. pyogenes*) and group B streptococci are responsible for a variety of clinical diseases in man. Although group C streptococci are primarily pathogens in various animals, including mice, strains can be isolated from the human respiratory tract as well (Davis *et al.,* 1969). However, we found no documented evidence that streptococci isolated from mice are transmitted to or acquired from man.

V. MYCOSES (RINGWORM)

Ringworm (favus) in the mouse was first recorded in England in 1850. A common house mouse had ringworm lesions identical to those on man (cited in Buchanan, 1919) Classical murine ringworm, reportedly caused by *Trichophyton quinckeanum,* is usually restricted to feral rodents. However, successful crossing of *T. quinckeanum* cultures with tester strains of the perfect state of *T. mentagrophytes, Arthroderma benhamiae,* demonstrates that *T. quickeanum* is not a distinct species and is indistinguishable from *T. mentagrophytes* (Ajello *et al.,* 1968). Many other zoophilic dermatophytes associated with infections of mice can cause ringworm in man, including *Epidermophyton floccosum, Microsporum gallinae, M. gypseum, T. erinacai, T. schoenleini,* and *T. (keratinomyces) ajello* (Dvorak and Otechenasek, 1964; Krempl Lamprecht and Bosse, 1964; Marples, 1967; Refai and Ali, 1970). In almost all mouse-associated ringworm infections in man, *T. mentagrophytes* has been isolated as the etiological agent (Table I).

A. Reservoir and Incidence

Dermatophytes are distributed throughout the world, with some species being reported more commonly in certain geographic locations. For example, in a study of small mammals in their natural habitat, *T. mentagrophytes* was isolated from 57 of 1288 animals representing 15 different species. The dermatophyte was isolated most commonly from the bank vole (*Clethrionomys glariolus*), followed by the common shrew (*Sorex araneus*) and the common house mouse (*M. musculus*) (Chmel *et al.,* 1975). In this survey, agricultural workers, exposed to these mammals in granaries and barns, risked contracting *T. mentagrophytes* infection. *Trichophyton mentagrophytes* was isolated from 77% of the 137 agricultural workers infected with ringworm, whereas *T. verrucosum* was isolated from only 23% of the cases. In the same study, of 445 ringworm-infected personnel working with farm animals, 75% were infected with *T. verrucosum* and 28% with *T. mentagrophytes.* Human infection with *T. mentagrophytes* has also followed handling of bags of grain in which mice had been living (Alteras, 1965; Blank, 1957). Thus, specific exposure to

Table I

Trichophyton mentagrophytes Infections Associated with Laboratory or Pet Mice

Probable source of infection	Number of persons infected	Lesions appearing on infected mice	References
Pet white mice	7 children	2 of 104, diffuse hair loss	MacKenzie (1961)
Inbred albino laboratory mice (VSBS, A2G)	2 laboratory technicians		
Laboratory mice	6 laboratory technicians		Alteras (1965)
Laboratory mice	2 laboratory technicians	0 of 96 (222 cultured), survey of commercial stock	Dolan *et al.* (1958)
BALB/c C3H/Bi mice	6 laboratory technicians	<1% of all mice, carrier rate 90%	Davies and Shewell (1964)
White mice	1 laboratory worker	% ND, loss of hair, increased scaling on head and back, 10 mice	Booth (1952)
White mice	1 bacteriologist	60 of 400, crusted or crustless plaques, circular with prominent periphery; general alopecia; mortality in some mice	Cetin *et al.* (1965)

reservoir hosts harboring different dermatophytes determines the type and incidence of infection in man.

Ringworm infection in laboratory mice is often asymptomatic and is not recognized until personnel become infected. A prevalence of *T. mentagrophytes* among laboratory mouse stocks as high as 80-90% has been recorded (Davies and Shewell, 1964). During an 8-month period, before infected mice were treated, 6 of 13 people handling the mice developed ringworm, although less than 1% of the mice showed any clinical signs of the disease. Dipping the animals in an aqueous solution of an acaricide containing a fungicide to remove mites reduced mice carriers from 90 to 21%. Other authors have reported that personnel were infected when handling mice clinically affected with *T. mentagrophytes* infection (Cetin *et al.*, 1965).

