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CHAPTER

14

Viral Diseases

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OUTLINE

INTRODUCTION

The major focus of this chapter is the naturally occurring viral diseases of rabbits and hares although asymptomatic infections are also discussed (Tables 14.1 and 14.2). Some viral infections of rabbits have provided fundamental information on basic mechanisms of agent–host interrelationships, e.g., *Myxoma virus*, and others have been useful as models for human diseases, e.g., *Rotavirus*. Although the principal emphasis is on virus infections of domestic rabbits of the genus *Oryctolagus*, naturally occurring and experimental infections of other rabbits and hares are also discussed.

In indoor facilities, it is unlikely that rabbits will encounter any of these viruses. Incoming rabbits should be obtained from sources free of these infections, however appropriate quarantine and screening measures should be standard operating procedure. With outdoor

The Laboratory Rabbit, Guinea Pig, Hamster, and Other Rodents
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TABLE 14.1 DNA Virus Infections of Rabbits

Family/subfamily	Genus	Species/strain	Host	Geographic Distribution
Poxviridae	*Leporipoxvirus*	*Myxoma virus*	*Sylvilagus brasilensis*	South America
			Sylvilagus bachmani	North America
			Oryctolagus cuniculus (wild and domesticated)	South America, North America, Europe, Australia, New Zealand
		Rabbit (Shope) fibroma virus	*Sylvilagus floridanus*	North America
		Hare fibroma virus	*Lepus europaeus*	Europe
	Orthopoxvirus	Rabbitpox	*Oryctolagus cuniculus* (domesticated)[a]	United States (laboratory colonies), Holland
Herpesviridae/ Gammaherpesvirinae	*Rhadinovirus*	Leporid herpesvirus 1 Leporid herpesvirus 2	*Sylvilagus floridanus* *Oryctolagus cuniculus* (domesticated)	United States England, United States (laboratory colonies)
Herpesviridae/ Alphaherpesvirinae	*Simplexvirus*	Leporid herpesvirus 4 *Human herpesvirus 1*	*Oryctolagus cuniculus* (domesticated) *Oryctolagus cuniculus* (domesticated)[a]	North America United States
Papillomaviridae	*Kappa-papillomavirus*	*Cottontail rabbit papillomavirus*	*Sylvilagus floridanus* *Oryctolagus cuniculus* (domesticated)	United States United States
		Rabbit oral papillomavirus	*Oryctolagus cuniculus* (domesticated)	United States, Mexico, New Zealand
Polyomaviridae	*Polyomavirus*	*Rabbit kidney vacuolating virus*	*Sylvilagus floridanus* *Oryctolagus cuniculus* (domesticated)	United States United States
Adenoviridae	*Mastadenovirus*	Adenovirus	*Oryctolagus cuniculus* (domesticated)	Hungary, Quebec[b]
Parvoviridae	*Parvovirus*	*Lapine parvovirus*	*Oryctolagus cuniculus* (domesticated)	Japan, United States, Switzerland[b]

[a]*Aberrant host.*
[b]*Serologic evidence only.*

TABLE 14.2 RNA Virus Infections of Rabbits

Family	Genus	Species/strain	Host	Geographic Distribution
Reoviridae	*Rotavirus*	*Rotavirus*	*Oryctolagus cuniculus* (domesticated)	North America, Japan, Europe,
			Sylvilagus floridanus	Canada[a]
			Lepus americanus[a]	Canada[a]
Coronaviridae	*Coronavirus*	Pleura effusion disease	*Oryctolagus cuniculus* (experimental)	Europe, United States, Japan
		Rabbit enteric coronavirus	*Oryctolagus cuniculus* (domesticated)	North America, Europe
Caliciviridae	*Lagovirus*	*Rabbit hemorrhagic disease virus*	*Oryctolagus cuniculus* (wild and domesticated)	Europe, Asia, North Africa, Middle East, Australia, New Zealand, Mexico, United States
			Lepus sp.	China
		European brown hare syndrome virus	*Lepus europaeus*	Europe, Argentina

(*Continued*)

TABLE 14.2 RNA Virus Infections of Rabbits (Continued)

Family	Genus	Species/strain	Host	Geographic Distribution
			Lepus timidus	Europe
		Rabbit Calicivirus	*Oryctolagus cuniculus* (wild and domesticated)	Europe, Australia
		Michigan Rabbit Calicivirus	*Oryctolagus cuniculus* (domesticated)	United States
	Vesivirus	Not assigned	*Oryctolagus cuniculus* (domesticated)	United States
Paramyxoviridae	Not assigned	Rabbit syncytium virus	*Sylvilagus floridanus*	United States
	Respivovirus	Sendai-like virus	*Oryctolagus cuniculus* (domesticated)[a]	Japan
Bunyaviridae	*Orthobunyavirus*	*California encephalitis virus*	*Sylvilagus floridanus*[a]	North America
			Lepus californicus[a]	North America
		Snowshoe hare	*Lepus americanus*	North America,
		Tahyna	*Lepus europeaus*[a]	Europe
			Oryctolagus cuniculus (wild)[a]	Europe
		lnkoo	*Lepus timidus*[a]	Finland
	Bunyamwera	Cache valley	*Sylvilagus audubonii*[a]	North America
			Sylvilagus floridanus	North America
			Lepus californicus[a]	North America
		Tenshaw	*Sylvilagus acquaticus*[a]	United States
			Sylvilagus palustris[a]	United States
			Sylvilagus transitionalis	United States
		Northway	*Lepus americanus*	Alaska, California
	Not assigned	Silverwater	*Lepus americanus*	Canada
Togaviridae	*Alphavirus*	*Western equine encephalitis virus*	*Sylvilagus* sp.[a] *Lepus californicus*[a]	North America North America
			Lepus americanus[a]	North America
			Oryctolagus cuniculus (domesticated)	North America
		Eastern equine encephalitis virus	*Lepus americanus*[a]	North America
		Venezuelan (VEE) equine encephalitis virus	*Lepus americanus*[a]	North America
			Sylvilagus floridanus[a]	North America
Flaviviridae	*Flavivirus*	*St. Louis encephalitis virus*	*Lepus americanus*[a]	North America
		West Nile virus	*Sylvilagus floridanus* (experimental)	North America
		Powassan virus	*Lepus americanus*	North America, Russia
Picobirnaviridae	*Picobirnavirus*	Not assigned	*Oryctolagus cuniculus* (domesticated)	United States
Rhabdoviridae	*Lysavirus*	*Rabies virus*	*Sylvilatus floridanus*	United States
			Oryctolagus cuniculus (domesticated)	United States

[a]*Serologic evidence only.*

facilities, appropriate measures should be undertaken, as described in the "Control" section for each of the viral diseases, to prevent spread of viruses from wild rabbits in the surrounding environment. None of the viral infections of rabbits are known to be of public health importance as there are no reports of the definitive spread of viruses from rabbits to humans.

