Chapter 25

Selected Zoonoses

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I. INTRODUCTION

Human risks of acquiring a zoonotic disease from animals used in biomedical research have declined over the past decade because higher quality research animals have defined microbiologic profiles. Even with diminished risks, the potential for exposure to infectious agents still exists, especially from larger species such as nonhuman primates, which are frequently obtained from the wild, and from livestock, dogs, ferrets, and cats, which are generally not raised in barrier facilities and are not subject to the intensive health monitoring performed routinely on laboratory rodents and rabbits. Additionally, when laboratory animals are used as models for infectious disease studies, exposure to microbial pathogens presents a threat to human health. Also, with the recognition of emerging diseases, some of which are zoonotic, constant vigilance and surveillance of laboratory animals for zoonotic diseases are still required.

Transmission of zoonotic agents between animals and personnel is either by direct contact with the infected animal or indirect contact by exposure to contaminated equipment or supplies. Many activities performed in laboratories and animal facilities result in the formation of aerosols. Aerosolization of infectious material remains the principal means of disease transmission. However, direct inoculation through bites and scratches, exposure to contaminated equipment, and accidental ingestion supplement spread of agents by aerosol.

As in a microbiologic laboratory or an infectious disease ward of a hospital, safety procedures can minimize potential zoonotic disease transmission to associated personnel in the biomedical laboratory. Some examples of sound procedures to follow in the control of exposure to zoonotic pathogens are (1) purchase of pathogen-free animals, (2) quarantine of incoming animals to detect any zoonotic pathogens, (3) appropriate treatment of infected animals or their removal from the facility, (4) vaccination of animal carriers and high-risk contacts where vaccines are available, (5) use of specialized containment caging or facilities and protective clothing, and (6) regular surveillance.

It is not within the scope of this chapter to discuss these issues in detail. A number of sources are available that offer additional information. In particular, the Centers for Disease Control and Prevention (CDCP) in conjunction with the National Institutes of Health (NIH) has published a monograph, "Biosafety in Microbiological and Biomedical Laboratories (CDCP–NIH, 1999). The National Academy of Sciences (NAS) has published "Occupational Health and Safety in the Care and Use of Research Animals" (National Research Council, 1997). "Occupational Medicine: State of the Art Reviews," dealing with animal handlers (Langley, 1999), is also available. All of these are important resources for personnel involved in biomedical research using animals.

The discussion that follows is a brief overview of select viral, rickettsial, chlamydial, bacterial, fungal, protozoal, and para-

sitic diseases shared by humans and the animals that are commonly used in biomedical laboratories.

II. VIRAL DISEASES

A. Poxviruses

Although there are numerous poxviruses capable of zoonotic transmission from laboratory animals to humans, with the possible exception of orf virus transmission from small ruminants, these infections appear to be mostly of historical interest (Fenner, 1990). The poxviruses involved in zoonotic transmission in the laboratory animal facility represent three genera, *Orthopoxvirus, Parapoxvirus,* and *Yatapoxvirus,* with the nonhuman primate serving as host for the majority of the potentially zoonotic poxviruses species. In humans, these infections usually are characterized by the development of proliferative cutaneous or subcutaneous self-limiting lesions. Humans occasionally manifest the clinical signs of systemic disease in these zoonotic infections, particularly when the poxviruses of nonhuman primates are involved.

1. Nonhuman Primate Poxvirus Infections

There are five nonhuman primate poxvirus infections that are either known to be zoonotic or are naturally occurring in humans. There is no evidence that smallpox, an *Orthopoxvirus* that is closely related to monkeypox virus, is naturally occurring in nonhuman primates, although it has been transmitted to nonhuman primates experimentally. Since 1980, smallpox has been considered to be eradicated on a worldwide basis by the World Health Organization, and the concomitant outbreaks of a smallpox-like disease in monkeys and humans have now been ascribed to monkeypox virus (Breman *et al.,* 1980).

a. Monkeypox

i. Reservoir and incidence. Monkeypox is an *Orthopoxvirus* causing sporadic cases of a human disease in Africa that mimics smallpox. Natural outbreaks of monkeypox have also been recorded in nonhuman primates in the wild and in laboratory settings (Fenner, 1990; CDCP, 1997). The virus appears to be naturally occurring in animals only on the continent of Africa, although Asian, African, and South American nonhuman primates are susceptible to infection (Fenner, 1990). Most of the infections in captive nonhuman primates have involved Asian macaques (Fenner, 1990). Recently, squirrels of the genera *Funisciurus* and *Heliosciurus* and nonhuman primates have been identified as hosts and significant reservoirs of the disease (Jerzek and Fenner, 1988).

ii. Mode of transmission. Within susceptible nonhuman primate populations, the disease spreads rapidly with high morbidity and variable mortality. However, the transmission of monkeypox from captive nonhuman primate populations to humans has not been recorded. Human-to-human transmission of this agent has occurred presumably through close contact with active lesions, recently contaminated fomites, or respiratory secretions (Fenner, 1990; CDCP, 1997). The possibility of zoonotic spread should be considered.

iii. Clinical signs. Clinical signs in the nonhuman primate host include fever followed in 4–5 days by cutaneous eruptions, usually on the limbs and less frequently on the trunk, face, lips, and buccal cavity.

Monkeypox in humans is primarily of interest and importance because it produces a disease similar to smallpox, characterized by fever, malaise, headache, severe backache, prostration, and occasional abdominal pain (Chin, 2000). Lymphadenopathy and a maculopustular skin rash develop subsequently. Some individuals develop a severe fulminating disease with fatality.

iv. Control and prevention. Smallpox vaccination will protect against monkeypox in humans and has also been used for the control of this disease in monkeys.

b. Benign Epidermal Monkeypox

Benign epidermal monkeypox (BEMP) is a *Yatapoxvirus* that has been zoonotic in the laboratory environment on numerous occasions.

i. Reservoir and incidence. Benign epidermal monkeypox, or tanapox, affects monkeys of the genus *Presbytis* in Africa and captive macaques in the United States. The African nonhuman primate genera *Cercopithecus* and *Cercocebus* and South American monkeys are apparently unaffected. Tanapox continues to be endemic in regions of Africa, and many cases of the disease in humans have also been detected in Africa during the course of surveillance for monkeypox (Jezek *et al.*, 1985).

ii. Mode of transmission. The rapid spread of BEMP among nonhuman primates housed in gang cages suggested direct viral transmission. The infections in animal handlers were attributed to viral contamination of skin abrasions.

iii. Clinical signs. Benign epidermal monkeypox is characterized by the development of circumscribed, oval to circular, elevated red lesions usually on the eyelids, face, body, or genitalia. These lesions regress spontaneously in 4–6 weeks. The localization of BEMP lesions in the epidermis and adnexal structures differentiates them from Yaba lesions histologically, but similar to Yaba, eosinophilic, intracytoplasmic inclusion bodies are present (Kupper et al., 1970).

iv. Control and prevention. Appropriate personal protective equipment should be sufficient to prevent the zoonotic transmission of this agent.

c. Yaba

Yaba monkey tumor poxvirus is a member of the genus *Yatapoxvirus* that was reported initially in a colony of rhesus monkeys (*Macaca mulatta*) housed outdoors in Yaba, Nigeria (Bearcroft and Jamieson, 1958). There have been subsequent outbreaks and experimental studies of the agent, as well as sporadic incidental cases of the disease in laboratory-housed nonhuman primates.

i. Reservoir and transmission. Natural cases of the disease have been reported in the rhesus monkey and the baboon (*Papio* spp.), and experimental studies have expanded the host range to include pigtail macaques (*Macaca nemestrina*), stumptail macaques (*Macaca arctoides*), cynomolgus (*Macaca fascicularis*), African green (*Cercopithecus aethiops*), sooty mangabey (*Cercocebus atys*) and patas monkeys (*Erythrocebus patas*) (Ambrus and Strandstrom, 1966; Ambrus *et al.*, 1969). Many African monkeys apparently originate from areas with endemic infection and are immune to the agent, and New World nonhuman primate species are resistant to infection (Ambrus and Strandstrom, 1966). The role of insect vectors in the natural spread of this disease is unproven. Experimental studies have demonstrated the spread of the agent by aerosol transmission; thus, aerosolized Yaba virus must be considered a potential hazard to humans.

ii. Clinical signs. Infected animals consistently have developed subcutaneous benign histiocytomas that reached a maximum size approximately 6 weeks postinoculation and regressed approximately 3 weeks thereafter. Natural tumor regression conferred immunity to reinfection (Niven, 1961), and the surgical removal of a Yaba tumor in a baboon prior to natural tumor regression was associated with subsequent susceptibility and reinfection with Yaba virus.

Six human volunteers have been inoculated experimentally with Yaba virus and developed similar, but smaller, tumors than those seen in monkeys; tumor regression was also earlier. Yaba tumor induction has also been recorded as a result of accidental self-inoculation (needlestick) in a laboratory worker using the virally infected tumor; complete tumor resection was curative.

2. Orf Virus (Contagious Ecthyma)

Orf virus is a *Parapoxvirus* disease of sheep, goats, and wild ungulates and is characterized by epithelial proliferation and necrosis in the skin and mucous membranes of the urogenital and gastrointestinal tracts.

i. Reservoir and incidence. Orf virus disease is an endemic infection in many sheep flocks and goat herds throughout the United States and worldwide. The disease affects all age groups although young animals are most frequently and most severely affected. In sheep, orf virus infection does not reliably confer protection against reinfection with different strains of virus, aiding in viral persistence within a population (Haig *et al.,* 1997).

ii. Mode of transmission. Orf virus is transmitted to humans by direct contact with scabs and exudates from viral-laden lesions. External lesions are not always readily apparent. Transmission of this agent by fomites or other animals contaminated with the virus is also possible due to the extended environmental persistence of this double-stranded DNA virus. Although the virus requires a break in skin for entry, rare cases of person-to-person transmission have been recorded (Chin, 2000).

iii. Clinical signs. Orf virus produces proliferative, pustular encrustations on the lips, nostrils, and mucous membranes of the oral cavity and urogenital orifices of infected animals.

The disease in humans is usually characterized by the development of a solitary lesion located on the hands, arms, or face (Fig. 1). The lesion is maculopapular or pustular initially and progresses to a weeping proliferative nodule with central umbilication. Occasionally, several nodules are present, each measuring up to 3 cm in diameter and persisting for 3–6 weeks, followed by spontaneous regression with minimal residual scarring. Regional adenitis is uncommon, and progression to generalized disease is considered a rare event (Chin, 2000).

iv. Control and prevention. Personnel should wear gloves and wash hands, as well as launder clothing and disinfect boots, after contact with sheep. Current herd-management practices often involve the use of live unattenuated orf virus vaccines that contribute to the perpetuation of environmental contamination and entail some risk to the individuals handling the vaccine product. Efforts are underway to explore the development of a subunit vaccine for orf virus to eliminate these problems (Mercer *et al.,* 1997).

Fig. 1. Human orf. Firm, raised, centrally necrotic lesion on the thumb of an animal technician who handled an infected goat. (Courtesy of Dr. J. Griffith.)

B. Hemorrhagic Fevers

The hemorrhagic fever viruses constitute a group of RNA viruses that produce a clinical syndrome in humans characterized by high fever, epistaxis, ecchymoses, diffuse hemorrhage in the gastrointestinal tract and other organs, hypotension, and shock. These diseases often are spread to humans by mosquitoes, ticks, or other arthropod vectors (hence, the term arthropod-borne or arboviruses for the causative agents); by direct contact with the excreta of infected rodents; or by the contaminated blood and bodily fluids of other infected animals. These viral agents have taken on increased importance in recent years and are receiving considerable attention within the context of emerging infections potentially impacting the United States and other regions of the globe. Contemporary society has catalyzed the process of emerging infections by introducing ecological disturbances affecting host and vector availability and distribution and by developing rapid means of international transportation, enhancing the potential dissemination and dispersion of these agents (Committee on Emerging Microbial Threats to Health, 1992; Le Guenno, 1997).

Nonhuman primates serve as reservoirs and are susceptible to numerous zoonotic viral hemorrhagic diseases, including yellow fever, dengue, Marburg virus disease, and Ebola, as well as to viral hemorrhagic diseases such as simian hemorrhagic fever, which is not considered zoonotic. However, these diseases are not of high concern in programs that follow an appropriate quarantine/importation process and are involved in the conventional care of nonhuman primates in indoor facilities. The salient features of natural and experimental infections by these agents in nonhuman primates have been reviewed in detail and will be discussed only briefly in this section (Adams, 1995; Mansfield and King, 1998). Rodent hantavirus infections have resulted in serious and fatal human zoonotic infection in association with laboratory animal studies and field studies involving wild animals and are covered in more detail.

1. Flaviviruses—Yellow Fever and Dengue

i. Reservoir, incidence, and transmission. Yellow fever is caused by an RNA flavivirus and is maintained in a monkey–mosquito–monkey cycle in the sylvatic or jungle form and in a monkey and human–mosquito transmission cycle in the urban or rural form of the disease (Adams, 1995). The main vectors are *Aedes aegypti* in the urban setting and *A. africanus* or *A. leucoelaenus* in the African or South American jungle settings, respectively. Cases of the disease in persons result from human forestry activities that disrupt the forest canopy, bringing mosquitoes to the ground, or from nonhuman primate epizootics, achieving a similar result.

There are four serotypes of dengue virus, any of which can cause dengue hemorrhagic fever. Dengue is endemic in tropical and subtropical Asia, Africa, Oceania, Australia, and the Americas and is widespread in the Caribbean basin. The virus persists in a nonhuman–mosquito cycle involving *A. aegypti* and *A. albopictus;* both of these vectors are now established in the United States (Committee on Emerging Microbial Threats to Health, 1992). Both dengue and yellow fever viruses are passed transovarially in the mosquito vector (Chin, 2000).

ii. Clinical signs. African monkeys apparently acquire yellow fever infection as young animals and develop a mild form of the disease with subsequent immunity as indicated by antibody titers. The disease in New World nonhuman primates and humans is fulminating and severe, characterized by fever, vomiting, anorexia, yellow to green urine, icterus, and albuminuria. At necropsy, the internal organs are hemorrhagic, necrotic, and bile-stained. The classic lesion is massive, midzonal necrotizing hepatitis with necrotic hepatocytes containing characteristic eosinophilic, intracytoplasmic inclusion bodies, or "Councilman bodies."

Human dengue infection is characterized by the abrupt onset of fever, intense headache, myalgia, arthralgia, retro-orbital pain, anorexia, gastrointestinal disturbances, and rash. The clinical presentation of dengue virus infection can be more severe, involving a generalized hemorrhagic syndrome with increased vascular permeability, thrombocytopenia, and unusual bleeding manifestations.

iii. Diagnosis and control. The variable expression of yellow fever in African versus New World nonhuman primates decreases the reliability of clinical signs as indicators of active infection. Consequently, imported monkeys should have a certificate that they have originated from a yellow fever–free area; have been maintained in double-screened, mosquito-proof enclosures; or have been vaccinated for yellow fever. The same general principles apply to the prevention of introduction of dengue virus in newly imported nonhuman primates.

The Center for Disease Control and Prevention (CDCP), which regulates nonhuman primate importation facilities, stipulates specific record-keeping procedures and requires the prompt (within 24 hr) reporting of any disease in a nonhuman primate suspected of being infected with yellow fever, Marburg, monkeypox, or Ebola disease (filovirus). This reporting requirement also applies to any illness among staff members that may have been acquired from nonhuman primates (Johnson *et al.,* 1995). Also, imported nonhuman primates that die within 10 days of arrival should be carefully examined at necropsy for the lesions suggestive of viral hemorrhagic fever.

2. Marburg Virus Disease (Vervet Monkey Disease)

The Marburg virus has been responsible for several highly fatal episodes of disease. The first outbreak occurred in Germany in 1967 and serves as the basis for most of the descriptive information about clinical disease (Siegart, 1972). The most recent case occurred in 1980 in an individual who was believed to have been exposed while visiting a site on the Kenya–Uganda

border located only 80 kilometers from the site where the vervet monkeys associated with the 1967 outbreak were maintained prior to shipment to Europe (Jahrling, 1989).

i. Reservoir and incidence. Originally classified as a rhabdovirus, the Marburg agent now has been reclassified into the genus *Filovirus* along with Ebola virus. In the initial outbreak of the disease, 31 persons became severely ill from infection and 7 died subsequently. Most of these individuals had handled fresh tissues or primary cell cultures from African green monkeys (*Cercopithecus aethiops*). Secondary infection occurred in 4 persons who had contact with the patients who had been exposed originally through blood, tissue, or cell cultures.

The natural reservoir for the Marburg disease agent has never been identified nor has the source of infection for the index case in any of the outbreaks (Jahrling, 1989). Experimental studies in nonhuman primates and other laboratory animals have shown that the virus produces a 100% fatal infection in African green monkeys, rhesus monkeys, squirrel monkeys, guinea pigs, and hamsters. Although African green monkeys were clearly incriminated in the original outbreak, their high fatality rate when infected experimentally with Marburg virus suggested that they would not be a likely reservoir (Jahrling, 1989).

ii. Mode of transmission. Transmission appears to be from direct contact with infected tissues and close contact with infected patients. Experimental infections in nonhuman primates suggest the possibility of airborne transmission because uninoculated monkeys housed in the same room as experimentally infected animals contracted the disease.

iii. Clinical signs. The incubation period for Marburg disease is 4–16 days. The disease in humans is manifested by the abrupt onset of fever, chills, myalgia, headache, anorexia, and conjunctival suffusion. Later, progressive involvement of the gastrointestinal tract with severe pain and gastrointestinal bleeding, maculopapular rash, and systemic bleeding disorders often occurs. Abnormalities in the coagulation pattern indicative of disseminated intravascular coagulation occur and may be the proximate cause of death in approximately a quarter of the cases. Treatment of Marburg virus disease consists of intensive supportive therapy directed at controlling the progressive pathophysiological events and the use of specific immune plasma if available (Jahrling, 1989).

iv. Diagnosis and prevention. Diagnostic studies for these agents must be conducted under biosafety level 4 conditions. These entail strict engineering controls, the use of primary barriers and personal protective equipment in conjunction with differential air-pressure gradients to ensure isolation, and complete standard operating procedures covering all aspects of facility function. The diagnosis of Marburg virus disease involves isolation of the virus from blood, other tissues, or bodily fluids in Vero cell culture or the detection of serum antibodies.

3. Ebola and Other Filovirus Infections

i. Reservoir and incidence. Ebola hemorrhagic fever is a rare disease caused by a filovirus that is morphologically identical to but antigenically distinct from Marburg disease virus. Human cases of Ebola have been confined to the continent of Africa. Although a case of the disease in a human has resulted from contact with infected chimpanzees (Formenty *et al.,* 1999b) and natural outbreaks of the disease have been recorded in a community of wild chimpanzees, the chimpanzee is not regarded as the natural reservoir (Formenty *et al.,* 1999a). Also, the Sudan and Zaire Ebola virus strains have been shown experimentally to produce lethal infection in nonhuman primates in about 8 days, but paralleling the situation with Marburg virus, monkeys have not been demonstrated to be the natural reservoir (Dalgard *et al.,* 1992). The natural reservoir for this agent has not been identified, although the bat, especially solitary microchiropteran species, has been suggested as a leading reservoir candidate (Monath, 1999).

The first and only non-African Ebola-like filovirus, Ebola–Reston, was isolated and identified from macaques recently imported into the United States from the Philippines during 1989. The infected monkeys died of an acute hemorrhagic disease and prompted the revision and implementation of nonhuman primate importation and handling guidelines (Centers for Disease Control [CDC], 1989, 1990). The natural reservoir for the Ebola–Reston strain is also unknown. Despite the novel epidemiological findings in this case, related to geography and natural reservoir, the deaths of imported monkeys were caused by another viral agent, simian hemorrhagic fever of a non-African Ebola-like filovirus, which is nonpathogenic for humans.

ii. Mode of transmission. Transmission appears in most cases to be from direct contact with infected tissues and close contact with humans or animals shedding the organism. Oral and conjunctival transmission of Ebola–Zaire in macaques has also been confirmed experimentally (Jaax *et al.,* 1996). However, in the natural outbreak of Ebola–Reston infection in a laboratory colony of nonhuman primates, transmission occurred among animals without apparent direct intimate contact, suggesting the possibility of airborne or aerosol transmission. Three of six animal technicians working with these animals developed antibody response to Ebola–Reston virus, but the details of transmission were not determined in all cases. One of these individuals was infected during postmortem examination of an infected monkey (Ksiazek *et al.,* 1999). Epidemiologic findings in animal caretakers working in the Philippine-source colony for Ebola–Reston suggest that the transmission of Ebola–Reston to humans is rare (Miranda *et al.,* 1999).

iii. Clinical signs. In experimental nonhuman primate infections with Ebola–Zaire or Sudan, animals rapidly develop a febrile, debilitating illness characterized by high titer viremia; virus dissemination and replication in multiple organs, produc-

ing tissue necrosis, effusions, coagulopathy, and hemorrhage; and death. Humans develop a similar pattern of infection, manifesting acute illness, fever, chills, headache, myalgia, and anorexia with progressive deterioration to vomiting, abdominal pain, sore throat, and bloody diarrhea. Although less virulent than the Sudan or Zaire strains of Ebola virus in nonhuman primates, Ebola–Reston produced a hemorrhagic disease in macaques involving multiple organ systems, resulting in death in 8–14 days. Clinical disease was not recognized in animal technicians who developed filovirus-specific serum antibodies associated with the disease outbreak in macaques due to Ebola–Reston (CDC, 1990; Dalgard *et al.,* 1992).

iv. Diagnosis and prevention. The gross and histopathologic findings of Ebola infection have been reported in numerous nonhuman primate species, including chimpanzees (Wyers *et al.,* 1999), baboons and African green monkeys (Ryabchikova *et al.,* 1999), and macaques (Dalgard *et al.,* 1992). In macaques, intracytoplasmic inclusion bodies associated with hepatocellular necrosis, adrenal necrosis, and patchy pulmonary interstitial infiltrates were noted in cases of Ebola–Reston infection and considered useful for the differentiation of this disease from simian hemorrhagic fever (Dalgard *et al.,* 1992).