B. Mode of Transmission

Transmission of dermatophytes from animal to man is a well-known and serious public health concern. Transmission from laboratory animals, including mice, to personnel is often unsuspected, because laboratory animals usually have a paucity of visible skin lesions. Various surveys have indicated that as few as 1% of infected laboratory rodents show clinical evidence of dermatophyte infection (Cotchin and Roe, 1967). Dolan *et al.* (1958) reported that 43% of healthy mice received from various breeders in the United States were infected with *T. mentagrophytes*, whereas only 2% displayed clinical lesions. Transmission occurs via direct or indirect contact with asymptomatic carrier animals or with skin lesions of infected mice, contaminated animal bedding, equipment, or causal fungi present in air, dust, or on surfaces of animal-holding rooms (MacKenzie, 1961). The infection is communicable as long as infected animals are maintained and viable spores persist on contaminated materials. To maintain laboratory mice free of infection, and thus preclude personnel exposure, newly purchased mice should be screened for dermatophytes, and the animal facility environment and caging should be sanitized regularly.

C. Clinical Signs

The disease, dermatomycosis or ringworm in man, is nonfatal, often self-limiting, sometimes asymptomatic, and thus often ignored by the affected person. In general, the dermatophytes cause scaling, erythema, and occasionally vesicles and fissures. The fungi cause thickening and discoloration of the nails. On the skin of the trunk and extremities, the lesion may consist of one or more circular lesions with a central clearing, forming a ring (Fig. 1) (Mescon and Grots, 1974). Fungal infections in man are catagorized clinically according to location; some examples are tinea capitis, a fungus infection

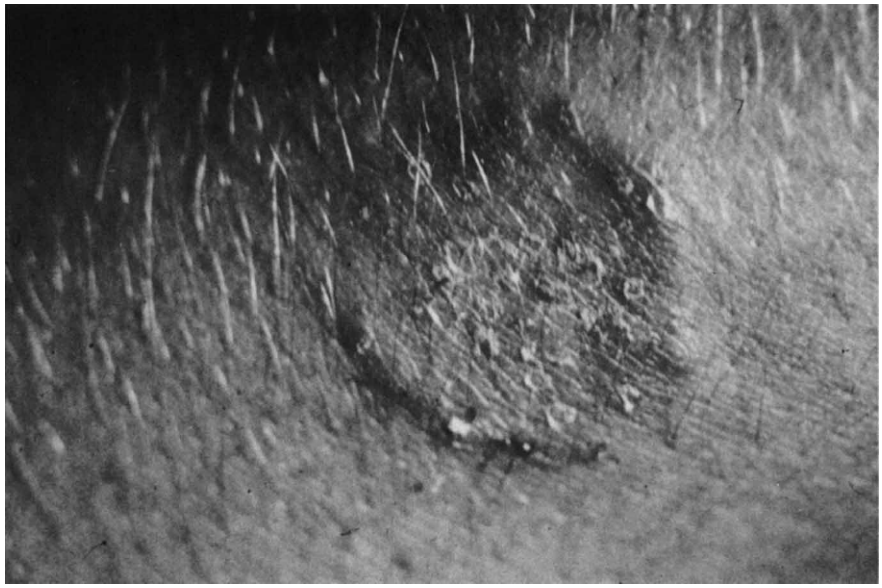

Fig. 1. A circular ringworm lesion on the arm of a man; contracted from a rodent infected with *Trichophyton mentagrophytes*. (Courtesy of Dr. William Kaplan.)

of the scalp and hair; tinea corporis, ringworm of the body; tinea pedis, of the foot; and tinea unguim, of the nails. Of the dermatophytes recovered from mice, when man is infected, the fungus is usually localized on the extremities or body, infection of the arm and hand being the most common. For instance, the zoophilic form of *T. mentagrophytes* is highly inflammatory and often undergoes rapid resolution. The infection may also produce furunculosis, deep involvement of the hair follicles, or a widespread tinea corporis, which is also seen in infections of *E. floccosum*. In a laboratory-acquired infection with *T. (keratinomyces) ajelloi,* a technician working with mice developed small, grayish-white, scaly lesions on both hands. The organism was isolated from the hand lesions and from 2 of 250 apparently healthy mice (Refai and Ali, 1970).