The viral diseases of rabbits are discussed in an order based on the taxonomic groups to which the viruses belong and are independent of the order of importance of the various diseases. The material is presented under uniform subject headings, including history, etiology, epidemiology, clinical signs, pathology, diagnosis, and control. Control is interpreted broadly and includes both prevention and eradication. This review uses the most widely accepted viral terminology. The recommendations of the VIII International Committee on Taxonomy of Viruses (Fauquet et al., 2005) are followed, but well-established common names for viruses are used when appropriate. Rabbits and hares are referenced by common names as indicated in *Mammals of the World, A Checklist* (Duff and Lawson, 2004).

DNA VIRUS INFECTIONS

Poxvirus Infections

Poxviruses cause several important diseases in domestic and wild mammals and birds. Infection with poxviruses usually results in relatively mild disease involving the skin of infected animals, but generalized and often fatal disease may also occur, as, for example, in myxomatosis in rabbits. Close antigenic relationships exist among many poxviruses derived from different animal species. In spite of close antigenic relationships, the poxviruses of rabbits which produce distinct disease syndromes are discussed as separate entities.

Myxoma Virus

HISTORY

The disease myxomatosis, caused by *Myxoma virus*, was first recognized by Sanarelli (1898) in Uruguay in 1896. European rabbits of the genus *Oryctolagus*, acquired for antiserum production, developed a highly fatal disease characterized by numerous mucinous skin tumors. Sanarelli (1898) named the disease "infectious myxomatosis of rabbits" and, since no microbial agents were detected, proposed that the disease was caused by a newly recognized group of infectious agents known as "filterable viruses." The virus which caused the first known outbreak of myxomatosis is believed to have originated from the Forest rabbit (*Sylvilagus brasiliensis*) in which the virus causes relatively mild disease. Transmission from wild to domestic rabbits probably occurred by mosquitoes of the genus *Aedes* (Aragao, 1943; Fenner and Ratcliffe, 1965).

Myxomatosis spread to other countries of South America where it occasionally causes sporadic outbreaks in domesticated rabbits. In Chile, the disease is considered endemic in the wild European rabbit population (Fenner and Ratcliffe, 1965). The disease was first recognized in North America in 1928 when natural outbreaks of a fatal disease of rabbits occurred in several rabbit colonies near San Diego, California (Kessel et al., 1931). The virus which caused the first outbreaks in southern California may have been introduced into the United States from Mexico by importation of infected domestic rabbits (Vail and McKenney, 1943). The disease is endemic in the western United States, where the Brush rabbit (*Sylvilagus bachmani*) is the natural reservoir (Marshall and Regnery, 1960; Regnery and Miller, 1972).

Myxomatosis was introduced intentionally into Australia in an effort to control what had become Australia's major animal pest, the European rabbit (*Oryctolagus cuniculus*). The virus was first introduced into Australia in 1926 and used only in experimental studies aimed at determining its feasibility as a control measure for rabbits. In 1950, the virus was released into the wild rabbit population where it decimated the rabbit population of the continent by 1953. The disease is now endemic in the wild rabbit population of Australia, where it occasionally assumes epidemic proportions when climatic conditions favor vector activity. Within a decade following release of *Myxoma virus* into the rabbit population, it became evident that through natural selection genetically resistant strains of rabbits had emerged. In these rabbits, a virulent strain of *Myxoma virus* caused only 25% mortality compared to 90% mortality in non-resistant strains of rabbits (Fenner and Ratcliffe, 1965). This selective pressure continues with regional increases in resistance of Australian rabbits (Williams et al., 1990).

Genetic modification of *Myxoma virus* was recognized soon after its release into the rabbit population, and by the fourth year markedly attenuated strains of virus had replaced virulent virus as the dominant strains. The naturally attenuated viruses caused a milder disease of longer duration, which favored vector transmission and thus persistence of the virus (Fenner and Woodroofe, 1965; Fenner et al., 1957). The evolution of myxomatosis in Australia is a classic example of natural modification of both a virus and host until a state of equilibrium is reached, permitting the continued existence of both.

The introduction of myxomatosis into Europe followed the early successes of the Australian campaign. In 1952, while French officials were considering the desirability of introducing the disease, a private individual acquired the virus and released it on his own estate in an effort to control the rabbit population. The

virus spread rapidly through the countryside, and by the end of 1953 myxomatosis had been diagnosed in Belgium, the Netherlands, Germany, Luxembourg, Spain, and England (Armour and Thompson, 1955; Fenner and Ratcliffe, 1965; Lubke, 1968). Myxomatosis is now endemic in rabbits of the genus *Sylvilagus* in both North and South America and in wild Europen rabbits (*Oryctolagus cuniculus*) in South America, Europe, Australia, and New Zealand.

ETIOLOGY

Myxomatosis is caused by one of several strains of the species, of which *Myxoma virus* is the type species of the genus *Leporipoxvirus* in the *Chordopoxvirinae* subfamily of the family *Poxviridae* (Fauquet et al., 2005). Antigenic differences, demonstrated among different strains of the virus (Fenner, 1965; Reisner et al., 1963), have prompted some to consider the California strains of virus as distinct from *Myxoma virus*, and the designation "California rabbit fibroma virus" has been used to describe this virus. However, the demonstrable antigenic differences are insufficient to justify this distinction, and California strains of virus are considered strains of *Myxoma virus* (Fauquet et al., 2005).