Many techniques have been used to detect Ebola virus or the viral antigen (Jahrling, 1989). Serologically, the infection is diagnosed by rising antibody titer using indirect immunofluorescence assay (IFA), radioimmunoassay, and enzyme-linked immunosorbent assay (ELISA) (Jahrling, 1989; Ksiazek *et al.,* 1999). The immunoglobulin M (IgM) capture assay proved useful for the detection of antibodies early in the course of infection (day 6) for both nonhuman primates and humans infected with Ebola–Reston. Also, the long-term persistence of IgG antibodies (> 400 days in nonhuman primates and up to 10 years in two humans) suggested that the ELISA would be very useful for field investigations.

Due to effective importation procedures mandated by CDC (1990), only those personnel employed in facilities involved in the importation of nonhuman primates have the potential for the occurrence of Ebola. These personnel should become familiar with the equipment and procedures used to minimize the potential for Ebola virus transmission in the event of an outbreak. Neither vaccination nor antiviral pharmaceuticals are available for the treatment of Ebola virus infection. The Subcommittee on Arbovirus Laboratory Safety of the American Committee on Arthropod-Borne Viruses recommends that biosafety level 4 procedures be employed in studies using Ebola virus (CDCP–NIH, 1999).

4. Hantaviruses (Hemorrhagic Fever with Renal Syndrome; Hantavirus Pulmonary Syndrome)

i. Reservoir and incidence. Hantavirus is one of several genera within the family Bunyaviridae that can cause severe hemorrhagic fever with renal syndrome (HFRS). The hantaviruses are widely distributed in nature among wild rodent reservoirs, but unlike other members of the family, they are usually not transmitted by insect vectors (Schmaljohn and Hjelle, 1997). At least 14 viruses are recognized in the genus, and the severity of the disease produced depends on the virulence of the virus involved (LeDuc, 1987; Schmaljohn and Hjelle, 1997). Viruses producing HFRS are prevalent in southeastern Asia, Japan, and focally throughout Eurasia; whereas variants producing a less severe form of the disease, known as nephropathia endemica, occur throughout Scandinavia, Europe, and western portions of the former Soviet Union. An outbreak of hantavirus infection resulting in numerous deaths in adults from fatal hantavirus pulmonary syndrome (HPS) was first recognized in the United States (Schmaljohn and Hjelle, 1997; CDCP–NIH, 1999). Since this initial outbreak, cases of HPS have been reported from 30 states, and about three-quarters of the patients have been from rural areas.

Rodents from numerous genera have been implicated in foreign outbreaks of the disease, including *Apodemus, Clethrionomys, Mus, Rattus, Pitymys,* and *Microtus.* In the United States, serological surveys have detected evidence of hantavirus infection in urban and rural areas involving *Rattus norvegicus, Peromyscus maniculatus, P. leucopus, Microtus pennsylvanicus, Tamias* spp., *Sigmodon hispidus, Reithrodontomys megalotis, Oryzomys palustris,* and *Neotoma* spp. (Tsai *et al.,* 1985; Schmaljohn and Hjelle, 1997; CDCP–NIH, 1999). Numerous cases of hantavirus infection have occurred among laboratory animal facility personnel from exposure to infected rats (*Rattus*), including outbreaks in Korea, Japan, Belgium, France, and England (LeDuc, 1987), although there have not been any cases reported in U.S. laboratories. Hantavirus pulmonary syndrome has been reported in the United States in persons associated with outdoor activities and occupations that place them in close proximity with infected wild rodents and their excrement (Hjelle *et al.,* 1996; Jay *et al.,* 1996; Schmaljohn and Hjelle, 1997). Several cases have involved individuals from academic institutions involved in field studies. There is also epidemiologic evidence that cats may become infected through rodent contact and serve as a potential reservoir.

ii. Mode of transmission. The transmission of hantavirus infection is through the inhalation of infectious aerosols, and extremely brief exposure times (5 min) have resulted in human infection. Rodents shed the virus in their respiratory secretions, saliva, urine, and feces for many months (Tsai, 1987). Transmission of the infection can also occur through an animal bite or from disturbing dried materials contaminated with rodent excreta, allowing wound contamination, conjunctival exposure, or ingestion to occur (CDCP–NIH, 1999). The recent cases that have occurred in the laboratory animal facility environment have involved infected laboratory rats. In this environment, the possibility of transmitting the infection from animal to animal by the transplantation of cells or tissues should also be considered (Kawamata *et al.,* 1987). Person-to-person transmission

apparently is a very rare feature of hantavirus infection (Schmaljohn and Hjelle, 1997).

iii. Clinical signs. The clinical signs are related to the hantavirus species involved. The form of the disease known as nephropathia endemica is characterized by fever, back pain, and nephritis and causes only moderate renal dysfunction from which the patient recovers. Recent cases of HPS in the United States developed a febrile prodrome, thrombocytopenia, and leukocytosis in common with HFRS. Patients proceeded rapidly to respiratory failure due to capillary leakage into the lungs, followed by shock and cardiac complications (Schmaljohn and Hjelle, 1997; CDCP–NIH, 1999). The form of the disease that has been noted following laboratory animal exposure fits the classical pattern for HFRS, characterized by fever, headache, myalgia, petechiae, and other hemorrhagic manifestations, including anemia and gastrointestinal bleeding, oliguria, hematuria, severe electrolyte abnormalities, and shock (Lee and Johnson, 1982).

iv. Diagnosis and prevention. Both antigenic and genetic methods have been used for the characterization of the hantaviruses. Routine serological tests include the IFA and ELISA for the demonstration of specific antibody, while plaque reduction neutralization is the most sensitive serological assay for virus differentiation (Committee on Emerging Microbial Threats to Health, 1992; Schmaljohn and Hjelle, 1997). Additional information about hantavirus serological testing is available through the Special Pathogens Branch, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention.

Hantavirus infections should be prevented through the detection of infection in incoming rodents and rodent tissues prior to their introduction into resident laboratory animal populations. Rodent tumors and cell lines can be tested for hantavirus contamination using a modified rat antibody production test as well as polymerase chain reaction (PCR)-based assays. Animal biosafety level 4 guidelines are recommended for animal studies involving hantavirus infections in permissive hosts such as *Peromyscus maniculatus,* and wild-caught rodents brought into the laboratory that are susceptible to hantaviruses producing HPS or HFRS should also be handled according to these guidelines (CDCP, 1994). Animal biosafety level 2 practices are sufficient for handling rodent strains known not to excrete the virus.

C. Lymphocytic Choriomeningitis Virus (LCM)

Of the many viruses present in the mouse, only LCM virus naturally infects humans. Recent cases and a review of the literature attest to the ease with which LCM virus can be transmitted from animals to humans (Dykewicz *et al.,* 1992).

i. Reservoir and incidence. Lymphocytic choriomeningitis virus (LCMV) is a member of the family Arenaviridae, which are single-stranded RNA viruses with a predilection for rodent reservoirs.

Other members of the family are also important zoonoses that produce a hemorrhagic fever syndrome, including Lassa fever (in Africa) and Argentine and Bolivian hemorrhagic fevers (in South America). In addition, a new zoonotic arenavirus that produced fatal infection in three persons, characterized by acute respiratory distress syndrome, liver failure, and hemorrhagic manifestations, has been identified in North America, specifically in California (CDCP, 2000). This agent shared 87% identity with the Whitewater Arroyo prototype strain isolated from *Neotoma albigula* (white-throated wood rats) in New Mexico in 1990, and one of these patients had cleaned rodent excreta in her home during the 2 weeks prior to illness. In parallel with the persistent and emerging importance of arenaviruses for humans with wild rodent contact, LCMV has remained an important natural infection of laboratory animals (Bowen *et al.,* 1975; Dykewicz *et al.,* 1992; Jahrling and Peters, 1992; Rousseau *et al.,* 1997).

The LCM virus is widely distributed among the wild mouse population throughout most of the world and presents a zoonotic hazard (Childs *et al.,* 1992; Smith *et al.,* 1993; Morita *et al.,* 1996). Mice, hamsters, guinea pigs, nonhuman primates, swine, and dogs are among the laboratory animal hosts that sustain natural infections. However, LCMV is especially well adapted to the mouse, living in a symbiotic relationship characterized by latent infection of the mouse for extended periods. The mouse, and in certain well-defined outbreaks, the hamster, have remained the species of primary concern as zoonotic reservoirs in the laboratory, as evidenced by a recent outbreak of LCMV in humans (Dykewicz *et al.,* 1992). Also, athymic and other immunodeficient mouse strains may pose a special risk of harboring silent, chronic infections and present a hazard to personnel (Dykewicz *et al.,* 1992; CDCP–NIH, 1999).

There have been numerous reports of epizootic infectious hepatitis (callitrichid hepatitis) with a high mortality rate in marmosets and tamarins in zoological parks in both the United States and England during the past 2 decades (Montali *et al.,* 1989). Early serological studies indicated that the same, or a closely related virus, was involved in five of six outbreaks studied and that the etiologic agent had a close antigenic relationship with LCMV (Stevensen *et al.,* 1990, 1991). Subsequently, LCMV was shown to be the etiologic agent for callitrichid hepatitis through cDNA genome analysis (Stevensen *et al.,* 1995). Rodent infestations are common in zoos, and mice, as known carriers of LCMV, are the probable source of infection in these outbreaks. Moreover, it had been a common practice in some facilities to supplement the diets of tamarins and marmosets with suckling mice (Richter *et al.,* 1984), a prime source for the infectious agent. Two veterinarians involved in the care of infected callitrichids became seropositive to the agent but did

not develop clinical signs of disease (Adams, 1995). Nevertheless, the wide geographic distribution of the outbreaks of callitrichid hepatitis underscores the need to better understand the public health implications of LCMV as a human pathogen as well.

ii. Mode of transmission. There are many forms of infection produced by LCMV in the laboratory mouse depending on host factors and variation in LCMV strain organotropism (Lehmann-Grube, 1982). Under some circumstances LCMV 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. In endemically infected mouse and hamster colonies, the infection is transmitted *in utero* or early in the neonatal period, producing a tolerant infection characterized by chronic viremia and viruria without significant clinical disease. Thus, bedding material and other fomites contaminated by LCMV-infected animals can also be important sources of infection for humans, as demonstrated in numerous outbreaks among laboratory animal technicians (Lehmann-Grube, 1982; Dykewicz *et al.,* 1992).

The experimental passage of tumors and cell lines appears to pose one of the biggest threats for the introduction of LCMV into animal facilities at the present time. Spread of LCMV among animals by contaminated tumors and cell lines has been widely recognized (Bhatt *et al.,* 1986; Dykewicz *et al.,* 1992; Nicklas *et al.,* 1993). Bhatt *et al.* (1986) reported 17 of 63 rodent transplantable tumors screened were positive for LCMV, and Nicklas *et al.* (1993) identified contamination in 4 of 14 hamster tumors and 2 of 81 mouse tumors that had been propagated in animals. Transmission by infected, bloodsucking ectoparasites has been demonstrated experimentally, and LCMV has been recovered from cockroaches. However, these sources for LCMV infection have not been shown to play a significant role in any of the LCMV infections (human or animal) in laboratory animal facilities to date.

Infection in humans may be by parental inoculation, inhalation, or contamination of mucous membranes or broken skin with infectious tissues or fluids from infected animals. Airborne transmission is well documented. In human LCMV infections associated with infected pet hamsters, the infection rate correlated with cage type and location in the household. Open wire cages were correlated with the highest rate of infection, whereas deep boxes and aquariums were associated with a lower human infection rate. Similarly, cage placement in an area of high human activity was associated with infection, but remotely located cages away from areas of frequent human activity (e.g., the basement) did not result in infection of occupants (Biggar *et al.,* 1975). Also, infections are known to occur in individuals who have not had direct physical contact with infected hamsters but who had simply entered the room housing the animals (Hinman *et al.,* 1975). These findings suggest that airborne transmission plays an important role in human infection.

Table I

Symptoms of Persons with Positive Titers for Lymphocytic Choriomeningitis

Symptom	Number of cases	
	49[a]	11[b]
None recognized	3	1
Fever	44	9
Headache	42	7
Myalgia	39	8
Pain on moving eyes	29	7
Nausea	26	9
Vomiting	17	9
Biphasic illness	12	NR[c]
Sore throat	12	NR
Photophobia	12	7
Cough	9	1
Swollen glands	8	NR
Diarrhea	8	1
Rash	6	1
Upper respiratory tract symptoms	6	NR
Orchitis	1	NR

[a]From Biggar *et al.* (1975).
[b]From Maetz *et al.* (1976).
[c]NR, None recognized.

iii. Clinical signs. Humans usually develop a flulike illness characterized by fever, myalgia, headache, and malaise following an incubation period of 1–3 weeks (Table I). However, there can be more serious manifestations of the disease in patients, including maculopapular rash, lymphadenopathy, meningoencephalitis, and rarely, orchitis, arthritis, and epicarditis (Johnson, 1990). Central nervous system involvement has resulted in death in several cases. The virus may pose a special risk during pregnancy because of potential infection of the human fetus (Wright *et al.,* 1997). Wright *et al.* (1997) reported 26 cases in human infants, with LCMV confirmed serologically over a 2-year period in a major U.S. medical center. These infants presented with ocular abnormalities, macrocephaly, and microcephaly. Fifty percent of the mothers reported having had illnesses compatible with LCMV infection, and over half reported exposures to rodents during their pregnancies. Intravenous ribavirin therapy significantly reduces mortality in patients infected with Lassa fever virus and may be of some benefit in patients with severe LCMV infections (Andrei and DeClerq, 1993).

iv. Diagnosis and prevention. Virus isolation from blood or spinal fluid in conjunction with the use of immunofluorescence assay (IFA) of inoculated cell cultures is the primary method of diagnosing acute disease. Antibody is detectable using an IFA approximately 2 weeks following the onset of illness. Prevention of this disease in the laboratory is achieved through the periodic serological surveillance of new animals

with inadequate disease profiles and resident animal colonies at risk, using ELISA and IFA tests. Screening all tumors and cell lines intended for animal passage for the presence of LCMV is another crucial element in the program to prevent the introduction of LCMV into established animal colonies. The elimination of ectoparasites and insect vectors in animal facilities as part of the overall scheme for disease prevention and control would also be prudent measures for the control of LCMV.

D. B Virus Infection (Cercopithecine Herpesvirus 1, CHV-1)

There are many herpesviruses of nonhuman primates and other animal species that might be studied as laboratory animals, but CHV-1 stands alone as a documented hazard with devastating potential for humans working in the laboratory animal facility environment. Among the many other nonhuman primate herpesviruses, *Herpesvirus saimiri* will replicate in human tissues and is classified as an oncogenic virus by the National Cancer Institute, and *H. tamarinus* has been shown to produce skin pustules, fever, and nonfatal encephalitis in humans (Adams, 1995; Mansfield and King, 1998). The reader is referred to the sources cited for more information on these latter two agents.

i. Reservoir and incidence.   First described in 1933 by Gay and Holden, B virus produces a life-threatening disease of humans that has resulted in several fatalities within the past decade (CDC, 1987, 1989, 1991; CDCP, 1998). In macaques, B virus produces a mild clinical disease similar to human *H. simplex* virus infection. During primary infection, macaques develop lingual and/or labial vesicles or ulcers that generally heal within a 1- to 2-week period; keratoconjunctivitis or corneal ulcer may also be noted. The virus persists latently in the trigeminal and genital ganglia of the macaque, and reactivation of viral shedding from peripheral sites in asymptomatic animals subjected to physical or psychological stressors or treated with immunosuppressive agents is known to occur. The infection is transmitted between macaques by virus-laden secretions through close contact involving primarily the oral, conjunctival, and genital mucous membranes (Weigler *et al.*, 1995).

In an endemically infected domestic macaque production colony, an age-related increase in the incidence of B virus infection occurred during adolescence as exposure to the agent continued, with the incidence approaching 100% in colony-born animals by the end of their first breeding season (Weigler *et al.*, 1993). Seroconversion to B virus among wild-caught rhesus monkeys also indicates that eventually 100% of the newly trapped individuals acquire the infection. Consequently, B virus should be considered endemic among Asian monkeys of the genus *Macaca* unless these animals have been obtained from specific breeding colonies known to be B virus–free. Several

species of New World monkeys and Old World monkeys other than macaques are known to succumb to fatal B virus infection, but only macaques are known to harbor B virus naturally (Holmes *et al.*, 1995). Eight of 25 langurs and 4 of 6 proboscis monkeys were seropositive to B virus in a survey, indicating that these Asian Old World monkey species may also be potential reservoirs (Kalter *et al.*, 1997).

Many of the human B virus infections have resulted from exposure to rhesus macaques (*Macaca mulatta*), leading to the supposition that there may be strain-specific pathogenicity of CHV-1. Several strains have now been identified by antigenic, restriction enzyme digest patterns, polymerase chain reaction (PCR), and phylogenetic analyses of B virus (Slomka *et al.*, 1993; Smith *et al.*, 1998). Three distinct genotypes have been described and associated with the macaque species of origin (Smith *et al.*, 1998). These B virus genotypes were composed of (1) isolates from the rhesus and Japanese macaques, (2) isolates from cynomolgus monkeys (*M. fascicularis*, and (3) isolates from pigtail macaques (*M. nemestrina*). However, it remains to be determined whether these strains will correlate with differences in pathogenicity for nonmacaque species.

ii. Mode of transmission.   The transmission of B virus to humans primarily occurs through exposure to contaminated saliva through bites and scratches. Exposure by the airborne route was believed to have played a role in several human cases (Palmer, 1987), and exposure of ocular mucous membranes to biological material, possibly fecal, has been confirmed in a human fatality (CDCP, 1998). Other types of B virus transmission to humans that have been confirmed are needlestick injury (Benson *et al.*, 1989) and exposure to infected nonhuman primate tissues (Wells *et al.*, 1989). The possibility of fomite transmission through an injury obtained in handling contaminated caging may be less likely but warrants consideration in an institution's hazard assessment and risk analysis. One case of human-to-human transmission has also been documented (CDC, 1987). In this case, the spouse of an infected animal handler, who applied ointment to herpetic skin lesions on her husband and subsequently to an area of dermatitis on her own hand, contracted B virus infection (Holmes *et al.*, 1990).

iii. Clinical signs.   The incubation period between the initial exposure and onset of clinical signs ranges from 2 days to, more frequently, 2–5 weeks. However, in one case, an individual developed severe clinical disease from B virus 10 years following his last known exposure to the agent. Researchers in the field have also suggested that asymptomatic human B virus infection may occur (Benson *et al.*, 1989), but it is not known whether viral reactivation resulting in severe clinical disease can occur later.

In most cases, following exposure by bite, scratch, or other local trauma, humans may develop a herpetiform vesicle at the site of inoculation. In the B virus fatality resulting from ocular

exposure, the patient did not develop a dendritic corneal lesion typical of ocular herpes infections; rather, she developed a swollen, painful orbit with conjunctivitis (CDCP, 1998). As the clinical signs in this patient progressed, she developed retro-orbital pain, photophobia, anorexia, nausea, and abdominal pain. Other early clinical signs of B virus include myalgia, fever, headache, and fatigue, which are later followed by progressive neurological disease characterized by numbness, hyperesthesia, paresthesia, diplopia, ataxia, confusion, urinary retention, convulsions, dysphagia, and an ascending flaccid paralysis.

iv. Control and prevention. A key provision to prevent B virus exposures within an institution's animal care and use program concerns the decision of whether or not the studies proposed warrant the use of macaques. Macaques should be used only when there are no suitable alternative animal models, and efforts to acquire macaques that are free of B virus infection and to maintain them appropriately to preserve this status should be pursued whenever feasible. In B virus endemically infected colonies with individually housed macaques, culling seropositive animals and replacement with seronegative stock might be useful in establishing a B virus–negative colony over time (Weir *et al.*, 1993). However, all macaques must be handled as though they are potentially infected because viral shedding is intermittent and viral serology does not adequately reflect the viral status of the animal.

After the outbreak of B virus infection in monkey handlers that occurred in 1987, guidelines were developed to prevent B virus infection in humans (CDC, 1987). Additional provisions for protection against B virus exposure via ocular splash were adopted following the death of a young woman exposed by this route (CDCP, 1998). Readers should refer to these sources or other detailed reviews before engaging in studies involving macaques or developing institutional programs for the prevention and control of B virus among monkey handlers (Adams, 1995; Holmes *et al.*, 1995). Briefly, these recommendations emphasize the need for nonhuman primate handlers to conform fully with a written comprehensive personal protective equipment (PPE) program based on a thorough hazard assessment of all work procedures, potential routes of exposure, and potential adverse health outcomes (CDCP, 1998). Approaches to hazard assessment and the development of occupational health and safety programs for research animal facilities have been reviewed extensively in other sources (Committee on Occupational Health and Safety in Research Animal Facilities, 1997). Protective clothing, including leather gloves or long-sleeved garments for hand and arm protection and protective goggles designed for splash protection, along with a mask, are considered essential equipment to protect other mucous membranes from exposure to macaque secretions. The use of a face shield is insufficient as the sole method for protection against ocular exposure because droplet splashes to the head may drain into the eyes and infectious materials may enter via the gap along the

margins of the shield. Importantly, personal eyeglasses are not considered PPE. The use of latex gloves alone for hand protection should be reserved for the handling of monkeys under full chemical restraint. Chemical restraint or specialized restraining devices should be used whenever possible for nonhuman primates to reduce personnel injuries.

The CDC recommendations further specify that institutions should be prepared to handle patients with a suspected B virus exposure promptly, and the patient should have direct and immediate access to a local medical consultant knowledgeable about B virus. This consultant should be available at any time the worker is concerned that potential occupational exposure to B virus may be relevant to worker symptoms. The wound should be cleansed thoroughly, and serum samples and cultures should be obtained for serology and viral isolation from both the patient and the monkey. The initiation of antiviral therapy with acyclovir or gangcyclovir may also be warranted if the history and symptoms are compatible with B virus infection. The management of antiviral therapy in B virus–infected patients is controversial because increasing antibody titer has been demonstrated in a patient following the discontinuation of acyclovir therapy (Holmes *et al.*, 1995). Physicians should consult the Viral Exanthems and Herpesvirus Branch, Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, for assistance in case management. Additional information about the B virus diagnostic resources is available through the B Virus Research and Resource Laboratory, Georgia State University, Atlanta, Georgia.