VI. PROTOZOAN DISEASES (*Entamoeba coli*)

Entamoeba coli, a nonpathogenic protozoan in man, is morphologically similar to *E. muris* seen in mice and rats. It is not definitely known whether transmission between humans and rodents is possible. An early report described the establishment of *E. coli* infection in rats; however, little attempt was made to reduce the possibility of cross-infection with *E. muris* (Kessel, 1923). In a later thorough study, *E. coli* was not transmitted to or established in either mice or rats (Neal, 1950). More recently, an attempt was made to establish human *E. coli* in laboratory rodents. Cysts of *E. coli* from 15 human and four primate stools were passaged in SPF guinea pigs, rats, and mice. In only one instance were cysts established in mice and eventually in rats (Owen, 1978). Because of the difficulty of differentiating between *E. coli* and *E. muris* morphologically, it is not possible to determine whether the *Entamoebe* that became established in rodents, originally isolated from an Ethiopian individual, was a true transmission of *E. coli* in the rodent or a contaminant of the human feces with *E. muris*. The author concluded that human–rodent contact is not responsible for the introduction of *Entamoeba* sp. (most likely *E. muris*) in SPF barrier-maintained rodent colonies. There is no evidence in the literature that humans are *E. muris* carriers.

The mouse can be infected experimentally with *E. histolytica,* but natural infections with this parasite have not been reported (Flynn, 1973).

VII. 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 (Wardle and McLeod, 1952); however, it is rarely encountered in man (Faust and Russell, 1970; Stone and Manwell, 1966).

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, man becomes infected only by 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 man is usually asymptomatic, but in moderate to heavy infections it may cause headaches, dizziness, and abdominal discomfort.

2. *Hymenolepis nana*, The Dwarf Tapeworm of Man

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, *H. nana* incidence is low compared to earlier reports of its high incidence in rodent colonies (Wescott, Chapter 20, this volume).

Stoll (1947) listed *H. nana* as infecting 100,000 persons in North America and 20 million in the world. Surveys conducted in Central Europe report that this tapeworm in man 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).

b. Mode of Transmission. *Hymenolepis 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 cysticeroid larva. *Hymenolepis 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 *H. 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. Convulsions have also occurred. A tapeworm identified as *H. nana* was found in a tumor removed from the chest wall (Jelliffe and Stanfield, 1978). The diagnosis was based on identification of the characteristic eggs or proglottids in the stool.

B. Roundworms (*Syphacia obvelata*)

1. Reservoir and Incidence

Syphacia obvelata is a ubiquitous parasite in both wild and laboratory mice. Although parasitology texts report that *Syphacia* is infectious to man, 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 collection of the feces, 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. C. 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 become 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 man. People working with infected mice probably ingest ova occasionally, but there is no evidence that active infection results from this exposure.

3. Clinical Signs

Because *Syphacia* infection in man 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 man (Markell and Voge, 1965). *Syphacia* is 3.5–5.8 mm long, whereas the *Enterobius* female reaches a length of 8–13 mm. The male *Syphacia* measures 1.1–1.5 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* would be misdiagnosed as *Enterobius*, assuming, of course, that the observer was aware of the size difference and measured the eggs.

VIII. ARTHROPOD INFESTATIONS

Though 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

Table II

Mouse Ectoparasites of Public Health Significance[a]

Vector	Disease	Reservoir
Mites		
Acarina (mites)	Allergic dermatitis	House mouse, laboratory mice, wild rodents
Ornithonyssus bacoti (tropical rat mite)	Biologic vector of murine typhus Rickettsialpox Q fever Plague Eastern equine encephalitis	
Liponyssoides (Allodermanyssus) sanguineus (house mouse mite)	Allergic dermatitis	House mouse
	Biologic vector of rickettsialpox Rash	Wild rodents
Haemalaelaps casalis	Allergic dermatitis	House mouse, laboratory mouse, wild rodents
Fleas		
Leptopsylla segnis	Biologic vector of plague and typhus Intermediate host of *H. nana* and *H. diminuta* Allergic dermatitis	
Xenopsylla cheopis	Allergic dermatitis Biologic vector of murine typhus	
Nasopsyllus fasciatus	Allergic dermatitis Biologic vector of murine typhus	

[a] For more information regarding life cycles, pathogenicity, and host range, see Flynn (1973).

mice (Fox, 1982); *L. sanguineus* has been identified only on wild mice (Table II). Bites from these mites, as well as from another mouse mite, *Haemalaelaps casalis*, are responsible for allergic dermatitis, or local inflammation, in man (Fig. 2).