Myxoma virus is antigenically closely related to the *Rabbit fibroma virus* as demonstrated by agar-gel diffusion microprecipitation techniques (Fenner, 1965). Heat-inactivated *Myxoma virus* has been reactivated by fibroma virus (Berry and Dedrick, 1936; Fenner, 1962), further demonstrating the close relationship between these two viruses. The Berry-Dedrick phenomenon of poxvirus reactivation was confirmed by Smith (1952), who demonstrated a spectrum of virulence for strains of myxoma and fibroma viruses. Fenner and Marshall (1957), in a study involving 92 strains of virus, established a virulence spectrum ranging from strains causing over 99% mortality in European rabbits to others causing less than 30% mortality. The most virulent strains were the Standard Laboratory, Lausanne, and California strains, whereas the least virulent were the neuromyxoma and Nottingham strains. Ecological pressures such as those previously described in Australia could have been responsible for the emergence of many of these strains of viruses. In many instances, however, viruses have been manipulated in the laboratory to the point of permanent modification (Kilham, 1957, 1958). The entire genome of the Lausanne strain has been sequenced (Cameron et al., 1999). Infection of *Oryctolagus cuniculus* with *Myxoma virus* has provided a model system for elucidating the immunopathogenesis of poxvirus in the host (Stanford et al., 2007).

The chemical and physical characteristics of *Myxoma virus* have been described (Andrewes and Porterfield, 1989; Fenner, 1953; Fenner and Ratcliffe, 1965). *Myxoma virus* is readily propagated at 35°C on the chorioallantoic membrane of embryonated hens' eggs, forming distinct pocks (Fenner and McIntyre, 1956). Different strains of virus cause pocks of various sizes, the variation being sufficiently distinct to allow tentative strain identification. The South American strains cause large pocks, whereas the California strains produce small focal lesions on the membrane (Fenner and Marshall, 1957). The virus can also be propagated in cell cultures derived from rabbits and other species, including chicken, squirrel, rat, hamster, guinea pig, and human (Andrewes and Porterfield, 1989; Woodroofe and Fenner, 1965). Distinct differences in plaque size on rabbit kidney cell cultures can be demonstrated between the South American and California strains, the former causing much larger plaques (Woodroofe and Fenner, 1965). The most sensitive method for isolation of *Myxoma virus* under laboratory conditions is inoculation of the skin of European rabbits (Fenner and McIntyre, 1956).

EPIDEMIOLOGY

Myxomatosis is endemic on four continents: Australia, Europe, North America, and South America. In Brazil and Uruguay, the virus is endemic in wild rabbits (*Sylvilagus*), particularly *Sylvilagus brasiliensis* (Aragao, 1943). A similar situation may exist in Panama and Colombia, where the strains of virus are similar in virulence to South American strains, but antigenically more closely related to the California strains (Fenner, 1965). In the forested area of Argentina, the virus is also endemic in *Sylvilagus* rabbits, but in the southern part of the country and in Chile the principal reservoir is the wild European rabbit (*Oryctolagus cuniculus*) (Fenner and Ratcliffe, 1965). The California strains of *Myxoma virus*, also known as the California rabbit fibroma virus (Andrewes and Porterfield, 1989), are endemic in wild rabbits (*Sylvilagus*), especially *Sylvilagus bachmani*, which serves as the principal source of infection for domestic rabbits (Marshall et al., 1963). A similar situation exists in Mexico, where *Sylvilagus bachmani* has been shown to be the reservoir in Baja California (Licón Luna, 2000). In Australia, the *Myxoma virus* has been endemic in wild European rabbits (*Oryctolagus cuniculus*) since its introduction into the rabbit population in 1950. Following the introduction of the virus into France in 1952, myxomatosis has become established in most countries of Europe, the wild European rabbit serving as the predominant host species. In Europe, *Myxoma virus* and *Rabbit hemorrhagic disease virus* occur endemically in the same free-living populations of *Oryctolagus cuniculus* (Calvete et al., 2002) and seropositivity to both viruses occurs significantly suggesting the possibility of predisposition (Marchandeau et al., 2004). In rabbit farms in Belgium, the Netherlands, and Germany, the seroprevalence of *Myxoma virus* was

higher in herds with recurrent respiratory or digestive diseases (Marlier et al., 2001).

The naturally susceptible species are the European rabbit (*Oryctolagus cuniculus*), the European hare (*Lepus europaeus*), the Mountain hare (*Lepus timidus*), the Forest rabbit (*Sylvilagus brasiliensis*), the Brush rabbit (*Sylvilagus bachmani*), and the Eastern Cottontail rabbit (*Sylvilagus floridanus*). Experimentally, several additional species of *Sylvilagus* can be infected (Fenner and Ratcliffe, 1965; Regnery and Marshall, 1971).

The principal mode of transmission of the virus is mechanical transport of virus on mouth parts by arthropod vectors, mosquitoes and fleas being most often incriminated (Grodhaus et al., 1963), but biting flies, gnats, mites, and lice may serve as vectors (Fenner and Woodroofe, 1953; Mykytowycz, 1957). The source of virus is usually the superficial layers of the skin, especially of the eyelids and at the base of the ears (Fenner and Woodroofe, 1953), where surface-feeding arthropods obtain the virus and serve as mechanical vectors. Experimentally, virus can spread by contact in the absence of arthropod vectors, and such transmission may occur under natural conditions in rabbit warrens (Mykytowycz, 1958, 1961). An outbreak in Hungary at a rabbit farm was attributed to airborne transmission as the disease occurred in winter when mosquitoes and fleas were uncommon (Farsang et al., 2003). Windborne spread was suspected in France (Arthur and Louzis, 1988). Transmission of *Myxoma virus* by contaminated spines of thistles (*Circium vulgare*) has been described (Dyce, 1961; Mykytowycz, 1961). The claws of predatory birds and carrion feeders, such as buzzards and crows, may be contaminated with virus, and such birds may play a role in dissemination of the virus (Borg and Bakos, 1963).