E. Rabies

Rabies is an acute, almost invariably fatal disease caused by a virus in the genus *Lyssavirus* of the family Rhabdoviridae (Johnson, 1989).

i. Reservoir and incidence. Rabies 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. Rabies virus infects all mammals; however, the main reservoirs are wild and domestic canines, cats, skunks, raccoons, bats, and other biting animals. In the United States the dog, cat, and other domestic animals have declined in importance as sources of exposure in confirmed human cases of the disease (CDCP, 1999). According to one study however, 18.4% of 3329 domestic animals that were reportedly exposed to rabies-positive wild animals are unvaccinated (Wilson *et al.*, 1997). The disease historically has not been a problem in the laboratory animal facility setting. Among the rodent and lagomorph species maintained in the laboratory, the wild-caught ground-hog and rabbit appear to represent a risk of transmitting rabies (Childs *et al.*, 1997; Karp *et al.*, 1999). However, because the

incidence of rabies in wildlife in the United States has risen, the possibility of rabies transmission to dogs, cats, or other species having uncertain vaccination histories and originating from an uncontrolled environment must be considered. In addition, rabies-susceptible wildlife species studied in the field or introduced into the laboratory for special research investigations could also have the potential to harbor rabies virus. In the skunk and some bat species, rabies virus strains appear to have adapted to growth in the lung, producing respiratory tract infections, and the virus is spread via the aerosol route (Johnson, 1989). Of the human cases of rabies in the United States reported since 1990, most have involved bat-associated viral variants; and the predominant strain has been associated with two insectivorous bat species, Eastern pipistrelle bats (*Pipistrellus subflavus*) and silver-haired bats (*Lasionycteris noctivagans*) (CDCP, 1999). Another rabieslike lyssavirus causing fatal human encephalitis has also been recently isolated from bats in Australia, a country believed to have a rabies-free status, further emphasizing the bat as a potential reservoir for these agents (Anonymous, 1997; Gerrard, 1997).

ii. Mode of transmission.   Rabies virus is transmitted by the bite of a rabid animal or by the introduction of virus-laden saliva into a fresh skin wound or an intact mucous membrane. Airborne transmission can occur in a laboratory setting and in caves where rabid bats roost (Johnson, 1989). In the bat-associated cases reported in the United States since 1990, a majority of patients handled bats but denied being bitten, and many had no known bat exposure (CDCP, 1999). The virus has also been transmitted through corneal transplants from individuals with undiagnosed central nervous system disease.

iii. Clinical signs.   Humans, as well as all other mammals, are generally regarded as susceptible to this disease. The course of the disease proceeds through several phases: incubation, prodromal, acute neurologic, coma, and rarely, recovery (Johnson, 1989). The incubation period in humans is ordinarily 1–3 months but may vary from 9 days to over 8 months. During the prodromal stage lasting 2–4 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 may also develop intermittent periods of excitation, nervousness, or anxiety interspersed with quiet periods when the mental state appears normal. Further progression of the disease is marked by 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.

iv. Diagnosis and prevention.   Rabies should be considered as a differential diagnosis in any wild-caught or random-source laboratory animal of unknown vaccination history exhibiting

encephalitic signs. Any wild animal that has bitten someone should be submitted for rabies examination in a manner that permits definitive identification of the species for epidemiologic purposes if the species is not already known.

The postmortem diagnosis of rabies virus infection can be based on the demonstration of Negri bodies, rabies virus antigen, or infectious virus from the brain of the infected animal (Johnson, 1989). Ammon's horn of the hippocampus is the best site for the demonstration of Negri bodies or rabies antigen by direct fluorescent antibody (DFA) test, but other brain areas should be sampled. Corneal impression smears or scrapings may also be a reliable site for the demonstration of antigen by DFA; mucosal scrapings and frozen skin biopsy specimens may also be used but are regarded as less reliable and have not been widely adopted by diagnostic laboratories. Many tissues are useful for virus isolation, especially brain and submaxillary salivary gland.

Vigorous first-aid and wound-care procedures for bites and scratches inflicted by animals are a crucial first step against the transmission of rabies virus to humans. General guidelines for proper administration of rabies postexposure prophylaxis (RPEP) treatments have been published by the Advisory Committee on Immunization Practices. Guidelines stipulate that unvaccinated persons potentially exposed to rabies should be treated with human rabies immune globulin and a 5-dose series of rabies vaccine administered (CDCP, 1999). Surprisingly, one study suggests that the use of RPEP is often inappropriate (Moran *et al.*, 2000). The authors urge the routine use of current published guidelines, physician education, and improved coordination with public health officials. The control of rabies through vaccination programs, animal control measures, and rabies surveillance efforts is an equally important factor in the prevention of rabies cases in the domestic animal population and therefore in humans. Whenever possible, animals brought into the laboratory should have histories that preclude their exposure to rabies or assure that they have been vaccinated for this disease. However, due to the potential for a long incubation in the natural history of the disease, the types of animal models utilized, or the prospect of vaccination failures, most institutions are likely to encounter situations where a rabies-free environment cannot be assured adequately. Thus, preexposure immunization to rabies should be available to personnel working in high-risk categories, such as veterinarians, people who are working with or involved in the care of high-risk or inadequately characterized animals, and field biologists who work in rabies-endemic areas.

F.   Viral Hepatitis Infections

Many of the nonhuman primate zoonoses causing systemic infections in humans include hepatitis as one component of the disease. However, of the viral infections that target the liver

as the primary site of involvement, only hepatitis A virus has proven to be a significant zoonotic pathogen in the laboratory animal facility environment. Nonhuman primates are important experimental hosts in viral hepatitis research and have been used to study hepatitis A, B, C, D, and E infections (Adams, 1995). The pig and wild rat are also natural hosts for hepatitis E infection and have been incriminated as zoonotic reservoirs for this agent, but no instances of transmission have been reported in the laboratory animal facility setting (Kabrane-Lazizi et al., 1999). Mouse hepatitis virus, a coronavirus, and infectious canine hepatitis, an adenovirus, are not transmissible to humans.

1. Hepatitis A

i. Reservoir and incidence. Hepatitis A virus (HAV) is a human enterovirus belonging to the family Picornaviridae (Purcell et al., 1989). The primary reservoirs for HAV infection are humans, with nonhuman primate infections resulting from contact with infected humans or other infected nonhuman primates. However, more than 100 cases of HAV infection in humans have been associated with newly imported chimpanzees. There are also many other nonhuman primate species that are naturally susceptible to HAV, including the other great apes, marmosets, owl monkeys, cynomolgus monkeys, and patas monkeys, and could serve as sources for human HAV infection (Shevtsova et al., 1988; Purcell et al., 1989; Lemon et al., 1990; Adams, 1995). A suspected outbreak of HAV infection in young domestically reared rhesus monkeys has demonstrated the need for continued attention to this zoonotic agent in the laboratory animal facility environment (Lankas and Jensen, 1987).

ii. Mode of transmission. Hepatitis A virus is transmitted by the fecal–oral route, and some outbreaks can be related to poor hygienic conditions or contaminated food and water.

iii. Clinical signs. The disease in nonhuman primates is much less severe than the disease in humans and is frequently subclinical. Clinical disease develops in the chimpanzee, owl monkey, and several marmoset species and is characterized by malaise, vomiting, jaundice, and elevated serum levels of hepatic enzymes.

The disease in humans varies from a mild illness lasting 1–2 weeks to a severely debilitating illness lasting several months (Hollinger and Glombicki, 1990). Following an incubation period of approximately 1 month, patients experience an abrupt onset of fever, malaise, anorexia, nausea, and abdominal discomfort followed within a few days by jaundice (Fig. 2). Children often have mild disease without jaundice, whereas HAV infections in older patients may be fulminant and protracted with prolonged convalescence. However, protracted HAV infection is considered an acute infection that is ultimately resolved by the patient; a chronic hepatitis A carrier state has never been shown to exist.
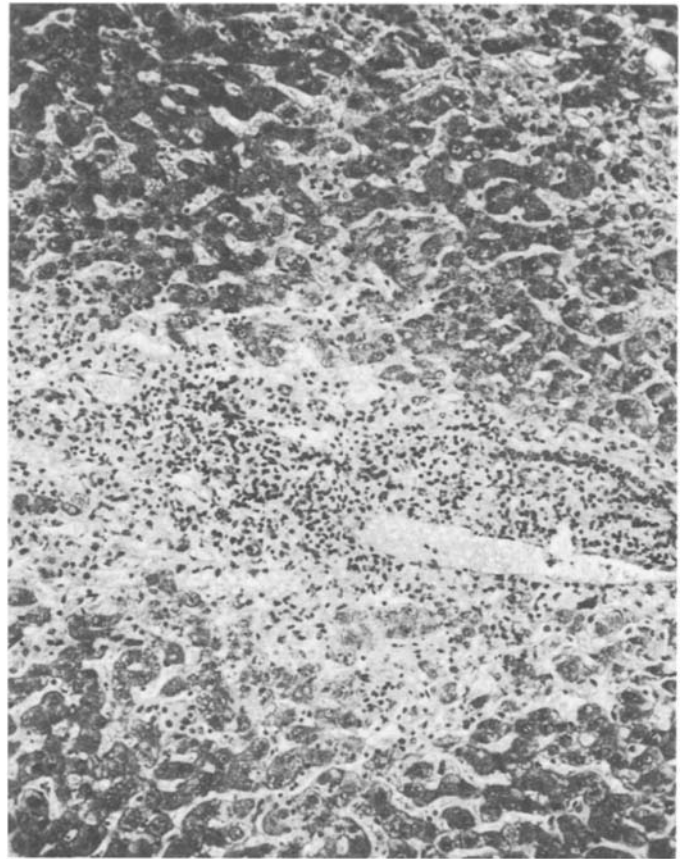

Fig. 2. Human liver with hepatitis A infection. Leukocytic infiltration of portal areas with hepatocellular necrosis in the peripheral areas of the lobules. Hematoxylin and eosin. ×250. (Courtesy of Dr. K. Ishak, Armed Forces Institute of Pathology.)

iv. Diagnosis and prevention. Enzyme immunoassay (EIA) and radioimmunoassay (RIA) for the demonstration of IgM-specific anti-HAV in the serum or plasma is useful early in the course of the infection. Later in the course of the infection (6 weeks), a fourfold rise in IgG antibody detected by the immune adherence hemagglutination assay can also be used to diagnose HAV infection. Alternatively, fecal samples can be tested for virus particles, viral antigen, or viral RNA to secure a definitive diagnosis (Purcell et al., 1989).

A safe, effective hepatitis A vaccine is now available in the United States and is recommended for individuals at high risk for exposure to HAV infection, such as persons involved with the care of nonhuman primates being used in experimental HAV-infection studies. Passive protection of such persons can also be undertaken through the intramuscular administration of specific immune serum globulin (ISG). Passive protection should be given before experimental animal HAV-infection studies begin because infected animals start shedding HAV at 7–11 days postinoculation and continue shedding for several weeks. The recommended dose of 0.02 ml/kg ISG provides

2–3 months of protection that is of sufficient duration for the period of nonhuman primate HAV shedding (Adams, 1995). Postexposure prophylaxis with ISG at the dose of 0.02 ml/kg within 2 weeks of exposure is also recommended (CDC, 1991). The use of protective clothing, personal hygiene, and appropriate sanitation practices for equipment and facilities will also minimize the potential for zoonotic transmission.

2. Other Viral Hepatitis Agents

Humans are considered natural hosts for viral hepatitis types B, C, D, and E. In the cases of hepatitis B, C, and D viruses, these agents are transmitted parenterally by exposure to blood or other bodily fluids. Hepatitis B virus (HBV), caused by human hepadnavirus, has been widely studied experimentally in the chimpanzee although the gibbon is known to be susceptible (Adams, 1995), and there has been one report of natural infection in a cynomolgus monkey (Kornegay et al., 1985). In the presumed natural HBV infection in cynomolgus monkeys, HBV infection was suggested by the demonstration of HBV surface antigen in hepatic cells but was not associated with zoonotic disease transmission. These animals developed mild clinical disease characterized by anorexia, elevated hepatic enzyme levels, and hyperbilirubinemia. Also, there are other natural hepadnavirus infections of animals (woodchuck, ground squirrel, and duck) that are used as animal models of HBV infection, but none are transmissible to humans (Adams, 1995). The chimpanzee has been used as an experimental model for the study of hepatitis C and D viruses. Thus, the concern for hepatitis B, C, and D as zoonoses is minimal in the laboratory animal facility environment except where these agents are being used in experimental animal studies. In these cases, personnel should adhere to appropriate precautions when handling nonhuman primates.

Hepatitis E virus (HEV) is an enterically transmitted calicivirus that causes acute, icteric, self-limiting disease that may have a high mortality. It has been experimentally transmitted to tamarins, owl monkeys, and cynomolgus monkeys, but there have not been any reports of natural HEV infections in monkeys (Adams, 1995). Other domestic and wild animals are also susceptible to HEV infection (Balayan, 1997). Reports have indicated that domestic pigs and wild rats may serve as reservoirs for this infection (Clayson et al., 1995), with infection in a majority of pigs over 3 months of age in some U.S. Midwestern herds (Meng et al., 1997). These pigs have been reported to appear clinically normal but developed viremia, positive serology, and microscopic signs of hepatic disease. Phylogenetic analyses have shown that the swine HEV is closely related to the human HEV strains in the United States forming a distinct phylogenetic branch (Meng et al., 1997, 1998). Although there have not been any recorded cases of HEV transmission in the laboratory animal facility environment from swine, nonhuman primates, or other laboratory animals, personnel should be instructed to observe proper PPE practices to prevent possible HEV transmission.

G. Retroviruses

In the wake of the human AIDS epidemic there has been an intense, multifaceted interest in the study of human and comparative retrovirology, and the zoonotic potential for animal retroviruses has clearly been identified. Notably, both HIV-1 and HIV-2 (human immunodeficiency virus) are known to have originated as zoonotic infections on the continent of Africa from the chimpanzee (Pan troglodytes troglodytes) and sooty mangabey (Cercocebus atys), respectively (Chen et al., 1996; Gao et al., 1999). These findings have heightened the concerns about zoonotic retroviral transmission, particularly in connection with the use of nonhuman primates as potential xenograft donors to humans requiring organ transplantation. Similar concerns have been raised about the pig as a donor for xenotransplants to humans because the porcine endogenous retrovirus has been demonstrated to grow in human cells in vitro (Wilson et al., 1998). However, although there are numerous retrovirus infections of wild, laboratory, and domestic animal species, the transmission of these agents from their natural host to humans under laboratory conditions has been documented in only a few cases, both involving nonhuman primates as source species. Further discussion herein is limited to these cases, and the reader should refer to Mansfield and King (1998) for an authoritative review of the retroviral diseases of nonhuman primates.

1. Simian Immunodeficiency Virus (SIV)

i. Reservoir and incidence. Simian immunodeficiency virus (SIV) is a lentivirus that infects a variety of Old World nonhuman primates and produces a clinical syndrome in rhesus monkeys and other susceptible macaque species with many important parallels to AIDS. Although the seroprevalence of SIV in Asian macaques is low and most SIV infections in these species are related to their use as animal models of HIV infection, the seroprevalence is much higher among wild-caught African nonhuman primate species with host-adapted SIV infections (Hayami et al., 1994).

ii. Mode of transmission. Transmission of SIV between monkeys is likely both horizontal and vertical. Vertical transmission may be by sexual contact, as seroconversion to SIV parallels sexual maturity. Direct inoculation of open wounds or mucous membranes with infectious secretions during other activities such as fighting may also play a role, but airborne transmission is regarded as unlikely (Lairmore et al., 1989). The blood, secretions, and tissues of SIV-infected monkeys should be presumed to be infectious for persons potentially exposed to these materials. Two human cases of seroconversion to SIV associated with known exposure incidents have been recognized (CDC, 1992b; Khabbaz et al., 1992), and a blind serological survey of other personnel working with SIV has identified perhaps an additional three seropositive individuals (CDC, 1992a). The possible inclusion of the aforementioned cases of known

SIV exposure and the cross-reactivity of SIV and HIV-2 in the assay employed confounded the interpretation of this survey (CDC, 1992a). In the first case, the individual's skin was punctured accidentally with a needle contaminated by the blood of an infected macaque. In the second case, a laboratory worker who had dermatitis on the hands and forearms and was under treatment with corticosteroids handled SIV-infected blood specimens without wearing gloves. The pattern of seroreactivity suggested the possibility of infection in the second case, and SIV infection was documented subsequently by PCR techniques (Khabbaz et al., 1994).

iii. Clinical signs. Clinical signs have not been recorded in these cases of human SIV exposure.

iv. Diagnosis and prevention. Serological techniques and viral isolation are available for the diagnosis of SIV in Asian macaques, which invariably seroconvert following natural infection (Mansfield and King, 1998), but African species may harbor the virus and not seroconvert.

Personnel should be instructed to observe the requirements for the use of PPE when working with potentially infected nonhuman primates and to follow safe syringe/needle handling practices. Potential SIV exposures should be cleansed immediately with soap and water, and supervisory personnel should be informed of the incident. Personnel should be advised to report and to seek medical attention for any acute febrile illness occurring within 12 weeks of exposure. The medical evaluation should include periodic monitoring for serum antibody to SIV at appropriate intervals. Written institutional policies should be in place to address confidentiality, counseling, and other issues related to potential SIV exposure. The absence of data related to the potential for SIV transmission between humans prevents any specific recommendations about the need for modifying personal behavior in the SIV-seropositive individual. However, the SIV-seropositive individual should not donate blood.

2. Simian Foamy Virus Infection

The simian foamy viruses are complex retroviruses that have been isolated from a number of New and Old World nonhuman primates and share considerable homology to the human foamy viruses (Mansfield and King, 1998). Although foamy viruses have not been demonstrated as the cause of any disease entity in humans or in the nonhuman primate, they have been linked to a number of human disorders. The transmission of simian foamy viruses to humans accidentally exposed or occupationally exposed to nonhuman primates has been reported (Neuman-Haeflin et al., 1993; Heneine et al., 1998). In the case of occupational exposure, 4 of 231 individuals surveyed serologically were positive, and proviral DNA detection and viral isolation were used to confirm the infection (Heneine et al., 1998). In 1 human case, the simian foamy virus originated from African green monkeys; and in the other 3 cases, baboons served as the

source. Clinical disease in humans has not resulted in any of these cases, and it is suggested that the virus persists in humans in a state of latency following accidental infection (Schweizer et al., 1997). The use of PPE as described in connection with the prevention of SIV transmission to humans should also be applied when handling simian foamy virus–infected nonhuman primates.

H. Measles Virus (Rubeola, Giant Cell Pneumonia)

i. Reservoir and incidence. Measles virus is a member of the genus *Morbillivirus,* which is known to cause infection in a wide variety of Old and New World nonhuman primate species (Mansfield and King, 1998). Humans serve as the reservoir with nonhuman primates becoming infected through contact with human populations with endemic measles. The disease spreads rapidly through infected nonhuman primate colonies, often with devastating consequences, and a 100% seroconversion rate to measles is common in wild-caught nonhuman primate populations within several weeks of capture. A recent serological survey in nonhuman primates from miscellaneous sources has indicated that in three macaque species commonly used in biomedical research, between 45 and 73% of the animals were seropositive for measles virus, but that less than 10% of the squirrel monkeys and marmosets surveyed were seropositive (Kalter et al., 1997). This finding possibly reflects the fact that these New World monkey species are more vulnerable and less likely to survive the disease than macaques. With the current emphasis on and success of domestic nonhuman primate production, it has become more likely that institutions will develop large populations of susceptible nonhuman primates that could contract measles and then transmit the disease to susceptible humans, as previously reported (Roberts et al., 1988).

ii. Mode of transmission. Measles is a highly communicable disease that is transmitted by infectious aerosols, contact with nasal or throat secretions, or contact with fomites freshly contaminated with infectious secretions. The virus is shed beginning in the prodromal stage and continuing through the exanthematous stage of the infection.

iii. Clinical signs. The clinical signs of measles are similar in both nonhuman primates and humans. In humans, after an incubation period of about 10 days, fever develops followed by conjunctivitis, coryza, cough, and Koplik's spots on the buccal mucosa. Subsequently, a characteristic exanthematous rash develops beginning on the face, becoming generalized over the body, and progressing to a dry and scaly desquamative dermatitis. Complications of viral replication or secondary bacterial infection can result in bronchopneumonia, otitis media, diarrhea, or rarely, encephalitis.

iv. Diagnosis and prevention. Characteristic clinical signs generally obviate the need for other diagnostic methods for

measles, but serology, immunofluorescent antibody, or PCR screening for virus in clinical specimens or viral isolation can be used. Vaccination of susceptible nonhuman primates with a modified live vaccine is effective in preventing the disease, and treatment of exposed animals with human gamma globulin may be useful in controlling disease during epizootics (Roberts *et al.*, 1988). Vaccination for measles should be assured for all handlers of nonhuman primates. The reader should refer to an excellent overview of the characteristics of a measles epizootic and the discussion of disease management in a nonhuman primate colony for additional information on factors relevant to the control and prevention of this disease (Willy *et al.*, 1999).

I. Newcastle Disease Virus

i. Reservoir and incidence. Newcastle disease is caused by a paramyxovirus and is seen among wild, pet, and domestic birds. Wild birds transmit the infection to domestic bird populations (Mufson, 1989). The zoonotic potential of this agent in the laboratory environment has been realized on numerous occasions (Barkley and Richardson, 1984).

ii. Mode of transmission. Aerosol transmission is the important means of spread to humans, but contaminated food, water, and equipment also transmit infection within bird populations.

iii. Clinical signs. The severity of the disease in birds depends on the pathogenicity of the infecting strain. Highly pathogenic strains have largely been excluded from flocks within the United States. Moderately pathogenic strains produce anorexia and respiratory disease in adult birds and neurologic signs in young birds. In humans, the disease is characterized by a follicular conjunctivitis that resolves without complications and without therapy. Mild fever and respiratory involvement ranging from cough to bronchiolitis and pneumonia can also be seen in humans.

iv. Diagnosis and prevention. This disease can be prevented in the laboratory environment by immunizing birds susceptible for this disease or obtaining birds from flocks known to be free of this agent. Personal hygiene practices should also be in place to prevent zoonotic transmission.