Fleas are seldom found in laboratory mice but are common parasites of feral rodents. The Oriental rat flea, *Xenopsylla cheopis*, and *Nasopsyllus fasciatus*, another flea, both naturally infest mice and rats; they are vectors for murine typhus. Apparently, *X. cheopis* is easily established in animal facilities. At a Midwestern United States university, it inhabited rooms housing laboratory mice where, on two separate occasions, the flea caused distress by biting students (Yunker,

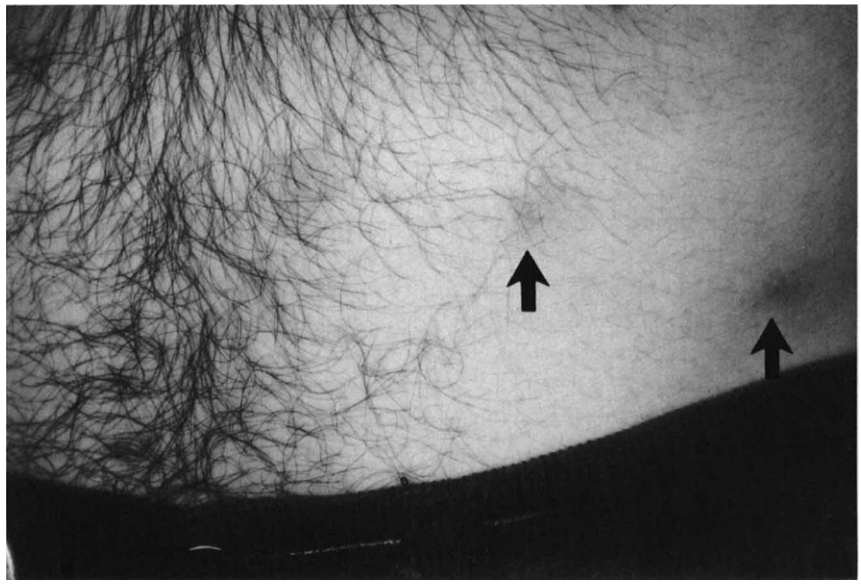

Fig. 2. Severe papular dermatitis with excoriations (arrows) on a man, caused by the bite of *Ornithonyssus bacoti*. Lesions are often noted on the stomach, above the belt line.

1964). *Leptopsylla segnis,* the mouse flea, bites man and is a vector for plague and typhus, serious diseases in man. Also, *L. segnis* can serve as an intermediate host for the rodent tapeworms *H. nana* and *H. diminuta,* which can infect man. The flea's bite can also be irritating and cause allergic dermatitis.

IX. BITES

During a 2-year surveillance period (1971-1972), 196,684 animal bite cases were reported from the 15 reporting areas in the United States (Moore *et al.,* 1977). The type of biting animal was reported for 196,117 persons bitten; 4% were rodents, type unspecified. By tradition, and public emotion, rabies has been the primary reason for investigating animal bite cases. Rodent bites (especially from wild rats), however, present other serious public health hazards, particularly in impoverished areas, where feral rodents are plentiful. Important effects of animal bites that must be considered are pain, anxiety, disfigurement, and infections caused by bacteria such as *Pasteurella* spp., *Clostridium tetani, S. moniliformis,* and *Sp. minus.* Reported incidences and severity of laboratory rodent-associated bites are few, except for published cases of rat-bite fever and *Pasteurella* infections (Hubbert and Rosen, 1970). Depending on the nature of the wound and the health status of the animal inflicting the bite, medical attention may be required. Minimally, for minor mice bites, the wound should be cleaned thoroughly and treated topically as necessary. Current tetanus immunizations should be maintained for personnel working with animals (ILAR, 1978).