In an attempt to improve the usefulness of myxomatosis in rabbit control, the European rabbit flea, *Spilopsyllus cuniculi,* was introduced into Australia in 1966 (Sobey and Menzies, 1969). The flea reproduced in wild rabbit populations and transmitted both introduced and field strains of *Myxoma virus* (Shepherd and Edmonds, 1977; Sobey and Conolly, 1971). As a result of flea introduction, myxomatosis has become more prevalent in drier tableland areas (Parer and Korn, 1989), and outbreaks of myxomatosis have shifted from summer to spring (Shepherd and Edmonds, 1978; Shepherd et al., 1978). In France, there is evidence that mosquitoes of the genus *Anopheles* are the principal vectors of summer epidemics. The rabbit flea, *Spilopsyllus cuniculi,* is probably a major vector, especially during winter months when mosquito activity is low (Fenner and Ratcliffe, 1965).

Myxomatosis in Britain is characterized by milder seasonal fluctuations in disease incidence than in Australia, California, and France (Ross and Tittensor, 1986). Mosquitoes play a minor role as vectors, whereas the rabbit flea, *Spilopsyllus cuniculi,* which is less influenced by seasonal changes, is the major vector (Andrewes et al., 1959; Armour and Thompson, 1955; Lockley, 1954; Mead-Briggs, 1964). The *Myxoma virus* in Britain has not undergone the rapid loss of virulence observed with the Australian and French viruses. The increase in resistance to myxomatosis in wild rabbit populations has resulted in the appearance of more virulent strains of *Myxoma virus* (Ross and Sanders, 1987). While mildly virulent strains have emerged in Britain, the predominant strains are moderately virulent (Chapple and Bowen, 1963; Chapple and Lewis, 1964; Fenner and Chapple, 1965), with recent estimates of between 47% and 69% mortality in infected rabbits (Ross et al., 1989). The different evolution of *Myxoma virus* in Britain has been attributed to the fact that the virus is predominantly flea-transmitted. The flea is less seasonal and less mobile than the mosquito. That fleas move in large numbers from dead animals while moving only occasionally from live ones would seem to favor transmission of virulent virus strains (Fenner and Marshall, 1957). The proportion of infective fleas produced is inversely related to the survival time of rabbits following infection (Mead-Briggs and Vaughan, 1975). The flea is also an effective reservoir of virus, possessing a longer life span than mosquitoes. The life span of active female mosquitoes is usually 2–3 weeks, whereas fleas have been known to feed actively for over 1 year. The *Myxoma virus* can persist for 105 days in rabbit fleas with no rabbit contact in artificial burrows (Chapple and Lewis, 1965).

In experimental studies of viral pathogenesis and host resistance, a virulent strain of *Myxoma virus* (SLS) inoculated into laboratory European rabbits (*Oryctolagus cuniculus*) resulted in fatal infections whereas wild European rabbits with naturally acquired innate resistance recovered (Best and Kerr, 2000). Conversely, inoculation of laboratory European rabbits with an attenuated, naturally derived field strain of *Myxoma virus* resulted in recovery from infection and rabbits with innate resistance experienced only mild disease. A similar study examined the pathogenesis of two Californian strains of *Myxoma virus*es (MSW and MSD) in European rabbits and found that both susceptible rabbits and rabbits that had naturally acquired innate resistance, experienced acute fatal infections with the MSW strain, whereas, the MSD strain caused classical signs of myxomatosis in both strains of rabbits (Silvers et al., 2006).

CLINICAL SIGNS

Considerable differences in the virulence of *Myxoma virus* strains complicate discussion of the clinical disease, as does the fact that different species and strains of rabbits vary considerably in susceptibility to *Myxoma virus*. Major emphasis is given to discussion of disease

in *Oryctolagus* by the major strains of virus found in Australia, California, Europe, and South America.

SIGNS IN SYLVILAGUS SPECIES Rabbits of the genus *Sylvilagus,* the natural host of the virus, are relatively resistant to infection and generally develop skin tumors and lesions, but rarely systemic disease, except in young rabbits (Aragao, 1943). Generally, the nodules occur at the site of infection, persist for a variable amount of time, and then regress. The size of the skin nodule and its persistence vary with the strain of rabbit and the strain of virus (Fenner and Ratcliffe, 1965; Marshall and Regnery, 1963; Regnery and Miller, 1972; Silvers et al., 2009).

SIGNS IN LEPUS SPECIES The European hare *(Lepus europaeus)* is resistant to *Myxoma virus* under experimental conditions, and field experience supports this observation. Occasionally, however, individual hares (*Lepus europaeus* and *Lepus timidus*) with mild to severe generalized myxomatosis have been encountered (Fenner and Ratcliffe, 1965).

SIGNS IN ORYCTOLAGUS CUNICULUS *Myxoma virus* infection in the European rabbit usually results in severe disease with high mortality (Marshall et al., 1963; Patton and Holmes, 1977). The severity and variety of clinical disease is largely determined by the strain of virus as well as the strain of rabbit (Sobey, 1969; Sobey et al., 1970) and have been described in detail (Fenner and Marshall, 1957; Fenner and Ratcliffe, 1965). The discussion which follows is a summation of the findings of these workers and others (Chapple and Bowen, 1963; Kessel et al., 1931).

Signs which develop following infection with California strains of the virus in susceptible rabbits can be categorized as peracute, acute, or chronic. Rabbits with the peracute form of disease die within 1 week after exposure to the virus, exhibiting only edema of the eyelids and lethargy prior to death. In the acute form of disease, in which rabbits survive for 1–2 weeks, usually edema of the eyelids, resulting in a "droopy" appearance of the eyes, appears at 6–7 days. Inflammation and edema around the anal, genital, oral, and nasal orifices are also observed. Skin hemorrhages and convulsions precede death on the ninth or tenth day. The few rabbits which survive beyond 10 days and have a chronic form may develop purulent blepharoconjunctivitis and edema at the base of the ears, signs more often associated with other myxoma strains (Figure 14.1). The nodule which develops at the site of inoculation is not a clearly defined tumor, and under natural conditions the development of myxomas is not characteristic. Although nodules on the ears, head, and legs have been reported (Kessel et al., 1934), other workers have been unable to induce nodule development (Fenner and Marshall, 1957).