J. Influenza Virus

i. Reservoir and incidence. Humans are considered the reservoir for human influenza virus infections. However, influenza virus infections from different antigenic strains occur naturally in many animals, including avian species, swine, horses, ferrets, mink, and seals (Harmon and Kendal, 1989).

Animal reservoirs are thought to contribute to the emergence of new human strains of influenza infection by the passage of avian influenza viruses through pigs, which act as intermediate hosts. This is believed to involve multiple mutational or reassortment events, and once established in the pig, transmission occurs by the airborne route (Webster, 1997). In the laboratory, ferrets are highly susceptible to human influenza and often are used as experimental models of influenza infection (Harmon and Kendal, 1989).

ii. Mode of transmission. Transmission occurs by airborne spread of the virus and by direct contact through droplet spread. The transmission of animal influenza strains from animals to humans is an uncommon occurrence. However, a study has shown that pigs experimentally infected with influenza virus in the laboratory can directly and readily spread this agent to persons working with these animals (Wentworth *et al.*, 1997). Also, ferrets housed in the laboratory will develop epizootic infection concomitant with human outbreaks of the disease. Ferret-to-human transmission of the virus has also been documented (Marini *et al.*, 1989).

iii. Clinical signs. Influenza is an acute disease of the respiratory tract and is characterized by fever, headache, myalgia, prostration, coryza, sore throat, and cough. Viral pneumonia and gastrointestinal involvement manifested by nausea, vomiting, and diarrhea may also develop.

iv. Diagnosis and prevention. Personnel should wear proper protective clothing and practice appropriate personal hygiene measures if contact is unavoidable with experimentally infected animals or with ferrets suspected of having natural influenza infection.

III. RICKETTSIAL DISEASES

A. Murine Typhus (Endemic Typhus)

Murine typhus is caused by *Rickettsia typhi*. Although this disease has been recognized for centuries, not until the 1920s was it distinguished from epidemic typhus. The absence of louse infestation in humans, seasonal occurrence, and sporadic nature help differentiate it from louse-borne typhus (i.e., epidemic typhus). Epidemic typhus is seen only in the eastern United States in association with flying squirrels (Duma *et al.*, 1981).

i. Reservoir and incidence. Murine typhus is worldwide, and in the United States it is usually diagnosed in southeastern or Gulf Coast states and in areas along the northern portion of the Mississippi River and southern California. It is also associ-

ated with human populations subjected to areas of high-density wild rat colonies, such as ports, granaries, farms, or rat-infested buildings in inner cities. Laboratory personnel have been infected with this agent when inoculating rodents and handling infected animals.

Since the 1970s, there has been a shift in the distribution of human cases of murine typhus to more rural locales in southern California and central and south Texas (Adams et al., 1970). Southern California was considered an unusual locale because Orange County was considered a wealthy suburb where rat infestation was uncommon. Epidemiologic studies indicated that opossums had a high seropositivity to murine typhus, and the cat fleas infesting the opossums were infected with either R. typhi or a newly recognized rickettsia first called ELB agent and later R. felis (Adams et al., 1990; Williams et al., 1992). Findings extended to a survey of fleas on dogs, cats, and opossums in California, Texas, and Georgia also confirmed that fleas were infected with R. typhi or R. felis, helping explain the spread of murine typhus into rural areas in the United States. Also, human cases of typhus caused by R. felis, based on PCR, have been recorded (Schriefer et al., 1994). Determining exact taxonomic specifications of R. felis has not been possible because no isolates have been obtained for detailed comparative analysis.

ii. Mode of transmission. Murine typhus is primarily a disease of rats, with its principal vectors being the oriental rat flea, *Xenopsylla cheopis,* and the flea *Nasopsyllus fasciatus.* These fleas will also naturally colonize the mouse *Mus musculus.* The cat flea, *Ctenocephalides felis,* (as well as seven other species of fleas) has also been implicated in the spread of the disease. Rickettsiae are ingested by a blood meal of the flea, where they multiply in the gut, and are subsequently passed out in the dejecta of the flea. Infection in the rat and the human is the result of contamination of the puncture wound by flea feces (Farhang-Azad et al., 1985). Experimental evidence indicates that a flea bite can also directly transmit the infection (Farhang-Azad et al., 1985). *Rickettsia typhi* are resistant to drying and remain infectious for up to 100 days in rat feces.

iii. Clinical signs. After infection with rickettsia, the incubation period is 7–14 days. Because murine typhus is difficult to differentiate either clinically or anatomically from other rickettsial diseases, specific serological tests or PCR-based assays are extremely important in making the correct diagnosis (Farhang-Azad et al., 1985). The acute febrile disease is usually characterized by general malaise, headache, rash, and chills, with signs ranging from mild to severe. An encephalitic syndrome can also occur (Mushatt and Hyslop, 1991). In one report, 25% of 180 patients with the disease had delirium, stupor, or coma. Fortunately, these findings resolve with lowering of the febrile response. Fatality rate for all ages is about 2% but increases with age. Proper antibiotic therapy is the most effective measure to prevent morbidity or mortality due to rickettsial infections. Tetracycline and chloramphenicol have proven to be

effective in hastening recovery and preventing neurologic sequelae, such as deafness due to eighth cranial nerve involvement (Mushatt and Hyslop, 1991).

iv. Diagnosis and control. Recovery of rickettsial organisms or antigens from biological specimens is inconsistent and is not routinely done except in labs equipped to process and identify these samples. It must be stressed that manipulation of rickettsia in the laboratory is hazardous and has accounted for numerous infections of laboratory personnel. Currently, serological diagnosis is accomplished by ELISA and RIA; however, the IFA technique remains the most commonly used. Unfortunately, this test cannot distinguish epidemic from endemic typhus. The CDC considers a fourfold rise in titer detected by any technique (except Weil–Felix) as evidence of rickettsial infection. Complement fixation titer of 1:16 or greater in a single serum sample from a patient with clinically compatible signs is also considered diagnostic (McDade and Fishbein, 1988). Newer PCR techniques specific for rickettsial species are increasingly being used, which in time may replace serological tests.

Fleas can be controlled by applying insecticides (organochlorines, as well as others) as residual powders or sprays in areas where rats nest or traverse. It is imperative that insecticides be applied prior to using rodenticides; this will prevent fleas from leaving the dead rodents and feeding on human hosts (Beaver and Jung, 1985). This disease should not be encountered in rat colonies in well-maintained research vivaria. However, with the cat flea being a newly recognized vector, its presence on random-source dogs, cats, and opossums raises the risk of transmission of murine typhus to personnel working with these flea-infested animals.

B. Rickettsial Pox

A variety of rodents are infected with other rickettsial diseases. *Mus musculus* is the natural host for the causative agent of rickettsial pox, *R. akari,* a member of the spotted fever group of rickettsia (Chin, 2000). This organism is also isolated from *Rattus rattus* and *R. norvegicus,* and the rat under certain circumstances may transmit the disease to humans. The disease is transmitted by the mite *Liponyssoides (Allodermanyssus) sanguineus* and has been diagnosed in New York City and other eastern cities, as well as in Russia, Egypt, and South Africa (Chin, 2000). The incubation period is approximately 10–24 days, and the clinical disease is similar to that noted in murine typhus. The rash of rickettsial pox commences as a discrete maculopapular rash, which then becomes vesicular. The palms and soles are usually not involved. About 90% of affected persons develop an eschar, with a shallow ulcer covered by a brown scab (Farhang-Azad et al., 1985; Chin, 2000). Although headaches are common and may be accompanied by stiff necks, lumbar cerebrospinal fluid (CSF) samples are normal. Pulmonary

and gastrointestinal involvement also are almost never encountered. Diagnosis, treatment, and control are similar to those described for murine typhus and *Yersinia pestis.*

C. *Coxiella burnetii* Infection (Q Fever)

i. Reservoir and incidence. *Coxiella burnetii,* the causative agent of Q fever, has a worldwide distribution perpetuated in two intersecting cycles of infection composed of domestic or wild animals and their associated ticks (Babudieri, 1959; Marrie, 1990). The domestic animal cycle involves mainly sheep, goats, and cattle. The prevalence of the infection among sheep is high throughout the United States, and sheep have been the primary species associated with disease outbreaks, including those occurring in research animal facilities (Asher, 1989). However, human cases of the disease have also been associated with nonruminants, such as pregnant cats (Langley *et al.,* 1988) and wild rabbits (Marrie *et al.,* 1986). Thus, a broad range of domestic and wild animal species, including birds, should be given consideration as potential sources for Q fever infection in animal care and use activities (To *et al.,* 1998).

ii. Mode of transmission. *Coxiella burnetii* are shed in the urine, feces, milk and especially placental tissues of domestic ungulates that generally are asymptomatic. The placenta of infected ewes can contain up to 10^9 organisms per gram of tissue, and milk may contain 10^5 organisms per gram (CDCP–NIH, 1999). The organism is highly infectious with possibly as few as 10 organisms inducing infection (CDCP–NIH, 1999). The primary method of transmission is through infectious aerosols. The organism produces a sporelike form that is resistant to desiccation and persists in the environment for long periods of time, contributing to the widespread dissemination of infectious aerosols and resulting in infections miles from the original organism source (Franz *et al.,* 1997; Tissot-Dupont *et al.,* 1999). The importance of these factors was illustrated in outbreaks of the disease associated with the use of pregnant sheep in research facilities in the United States (Bernard *et al.,* 1982). In these outbreaks, personnel who did not have direct contact with infected sheep but who worked along the transport routes for these animals became serologically positive for Q fever (Bernard *et al.,* 1982; Reimer, 1993). Also, five of nine laundry workers without direct sheep contact but who processed linens soiled during sheep surgery developed serological evidence of infection.

iii. Clinical signs, susceptibility, and resistance in humans. Q fever in humans varies in duration and severity, and asymptomatic infection may occur. The disease often presents as a flulike illness with fever, frontal headache with retro-orbital pain, and chest pain with a nonproductive cough and pneumonia, resolving within 2 weeks of infection. However, serious extrapulmonary complications, such as acute or chronic hepatitis,

nephritis, epicarditis, and endocarditis, may also occur. Individuals with valvular heart disease should not work with *C. burnetii* due to the prospect of serious, chronic, relapsing infection (Asher, 1989; CDCP–NIH, 1999).

iv. Diagnosis, prevention, and control. Whenever possible, male or nonpregnant sheep should be used in research programs; however, many research applications specifically call for the use of pregnant animals. Several commercial vendors now supply sheep from flocks that have not had serological evidence of infection for an extended period. Although serological status is not a useful indicator of organism shedding in individual sheep, many institutions have elected to use these animals, reasoning that cumulative and consistent negative Q fever serology on a herd basis provides a reasonably strong assurance of Q fever–free status. Advances in polymerase chain reaction (PCR) methods have improved the sensitivity of *C. burnetii* detection over that of the antigen capture ELISA, as well as improved the speed, safety, and convenience of the assay. The PCR method may offer some hope that the potential for organism shedding could be assessed on an individual animal basis to minimize the potential risk of Q fever outbreaks in animal facilities (Lorenz *et al.,* 1998; Yanase *et al.,* 1998).

Sheep and other animals harboring Q fever infections should be maintained under animal biosafety level 3 (ABSL-3) conditions to prevent the transmission of the organism in the research animal facility environment (CDCP–NIH, 1999). Additional detailed recommendations have been published concerning sheep handling in biomedical research programs (Bernard *et al.,* 1982). In many institutions, ABSL-3 conditions would prove to be unachievable for sheep held under agricultural conditions for food and fiber production or for instructional exercises. The use of personal protective equipment conforming to ABSL-3 practices is important in these settings even though the facilities may be deficient in meeting ABSL-3 criteria. An effective Q fever vaccine is licensed in Australia (Q-Vax), and an investigational new phase 1 Q fever vaccine (IND) is available from the Special Immunizations Program, U.S. Army Medical Research Institute for Infectious Disease (USAMRIID), Fort Detrick, MD 21701 (Franz *et al.,* 1997; CDCP–NIH, 1999). The use of this vaccine should be limited to personnel at high risk of exposure and who have no demonstrated sensitivity to Q fever antigen.

IV. CHLAMYDIAL INFECTIONS

A. Chlamydiosis (Psittacosis, Ornithosis, or Parrot Fever)

i. Reservoir and incidence. The taxonomy for the order Chlamydiales has recently been revised based upon ribosomal

operon genes and phenotypic characteristics of the chlamydial organisms, and many of the new species may be unfamiliar to the reader (Everett *et al.*, 1999). Chlamydial agents are widely distributed among birds and mammals worldwide and occur naturally among many laboratory animal species, including birds, mice, guinea pigs, hamsters, rabbits, ruminants, swine, cats, ferrets, muskrats, and frogs (Storz, 1971; Newcomer *et al.*, 1982). Of these host species, birds with *Chlamydophila psittaci* comb. nov. (previously *Chlamydia psittaci*) infection, particularly psittacines, have proven to be the most frequent sources of virulent human infection (CDCP, 1997); however, infections in ruminants (Hyde and Benirschke, 1997; Jorgesen, 1997) and cats (Cotton and Partridge, 1998) have also been involved in serious human cases of the disease. The most common human chlamydial infection, *Chlamydia trachomatis,* is not naturally transmissible to animals but is used to produce experimental infections in nonhuman primates. *Chlamydia muridarium* occurring in the mouse and *C. suis* occurring in the pig are closely related to *C. trachomatis* but are not infectious for humans. Also, *Chlamydophila pecorum* comb. nov. (previously *Chlamydia pecorum*) produces intestinal infection in ruminants and other animals but not in humans, and *Chlamydophila pneumoniae* comb. nov. (previously *Chlamydia pneumoniae*) produces respiratory infections in humans and has been isolated from only the koala, horse, and frog (Berger *et al.*, 1999). Zoonotic infections from *Chlamydiophila pneumoniae* have not been recorded.

ii. Mode of transmission. The organism is spread to humans from infectious material present in exudates, secretions, or desiccated fecal material by direct contact or the aerosol route. Latent infection is an important feature of epizootology of the *Chlamydiophila psittaci* infection in birds; stress can reactivate enteric shedding of the organism and clinical signs (Storz, 1971).

iii. Clinical signs, susceptibility, and resistance in humans. Chlamydiae produce a diverse spectrum of animal disease, including conjunctivitis, pneumonitis, air sacculitis, pericarditis, hepatitis, enteritis, arthritis, meningoencephalitis, urethritis, endometritis, and abortion. Zoonotic infections in humans are characterized mainly by upper and lower respiratory tract complaints; however, conjunctivitis, thrombophlebitis, myocarditis, hepatitis, and encephalitis have also been reported (Smith, 1989; Leitman *et al.*, 1998). Although the avian strains of the organism are considered to be more pathogenic for humans than are the mammalian strains, ovine strain–related (*Chlamydophila abortus* gen. nov. sp. nov.) human gestational infections (Hyde and Benirschke, 1997; Jorgesen, 1997) and feline pneumonitis strain–related (*Chlamydophila felis* gen. nov. sp. nov.) conjunctivitis, pneumonia, and extrapulmonary infection (Cotton and Partridge, 1998) emphasize the relevance of diverse reservoir hosts in the human disease.

iv. Diagnosis and control. The diagnosis of *C. psittaci* in birds is based upon positive complement fixation serology (titer

> 1 : 16), ELISA-based fecal antigen tests, identification of inclusions in tissue specimens, or impression smears or organism isolation. Birds used in research animal facilities should be acquired from flocks free from *C. psittaci* infection. Antibiotic treatment should be provided to wild-caught birds or birds of unknown disease status, as well as to mammalian or amphibian species with chlamydial infection if these are used in research programs. Personnel protection adhering to ABSL-2 procedures along with respiratory protection is generally adequate, but ABSL-3 procedures are warranted for activities with the high potential for droplet or infectious aerosol production (CDCP–NIH, 1999).

V. BACTERIAL DISEASES

A. Trauma-Associated Bacterial Diseases

1. Bites and Scratches

Several million Americans annually suffer animal bites, which continues to be a major health problem in the United States and accounts for approximately 1% of emergency room visits. Dogs and cats are responsible for 90% of the recorded bites (Weber and Hansen, 1991; Talan *et al.*, 1999), and each year dog attacks account for 10 to 20 deaths in the United States. Veterinarians, animal control officers, and presumably animal care personnel in research facilities as well as in municipal pounds are at higher risk of bites than the general population. Although rabies is the most serious public health threat from bites and scratches, the risk of bacterial infection from dog bites is lower (approximately 3–18%) than that from cat bites, which is reported to be approximately 28–80% (Weber and Hansen, 1991). It is estimated that 400,000 persons in the United States are bitten or scratched by cats annually. According to one report, approximately 40,000 rat bites are recorded annually (Committee on Urban Pest Management, 1980). As with bites from dogs and cats, the majority of rat bites occur in children. It is estimated that 2% of rat bites become infected (Ordog, 1985).

Animals in general have a complex oral microflora consisting of numerous bacterial species; both aerobic and anaerobic bacteria are therefore routinely isolated from traumatic bite wounds inflicted by domestic and wild animals. Common organisms isolated from dog bites include *Staphylococcus* species, *Streptococcus* species, a variety of anaerobes, and *Pasteurella multocida*. In a comprehensive multicenter study, 60% of dog-bite wounds were punctures, 10% were lacerations, and 30% were a combination of both. This compared to 85% of cat-bite wounds being punctures, 3% lacerations, and 12% a combination of both. In this study, 39% of 57 patients with cat bites presented as purulent wounds, whereas abscesses were present in 19% of the cases reviewed (Talan *et al.*, 1999). Of the

50 patients with dog bites, 58% had purulent wounds, 30% were nonpurulent, and 12% were noted to have abscesses. Dog and cat bites had a mean of 5 bacterial species per wound; 63% of the cat bites analyzed compared to 48% of dog bites had a mixed anaerobic and aerobic population (Talan et al., 1999). Only aerobes grew in 36% of the cases (42% of dog bites and 32% cat bites), whereas anaerobes were the only species grown in 1% of the cases. Capnocytophaga canimorsus, an invasive organism, was recovered from 4.7% of the wounds. It should be noted that if fever occurs in immuncompromised patients after a bite wound, this organism should be considered in the differential diagnosis. Erysipelothrix rhusiopathiae was isolated from two cat-bite wounds, whereas Pasteurella spp. were present in the wounds 75% of the time in cats and 50% in dogs. Geographic locale is also important in defining bacterial flora of bites and scratches. In a study conducted in the southwestern and central United States, 17 of 1041 (1.6%) of the cases of tularemia in humans diagnosed from 1981 to 1987 were associated with cat scratches or bites (Taylor et al., 1991).

Several bacterial pathogens have been isolated from rat bites, including Leptospira interrogans, Pasteurella multocida, and Staphylococcus species; however, the most commonly isolated pathogens are Streptobacillus moniliformis and Spirillum minus (Fox, 1999). Bite wounds from primates and ferrets (and other laboratory animals) can also result in bacterial infection. For example, a chronic Mycobacterium bovis infection on the hand of a human resulted from a ferret bite that had occurred 22 years previously (Jones et al., 1993). The greatest concern from macaque bites still remains the threat of B virus infection.

2. Atypical Mycobacteriosis

i. Reservoir and incidence. The rapidly growing mycobacteria (RGM) Mycobacterium fortuitum, M. chelonae, and M. abscessus are ubiquitous, being found in soil throughout the world. Mycobacterium chelonae was first isolated from sea turtles; M. fortuitum from frogs (originally called ranae); and M. abscessus, as the name implies, from soft tissue abscesses of a patient. Of the nontuberculosis mycobacterium belonging to Runyon group I, M. marinum is by far the most common. The organism was first isolated from cutaneous lesions in 1826 and was responsible for the death of saltwater fish in a Philadelphia aquarium 100 years later; the authors named the mycobacterium M. marinum.

ii. Mode of transmission. The RGM most commonly are associated with a traumatic injury with potential soil contamination and result in skin, soft tissue, or bone disease. Mycobacterium marinum is pathogenic only on abraded skin; a disruption of the epidermis must be present for development of disease. Because this organism is recognized as a pathogen in zebrafish, it can be a source of infection in personnel working with this species in a research environment.

iii. Clinical signs. Mycobacterium marinum is a free-living mycobacterium that causes disease in fresh-water and saltwater fish and occasionally in humans. It is often called swimming pool granuloma or fish tank granuloma because of the association with these two environmental exposures and human infections. Importantly, M. marinum, because of its optimum growth at 30°–32°C, is primarily localized to skin infections. However, it can extend to deeper tissues, including joints and tendons. For individuals exposed to diseased fish and/or their environment, the lesions are in general located on the backs of hands or fingers or forearms. Infections have also resulted from the bite of a dolphin (Flowers, 1970).

iv. Diagnosis and control. Identification for the common RGMs and M. marinum has been given low priority and is only performed routinely in reference laboratories. Fortunately however, PCR-based assays have become available for rapid diagnosis of atypical mycobacteria.