X. ALLERGIC SENSITIVITIES

A. Incidence and Clinical Signs

Allergic skin and respiratory reactions are quite common in laboratory workers working with mice. Hypersensitivity reactions to mouse dander and urine are serious occupational health problems. Because of the large number of mice used in biomedical fields, numerous people are constantly exposed to laboratory mouse allergens. Historically, it was believed that only rabbit and cat danders produced laboratory animal-related asthma. This notion has been disproven and the mouse has been incriminated in producing asthma (Rajka, 1961; Newman-Taylor *et al.,* 1977). A biologist developed a typical mild anaphylactic reaction with hypotension, asthma, and giant urticaria after a mouse bite (Lincoln *et al.,* 1974). Hypersensitivity reactions include nasal congestion, rhinorrhea, sneezing, itching of the eyes, angioedema, and asthma. These would also include various skin manifestations such as localized urticaria and eczema (atopic dermatitis). Skin wheal and flare reactions were demonstrated in eight subjects sensitive to mice when tested with mouse pelt extracts (Ohman *et al.,* 1975). Maximal allergenic activity was demonstrated when the skin testing was done using the extract fraction which had the electrophoretic mobility of albumin. Figs. 3 and 4 illustrate a typical wheal and flare reaction on the skin of a patient who is hypersensitive to mouse urine. The patient developed hypersensitivity after working with mice for several years. A mouse whose feet were contaminated with urine walked across the patient's arm and produced these lesions. Often the complaint is manifested by intense itching when the mouse urine or serum has touched the skin (Ohman, 1978). Delayed reactions are also seen. Asthma may develop during the night after an exposure during the working day.

Some allergic disorders exhibit a familial prevalence. This familial predisposition to respond to allergies is called *atopy* and suggests that inheritance plays a role in the pathogenesis of atopic diseases (Gupta and Good, 1979). Members of the same family may manifest their atopy in different ways, with some having asthma and others eczema. These clinical manifestations of atopy are determined by the location of the shock organ, i.e., the skin, mucous membranes, respiratory or gastrointestinal tracts (Criep, 1976).

It appears that the major sources of antigen for personnel working with mice would be mouse dander (Sorrell and Gottesman, 1957; Lincoln *et al.,* 1974) and mouse urine (Newman-Taylor *et al.,* 1977). Newman-Taylor evaluated five patients, all of whom had a history of hay fever or asthma. Four of these patients handled mice. Symptoms appeared within 1 year in four patients and after 4 years in the fifth patient. Initial symptoms were rhinitis and conjunctivitis of rapid onset after animal exposure. Urticaria developed when the animal's feet, contaminated with urine, touched the patient's skin. Asthma developed in the five patients after a few weeks to 2 years of exposure to the animals. Initially, the asthmatic episodes would occur several hours after exposure to the animals. Within a year after the first asthma attack, all five patients developed asthma after a few minutes of exposure. After being separated from the animals for a few days, the patients were clinically normal. All four patients handling mice had immediate skin test reactions to mouse urine, mouse hair extract, and the prealbumin urine protein fraction. The four patients exhibited asthmatic reactions to inhalation tests using mouse urine. No asthmatic reactions were produced by mouse hair extract. Three of the four mouse handlers had immediate skin test reactions to mouse serum. The mouse prealbumin allergen in serum is in concentrations 200-400 times less than in urine.