The original South American isolate of Moses (1911), results in an acute disease with a mean survival time of 11 days. From 3–4 days following inoculation or natural infection with virus, a primary tumor may become evident, and generalized tumors usually appear by the sixth or seventh day. Edema of the eyelids occurs followed by mucopurulent blepharoconjunctivitis, often resulting in complete closure of the eyes. Mucopurulent nasal discharge and pronounced edema of the base of the ears, the perineal region, the external genitalia, and lips are frequently seen. By the tenth day, hard convex lumps may cover the body, head, and ears and occasionally the legs. The lumps are not sharply demarcated but may become markedly congested and ultimately necrotic in rabbits surviving for 2 weeks. Dyspnea is often seen in protracted cases, but appetite may be maintained until shortly before death. Terminal convulsions frequently precede death, which usually occurs 8–15 days after infection. Infection with less virulent South American and Australian strains results in milder disease with less edema and nasal and ocular discharge, more clearly demarcated nodules, and lower mortality. The laboratory-attenuated neuromyxoma virus induces a mild disease with little or no mortality (Hurst, 1937b).

The predominant myxoma strains in Europe are the virulent Lausanne strain and its naturally attenuated derivatives originating from the virus introduced into France from Brazil in 1952. The more virulent European viruses cause severe disease in rabbits, resulting in mortality of up to 100%, but modified strains which have emerged are of lower morbidity and mortality (Arthur and Louzis, 1988). With some of the naturally attenuated British viruses, mortality is also decreased, and tumors are flat rather than convex, resembling some of the attenuated field strains in Australia (Chapple and Bowen, 1963). In France and Belgium, two forms of the disease are recognized, nodular and amyxomatous forms (Marlier et al., 1999). The former is characterized by florid skin lesions and severe immunosuppression, accompanied by bacterial infections of the respiratory tract, whereas in the latter, skin nodules are few and small, with acute respiratory distress and copious nasal discharge.

PATHOLOGY

The gross and microscopic pathology of myxomatosis has been comprehensively reviewed (Fenner and Ratcliffe, 1965; Hurst, 1937a; Rivers, 1930). In adult *Sylvilagus, Myxoma virus* usually causes localized skin tumors. The tumors resemble the fibromas in European rabbits produced by the *rabbit fibroma virus* (see later). Hares or young *Sylvilagus* usually develop a mild localized infection, although disseminated cutaneous

FIGURE 14.1 Rabbit with myxomatosis displaying facial edema with mucopurulent conjunctivitis. *Courtesy of Dr. G. Van Hoosier.*

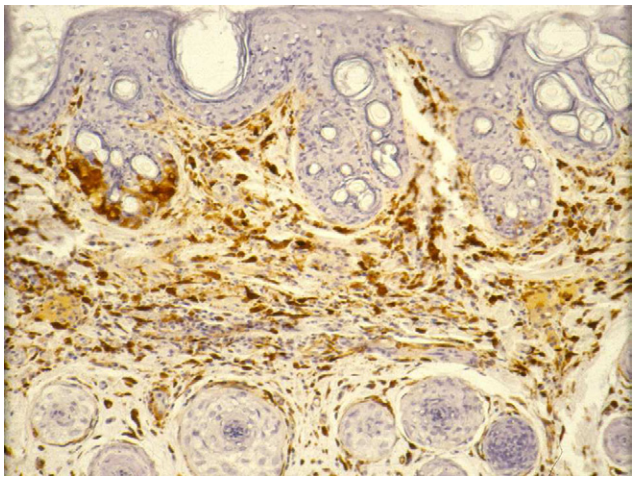

FIGURE 14.2 Myxoma virus expressing lacZ-infected primary skin lesion immunostained with antibody to β-galactosidase demonstrates the wide distribution of the virus within the dermis and subcutis. Hematoxylin and eosin counterstain. *Courtesy of Dr. G. McFadden.*

fibromatous to myxomatous nodules similar to those in acute myxomatosis may be found. Prominent gross lesions in European rabbits with myxomatosis are skin tumors (not characteristic of the California disease) and pronounced cutaneous and subcutaneous edema, especially of the face and around body orifices. Hemorrhages of the skin, heart, and subserosa of the gastrointestinal tract may be observed, especially following infection with the California virus.

Lesions in the skin involve epithelial cells, fibroblasts, and endothelial cells and range from proliferative to degenerative, depending on the strain of virus. The skin tumors result from proliferation of undifferentiated mesenchymal cells, which become the characteristic large stellate (myxoma) cells surrounded by a homogeneous matrix of mucinous material interspersed with capillaries and inflammatory cells (Figure 14.2). There is typically vascular endothelial proliferation and hypertrophy with narrowing of the lumen (Hurst, 1937a; Percy and Barthold, 2007). Central necrosis of myxomas may be attributed to occlusion of blood vessels by endothelial proliferation. Epithelial cells overlying the tumor may appear normal in early tumors, or show hyperplasia or degeneration. Intracytoplasmic inclusions, in various cells types, are especially prominent in the epidermis (Patton and Holmes, 1977; Rivers and Ward, 1937).

Lesions in other organs, although not consistently present, reflect the potential generalized nature of myxomatosis. Cellular proliferation, invariably present in the skin, has also been described in pulmonary alveolar epithelium and in reticulum cells of lymph nodes and spleen (Hurst, 1937a). Focal hemorrhages may be observed in skin, kidneys, lymph nodes, testes, heart, stomach, and intestines. Degeneration and necrosis occur frequently in lymph nodes, pulmonary alveoli, spleen, and central veins of hepatic lobules. Stellate cells may occur in lymph nodes, bone marrow, uterus, ovaries, testes, and lungs (Marcato and Simoni, 1977).

In a survey of 66 rabbits, presumably *Oryctolagus cuniculus*, that died of respiratory disease, *Myxoma virus* was isolated from seven (10%), mainly from rabbits with acute hemorrhagic pneumonia (Marlier et al., 2000). The mechanisms by which the virus manifests the development of disease in rabbits have been described (Stanford et al., 2007).