3. Rat-Bite Fever

Rat-bite fever (RBF) can be caused by either of two microorganisms: Streptobacillus moniliformis or Spirillum minus. Streptobacillus moniliformis causes the diseases designated as streptobacillary fever, streptobacillary rat-bite fever, or streptobacillosis (McEvoy et al., 1987; Rupp, 1992; Chin, 2000). Haverhill fever and epidemic arthritic erythema are diseases associated with ingestion of water, food, or raw milk contaminated with S. moniliformis. Sodoku is derived from the Japanese words for rat (so) and poison (doku), and is used to designate infection with Spirillum minus. Spirillosis and spirillary rat-bite fever are other names given to the infections caused by Spirillum minus.

i. Reservoir and incidence. These organisms are present in the oral cavity and upper respiratory passages of asymptomatic rodents, usually rats (Wilkins et al., 1988). Streptobacillus moniliformis has been isolated as the predominant microorganism from the upper trachea of laboratory rats in one study (Paegle et al., 1976). Other surveys indicate isolation of the organism in 0/15, 7/10, 2/20, 7/14 laboratory rats and 4/6 wild rats (Geller, 1979). The incidence of S. moniliformis is probably lower in high-quality, commercially reared specific pathogen–free rats. Surveys in wild rats indicate 0–25% infection with Spirillum minus (Hull, 1955) or 50–100% for Streptobacillus moniliformis.

ii. Mode of transmission. The bite of an infected rat is the usual source of infection. In some cases, bites from other animals, including mice, gerbils, squirrels, weasels, ferrets, dogs, and cats, or rare traumatic injuries unassociated with animal contact cause the infection.

iii. Clinical signs. Rat-bite fever is not a reportable disease, which makes its prevalence, geographic location, racial data,

and source of infection in humans difficult to assess. The disease, though uncommon in humans, has nonetheless appeared among researchers or students working with laboratory rodents, particularly rats (Anderson *et al.,* 1983). Historically, bites from wild rats and subsequent illness (usually in small children) relate to poor sanitation and overcrowding (Hull, 1955). One survey of rat bites in Baltimore tabulated rat-bite fever in 11 of 87 cases (Brooks, 1973). The disease can also occur in individuals who have no history of rat bites but reside or work in rat-infested areas. Exposure to dogs and cats who prey on wild rodents may also be the source of the organism. Ingestion of milk, food, or water contaminated with rat feces can result in RBF (CDC, 1995).

The incubation period for *S. moniliformis* infection varies from a few hours to 2–10 days, whereas the incubation period for *Spirillum minus* infection, most commonly seen in Asia, ranges from 1 to 6 weeks (Table II). Fever is present in either form. Inflammation associated with the bite and lymphadenopathy are frequently accompanied by headache, general malaise, myalgia, and chills. 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 *Streptobacillus moniliformis* but is less common in *Spirillum minus. Streptobacillus moniliformis* may be cultured from serous to purulent effusion that is recovered from affected larger joints.

Most cases of RBF resolve spontaneously within 14 days; however, 13% of untreated cases are fatal (Sens *et al.,* 1989). Prophylactic efficacy of antibiotic treatment following rat bites has not been thoroughly investigated. If antibiotic treatment (intravenous penicillin for 5–7 days, followed by oral penicillin for 7 days) is not instituted early, complications such as pneumonia, hepatitis, pyelonephritis, enteritis, and endocarditis may develop (Anderson *et al.,* 1983). If endocarditis is present, the penicillin should be given parenterally at doses of 15–20 million units daily for 4 to 6 weeks. Streptomycin and tetracyclines are also effective antibiotics for those individuals with penicillin-associated allergies. Death has occurred in cases of *Streptobacillus moniliformis* involving preexistent valvular disease.

iv. Diagnosis and prevention. Spirillum minus does not grow *in vitro* and requires inoculation of culture specimens into laboratory animals, with subsequent identification of the bacteria by dark-field microscopy. Streptobacillary rat-bite fever can be diagnosed only by blood culture. *Streptobacillus moniliformis* grows slowly on 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 (Fox and Newcomer, 1990). Because of its properties as a bacterial growth promoter, sodium polyanethol sulfonate, which is sometimes found in blood-based media, should not be used due to its inhibitory effects on *S. moniliformis.* Growth on agar consists of 1–2 mm gray, glistening colonies. The API-ZYM diagnostic system can be used for rapid biochemical analysis and diagnosis. Unfortunately, no serological test is available. Acute febrile diseases, especially if associated with animal bites, are routinely treated with penicillin or other antibiotics.

4. Cat Scratch Disease

Histopathologic examination of lymph nodes from 39 patients with clinical criteria for cat scratch disease (CSD) revealed pleomorphic, gram-negative bacilli in 34 of the 39 nodes. Organisms in lymph node sections exposed to convalescent serum from 3 patients and to immunoperoxidase stained equally well with all three samples. The authors concluded that the bacilli appear to be the causative agents of CSD. *Bartonella* (formerly *Rochalimaea*) *henselae,* a recently described fastidious gram-negative bacteria, is now recognized as the primary cause of cat scratch disease. *Bartonella henselae* has been isolated from lymph nodes of CSD patients, and elevated serological titers to *B. henselae* are also noted in these individuals (Dolan *et al.,* 1993; Zangwill *et al.,* 1993). A second organism,

Table II

Clinical Signs of Rat-Bite Fever[a]

Clinical features	Streptobacillary fever (*Streptobacillus moniliformis*)	Spirillosis (*Spirillum minus*)
Incubation period	2–10 days	1–6 weeks
Fever	+++	+++
Chills	+++	+++
Myalgia	+++	+++
Rash	++	++
	Morbilliform, petechial	Maculopapular
Lymphadenitis	+	++
Arthralgia, arthritis	++	±
Indurated bite wound	—	+++
Recurrent fever/ constitutional signs (untreated)	Irregular periodicity	Regular periodicity

[a]Modified from Lipman (1996).

Afipia felis, has also been isolated from CSD lesions but is not considered the common etiologic agent of CSD.

i. Reservoir and incidence. An estimation of 22,000 cases of cat scratch disease in the United States, of which approximately 2000 require hospitalization, is based on an analysis of three databases (Jackson *et al.,* 1993). Almost all *B. henselae* infections are associated with exposure or ownership of cats; however, not all cases of CSD are associated with a scratch or bite.

ii. Mode of transmission. Patients with CSD commonly have a history of exposure to a cat and of these patients, the majority have either been bitten or scratched. Most of the patients are under 20 years of age. It is now known that cat fleas are infected with *B. henselae.* It is suspected that the organism is shed in the feces of the flea and can result in the transmission of the organism from cat to cat and from cat to human via mucous membrane or skin contact. Subsequently there is self-inoculation by scratching the flea bite, or alternatively by having the contaminated claws or teeth of cats inoculate the organism into traumatized skin. Importantly, several surveys have shown that cats can be chronically infected with *B. henselae,* with the organism capable of being isolated from blood of asymptomatic cats over an extended period of time (Koehler *et al.,* 1994).

iii. Clinical signs. The natural course of CSD, which consists of a mild or absent fever, few systemic sequelae, and localized lymphadenitis with little or no discomfort, probably results in a large number of unrecognized cases. A primary lesion will develop in 50% of the cases about 10 days after a cat bite or scratch; the erythematous pustule will usually persist for 1–2 weeks (Fig. 3). A regional lymphadenopathy develops 14 days after the initial lesion in most cases. Lymphadenitis regresses in about 6 weeks, with 30–50% of the nodes becoming suppurative. Of the approximately 65% of people who develop systemic illness, fever and malaise are the symptoms most often noted. Occasionally observed are generalized lymphadenopathy, thrombocytopenia, encephalitis, osteolytic lesions, and erythema nodosum. The disease is benign, and most patients recover spontaneously without sequelae within 2 months, although lymphadenopathy can persist up to a year. In immunocompromised individuals, CSD is manifested by an unusual vascular growth seen on the skin and given the name bacillary epithelioid angiomatosis (LeBoit *et al.,* 1988; Kemper *et al.,* 1990). Systemic disease involving spleen and liver also occurs in these patients.

iv. Diagnosis and control. If lymphadenitis is present, three of the four following criteria should be fulfilled to diagnose CSD: (1) positive serology for *B. hensalae;* a positive titer of 1:64 or greater by IFA assay is considered positive, (2) history of contact with a cat, (3) characteristic histopathologic changes present on involved lymph node biopsy, (4) absence of

other disease, and (5) growth of the organism on rabbit blood agar in 5% CO_2.

Prevention is based on flea control as well as thorough cleansing of cat bites and scratches.

5. *Pasteurella* spp.

i. Reservoir and incidence. *Pasteurella* spp. colonize the respiratory and intestinal tracts of a variety of domestic and wild animals, including birds. The bacteria are gram-negative rods that grow readily on blood agar.

ii. Mode of transmission. Human infection caused by *P. multocida* is commonly the result of contact with animals, particularly when bitten or scratched.

iii. Clinical signs. Traumatic wounds resulting from bites or scratches are clinically recognized by acute onset of pain, erythema, cellulitis, and purulent discharge. Osteomyelitis can also occur in bone underlying the wound, and septicemia can result on occasion (Hombal and Dincsoy, 1992). Cat scratches have also resulted in *P. multocida*–associated corneal ulceration and keratitis (Ho and Rapuan, 1993).

iv. Diagnosis and control. Bacterial culture of the wound is undertaken prior to local cleansing and antisepsis of the traumatic site of injury.

6. *Streptococcus iniae*

i. Reservoir and incidence. *Streptococcus iniae* is now recognized as a cause of high mortality in rainbow trout and tilapia (members of the cichlid group of fish) being raised in fish farming environments. *Streptococcus iniae* was recognized as a pathogen in 1976 when the bacteria was first cultured from cutaneous abscesses in aquaria-maintained Amazon freshwater dolphins (Pier and Madin, 1976).

ii. Mode of transmission. Many infected patients sustain an injury to the hand when preparing infected fish for consumption. The organism can be readily cultured from these infected fish (Goh *et al.,* 1998).

iii. Clinical signs. *Streptococcus iniae* was identified as a zoonotic agent in 1995–1996 when a cluster of cases presented with fever and lymphangitis in individuals handling whole or live fish purchased in Toronto, Canada (CDCP, 1996; Weinstein *et al.,* 1997). *Streptococcus iniae* was cultured from the blood of each of these patients.

iv. Diagnosis and control. The organisms are gram-positive cocci, β-hemolytic on 5% sheep blood agar and are nonreactive in the Lancefield sero-grouping system. A nested PCR assay specific for the 16S-23S ribosomal intergenic spacer,
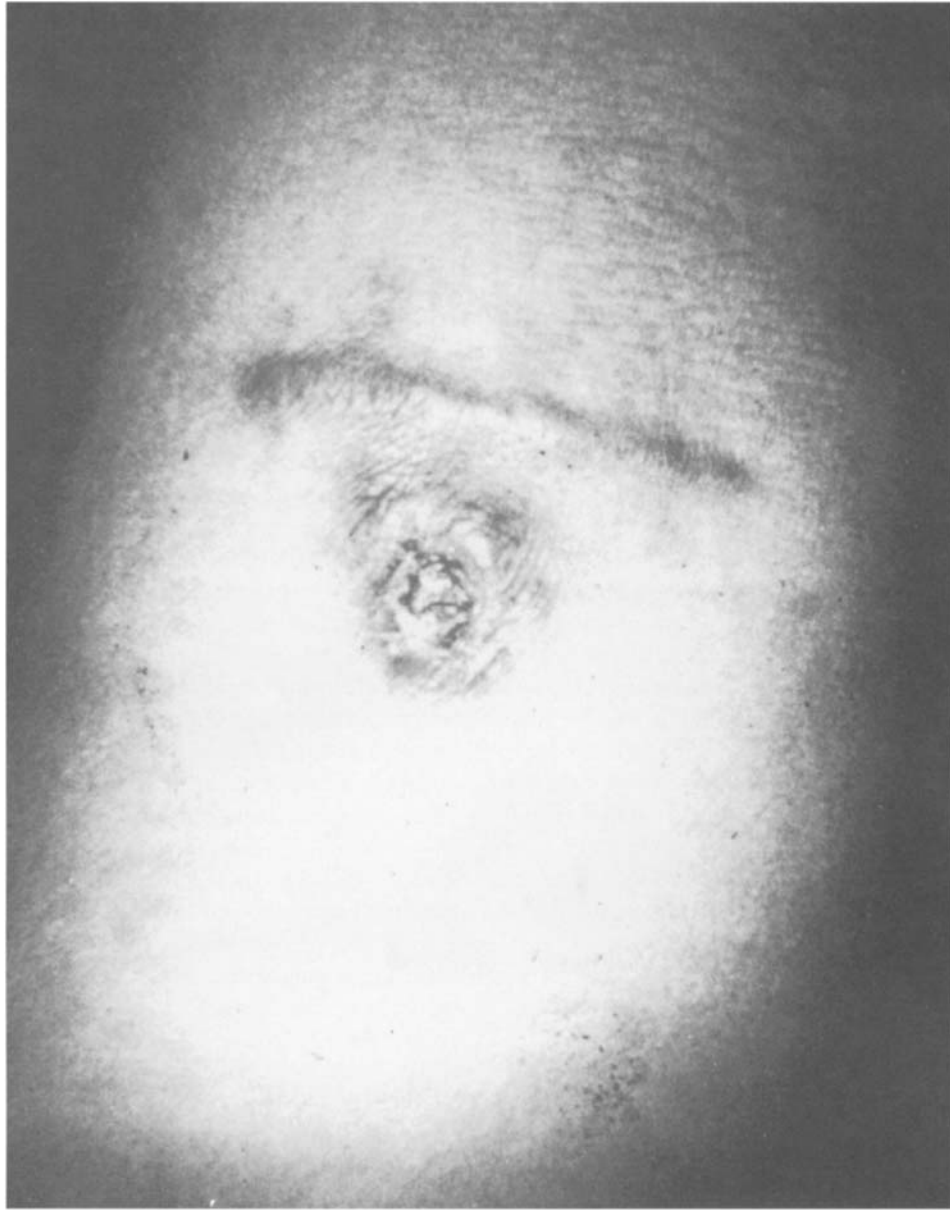
Fig. 3. Cat scratch disease. Ulcerated, circular lesion adjacent to cat scratch. (Courtesy of Dr. J. H. Graham, Armed Forces Institute of Pathology.)

or alternatively, a chaperonin 60 (cpu 60) gene identification method, are two molecular techniques that provide accurate, rapid, and specific diagnosis of this organism (Berridge *et al.,* 1998; Goh *et al.,* 1998). Infected individuals respond to parenteral antibiotics within 2–4 days after initiation of treatment.

B. Systemic Diseases

1. Brucellosis

i. Reservoir and incidence. Of the *Brucella* spp., *Brucella canis* is the most likely zoonotic agent in the laboratory animal facility due to the extensive use of random-source and

laboratory-bred dogs in comparison to other large domestic animals known to be infected with other *Brucella* spp.

ii. Mode of transmission. In one study, investigators considered the zoonotic transmission of *B. canis* unlikely, as evidenced by negative serological tests among 12 individuals exposed to five infected dogs. Since 1967, when the first human *B. canis* infection was identified, more than 35 natural and laboratory-acquired infections have been reported; most resulted from contact with aborting bitches. Fortunately, humans are relatively resistant to infection; however, *B. canis* is not a reportable disease, and prevalence data are not available. Although *B. canis* is particularly well adapted to dogs and is not readily transmitted

to other species, susceptibility has been reported in several wild species of Canidae (Carmichael and Greene, 1998).

iii. Clinical signs. Bacteremia occurred in several infections; other systemic involvement included painful generalized lymphadenophathy and splenomegaly. Additional signs include fever, headache, chills, sweating, weakness, malaise, myalgia, nausea, and weight loss. Rare complications include endocarditis, meningitis, hepatitis, and arthritis. Although *B. canis*-produced clinical disease in humans is similar to that caused by other *Brucella* spp., it is generally not as severe. Seroconversion to *B. canis* has been reported in 0.5% of asymptomatic military personnel who had contact with infected dogs, indicating that inapparent infection may occur (Polt *et al.,* 1982).

iv. Diagnosis and control. When a canine's history includes abortions, infertility, testicular abnormalities, and poor semen quality, infection should be considered. A rapid slide agglutination test that produces presumptive diagnostic information is commercially available. To confirm the results of the slide test, one should perform blood cultures and additional serological tests, such as the tube agglutination test (Polt *et al.,* 1982; Serikawa *et al.,* 1989). There have not been any large-scale efforts to eradicate *B. canis* in the general canine population as there have been with *Brucella* spp. of large domestic animals (Forbes and Pantekoek, 1988). Because of the intracellular location of *B. canis,* efficacy of antibiotic therapy is variable, and failures or relapses after therapy are reported in dogs. Ultimate control of *B. canis* in humans relies on elimination of dogs with the disease.

2. Plague

Human infections due to *Yersinia pestis,* a gram-negative coccobacillus, in the United States are sporadic and limited, usually resulting from infected flea or rodent contact. Since 1924–1925, when a plague epidemic ravaged Los Angeles, neither urban plague nor rat-borne plague has been diagnosed in the United States (Craven and Barnes, 1991). All reported cases since then have occurred in states located west of the 101st meridian.

i. Reservoir and incidence. Although plague has occurred repeatedly in recorded history, by the fourteenth century the disease had appeared in the Far East, spread to Asia Minor, and followed the trade routes to Europe. Plague, however, did not make its arrival in the United States until the disease appeared in California in the early 1900s, where it still exists endemically in the ground squirrel and chipmunk.

Wild rat populations still act as the primary reservoir in many parts of the world and remain a continued threat in the United States. Sciurid rodents (rock squirrels, California ground squirrels, chipmunks, and prairie dogs) account for the primary plague reservoir in the western parts of the United States

(Kaufman *et al.,* 1980; Rosner, 1987). Cricetid rodents, such as the wood rat, are occasionally cited as reservoir hosts. The oriental rat flea, *Xenopsylla cheopis,* the common vector of plague, is well established throughout the United States, particularly in the southern United States and southern California. It is important to remember that more than 1500 species of fleas and 230 species of rodents are infected with *Yersinia pestis.* Only 30 to 40 rodent species, however, are permanent reservoirs of the infection (Macy, 1999). Plague is infrequently reported in the United States, with a low of 1 case in 1972 and a high of 40 cases in 1983 (Craven and Barnes, 1991). Ninety percent of the cases have been diagnosed in New Mexico, Colorado, and California. Urban development (particularly in New Mexico) encroached into plague-enzootic rodent habitats, placing human populations at increased risk of contracting the disease. In addition to rodent epizootics, dogs, and increasingly cats, either have served as passive transporters of the disease or have been actively infected (Rosner, 1987). The disease has seasonal peaks, with the highest proportion occurring May through September.

ii. Mode of transmission. An individual is usually infected by the bite of an infected flea, but infection can also occur via cuts or abrasions in the skin or via infected aerosols coming in contact with the oropharyngeal mucous membrane.

Primary pneumonic plague historically occurred by inhalation of infectious droplets from a pneumonic plague patient. However, in the last several decades, this form of the disease has occurred from exposure to infected animals (usually cats) that have developed secondary pneumonia due to septicemic spread of the organism (Rosner, 1987; Craven and Barnes, 1991). Personnel attending these sick animals are then infected by inhaling infected aerosols.

iii. Clinical signs. Bubonic plague in humans is usually characterized by fever (2–7 days postexposure) and the formation of large, tender, swollen lymph nodes, or buboes. If untreated, the disease may progress to severe pneumonic or systemic plague. Inhaled infective particles, particularly from animals with plague pneumonia, may also result in the pneumonic form of the disease.

iv. Diagnosis and control. A presumptive diagnosis can be made by visualizing bipolar-staining, ovoid, gram-negative rods on the microscopic examination of fluid from buboes, blood, sputum, or spinal fluid; confirmation can be made by culture. Complement fixation, passive hemagglutination, and immunofluorescence staining of specimens can be used for serological confirmation.

Mortality without antibiotic therapy, particularly in cases of pneumonic plague, exceed 50% in untreated cases. Although *Y. pestis* is susceptible to a wide variety of antibiotics, multiple antibiotic-resistant strains are being isolated with increasing frequency (Dennis and Hughes, 1997). Aminoglycosides, such

as streptomycin and gentamicin, are the most effective antibiotics *in vivo* against *Y. pestis.* Chloramphenicol is the drug of choice for treating plague meningitis and endophthalmitis (Craven and Barnes, 1991; Mushatt and Hyslop, 1991). In people exposed to *Y. pestis,* prophylactic therapy with tetracycline for a 7-day period is often prescribed.

An inactivated plague vaccine is available for laboratory personnel working with the organism and in high-risk individuals working in areas where the disease is endemic (e.g., wildlife management employees, Peace Corps volunteers) and where they are exposed to plague reservoirs.

Rodent and flea control, particularly in endemic areas, is an indispensable part of containing exposure to plague, as is restricting certain locales for recreational use. Animal facilities should be constructed and maintained to prevent wild rodent egress. Furthermore, feral or random-source animals acquired from plague-endemic areas should be quarantined and treated with appropriate insecticides to kill fleas.