Levy (1974) studied and quantitated allergic activity of pro-

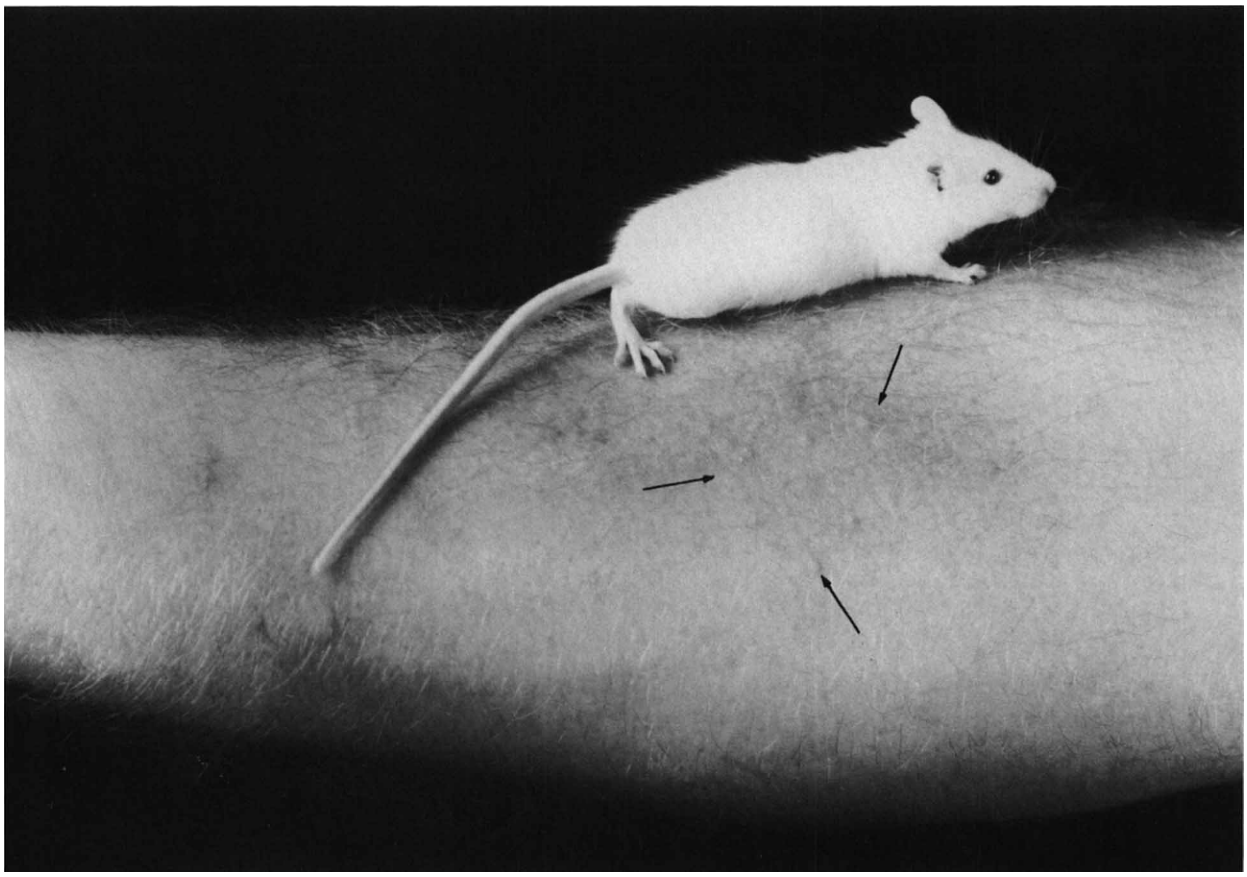

Fig. 3. Small wheals on the mid-forearm (arrows) and a large wheal adjacent to the tip of the tail of the mouse in the skin of a patient sensitive to mice.

teins from mice. He found that albumin was the major component of mouse skin extracts and that it was highly allergenic in some patients who were allergic to mice. Furthermore, Siraganian and Sandberg (1979) demonstrated the presence of at least two major allergens in mouse skin, serum, and urine. Patients sensitive to mice may react predominantly with either or both of these allergens. Further characterization of allergens from urine and animal pelts of inbred laboratory mice identified potent allergens in the mouse urine within the major urinary protein complex (MUP). In the three mouse strains studied, purified MUP proteins that bound to IgE antibodies cross-reacted extensively with each other and with allergens in dust from a mouse room. In addition, allergens from mouse pelts cross-reacted with MUP protein, suggesting that part of the allergenicity of pelt material may result from its content of components of the MUP complex. Other allergens with a high molecular weight were also found in the mouse pelt preparations. This study, which demonstrates cross-reactivity between urinary proteins and antigens in dust from a mouse room, suggests that a possible cause of sensitization in laboratory personnel is the dispersal of urinary protein from litter in mouse cages (Schumacher, 1980).

Other antigens in laboratory animal quarters may cause allergic reactions; these include mold spores and proteins in food that might be aerosolized (Patterson, 1964).

B. Pathogenesis

Because allergic sensitivities are the most common significant health hazard in mouse-associated employee activity, the pathogenesis will be discussed in some detail.