DIAGNOSIS

Myxomatosis in European rabbits can usually be diagnosed by the clinicopathological features, particularly the nodular form, due to the characteristic skin lesions. Infection with the California viruses may be harder to diagnose, however, owing to the frequent absence of skin nodules and other signs of disease. Diagnosis should be confirmed by virus isolation. Intracutaneous inoculation of young susceptible rabbits with fresh tissue collected from lesions free of bacterial contamination results in lesions at the site of inoculation within 1 week. The virus can be isolated by chorioallantoic membrane inoculation of 11–13-day-old embryonated chicken eggs followed by incubation at 35°C for 4–6 days. Distinct focal pocks develop if the virus is present. The South American viruses cause large pocks, the California virus intermediate-sized pocks, and the fibroma virus minute pocks. Virus isolation on chicken embryo fibroblast, Vero or RK13 cells can also be accomplished. A cytopathic effect typical of poxviruses usually develops in 1–2 days but may take up to 7 days with some strains. The virus isolated can be identified as *Myxoma virus* by direct fluorescent antibody test (Takahashi et al., 1958, 1959), the plaque-neutralization test (Woodroofe and Fenner, 1965), the agar-gel diffusion microprecipitation test (Fenner, 1965), or the

indirect immunoperoxidase test (Marlier et al., 1999). Myxoma virus DNA in tissue samples can be detected by polymerase chain reaction (PCR) (Barcena et al., 2000; Kritas et al. 2008; Pérez de Rozas et al., 2008).

Rabbits that survive infection develop antibodies to the virus, which can be detected by an enzyme-linked immunosorbent assay (ELISA) that has been shown to be more sensitive and specific than agar gel immunodiffusion, complement fixation (CF), or indirect immunofluorescence (Gelfi et al., 1999). Serum neutralization has also been used to detect antibodies (Marlier et al., 1999). Infection of *Sylvilagus* rabbits with *Myxoma virus* clinically resembles fibromatosis and should be differentiated from the latter disease by PCR or inoculation of young susceptible rabbits of the genus *Oryctolagus*. Myxomatosis causes severe to fatal disease, whereas fibromatosis causes a localized fibroma.

CONTROL

Control of myxomatosis is of prime importance in areas where the virus is endemic in wild rabbit populations. Vector control, including adequate screening to exclude mosquitoes, serves to keep the disease under control. Newly introduced rabbits should be quarantined in an insect-proof facility for 2 weeks. To prevent spread within a colony, all sick rabbits should be isolated. Fibroma virus has been used as a live vaccine for myxomatosis, but results have been variable (Fenner and Ratcliffe, 1965). A live attenuated myxomatosis vaccine (the MSD strain) results in a mild reaction followed by immunity persisting for 9 months (McKercher and Saito, 1964). Jiran et al. (1970) found this virus to be too virulent for use as a vaccine and further attenuated it by serial passage in rabbit kidney cell cultures. The additionally modified virus, designated MSD/B, was safe and highly immunogenic.

However, efficacy of a vaccine has yet to be demonstrated in commercial rabbits. In an outbreak of atypical myxomatosis in Hungary, fibroma vaccine was not protective, whereas in experimental studies, a live myxomatosis vaccine protected rabbits (Farsang et al., 2003). An assessment of the Borgi strain vaccine of *Myxoma virus* was reported during an outbreak of myxomatosis in Greece (Kritas et al., 2008). Two-month-old vaccinated pregnant does were obtained by two commercial rabbitries, only one of which had vaccinated resident does. Within several weeks of their arrival, an explosive outbreak of myxomatosis with high morbidity and mortality occurred on both farms in both unvaccinated and vaccinated rabbits, both imported and resident, with the Lausanne strain of *Myxoma virus*. Since vaccinated rabbits were affected within 6 months of vaccination, the efficacy of the vaccine was questionable.

Field trials using various strains have been conducted in free-living rabbit populations. A field trial of a recombinant vaccine, using a naturally attenuated myxoma field strain (6918) that expressed a *Rabbit hemorrhagic disease virus* VP60 protein, conducted on an island off the coast of Spain, revealed that the vaccine induced antibodies to both viruses in vaccinated rabbits without any adverse side effects (Torres et al., 2001). Furthermore, the vaccine exhibited limited horizontal transmission, either by direct contact or fleas, as uninoculated rabbits also exhibited seroconversion. Although the observation period was brief (32 days), the vaccine appeared to be both safe and efficacious. An attenuated strain (SG33) was used in a field trail in juvenile rabbits in France and vaccinated rabbits had a 1.8-fold greater odds of surviving than unvaccinated rabbits over 4 years of surveillance (Guitton et al., 2008). In a field trial in Zaragoza province in northeast Spain, young European rabbits (*Oryctolagus cuniculus*) born in the current year and unvaccinated, were 13.6 times more likely to die than rabbits vaccinated against both myxomatosis (POX-LAP) and *Rabbit* hemorrhagic disease (CYLAP-VHD), over a 90-day observation period after vaccination (Calvete et al., 2004).

Rabbit (Shope) Fibroma Virus

HISTORY

The transmissible tumor-inducing agent now known as rabbit or Shope fibroma virus was isolated from an Eastern Cottontail rabbit *(Sylvilagus floridanus)* in 1932 (Shope, 1932a). The virus was transmissible to Eastern Cottontail and European rabbits *(Oryctolagus cuniculus),* producing localized fibromas in both species. Shope (1932a) described the gross and microscopic lesions of both the natural and experimental disease and identified the causative agent as a virus antigenically related to *Myxoma virus* (Shope, 1932b). Similarities between *Rabbit fibroma* and *Myxoma virus*es have subsequently been confirmed by cross-immunity tests (Shope, 1936), ether sensitivity (Andrewes and Horstmann, 1949; Fenner, 1953), virus-reactivation studies (Berry and Dedrick, 1936), microprecipitation procedures (Fenner, 1965), and sequence comparison (Willer et al., 1999). The *Rabbit fibroma virus*, initially believed to cause only localized benign fibromas, was later shown to cause severe generalized disease in newborn European (Duran-Reynals, 1940; Joiner et al., 1971) and Eastern Cottontail rabbits (Yuill and Hanson, 1964). The disease is historically considered a benign endemic disease of wild *Sylvilagus* rabbits, of little economic significance to commercial rabbit producers or laboratory investigators. However, an outbreak of fibromatosis in a commercial rabbitry resulting in high morbidity and mortality in newborn rabbits was reported in 1971 (Joiner et al., 1971). Thus, the disease can be a threat to commercial rabbits in areas where it is endemic in wild rabbit populations and outdoor husbandry practices permit contact with arthropod vectors.