3. Leptospirosis

Leptospirosis is solely a zoonotic disease of livestock, pet and stray dogs, and wildlife, including wild rodents. Human-to-human transmission is extremely rare. *Leptospira interrogans* (comprising > 200 serovars) has been isolated worldwide. Although particular serotypes usually have distinct host species, most serotypes can be carried by several hosts. *Leptospira* spp. are well adapted to a variety of mammals, particularly wild animals and rodents.

i. Reservoir and incidence. *Leptospira icterohaemorrhagiae* was first recovered in 1918 in the United States from wild rats sampled in New York City. In the 1950s, in a study conducted in Baltimore, 45.5% of 1643 rats were infected with *Leptospira;* higher prevalence rates occurred in older rats (approximately 60%). In the late 1970s, more than 90% of adult Brown Norway rats sampled in Detroit were infected with *L. icterohaemorrhagiae* (Thiermann, 1977). Other studies confirm the high prevalence of this organism in wild rats inhabiting U.S. cities (Alexander, 1984; Sanger and Thiermann, 1988). Rodent reservoir hosts of leptospirosis, in addition to rats, include mice, field moles, hedgehogs, gerbils, squirrels, rabbits, and hamsters (Torten, 1979; Fox and Lipman, 1991). Livestock serve as a significant source of primary long-term shedding of at least three serovars. Cattle are the natural carriers of the serotype *L. hardjo,* whereas swine carry *L. pomona* and *L. bratislava;* each animal can shed the organism for extended periods in their urine. Dogs also commonly harbor two other serotypes; feral dogs harbor *L. icterohaemorrhagiae* as well as serve as natural carrier hosts of *L. canicola.* Sheep, goats, and horses can also be infected with a variety of serotypes. Raccoons are reservoirs of *L. antumnalis,* whereas rats, mice, and other wild rodents are common animal hosts for another serotype, *L. ballum.* In wild mice, the infection can persist unnoticed for the ani-

mal's lifetime and can also be harbored by laboratory mice, although their carrier rates in the United States are unknown (Torten, 1979). There was, however, a report of leptospirosis in a research colony of mice in the United States in the early 1980s (Alexander, 1984). In several European laboratories, personnel have contracted leptospires from laboratory rats (Geller, 1979).

ii. Mode of transmission. Infection with *Leptospira* most frequently results from handling infected animals (contaminating the hands with urine) or from aerosol exposure during cage cleaning. Skin abrasions or mucous membrane exposure may serve as the portal of entry in humans. 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. Handling infected wild rats increases the risk of contracting leptospires (Luzzi *et al.,* 1987). Also, a young man died of acute leptospirosis by falling into a heavily polluted river contaminated with *L. icterohaemorrhagiae* (Sanger and Thiermann, 1988). In addition, rodent bites can transmit the disease. Children living in rat-infested tenements may be at increased risk of infection. For example, children from inner-city Detroit had significantly higher *L. icterohaemorrhagiae* antibody titers when compared to those of children living in the Detroit suburbs (Demers *et al.,* 1983). Outbreaks of leptospirosis in humans with varying mortality in underdeveloped countries were documented in 1995–1998.

iii. Clinical signs. The disease may vary from inapparent to severe infection and death. Infected individuals experience a biphasic disease (Stoenner and Maclean, 1958; Sanger and Thiermann, 1988; Faine, 1991). 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. On examination, renal, hepatic, pulmonary, and gastrointestinal findings may be abnormal. Penicillin is the drug of choice in treating early onset of leptospirosis infection (Faine, 1991). Ampicillin and doxycycline have also been effective in treating people with leptospirosis.

iv. Diagnosis and control. Leptospirosis in humans is often difficult to diagnose; therefore, the low incidence of reported infection in humans may be misleading. Outbreaks have been documented in the United States from personnel working with laboratory mice (Stoenner and Maclean, 1958; Barkin *et al.,* 1974). In one study, 8 of 58 employees handling infected laboratory mice (80% of breeding females were excreting *L. ballum* in their urine) contracted leptospirosis (Stoenner and Maclean, 1958).

Because of the variability in clinical symptoms and lack of pathognomonic findings in humans and animals, serological 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. 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). Serological assessment is accomplished by indirect hemagglutination, agglutination analysis, complement fixation, microscopic agglutination, and fluorescent antibody techniques (Faine, 1991). The serological test most frequently used is the microscopic agglutination test, which employs dark-field microscopy. Titers of 1:100 or greater are considered significant. Personnel hygiene and protective garments that minimize exposure to infected urine and other infected animal tissue are important for control of zoonotic infection with leptospires.

C. Enteric Diseases

1. Campylobacteriosis

Campylobacter has been known as a pathogenic and commensal bacterium in domestic animals for decades. During the last several years, *C. jejuni* and *C. coli* have gained recognition as a leading cause of diarrhea in humans.

i. Reservoir and incidence.   *Campylobacter jejuni, C. coli, C. upsaliensis,* and *C. helveticus* have been isolated from a variety of laboratory animals, including dogs, cats, guinea pigs, hamsters, ferrets, nonhuman primates, poultry, and rabbits (Fox, 1982a) and also from healthy swine, sheep, and cattle. *Campylobacter* spp. commonly cause abortion in livestock. *Campylobacter* spp. can be shed in the stool for variable periods of time in asymptomatic carriers, and multiple species of *Campylobacter* as well as *Helicobacter* spp. can be isolated from the feces of a single individual or animal (Allos *et al.,* 1995; Shen *et al.,* 1999).

ii. Mode of transmission.   In most reports citing pet-to-human transmission of *C. jejuni,* diarrheic puppies or kittens recently obtained from animal pounds were the source of the infection (Blaser *et al.,* 1980; Deming *et al.,* 1987). In a laboratory animal setting, personnel performing husbandry chores have become infected when handling *Campylobacter*-infected animals (Fox *et al.,* 1989b). Prevalence studies of dogs, cats, newly imported primates, or animals housed in groups suggest that younger animals more easily acquire the infection and, hence, commonly shed the organism. More recently, *C. upsaliensis* and *C. helveticus* have been isolated from dogs and cats. *Campylobacter upsaliensis* has also been associated with diarrheal disease in humans (Fox *et al.,* 1989a).

iii. Clinical signs.   The clinical features of campylobacter enteritis in humans are usually consistent with an acute gastrointestinal illness. Diarrhea—sometimes watery—with or without blood and leukocytes, abdominal pain, and constitutional symptoms, especially fever, occur routinely. The severity of the illness can be variable, but in most cases it is brief and self-limiting. In protracted or severe cases, antimicrobial therapy (e.g., erythromycin) is instituted (Blaser, 1985).

iv. Diagnosis and control.   There are multiple *C. jejuni/coli* serotypes; the use of serotyping schemes and restriction enzyme analysis of isolates aids in confirming zoonotic spread of the organism (Russell *et al.,* 1990). Because animals can be asymptomatic carriers of campylobacters, protective measures preventing fecal contamination and inadvertent oral ingestion are important for prevention of infection.

2. Enteric Helicobacteriosis

i. Reservoir and incidence.   *Helicobacter cinaedi* is primarily recovered from immunocompromised individuals; the organism is also recovered from chronic alcoholics as well as immunocompetent men and women. The hamster is suspected to be the reservoir host for *H. cinaedi* (Gebhart *et al.,* 1989). Even though *H. canis, H. cinaedi, H. fennelliae,* and *H. rappini* have been isolated from both dogs and humans and *H. canis* and *H. cinaedi* from cats, additional investigations will be required to ascertain whether these enteric helicobacters in dogs, cats, and other unrecognized mammalian hosts constitute a potential reservoir for zoonotic transmission to people.

ii. Mode of transmission.   Fecal–oral transmission is the likely route of infection. *Helicobacter cinaedi,* a fastidious microaerophile, has been recovered from blood and fecal specimens of children and of a neonate with septicemia and meningitis. The mother of the neonate had cared for pet hamsters during the first two trimesters of her pregnancy (Orlicek *et al.,* 1993). Because *H. cinaedi* has been isolated from normal intestinal flora of hamsters, it was suggested that the pet hamsters served as a reservoir for transmission to the mother. The mother had a diarrheal illness during the third trimester of pregnancy; the newborn was likely to have been infected during the birthing process, although this was not proven (Orlicek *et al.,* 1993). Furthermore, the hamster has been suggested as possibly infecting other humans with *Helicobacter cinaedi* (Gebhart *et al.,* 1989). Studies are needed to confirm zoonotic risk of handling *H. cinaedi*-infected hamsters (Gebhart *et al.,* 1989). Also of interest is the isolation, based on cellular fatty acid and biochemical identification analysis, of *H. cinaedi* from the feces of dogs and a cat and from a rhesus monkey with chronic colitis (J.G. Fox, unpublished observations) (Kiehlbauch *et al.,* 1995).

iii. Clinical signs.   *Helicobacter cinaedi* (previously *Campylobacter cinaedi*) was first isolated from the lower bowel of

homosexuals with proctitis and colitis. It has also been isolated from the blood of homosexual patients with human immunodeficiency virus (HIV) as well as children and adult women (Orlicek *et al.*, 1993). In a retrospective study of 23 patients with *H. cinaedi*–associated illness, 22 of the cases had the organism isolated from blood by using an automated blood culture system in which a slightly elevated growth index was noted (Kiehlbauch *et al.*, 1994). This study also described a new *H. cinaedi*–associated syndrome consisting of bacteremia and fever, and accompanied by leukocytosis and thrombocytopenia. Recurrent cellulitis and/or arthritis are also noted in a high percentage of infected immunocompromised patients (Kiehlbauch *et al.*, 1994; Burman *et al.*, 1995). Other enteric helicobacters have been isolated from diarrheic patients as well as bacteremic immunocompromised individuals.

iv. Diagnosis and control. It should be stressed that many hospital and veterinary laboratories have difficulty isolating this organism. Because of the slow growth of *H. cinaedi* and other enteric helicobacters, laboratory diagnosis is unlikely if blood culture procedures that rely on visual detection of the culture media are used (Kiehlbauch *et al.*, 1994; Burman *et al.*, 1995; Kiehlbauch *et al.*, 1995). Use of dark-field microscopy or acridine orange staining of blood culture media, rather than gram staining, increases likelihood of seeing the organism. Likewise, fecal isolation is difficult; selective antibiotic media are required, and recovery is facilitated by passing fecal homogenates through a 0.45 μm filter (Gebhart *et al.*, 1989). In one study, several strains of both *H. cinaedi* and *H. fennelliae* were inhibited by concentrations of cephalothin and cetazolin used frequently in selective media for isolation of enteric microaerophilic bacterium. These organisms also require an environment rich in hydrogen for optimum *in vitro* growth. Until diagnostic laboratories embark on routine isolation attempts of *Helicobacter* spp. from feces, the extent of their presence in companion and pocket pets and their zoonotic potential will be unknown.

3. Gastric Helicobacter Infections

i. Reservoir and incidence. Because gastric helicobacter-like organisms (GHLO) (i.e., "*H. heilmannii*" or *H. felis*, currently referred to as *H. bizzozeronii* in dogs) cause a small percentage of gastritis in humans and no environmental source for these bacteria has been recognized, various animals, particularly dogs and cats, have been implicated in zoonotic transmission. In colony-reared animals, GHLO infection may approach 100%. *Helicobacter pylori*, the primary gastric pathogen in humans, has been isolated from only one colony of commercial cats and macaque species. If *H. pylori*, as demonstrated in commercially reared cats (Handt *et al.*, 1994; Fox *et al.*, 1996), is isolated from pet cats, the zoonotic potential of helicobacteriosis from cats would obviously increase substantially. *Heli-*

cobacter pylori infection is an important cause of human gastritis; however, most epidemiologic studies do not incriminate animal contact as a cause of human infection. An epidemiologic survey conducted in Germany did not show an increased risk of *H. pylori* because of cat ownership. In a serological survey measuring antibodies to *H. pylori*, lower socioeconomic status, and not pet ownership or day care, was associated with seropositivity (Staat *et al.*, 1996).

ii. Mode of transmission. Oral–oral transmission is likely, but fecal–oral transmission may also occur. In one case study, a researcher performing physiologic studies with cat stomachs developed an acute gastritis, presumably resulting from *H. felis* on the basis of electron microscopy (EM) (Lavelle *et al.*, 1994). Gastric spiral bacteria were demonstrated in gastric mucosa of cats being used by this scientist. In Germany, a survey of 125 individuals infected with GHLOs provided information in a questionnaire regarding animal contact. Of these patients, 70.3% had contact with one or more animals compared with 37% in the clinically healthy control population (Stolte *et al.*, 1994).

iii. Clinical signs. Infection with GHLOs and *H. pylori* in animals (although associated with gastritis in the majority of humans) does not cause characteristic clinical illness with any consistency or reproducibility. In people with GHLO infections, bismuth subsalicylate, amoxicillin, tetracycline, and metronidazole in various combinations successfully eradicated GHLOs from the gastric mucosa with resolution of gastritis (Heilmann and Borchard, 1991). No systematic antibiotic trials have been conducted in dogs and cats to test for efficacy in eradicating either "*H. heilmannii*" or *H. felis* from gastric mucosa.

iv. Diagnosis and control. A diagnosis of chronic gastritis in animals, as in humans, cannot be made by gross visual examination of the gastric mucosa by endoscopy. Histologic evaluation of gastric biopsy samples is required, utilizing a special silver stain or modified Giemsa stain to reveal the presence of GHLOs. Unfortunately, *H. bizzozeronii* is the most common spiral organism in dogs and cats, and it has been extremely difficult to culture on artificial media (Hanninen *et al.*, 1996). "*Helicobacter heilmannii*," also common in primates, has not been cultured. *Helicobacter felis* is also difficult to isolate. In practice, histological findings of inflammatory changes accompanied by gastric spiral organisms on the gastric mucosa or in the gastric mucous layer have been used for diagnosis. *Helicobacter felis* cannot be distinguished from "*H. heilmannii*" by histologic examination; EM evaluation is necessary.

Because oral bacteria and bacteria refluxed from the duodenum may overgrow the fastidious *Helicobacter* species, selective antibiotic media are available for isolation. Helicobacters, like campylobacters, require special environmental and cultural conditions for their growth. The organisms are thermophilic and grow at 37°C, and some species at 42°C. Growth on chocolate

or blood agar takes 3 to 5 days (Hanninen *et al.,* 1996). For *H. bizzozeronii* isolation, incubation requires 5 to 10 days. A provisional diagnosis of gastric helicobacters takes advantage of a biochemical feature of these organisms: the ability to produce large quantities of urease. Gastric biopsy samples can be placed in a urea broth containing a pH indicator (phenol red) and a preservative (sodium azide). A similar test is available commercially. Serological assays are being employed to diagnose *H. pylori* in humans (Staat *et al.,* 1996; Versalovic and Fox, 1999). However, serological tests currently do not provide a reliable, noninvasive diagnostic test for gastric helicobacter infection in dogs and cats or primates.

4. Salmonellosis

The genus *Salmonella* are gram-negative bacteria with approximately 2400 serotypes that require antigenic analysis for identification. Nontyphoidal salmonellosis is caused by any of these serotypes. *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.

i. Reservoir and incidence. Salmonellosis occurs worldwide and is important in humans and animals. *Salmonella* isolates, because of molecular taxonomics, are now classified under a single species, *S. choleraesuis.* This species is further subclassified into seven subgroups. References to serotypes, however, are abbreviated such that "choleraesuis" is dropped, e.g., *S. choleraesuis* serotype *typhimurium* is called *S. 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 *S. heidelberg, S. agona, S. montevideo,* and *S. newport.* Salmonellae are pathogenic to a variety of animals.

Although the reported prevalence of *Salmonella* spp. in laboratory animals has decreased in the last several decades because of management practices (e.g., pasteurizing animal feeds), environmental contamination with *Salmonella* spp. continues to be a potential source of infection for these animals and for the personnel handling them. Until all animal feeds in the United States and Europe are *Salmonella*-free and animals are procured from *Salmonella*-free sources, laboratory animal–associated cases of salmonellosis in humans will continue. Endemic salmonellosis in commercially raised guinea pigs as well as dogs, cats, and nonhuman primates has also been a source of infection in personnel working with these animals. Prevalence data from eight studies conducted worldwide indicated that a wide range (0.6–27%) of cats were culture-positive for *Salmonella,* and a conservative estimate for the U.S. canine population would be 10%. Rats are extremely susceptible to infection with *Salmo-*

nella spp. In studies performed in the 1920s through 1940s, prevalence of *Salmonella* in wild rats surveyed in the United States varied from 1 to 18%, compared to 19% in Europe (Geller, 1979; Weisbroth, 1979; Alexander, 1984). In experimental studies, when rats were dosed orally with *Salmonella,* 10% shed the organism in the 2 months after inoculation, and a few remained carriers when examined 5 months after experimental challenge. These rats, when placed with other naive rats, were capable of initiating new epizootics. Fortunately, the disease in laboratory rats, although common prior to 1939, has been isolated rarely in U.S. commercially reared rats since that time. Birds and reptiles are particularly dangerous sources of *Salmonella;* as much as 94% of all reptiles harbor *Salmonella* spp. (Chiodini and Sundberg, 1981). Turtles have received a great deal of zoonotic attention and in 1970 alone may have caused 280,000 human cases of salmonellosis. In the late 1960s, with annual sales of 15 million turtles, zoonotic salmonellosis became a growing problem. In 1972, the U.S. Food and Drug Administration (FDA) banned importation of turtles and turtle eggs and the interstate shipment of turtles that were not certified as free of *Salmonella* or *Arizona hinshawii* in their state of origin. However, the unreliable effectiveness of this method forced the FDA in 1975 to rule against the sale of viable turtle eggs or live turtles with a carapace length less than 10.2 cm, with exceptions made for educational or scientific institutions and marine turtles. Subsequently, there was a substantial decrease in turtle-associated salmonellosis, indicating the efficacy of this regulation. These restrictions are difficult to enforce, and other reptiles, e.g., iguanas, are increasingly cited in zoonotic outbreaks of salmonellosis, particularly in children. Also of note, because of repeated reports of chick- and duckling-associated salmonellosis, some states have also restricted their sale as pets.

ii. Mode of transmission. *Salmonella* spp. 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 spread of infection from animal to animal or to humans. Rat feces can remain infective for 148 days when maintained at room temperature. *Salmonella* is routinely associated with food-borne disease outbreaks, is a contaminant of sewage, and is found in many environmental water sources. Transmission is enhanced by crowding and poor sanitation.

Both humans and animals can be asymptomatic carriers and periodic shedders; they may have mild, unrecognized disease, or they may be completely asymptomatic. In the biomedical laboratory, asymptomatic animals can easily infect other animals, technicians, and investigators. Personnel at veterinary hospitals are at increased risk because of outbreaks of salmonellosis in hospitalized animals (Ikeda *et al.,* 1986). The prevalence of human salmonellosis acquired from laboratory animals or vice versa is unknown; however, the literature is replete with

examples of cases of this infection obtained from pets; this is particularly true for exotic pets such as iguanas, turtles, sugar gliders, and hedgehogs (Woodward *et al.,* 1997).

iii. 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 serotype of the organism, the number of bacteria ingested, and the susceptibility of the host. In experimental studies with volunteers, several serovars induced a spectrum of clinical disease, from brief enteritis to serious debilitation. Incubation varied from 7 to 72 hr. Cases of asymptomatic carriers, persisting for several weeks, were common (Hull, 1955).

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* spp. is 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* spp. carriage. Bacteriological 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). Also of interest is the fact that in recent outbreaks of DT104 *Salmonella typhimurium* infection, a high percentage of patients had been recently on antibiotics before becoming infected with the *Salmonella typhimurium* strain DT104 (Molba *et al.,* 1999).

iv. Diagnosis and control. 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 min) effectively destroy *Salmonella.* In the laboratory, control and prevention of salmonellosis depends on the rapid detection, removal, or treatment of both acute and chronic animal infections, particularly during the quarantine period. Multiple antibiotic resistance is commonly encountered in *Salmonella* strains. For example, multiple-resistant *S. typhimurium* strain DT104 has been increasingly cited (in Europe and recently in the United States) as a cause of human infections (Tauxe, 1999). Importantly, this organism has been isolated from farm animals, cats, wild birds, rodents, foxes, and badgers. It definitely has been transmitted from cattle and sheep

to humans and has caused epizootic gastroenteritis and fatal bacteremia in dairy cattle (Besser *et al.,* 1997).

5. Shigellosis

i. Reservoir and incidence. Shigellosis is a significant zoonotic disease in nonhuman primates (Fox, 1975; Richter *et al.,* 1984). *Shigella flexneri, S. sonnei,* and *S. dysenteriae* are the most common species found in nonhuman primates. Humans are the main reservoir of the disease, which occurs worldwide. Nonhuman primates acquire the disease following capture and subsequent contact with other infected primates or contaminated premises, food, or water. Shigellosis is one of the most commonly identified causes of diarrhea in nonhuman primates.

ii. Mode of transmission. *Shigella* organisms may be shed from clinically ill as well as asymptomatic humans and nonhuman primates. In humans, transmission occurs by ingestion of fecally contaminated food or water, or by direct contact (even if only minimal) with infected animals. Pet monkeys shedding *Shigella* are a particular threat to owners, and pet store proprietors, unless cautious, can contract the disease (Fox, 1975).

iii. Clinical signs. Humans are generally susceptible to shigellosis, although it is much more severe in children than in adults. The disease varies from completely asymptomatic to a bacillary dysentery syndrome characterized by blood and mucus in the feces, abdominal cramping, tenesmus, weight loss, and anorexia. Usually, the disease presents only as a clinically mild diarrhea. However, fatal shigellosis has been reported in children and adults who have had contact with infected pet or zoo monkeys (Fox, 1975); survivors can remain asymptomatic carriers. The clinical disease in nonhuman primates is similar to that in humans but may be associated with higher mortality rates.

iv. Diagnosis and control. When humans or nonhuman primates experience acute diarrhea (especially if traced with blood or mucus), *Shigella* spp. may be the cause (Richter *et al.,* 1984; Dupont, 2000). A definitive diagnosis requires the isolation of the organism from inoculation of fresh feces onto selective media. An identification can be confirmed by agglutination with polyvalent *Shigella* antisera. Because many *Shigella* spp. from nonhuman primates have plasmid-mediated antibiotic resistance markers, determination of antibiotic sensitivities of these isolates is mandatory before instituting treatment (Fox, 1975).

To prevent shigellosis in the laboratory, quarantine and screening of all newly arrived primates to detect microbial carriers are required. As in the treatment of the disease in humans, trimethoprim and sulfamethodoxazole can be effective in eliminating the

Shigella spp. carrier state in rhesus monkeys. Enrofloxacin is also used to eliminate subclinical *Shigella* in macaques.

D. Respiratory Infections

1. *Bordetella bronchiseptica*

Bordetella bronchiseptica is commonly recovered from the respiratory tract of dogs, cats, rabbits, and a variety of laboratory rodents. Despite its widespread occurrence in animals, it is seldom cultured from diseased tissues of humans, with fewer than 50 cases reported in the literature. Its isolation is often from immunocompromised patients (Woolfrey and Moody, 1991) who have pneumonia and/or bacteremia. It has also been isolated from AIDS patients (Ng *et al.*, 1992). In children with respiratory infection due to *B. bronchiseptica*, a "whooping cough"–like syndrome is described. This is not surprising given that *B. bronchiseptica* produces a dermatonecrotoxin, tracheal cytotoxin, and adenylate cyclase similar to that isolated from *B. pertussis*. In one interesting report, three children with *B. bronchiseptica* infection developed whooping cough–like symptoms; both their pet rabbits and cats subsequently died of *B. bronchiseptica* pneumonia (Kristensen and Lautrop, 1962).