The pathogenesis of immediate hypersensitivity is initiated by an interaction of the mast cell and/or basophils. This degranulation releases preformed chemical mediators such as histamine, serotonin, and heparin. Other mediators are generated by the basophil or mast cell after it has been appropriately sensitized. An example of this type of mediator is the slow-reacting substance of anaphylaxis (SRS-A) (Gupta and Good, 1979). These mediators of immediate hypersensitivity act as messengers between the primary target cell population and populations of secondary effector cells or tissues. Effector cells, such as eosinophils, platelets, T lymphocytes, and monocytes, in turn amplify or modulate the inflammatory host

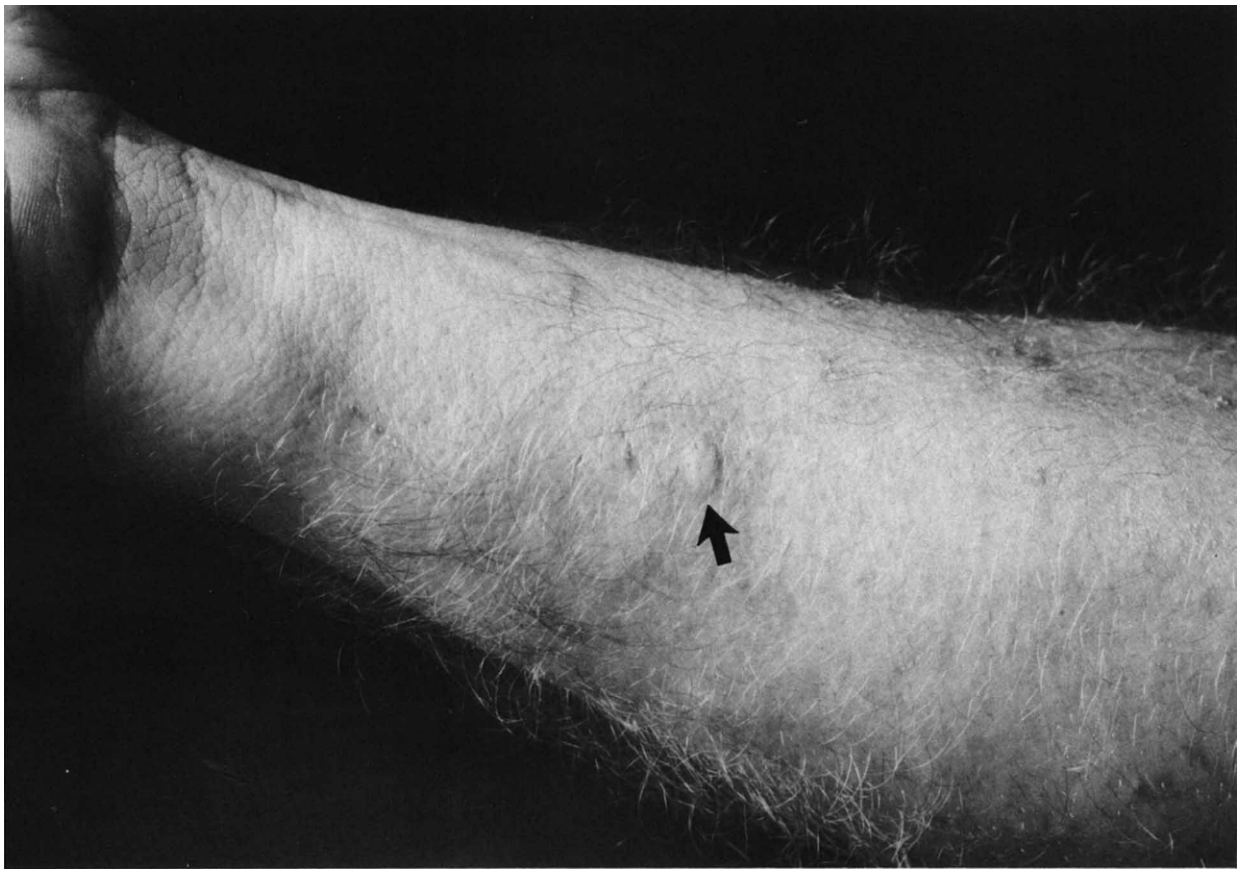

Fig. 4. Large wheal and flare in the skin (arrow) of a patient sensitive to mice.

responses, including smooth muscle contraction, vascular dilatation, and increased vascular permeability. The allergic reaction described above is often classified as type I.

Type II reactions occur when an IgG or IgM antibody reacts with an antigen on target cells. This reaction activates complement which causes cell lysis (Lutsky and Toshner, 1978). This type of reaction is most often seen when drugs act as the antigen and therefore is relatively unimportant in people working with laboratory mice.