Another tumor-producing virus, designated malignant rabbit fibroma virus, has been recovered from *Oryctolagus cuniculus* with experimentally induced Shope fibromas (Strayer et al., 1983a). Although the virus was present in a stock of *Rabbit fibroma virus*, its origin is unclear. The virus is antigenically similar to both *Rabbit fibroma* and *Myxoma virus*es and is considered a recombinant of the two viruses (Block et al., 1985). The virus induces a syndrome of severe immunosuppression resulting in disseminated malignancy and opportunistic infections (Corbeil et al., 1983; Skaletsky et al., 1984; Strayer and Sell, 1983; Strayer et al., 1983a, 1983b, 1983c). The disease may be a useful model for the study of virus-induced immunologic impairment (Strayer et al., 1985).

ETIOLOGY

Rabbit fibroma virus is a *Leporipoxvirus* of the family *Poxviridae* (Fauquet et al., 2005) and is closely related to *Myxoma virus* (Fenner, 1953) and the hare and squirrel fibroma viruses (Fenner, 1965). The complete genome of *Rabbit fibroma virus* has been sequenced (Willer et al., 1999). The chemical and physical characteristics of fibroma virus have been summarized by Gross (1983). The virus can be propagated on the chorioallantoic membrane of chicken embryos, but characteristic lesions as observed with *Myxoma virus* are not produced (Gross, 1983). The virus has been propagated in cell cultures derived from rats, guinea pigs, and humans (Chaproniere and Andrewes, 1957) and also in rabbit cell cultures derived from Eastern Cottontail and domestic rabbits (Constantin et al., 1956; Hinze and Walker, 1964; Kasza, 1974; Kilham, 1956; Padgett et al., 1962). Fibroma virus in cultured rabbit kidney cells induces pronounced changes in cell growth and morphology, and inoculation of virus-transformed cells into the cheek pouch of hamsters results in tumor formation (Hinze and Walker, 1964).

EPIDEMIOLOGY

Since *Rabbit fibroma virus* was first isolated from an Eastern Cottontail rabbit in New Jersey (Shope, 1932a), the disease has been recognized in several other states, as well as in Canada. Herman et al. (1956) found that more than 50% of wild *Sylvilagus* rabbits trapped in the Patuxent Wildlife Refuge in Maryland had *Rabbit fibroma virus* or antibodies to *Rabbit fibroma virus*. The virus has also been isolated from *Sylvilagus* rabbits in Wisconsin (Yuill and Hanson, 1964), Michigan (Herman et al., 1956), and Ohio (Kasza, 1974). Recognition of the disease in Texas (Joiner et al., 1971) indicates that it may be more widespread in the U.S. than was formerly believed.

The natural transmission cycle of *Rabbit fibroma virus* has not been completely elucidated. The virus may persist in the epidermis of experimentally infected *Sylvilagus* rabbits for 5–10 months (Kilham and Dalmat, 1955; Kilham and Fisher, 1954), which would enhance the likelihood of mechanical arthropod transmission. Experimentally, several species of mosquitoes as well as triatomes, fleas, and bedbugs can serve as vectors (Dalmat, 1959; Kilham and Dalmat, 1955; Kilham and Woke, 1953). Infected mosquitoes are capable of infecting wild *Sylvilagus* rabbits (Kilham and Dalmat, 1955). Experimental and circumstantial evidence suggests that the principal mode of transmission for fibroma virus is biting arthropods, a situation similar to that described for myxomatosis. Infection may also occur by direct contact with skin injuries being a predisposing factor (Grilli et al., 2003).

The natural host of fibroma virus is the Eastern Cottontail rabbit (*Sylvilagus floridanus*). Three other species of *Sylvilagus* (*Sylvilagus bachmani*, *Sylvilagus nuttalli*, and *Sylvilagus auduboni*) are refractory to fibroma virus (Fenner and Ratcliffe, 1965). A closely related virus, isolated from fibromas in *Sylvilagus bachmani*, failed to induce lesions in other *Sylvilagus* species (Marshall and Regnery, 1960). This virus, considered a strain of *Myxoma virus*, is a related virus named California *Rabbit fibroma virus* (Andrewes and Porterfield, 1989). The European rabbit (*Oryctolagus cuniculus*) is susceptible to fibroma virus (Shope, 1932a) as is the Snowshoe hare, *Lepus americanus* (Yuill, 1981), but the European hare, *Lepus europaeus*, is refractory to the virus (Fenner and Ratcliffe, 1965). Whereas the European rabbit is readily infected, it does not serve as a good source of infection for mosquitoes because of low virus concentrations in the skin (Fenner and Ratcliffe, 1965).

CLINICAL SIGNS

The clinical signs are largely those described by Shope (1932a, 1932b, 1936). The tumors observed in natural fibromatosis of Eastern Cottontail rabbits are almost invariably on the legs or feet, usually one to three tumors occurring on an infected rabbit. Tumors may occur on the muzzle and around the eyes, and measure up to 7 cm in diameter and 1–2 cm in thickness. The tumors are subcutaneous, unattached to underlying tissues, and may persist for several months, and in some instances for nearly a year (Kilham and Dalmat, 1955). Other clinical signs are usually absent, the tumor-bearing rabbit remaining apparently normal throughout the disease. Metastases do not occur (Shope, 1932a). The clinical signs in experimentally infected European rabbits resemble those in *Sylvilagus* rabbits. However, regression of tumors is usually more rapid than in *Sylvilagus* rabbits. Inoculation of newborn European rabbits frequently results in fatal systemic infections (Duran-Reynals, 1945). Systemic infections of adult European rabbits have also been described (Hurst, 1937c), but the usual result of infection is the development of localized benign tumors. In the only reported

natural outbreak of fibromatosis of European rabbits, diffuse subcutaneous induration involving the underlying tissues occurred (Joiner et al., 1971). Subcutaneous tumors were the predominant sign in adult rabbits but suckling rabbits had lethargy and loss of condition, in addition to the skin lesions. Hyperemia and edema of the external genitalia of male and female rabbits were also observed.