2. Tuberculosis

i. Reservoir and incidence. Tuberculosis is an important zoonosis associated with laboratory animals. It is caused by acid-fast bacilli of the genus *Mycobacterium*. Natural reservoir hosts for the etiologic agent of this disease correspond to the three most common species of *Mycobacterium: M. bovis, M. avium* complex, and *M. tuberculosis*. Although cattle, birds, and humans are the major reservoir hosts, many animals, including swine, sheep, goats, monkeys, cats, dogs, and ferrets, are susceptible and contribute to the spread of disease (Marini *et al.*, 1989; Fox, 1998). This susceptibility varies according to the immune response of the host and to the particular *Mycobacterium* sp. infecting the host. In nonhuman primates, outbreaks of tuberculosis still occur, particularly in the Old World species of monkeys. They initially contract the disease in the wild through human contact, and then the organism is transmitted from monkey to monkey (Richter *et al.*, 1984).

ii. Mode of transmission. *Mycobacterium* bacilli are transmitted from infected animals or tissue samples via the aerosol route. The disease is spread beyond the natural host range through animal-to-animal and human-to-human contact, usually by airborne infectious particles. Laboratory workers have the highest risk of contracting the disease when caring for or performing autopsies on infected animals. In the laboratory, certain situations can enhance disease transmission, such as exposure to (1) dusty bedding of infected animals, (2) aerosolized organisms from a high-pressure water sanitizer, and (3) the coughing of clinically affected animals. The disease may also be contracted by direct ingestion of bacilli. Reports have documented an increase of tuberculin skin conversion in personnel working with primates infected with *Mycobacterium* spp. (Kalter *et al.*, 1978).

iii. Clinical signs. Clinical signs of tuberculosis in humans are dependent on the organ system or systems involved. Most familiar are the signs related to the pulmonary form. Although this form of the disease often remains asymptomatic for months or years, it may eventually produce a cough with sputum and hemoptysis. In addition, general symptoms include anorexia, weight loss, lassitude, fatigue, fever, chills, and cachexia (Division of Tuberculosis Elimination, 2000).

iv. Diagnosis and control. A positive diagnosis is often quite difficult to obtain. Three widely used tools for a presumptive diagnosis are the intradermal tuberculin test, radiographic analysis, and positive acid-fast–stained sputum smears. A more definitive diagnosis of the organisms from body fluids or biopsy specimens is obtained by culture, PCR analysis, and confirmation using standard biochemical techniques.

Control of tuberculosis infection, particularly within the biomedical research arena, requires a multifaceted approach. This includes personnel education, a regular health surveillance program for personnel and nonhuman primates, isolation and quarantine of suspect animals, and rapid euthanasia and careful disposal of confirmed positive animals. Vaccination or chemoprophylaxis may be considered, but certain precautions are necessary (Division of Tuberculosis Elimination, 2000). Vaccination with Bacillus Calmette-Guerin (BCG), a strain of *M. bovis*, is an effective means of preventing active tuberculosis. Vaccination is suggested in high-risk groups. However, this vaccine often elicits a positive tuberculin test, thereby negating the best diagnostic indicator of early disease. Vaccination in the United States is therefore reserved for demonstrated high-risk individuals and children in locations where 20% or more of school-age children are tuberculin-positive (Division of Tuberculosis Elimination, 2000).

Chemoprophylaxis with effective antituberculosis agents used to treat humans, such as isoniazid, rifampin, and ethambutol, has been used to treat valuable nonhuman primates (Wolf *et al.*, 1988). A well-conceived tuberculosis control program will include some or all of the above methods tailored to the needs and special circumstances of individual animal resource programs.

VI. FUNGAL DISEASES

The superficial mycoses are commonly referred to as ringworm due to the characteristic circular erythematous lesion

found on the skin of the host. The most common of the fungi responsible for disease in animals and humans are the three genera of the dermatophytes: *Microsporum, Epidermophyton,* and *Trichophyton.* Species of dermatophytes are subcategorized as anthropophilic (primarily infect humans), geophilic (soil inhabitants), and zoophilic (parasitic on animals). The zoophilic dermatophytes are known to infect humans.

i. Reservoir and incidence. Dermatophytes are distributed worldwide, with particular species found more frequently in specific geographic regions. Ringworm in laboratory animals is common, particularly among random-source animals, such as dogs, cats, and livestock. *Microsporum canis* is the common isolate from dogs and cats, whereas *Trichophyton verrucosum* is the species usually isolated from livestock, and *T. mentagrophytes* from laboratory rodents.

ii. Mode of transmission. Transmission to humans occurs from direct or indirect contact with symptomatic or asymptomatic carrier animals; contaminated bedding, caging, or other equipment; or fungal contamination of the environment. The resultant disease in humans, tinea, is frequently self-limiting and often goes unnoticed. When lesions occur, they are generally on the extremities, particularly on the arm or hand. Lesions are focal, annular, scaling, and erythematous with central clearing resembling a ring. Occasionally, vesicles or fissures are reported. In contrast with anthropophilic species, zoophilic dermatophytes generally produce more eczematous and inflammatory lesions, which regress rapidly.

iii. Clinical signs. Generally, dermatophytes grow only in dead, keratinized tissue. Advancing infection is halted when contact with live cells and inflammation occurs. Dermatophytes are species-adapted and rarely cause severe inflammatory lesions in the specific-host species. When zoophilic species infect humans, the inflammatory response usually restricts the progress of the infection. Contact with the dermatophyte does not necessarily result in infection in the animal or human host. A number of factors, including but not limited to, age; immune, hormonal, and nutritional status; and prior exposure all are important in disease expression.

When observed, disease in animals is often mild and goes undetected. Disease in cats, usually seen in kittens, is quite variable. Lesions, generally seen on and around the head, are crusting and mildly erythemic. The areas may be alopecic with numerous broken hairs. In dogs, lesions consist of circular, alopecic, crusting patches. In laboratory rodents, lesions are generally absent. Presence of the organism may not be detected until personnel become infected and manifest lesions (Fig. 4).

iv. Diagnosis and control. Diagnosis in humans and animals is similar. Fungal culture is the most effective and specific means of diagnosis. Specialized dermatophyte test media
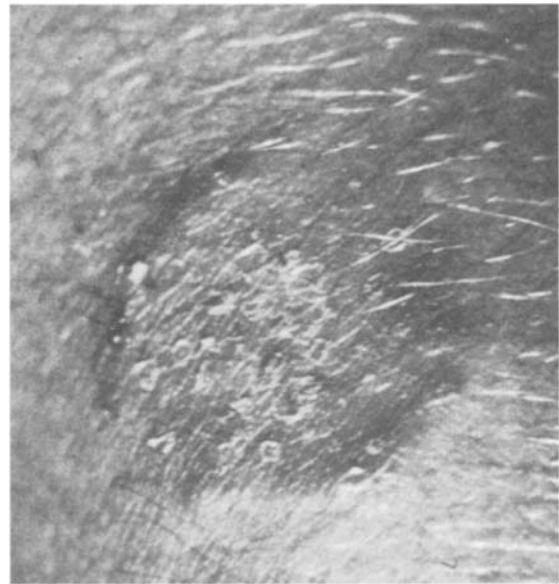

Fig. 4. Circular ringworm lesion on the arm of a man. Contracted from a rodent infected with *Trichophyton mentagrophytes* (Courtesy of Dr. W. Kaplan.)

(DTM) or Sabouraud's agar may be used. A Wood's lamp can be used to screen lesions, scrapings, or cultures, as approximately 50% of *Microsporum canis* isolates fluoresce when examined with the cobalt-filtered ultraviolet lamp. Direct microscopic examination of hairs and skin scrapings may allow for definitive diagnosis.

The risk of zoonotically acquired dermatophytosis can be reduced among laboratory and animal care personnel by wearing protective garments, specifically long-sleeved clothing or laboratory coats; practicing effective personal hygiene; handling random-source animals with disposable gloves; screening newly acquired animals for suggestive lesions; and isolating and treating animals with lesions.

Treatment consists of either systemic therapy with griseofulvin or topical therapy with any one of a number of antifungal agents, such as miconazole. Infectious spores will persist on the animal despite successful treatment of active lesions. Eradication of spores is generally unfeasible, as it may require extensive depilation and the use of sporicidal dips.

VII. PROTOZOAL DISEASES

A. Enteric Diseases

1. Amebiasis

Amebiasis is a parasitic infection of the large intestine caused by the protozoan parasite *Entamoeba histolytica* (Ravdin, 1995).

i. Reservoir and incidence. The disease occurs worldwide in humans, with a greater prevalence in tropical areas. The parasite is found routinely in clinically normal monkeys and anthropoid apes and may cause severe clinical disease in these animals. The reported incidence of *E. histolytica* has ranged from 0 to 21% in rhesus monkeys, 2 to 67% in chimpanzees, and up to 30% in other nonhuman primates.

ii. Mode of transmission. *Entamoeba histolytica* exists as either resistant cysts or the more fragile trophozoites (Visvesvar and Stehr-Green, 1990). Cysts are the infectious form of the parasite and are usually found in the normal stool of asymptomatic carriers or humans with mild disease (Ravdin, 2000). Cysts may remain viable in moist, cool conditions for over 12 days and in water for up to 30 days. Epidemics of amebiasis in humans usually result from ingestion of fecally contaminated water containing amebic cysts. Laboratory animal workers handling nonhuman primates are potentially exposed to infection from infected fecal matter transferred through the workers' skin or clothing. The infective cyst forms may be subsequently ingested.

iii. Clinical signs. Most human infections with *E. histolytica* have few or no detectable symptoms (Ravdin, 2000). Clinical signs result when trophozoites invade the large bowel wall causing an amebic colitis. Signs begin with a mild, watery diarrhea with bad-smelling stool, which is frequently preceded by constipation in early stages. There may be gas, abdominal cramps, and tenderness progressing to an acute fulminating bloody or mucoid dysentery with fever, chills, and muscle ache. The disease may have periods of remission and exacerbation over months to years (Ravdin, 2000). Rarely, extraintestinal amebic abscesses may form in the liver, lung, pericardium, or central nervous system. Involvement of the liver may lead to tenderness in the right abdomen and can progress to jaundice.

iv. Diagnosis and control. The diagnosis of amebiasis requires the microscopic identification of trophozoites or cysts in fresh stool specimens. The organism must be carefully measured to differentiate it from other nonpathogenic amebas. Control measures to prevent amebiasis should include strict adherence to sanitation and personal hygiene practices. Water supplies should be protected from fecal contamination since usual water-purification chlorine levels do not destroy the cysts (Chin, 2000). A chlorine concentration of 10 ppm is necessary to kill amebic cysts (Ravdin, 2000). Cysts may also be killed by heating to 50°C. Nonhuman primates should be screened during quarantine to identify carriers of *E. histolytica* and should be appropriately treated. Nonhuman primates with acute diarrhea or dysentery should also have stool examined for the presence of *E. histolytica* and should be treated as necessary. Recommended drugs for treatment of *E. histolytica* infection include metronidazole, paromomycin, emetine, and diiodohydroxyquin (iodoquinol). Both asymptomatic carriers and symptomatic patients should be treated (Ravdin, 2000).

2. Balantidiasis

Balantidiasis is a zoonotic disease caused by the large ciliated protozoan *Balantidium coli*.

i. Reservoir and incidence. *Balantidium coli* is distributed worldwide and is common in domestic swine. It may also be found in humans, great apes, and several monkey species. The incidence in nonhuman primate colonies has ranged from 0 to 63%. These infections are usually asymptomatic in most animals, although clinical disease characterized by diarrhea or dysentery may occur.

ii. Mode of transmission. Infection usually results from the ingestion of trophozoites or cysts from the feces of infected animals or humans. Transmission may also occur from ingestion of contaminated food or water.

iii. Clinical signs. Balantidiasis may cause ulcerative colitis characterized by diarrhea or dysentery, tenesmus, nausea, vomiting, and abdominal pain. In severe cases, blood and mucus may be present in the stool. Humans apparently have a high natural incidence, and infections are often asymptomatic (Chin, 2000).

iv. Diagnosis and control. Balantidiasis is diagnosed by the detection of trophozoites or cysts in fresh fecal samples. Control measures to prevent balantidiasis should be directed at maintaining good sanitation and personal hygiene practices in nonhuman primate and swine colonies. Water supplies should be protected from fecal contamination, especially since usual water chlorination does not destroy cysts (Chin, 2000). Nonhuman primates exhibiting acute diarrhea should be examined for the presence of *B. coli* organisms in the feces. Positive animals should be isolated and the infection appropriately treated. Tetracyclines, metronidazole, paromomycin, and ampicillin have been used successfully to eliminate *B. coli* infections (Teare and Loomis, 1982).

3. Cryptosporidiosis

Cryptosporidiosis was first described in the mouse. The genus *Cryptosporidium* now contains over 10 named species (Levine, 1980), many of which have been incriminated as opportunistic, pathogenic parasites (Angus, 1983). Cryptosporidiosis, once considered an infrequent, inconsequential protozoan infection in mammals and reptiles, is now considered a significant enteric pathogen. *Cryptosporidium parvum* is considered the human pathogen.

i. Reservoir and incidence. *Cryptosporidium* spp. are coccidian parasites known to infect a variety of mammals, including humans, monkeys, livestock, ferrets, pigs, guinea pigs, mice, fish, reptiles, and birds. Neonates of mammalian domes-

tic species are uniquely susceptible to this infection, in comparison to the adults, who are resistant. In humans, however, both children and adults are susceptible. Cryptosporidia isolated from mammals are not host-specific, and zoonotic transmission from calves to humans has been reported (Levine *et al.,* 1988). Bovine cryptosporidia from calves can also cause infection in newborn pigs, lambs, chicks, mice, rats, and guinea pigs.

ii. Mode of transmission. The life cycle of cryptosporidia is direct, with infection generally limited to the small intestine; however, infections of the respiratory tract, stomach, and conjunctiva have been reported. The life cycle of cryptosporidia is similar to that of other coccidia except that cryptosporidial oocysts do not require time outside the host to sporulate but are infectious at the time of excretion. Large epidemics have occurred in humans ingesting the organism in contaminated municipal drinking water. Sporulated oocysts can exist in the intestine before being excreted. Disease transmission is through ingestion of infectious oocysts. The organisms are small (4–5 μm in diameter) and are located on the apical surface of the parasitized epithelial cell, where they protrude from the brush border. The organisms are intracellular, as the plasma membrane of the host cell envelops the parasite.

iii. Clinical signs. Recorded cases of this disease generally occur in children, particularly in developing countries with poor sanitation, and in immunosuppressed (compromised) individuals. Zoonotic disease has been reported among animal handlers and veterinary students working with neonatal ruminants, principally calves, infected before 6 weeks of age (Levine *et al.,* 1988). Another transmission was recorded in an individual who became infected performing a survey of *Cryptosporidium* spp. in calves (Reese *et al.,* 1982). In this patient, clinical remission occurred by day 13, and oocytes of cryptosporidium were no longer apparent on fecal flotation (Fig. 5). Disease in neonatal ruminants may be subclinical or may present with protracted watery diarrhea, very similar to what occurs in humans. Symptoms in humans occur 1 to 2 weeks after contact with infected calves, and diarrhea may be accompanied by vomiting, severe abdominal cramps, lassitude, fever, and headache. Disease is generally self-limiting except in immunocompromised individuals (Fayer and Ungar, 1986). Most of the recorded cases of protracted human cryptosporidiosis have occurred in immunodeficient individuals, particularly AIDs patients, and are regarded as opportunistic infections (Chin, 2000). Disease in these individuals produced low-grade fever, malaise, anorexia, nausea, abdominal cramps, and a protracted, watery diarrhea. Repeated intestinal biopsies in a patient have documented indigenous cryptosporidial stages for as long as 1 year; clinical signs also persisted in this patient.

iv. Diagnosis and control. Diagnosis is made by examination of feces for the characteristic oocysts. Direct wet mounts may be satisfactory in heavy infections; the organism can be
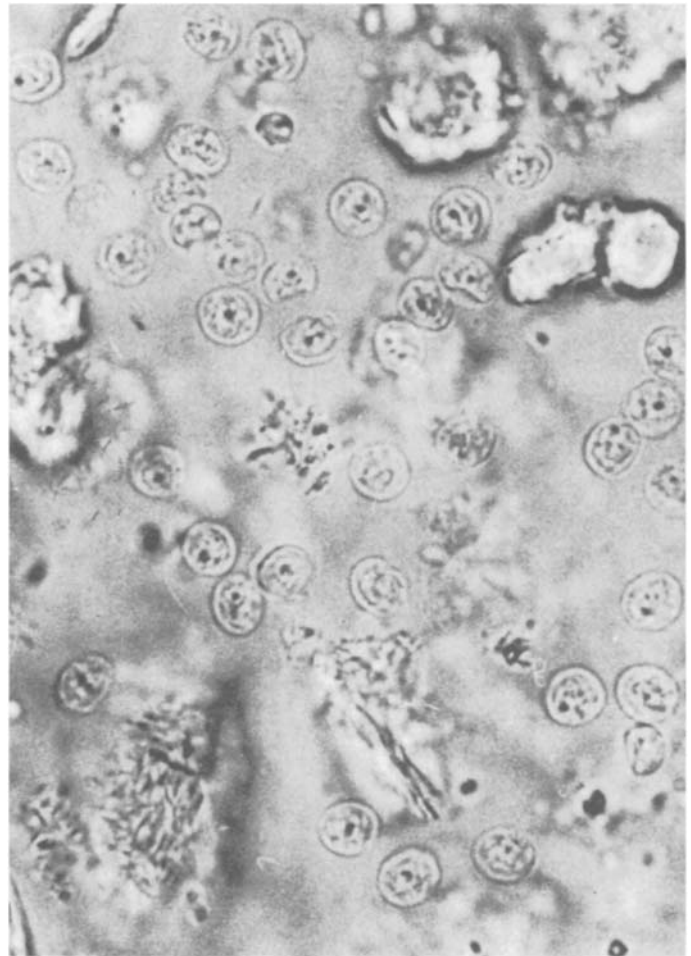

Fig. 5. Cryptosporidial oocysts in an unstained wet mount from calf feces. Note single prominent black dot, which is central or slightly eccentric. Some oocysts are indented. ×1280. (Courtesy of Dr. B. Anderson.)

concentrated by the Sheather sugar flotation or the Formalin–ethyl acetate method. Histologic evaluation of intestinal and rectal biopsies can also be used for diagnosis. Currently, no pharmaceutic agent is effective in treating cryptosporidiosis. More than 50 antibiotics have been tried without effect. Immunocompromised patients are persistently infected. Some drugs, such as paromomycin, may reduce the symptoms, and new drugs are being tested. The infection persists until the host's immune response clears the parasite.

4. Giardiasis

Giardiasis is usually a mild intestinal illness, caused by the protozoan parasite *Giardia lamblia.* The parasite can be found in the feces of infected animals (dogs, cats, beavers, and rodents).

i. Reservoir and incidence. *Giardia* spp. are found worldwide among all classes of vertebrates and occur among numerous laboratory animals. *Giardia* cysts isolated from a human

produced infections when fed to eight different species of test animals, including dogs.

ii. Mode of transmission. Historical classification schemes have speciated *Giardia* based on host origin. Studies conducted over the past decade have demonstrated a lack of host specificity, at least for some species of *Giardia*. Epidemiologic studies and zoonotic transmission have corroborated the lack of host specificity exhibited by *Giardia* spp. Contamination of drinking water with *Giardia* cysts from beavers has been implicated in several human giardiasis outbreaks (Dykes *et al.,* 1980; Keifer *et al.,* 1980), and cysts from this source have infected human volunteers and dogs. Other studies have produced patent infections in dogs, using *Giardia* cysts isolated from municipal drinking water known to have infected humans (Shaw *et al.,* 1977; Dykes *et al.,* 1980). Nonhuman primates have also been implicated. A clinically ill gibbon was presumed to be the source of infection for three zoo attendants and six apes who subsequently developed clinical giardiasis (Armstrong and Hertzog, 1979). The life cycle of *Giardia* is direct, with trophozoites, the feeding stage of the organism, residing in the upper gastrointestinal tract. They multiply and develop into infective cysts that are shed in the feces and ingested by subsequent hosts.

iii. Clinical signs. The disease in humans and animals is often similar. Giardiasis in humans is characterized by chronic or intermittent diarrhea, bloating, abdominal cramping, anorexia, fatigue, and weight loss. The stool frequently is mucus-laden, light-colored, and soft, but not watery. Symptoms may persist for several weeks and then resolve spontaneously. Fever is usually not present, and many persons infected with *Giardia* may have no symptoms at all. Individuals with the disease are contagious for the entire period of infection and may recover without treatment.

iv. Prevention and control. Although many species of laboratory animals can be infected experimentally with *Giardia* pathogenic for humans, they have not been demonstrated to harbor these organisms naturally. *Giardia* infections of dogs, nonhuman primates, and other animals probably present a greater public health risk, and infected animals may warrant treatment. Personnel handling these animals should take appropriate safety measures. Quinacrine is the drug of choice for treating giardiasis. Metronidazole and furazolidone are also used for treatment in the United States.