Type III allergic reactions are characterized by damage initiated by immune complexes. These complexes activate the complement system which enhances the inflammatory response. This arthus reaction is a vasculitis initiated by the deposition of immune complexes of antigen and immunoglobulin (IgG) on the vessel endothelium. Examples include serum sickness, delayed tuberculin hypersensitivity, and hypersensitivity pneumonitis. Type III reactions may be involved in people working with laboratory animals who develop asthma several hours after being exposed to mice.

Type IV allergic reactions are cell mediated. Antigens are deposited locally and react with sensitized T lymphocytes which release certain cell-free factors (lymphokines). Examples of this type of reaction include homograph rejection, graft versus host reactions, and allergic-contact dermatitis. Type IV reactions may be involved in cases in which mouse dander, urine, or serum produces erythema and pruritis locally on the skin (Sorrell and Gottesman, 1957; Lincoln *et al., 1974).*

C. Diagnosis

To diagnose occupational allergic disease resulting from working with mice, one must establish a clinical diagnosis and incriminate the etiologic factors. A careful, detailed history, including patients' complaints as well as clinical symptoms, must be evaluated. The history of the appearance of clinical symptoms concomitant with or following environmental exposure often helps to narrow the number of allergens considered in the differential diagnosis. Nonoccupational exposure to potential allergens must also be considered. The family history of allergy is also important, since atopy predisposes a person to type I allergic reactions.

The physical examination must be thorough and well documented; often a repeat physical examination is helpful if

performed when the patient is not having an acute allergic attack. Repeated pulmonary function tests, especially when the lungs are the target organ, are often helpful; radiological examinations are occasionally used. Bronchial challenge tests with suspected allergens, though rarely indicated and difficult to evaluate, together with pulmonary function tests may detect the etiologic allergen. Skin testing with suspected antigens often identifies the hypersensitivity. Skin tests are almost always positive when properly done on a patient who has type I sensitivity to animal dander. Useful laboratory tests include a complete blood count; immunoglobulins and IgE antibody specific to one allergen, as measured by the radio-allergosorbent test (RAST); nasal smears for eosinophilia; and serum precipitants to specific allergens. The *in vitro* RAST, however, is less sensitive and no more specific than the skin test. The direct eosinophil count is another useful laboratory test; it is often elevated in the presence of nasal allergy and is almost always elevated in patients with asthma.

D. Treatment and Prevention

After an allergic disorder associated with exposure to mice has been diagnosed definitely, pharmacological agents are often used to relieve the acute attack. Useful agents include antihistamines, sympathomimetic agents, corticosteroid, and bronchodilators. Some pharmacological agents are somewhat useful on a long-term basis; these include antihistamines for allergic rhinitis, allergic conjunctivitis, and allergic skin reactions. β-Adrenergic agonists, cromolyn sulfate, and xanthines are sometimes useful in asthmatic patients.

Immunotherapy has been employed to reduce symptomatology of a laboratory worker sensitive to mice (Sorrell and Gottesman, 1957). Allergen immunotherapy is the systemic administration of etiological antigens in increasing dosages to produce hyposensitivity to animal proteins in the patient. This type of therapy may not be recommended because in highly sensitive individuals, it can be accompanied by uncomfortable local and systemic reactions. There is also a serious risk of inducing anaphylaxis in the patient (Gupta and Good, 1979). The risk of treatment of patients with animal dander extract, however, is probably no greater than that of treatment with pollen extracts. Newer forms of immunotherapy are still experimental, but some may prove clinically useful. Complete avoidance of the offending antigen is the method of choice for preventing an allergic reaction to mice. However, when complete avoidance of the allergen is unfeasible for socioeconomic reasons such as earning a living, other avenues of treatment and control must be considered (Lutsky and Toshner, 1978). Reduction of the contact intensity of the offending allergen is frequently used. Methods include reduction of direct animal contact time, increasing the room ventilation, employing filter caps on animal cages, using exhaust hoods when working with mice, and using protective clothing, masks, or respirators when working with mice.

XI. CONCLUSION

With the adoption of modern laboratory animal management, which includes routine disease surveillance, proper sanitary regimens, acceptable personal hygiene, and personnel health monitoring, laboratory mice usually do not present a zoonotic or health hazard. Well-designed animal facilities to prevent ingress of wild rodents and other vermin help preclude the introduction of animal and human pathogens. Careful attention to design of caging and air-flow dynamics within animal rooms is necessary to minimize exposure to allergens.

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