B. Systemic Infections

First discovered in 1908, toxoplasmosis is caused by infection with a microscopic parasite called *Toxoplasma gondii.* Toxoplasmosis has been found in humans and most warm-blooded animals. An estimated 500 million humans have been infected with the organism, and nearly one-third of all adult humans in the United States and in Europe have antibodies to toxoplasma, which provides evidence that they have been exposed to this parasite.

i. Reservoir and incidence. The life cycle of *T. gondii* consists of definitive and intermediate hosts. *Toxoplasma* infection has spread throughout the animal kingdom to include hundreds of species of mammals and birds as its intermediate hosts. Mice, rats, hamsters, guinea pigs and other rodents, rabbits, dogs, sheep, cattle and nonhuman primates include some of the laboratory animals that could serve as intermediate hosts (Teusch *et al.,* 1979; Wright, 1985). These laboratory animal hosts have not been shown to be important in zoonotic infection by *T. gondii* in the laboratory environment because the organism replicates only asexually in extraintestinal sites (Parker and Holliman, 1992; Herwaldt and Juranek, 1993). Serological surveys conducted in the United States during the early 1980s using the Sabin–Feldman dye test have demonstrated *T. gondii* infection in 30–80% of cats (Ladiges *et al.,* 1982). Presumably, all serologically positive cats have shed *Toxoplasma* oocysts and could again shed organisms by reinfection or by reactivation.

ii. Mode of transmission. Domestic and wild felids develop extraintestinal invasion with *T. gondii* analogous to that of the nonfelid hosts. In addition, as the definitive hosts in the *T. gondii* life cycle, felines develop intestinal infection, with the shedding of oocysts. Thus, the domestic cat is the primary reservoir for the zoonotic transmission of *T. gondii* in the laboratory environment. The three common modes of transmission are congenital infection, ingestion of *T. gondii*–infected tissue, and ingestion of toxoplasma oocytes or from direct exposure and consumption of contaminated food or water (Dubey, 1998). Most postnatally acquired infections in cats are asymptomatic and have a variable prepatent period and pattern of oocyst shedding. The prepatent period can be as brief as 3 days if the cat has ingested mice or meat containing *T. gondii* cysts, or it can be as long as several weeks if oocysts have been ingested. Shedding of oocysts in the feces occurs for 1–2 weeks, during which time cats are considered a public health risk (Dubey, 1998). Oocysts become infectious after sporulation, which occurs in 1–5 days. Oocysts survive best in warm, moist soil. Oocyst shedding is less likely to occur if the cat was infected by oocysts or tachyzoites than if infection resulted from the ingestion of *Toxoplasma* cysts. Oocyst shedding can be reactivated by induction of hypercorticism or by superinfection with other feline microorganisms, such as *Isospora felis* (Chessman, 1972). Oocysts of *T. gondii* have been observed infrequently in the feces of naturally infected cats (Ladiges *et al.,* 1982), and shedding usually precedes the development of antibody titers to *T. gondii.* The oocyst is very hardy and can survive freezing and as much as several months of extreme heat and dehydration. Importantly,

high IgG titers do not prove recent or active infection (Dubey *et al.,* 1995).

iii. Clinical signs. *Toxoplasma* infection in humans and animals is very common, but clinical disease occurs only sporadically and has a low incidence. Sporadic clinical cases and occasional epidemics do occur. Outbreaks have occurred when humans are exposed to oocyst-contaminated dust, either by inhalation or ingestion. Populations at high risk for infection are pregnant women and immunodeficient individuals. Congenital infection in humans results in systemic disease, frequently with severe neuropathological changes. Postnatal infection results in disease that is less severe and commonly presents as nondescript, consisting of fever, myalgia, and generalized lymphadenopathy that may resolve without treatment in a few weeks. Asymptomatic infection may recrudesce with encephalitis if patients become immunocompromised. Although rare, serious systemic toxoplasmosis can be acquired by older individuals. This is manifested by fever, maculopapular eruption, malaise, myalgia, arthralgia, posterior cervical lymphadenopathy, pneumonia, myocarditis, and meningoencephalitis. Ocular toxoplasmosis, usually chorioretinitis, is commonly seen in postnatal infections but can also occur in infections of older individuals. Clinically severe and progressive illness is most likely to develop in immunocompromised individuals. As high as 10% of AIDS patients have toxoplasmosis (Gill and Stone, 1992). These patients develop neurologic disease and can experience convulsions, paralysis, or coma or even die from toxoplasmosis, even after treatment is administered.

iv. Diagnosis and control. Diagnosis can be made by histopathologic demonstration of the organisms, demonstration of serum antibody, testing for antigenemia, or skin test. Chemotherapeutic treatment is indicated in patients with diagnosed clinical disease, active ocular lesions, or congenital infection, and in immunocompromised individuals with disease suggestive of toxoplasmosis. The preferred therapy is pyrimethamine administered in combination with sulfonamide. Laboratory-acquired infections are likely restricted to the use and handling of laboratory cats (DiGiacomo *et al.,* 1990). Rigorous sanitation should effectively prevent human toxoplasmosis from occurring in the laboratory environment. Since oocysts must sporulate before they are infectious, daily cleaning of litter plans will prevent accumulation of infectious oocysts. Personnel should wear gloves when handling litter pans and wash their hands thoroughly before eating. Pregnant women should completely avoid contact with cat feces. Interestingly, there is no correlation between toxoplasmosis in adults and cat ownership. Most cats acquire infection shortly after weaning and shed the oocysts for a short period of time (< 3 weeks). Nevertheless, unsporulated oocysts are more susceptible to proper disinfection, and control of exposure should be centered around disinfection of litter pans at this stage.

VIII. HELMINTH INFECTIONS

Many of the helminth parasites common to animals and humans have an indirect life cycle that is interrupted in the laboratory environment, thus precluding cross-infection of animals and humans. Although numerous helminths of laboratory animals should be regarded as zoonotic (Soulsby, 1969; Flynn, 1973), the risk of human infection from laboratory-housed animals appears to be minimal. One exception may be the dwarf tapeworm of humans, *Hymenolepis nana,* a common parasite of house mice and occasionally diagnosed in mice used for research. It is conservatively estimated that over 20 million people (mostly children) are infected with this parasite (Markell *et al.,* 1999). *Hymenolepis nana* is unique among cestodes in that the adult worm develops following ingestion of the egg by humans and does not require an intermediate host for its life cycle (Table III).

Nematodes in aberrant hosts are a potential cause of visceral and ocular larval migrans. Ingested eggs of several nematode larvae may be shed in the feces and ingested by humans. These ingested eggs hatch in the abnormal host and migrate into deep tissues, but development proceeds no further. Larvae may persist in the visceral organs or the eyes and cause granulomatous lesions, resulting in hepatosplenomegaly, fever, and eosinophilia (visceral larval migrans) (Edelglass *et al.,* 1982; Davies *et al.,* 1993) or leucocoria, eye pain, strabismus, or loss of vision (ocular larval migrans) (Bathrick, 1981). The most frequent cause of these diseases is *Toxocara canis* (dog) (Wolfrom *et al.,* 1995) and *Toxocara cati* (cat) (Glickman and Magnava, 1993), but *Baylisascaris procyonis* in the raccoon is much more aggressive and therefore more pathogenic (Fox *et al.,* 1988). Fatal or severe central nervous system disorders have been documented for mice, woodchucks, pigeons, domestic quail, turkeys, captive prairie dogs, and armadillos, and two human fatalities have been reported. Several other animal parasites have been associated with larval migrans–like syndromes. These include *Ascaris suum* (swine), *Capillaria hepatica* (rat), *Angiostrongylus cantonensis* (rat), *Gnathostoma spinigerum* (dogs and cats) (Bathrick, 1981), and *Angiostrongylus costaricensis* (cotton rats) (Levine, 1980). Human involvement has been reported with each of the above.

The practices encountered in a properly managed animal facility are not conducive to the transmission of these parasites. Proper quarantine, surveillance, and treatment procedures drastically reduce the endoparasitic burden of laboratory animals. Routine sanitation eliminates most parasitic ova before they have undergone the embryonation necessary for infectivity. Education of personnel on standard hygiene practices further reduces the likelihood of zoonotic infection.

Laboratory-housed nonhuman primates are presumed to be the most likely, although infrequent, source of parasitic infection for animal handlers (Orihel, 1970; Nasher, 1988).

Table III

Zoonotic Helminth Parasites in the Laboratory Environment

| Disease	Etiology	Natural host(s)	Aberrant hosts	Comments
Cestodiasis	*Hymenolepis nana*	Rats, mice, hamsters, nonhuman primates	Humans	Intermediate host is not essential to the life cycle of this cestode. Direct infection and internal autoinfection can also occur. Heavy infections result in abdominal distress, enteritis, anal pruritis, anorexia, and headache
Strongyloidiasis	*Strongyloides stercoralis, S. fulleborni*	Nonhuman primates, dogs, cats, humans, Old World nonhuman primates	Humans	Oral and transcutaneous infections can occur in animals and humans. Heavy infections can produce dermatitis, verminous pneumonitis, enteritis. Internal autoinfection can occur
Ternidens infection	*Ternidens deminutus*	Old World primates	Humans	Rare and asymptomatic
Ancylostomiasis	*Ancylostoma duodenale*	Humans	Nonhuman primates, pigs	Oral and transcutaneous routes of infection occur. Heavy infections produce transient respiratory signs during larval migration followed by anemia due to gastrointestinal blood loss
	Necator americanus	Humans	Nonhuman primates, pigs	
Trichostrongylosis	*Trichostrongylus colubriformis, T. axei*	Ruminants, pigs, dogs, rabbits, Old World nonhuman primates	Humans	Heavy infections produce diarrhea
Oesophagostomiasis	*Oesophagostomum* spp.	Old World primates	Humans	Heavy infections result in anemia. Encapsulated parasitic granulomas are usually an inocuous sequella to infection
Ascariasis	*Ascaris lumbricoides*	Old World primates	Humans	Infection occurs by ingestion of embryonated eggs only. Embryonation, requiring 2 or more weeks, ordinarily would not occur in laboratory. Heavy infections can produce severe respiratory and gastrointestinal tract disease
Enterobiasis	*Enterobias vermicularis*	Humans	Old world primates	Oral and inhalational infection can occur. Disease in humans characterized by perianal pruritis, irritability, and disturbed sleep
Trichuriasis	*Trichuris trichiura*	Humans	Old world primates	Three-week embryonation makes laboratory infection highly unlikely. Heavy infection in humans results in intermittent abdominal pain, bloody stools, diarrhea, and occasionally rectal prolapse
Larval migrans (viscera)	*Toxocara canis*	Dogs and other canids	Humans	Chronic eosinophilic granulomatous lesions distributed throughout various organs. Should not be encountered in laboratory
	Toxocara cati	Cats and other felids	Humans	
	Toxocara leonina	Dogs, cats, wild canids, felids	Humans	
	Baylisascaris procyonis	Raccoons	Humans and other animals	Infections in aberrant host produces granulomas in visceral organs with a predilection for the central nervous system
Larval migrans (cutaneous)	*Ancylostoma caninum*	Dogs	Humans	Transcutaneous infection causes a parasitic dermatitis called "creeping eruption"
	Ancylostoma braziliense	Dogs, cats	Humans	
	Ancylostoma duodenale	Dogs, cats	Humans	
	Uncinaria stenocephala	Dogs, cats	Humans	
	Necator americanus	Dogs, cats	Humans	
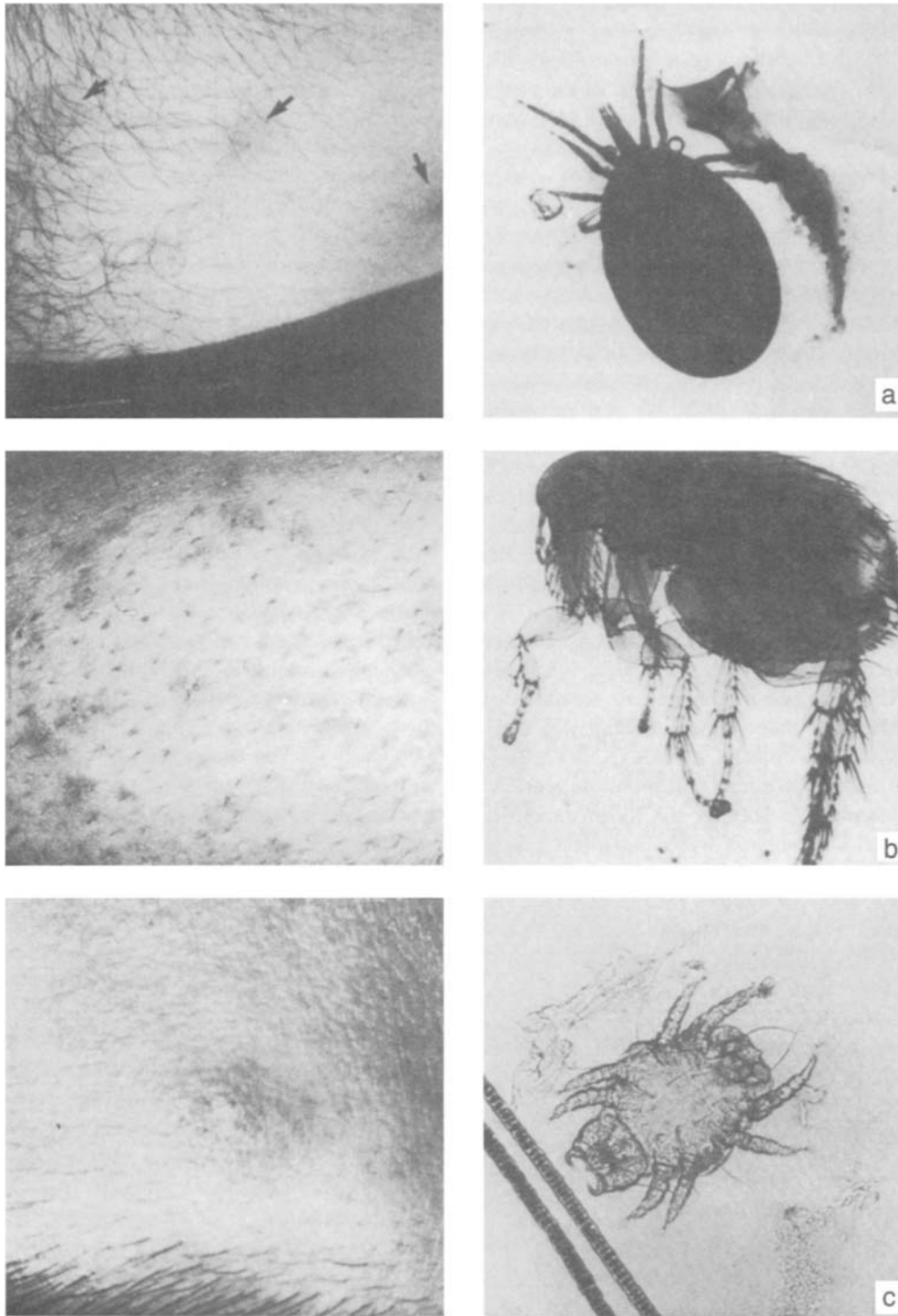
Fig. 6. Maculopapular dermatoses in humans associated with mite and flea bites. (a) Tropical rat mite; (b) flea (courtesy of American College of Laboratory Animal Medicine and Washington State University College of Veterinary Medicine); (c) cheyletiella mite.

Table IV

Ectoparasites[a,b]

Species	Disease in humans	Animal host	Agent
Mites			
Obligate skin mites			
Sarcoptes scabiei subspecies	Scabies	Mammals	
Notoedres cati	Mange	Cats, dogs, rabbits	
Nest-inhabiting parasites			
Ornithonyssus bacoti	Dermatitis, murine typhus	Rodents and other vertebrates, including birds	WEE,[c] SLE[d] virus *Rickettsia mooseri*
Ornithonyssus bursa	Dermatitis	Birds	WEE, EEE,[e] SLE viruses
Ornithonyssus sylviarum	Dermatitis, encephalitis	Birds	
Dermanyssus gallinae	Dermatitis, encephalitis	Birds	
Allodermanyssus sanguineus	Dermatitis, rikettsialpox	Rodents, particularly *Mus musculus*	*Rickettsia akari*
Ophionyssus natricis	Dermatitis	Reptiles	
Haemogamasus pontiger	Dermatitis	Rodents, insectivores, straw bedding	
Haemolaelaps casalis	Dermatitis	Birds, mammals, straw, hay	
Eulaelaps stabularis	Dermatitis, tularemia	Small mammals, straw bedding	*Francisella tularensis*
Glycyphagus cadaverum	Dermatitis, psittacosis	Birds	*Chlamydophila psittaci*
Acaropsis docta	Dermatitis, psittacosis	Birds	*Chlamydophila psittaci*
Trixacarus caviae	Dermatitis	Guinea pigs	
Facultative mites			
Cheyletiella spp.	Dermatitis	Cats, dogs, rabbits, bedding	
Dermatophagoides scheremtewskyi	Dermatitis, urinary infections, pulmonary acariasis	Feathers, animal feed, bird nests	
Eutrombicula spp.	Human pest (chiggers), local pruritis	Chickens, occasional mammals obtained from natural habitat	
Laelaps echidninus			Potential Argentine hemorrhagic fever
Ixodids (ticks)			
Rhipicephalus sanguineus	Irritation, RMSF,[f] tularemia, other diseases	Dogs	*Rickettsia rickettsii, Francisella tularensis*
Dermacentor variabilis	Irritation, RMSF,[f] tularemia tick paralysis, other diseases	Wild rodents, cottontail rabbits, dogs from endemic areas	See above
Dermacentor andersoni	Irritation, Colorado tick fever, Q fever, RMSF,[f] other diseases	Small mammals, uncommon on dogs	See above Ungrouped rhabdoviruses
Dermacentor occidentalis	Irritation, Colorado tick fever, RMSF,[f] tularemia	Small mammals, uncommon on dogs	See above
Ambylomma americanum	Irritation, RMSF,[f] tularemia	Wild rodents, dogs	
Ixodes scapularis	Irritation, possible tularemia	Dogs, wild rodents	
Ixodes spp.	Lyme disease	Dogs, cats, wild rodents	*Borrelia burgdonferi*
Ornithodorus spp.	Irritation, relapsing fever	Captive reptiles, wild animals, pigs	*Borrelia recurrentis*
Argas persicus	Irritation, seldom bites humans, but can transmit anthrax, Q fever	Domestic fowl	*Borrelia recurrentis*

Table IV (*Continued*)

Species	Disease in humans	Animal host	Agent
Fleas			
Ctenocephalides felis	Dermatitis, vector of *Hymenolepis diminuta, Dipylidium caninum*	Dogs, cats	
Ctenocephalides canis (cat and dog fleas)			
Xenopsylla cheopis	Dermatitis, plague vector, *Hymenolepis nana, H. diminuta*	Mouse, rat, wild rodents	*Yersinia pestis*
Nasopsyllus fasciatus	Dermatitis, plague vector, *Hymenolepis nana,* *H. diminuta* murine typhus	Mouse, rat, wild rodents	*Yersinia pestis*
Leptopsylla segnis	*Hymenolepis diminuta,* *H. nana,* murine typhus vector	Rat	Harbors salmonella
Echidnophaga gallinacea (sticktight flea)	Potential plague vector	Poultry	
Pulex irritans	Irritation	Domestic animals (esp. pigs) and humans	

[a] Found in laboratory animals that cause allergic dermatitis or from which zoonotic agents have been recovered in nature.
[b] Modified from Fox *et al.* (1984).
[c] WEE, Western equine encephalitis.
[d] SLE, St. Louis encephalitis.
[e] EEE, Eastern equine encephalitis.
[f] RMSF, Rocky Mountain spotted fever.

However, a review cited only three cases of zoonotic helminth infections resulting from nonhuman primates. These animals had been kept as pets and not as laboratory animals. Thus, although helminth parasites should be recognized as potentially zoonotic in the laboratory environment, they represent a significantly smaller problem than that posed by possible viral and bacterial zoonosis.

IX. ARTHROPOD INFESTATIONS

Health hazards to humans due to ectoparasite infestations from arthropods associated with laboratory animals are most often mild and limited to manifestations of allergic dermatitis. However, arthropods can serve as vectors to systemic illnesses such as rickettsial pox, tularemia, and Lyme disease. Those working with laboratory animals, particularly those species arriving directly from their natural habitat, should be familiar with the arthropods capable of transmitting these diseases.

Mites probably pose the greatest health hazard, not only because they are the most common inhabitant in number and variety of species, but because they also readily transmit agents from almost every major group of pathogens: bacteria, chlamydia, rickettsia, viruses, protozoa, spirochetes, and helminths (Yunker, 1964). In addition, most of these mites are capable of producing severe allergic papular dermatitis in humans (Fox and Reed, 1978; Fox, 1982b) (Fig. 6). Control of mite infestation is primarily dependent on their habitats. Some, such as *Sarcoptes* sp. and *Notoedres* spp. are obligate parasites that require treatment of the host. Other mites, such as *Ornithonyssus bacoti*, which live most of the time off the animal, require treatment of the environment with appropriate insecticides (Markell *et al.*, 1999).

Ticks, with the exception of those in newly arrived dogs or wild animals brought into the laboratory, are rarely found in the well-managed animal facility. The brown dog tick, *Rhipicephalus sanguineus*, is an exception. It readily infests kennels and vivaria. Ticks, like mites, can transmit a variety of diseases, including Rocky Mountain spotted fever, tick-borne typhus, Lyme disease, and others (Table IV). Lyme borreliosis is a commonly reported tick-borne infection in Europe and North America. The illness is caused by a spirochete, *Borrelia burgdorferi*, which is transmitted during the blood feeding of ticks of the genus *Ixodes*. The larvae and nymphs feed readily on a wide range of hosts, including birds, and an abundance of reservoir hosts exists, usually small and medium-sized animals. Larger animals, such as deer, sheep, cows, or horses, must be present for the maintenance of the tick population since adult ticks only engorge successfully on larger animals. Transmission occurs through salivation during the feeding process on a host.

Control of ticks indoors is aimed primarily at the resting places of the unattached ticks and proper treatment of newly arrived animals, which are noted for harboring ticks.

Fleas are notorious for their ability to transmit disease to humans, particularly plague and murine typhus. Three rodent fleas, *Xenopsylla cheopis*, *Nasopsyllus fasciatus*, and *Leptopsylla segnis*, have been found in a high percentage of urban dwellings in certain areas of the United States and are potential transmitters of disease in the laboratory. Apparently, *X. cheopis* in the past was readily established in animal facilities. At a Midwestern U.S. university, it inhabited rooms housing laboratory mice, where on two separate occasions fleas bit students (Yunker, 1964). *Leptopsylla segnis*, the mouse and rat flea, bites humans and is a vector for plague and typhus, serious diseases in humans. *Leptopsylla segnis* can also serve as an intermediate host for the rodent tapeworms *Hymenolepis nana* and *H. diminuta*, both of which can infect humans (Markell *et al.*, 1999). The flea bite can be irritating and can cause allergic dermatitis. The cat flea, *Ctenocephalides felis*, is the most common flea in and around human dwellings in the United States. This flea is capable of experimentally transmitting plague and murine typhus, and therefore the potential exists for transmitting the disease to humans. Control of fleas consists of treatment of infested areas as well as the primary host; in the case of rodent fleas, the animal facility must be free of feral rodents and their entry to prevent introduction of these arthropods.

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