A survey of tumors in pet rabbits submitted to the surgical biopsy service of a veterinary school in Pennsylvania over a 16-year period revealed that Shope fibroma was diagnosed in 19 tumors from 179 rabbits (von Bomhard et al., 2007). The species of rabbits was not provided and diagnosis was based on histopathologic findings. The limbs, head, and pinna were affected in 75% of cases. Case reports of keratitis with a perilimbal mass due to fibroma virus have been diagnosed in individual European rabbits (*Oryctolagus cuniculus*) (Keller et al., 2007; McLeod and Langlinais, 1981).

PATHOLOGY

The gross and microscopic changes associated with fibroma virus infection in naturally and experimentally infected *Sylvilagus* rabbits and in experimentally infected European rabbits have been described by several workers (Ahlstrom, 1938; Andrewes, 1936; Dalmat and Stanton, 1959; Fisher, 1953; Grilli et al., 2003; Kilham and Fisher, 1954; Shope, 1932a; Yuill and Hanson, 1964). The pathological changes in the only reported natural outbreak of fibromatosis in European rabbits were described by Joiner et al. (1971). The earliest gross lesion in experimentally infected *Sylvilagus* rabbits is a slight thickening of the subcutaneous tissue, followed by development of clearly demarcated soft swellings usually evident 6 days after inoculation. The tumors enlarge, increase in density, and usually reach maximum size by 12 days. The average size of the tumors is 4–6 cm with a thickness of 2 cm. Tumors may persist for months before regressing, leaving the rabbit essentially normal. Experimentally infected newborn *Sylvilagus* rabbits may die of generalized fibromatosis. Under natural conditions, however, this form of the disease has not been observed. Gross lesions in experimentally infected European rabbits are similar to those observed in *Sylvilagus* rabbits but regression of the tumors occurs more rapidly.

The earliest microscopic lesions in *Sylvilagus* rabbits are an acute inflammation followed by localized fibroblastic proliferation, accompanied by both mononuclear and polymorphonuclear leukocyte infiltrations. Fibroblasts proliferate until a distinct tumor is formed, consisting of spindle-shaped and polygonal connective tissue cells with abundant cytoplasm. Mitotic figures are few. Many tumor cells may have large intracytoplasmic inclusions characteristic of poxvirus infections. Mononuclear leukocyte cuffing of vessels adjacent to the tumor may be observed, and a pronounced accumulation of lymphocytes at the base of the tumor is often seen. Degeneration of the overlying epidermis may result from pressure ischemia, followed by necrosis and sloughing of the epithelium and tumor. In many instances, however, the tumors regress without epithelial sloughing. Regression is usually complete within 2 months after appearance of tumors. Andrewes (1936) described a strain of fibroma virus which caused a more inflammatory and less proliferative lesion than the fibroma virus isolated by Shope (1932a).

Histologically, typical fibromas are observed in European rabbits experimentally infected with fibroma virus. The lesions differ only slightly from those in *Sylvilagus* rabbits, the principal difference being the absence of epidermal degeneration often observed in the latter species (Shope, 1932a). However, Ahlstrom (1938) described epidermal degeneration in European rabbits. Microscopic lesions in the natural outbreak of fibromatosis in European rabbits ranged from tumors resembling myxomas to typical fibromas (Joiner et al., 1971). Eosinophilic cytoplasmic inclusions were occasionally observed in tumor cells, and similar inclusions, possibly of viral origin, were seen in epithelial cells overlying the tumors. The lesions encountered in adult and newborn rabbits did not differ significantly.

DIAGNOSIS

Fibromatosis should be differentiated from papillomatosis and myxomatosis. Clinically, differentiation from papillomatosis can be readily accomplished as fibromas are essentially flat, subcutaneous, loose, rubbery tumors, whereas papillomas are tumors of the skin which are heavily keratinized and project in irregular fashion from the skin surface. Histopathological differentiation is also easily accomplished, especially when intracytoplasmic inclusion bodies are observed. Historically, subcutaneous inoculation of young European rabbits with a tumor cell suspension was used to differentiate the two viruses. *Rabbit fibroma virus* induces local fibromas, whereas *Myxoma virus* causes severe systemic and often fatal disease. Virus isolation in cell cultures or on the chorioallantoic membranes of chicken embryos should be attempted to confirm the diagnosis. The virus can be identified by serum neutralization tests (Yuill, 1981).

CONTROL

Because the disease is endemic and of little significance in *Sylvilagus* rabbits, no control measures have been developed. Fibromatosis is also not an important problem in domestic rabbits; however, since the disease has been encountered in a rabbitry in an area where the disease is apparently endemic in wild rabbits, control measures might be considered. In such areas, the

method of choice for preventing infection of rabbits held in outdoor enclosures is vector control. Careful analysis of the role of possible vectors in natural outbreaks should be made in preparation for the establishment of vector control methods.

Hare Fibroma Virus

HISTORY

Epidemics of a fibromatous disease in European hares (*Lepus europaeus*) occurred in France and Northern Italy in 1959 (Lafenetre et al., 1960; Leinati et al., 1959). The causative agent was a poxvirus related to *Myxoma virus* (Leinati et al., 1961). In retrospect, a nodular skin disease of hares in Germany designated hare sarcoma was probably hare fibromatosis (Dungern and Coca, 1909).

ETIOLOGY

The causative agent of hare fibromatosis is a *Leporipoxvirus* in the family *Poxviridae* (Fauquet et al., 2005), which has been shown by plaque-neutralization and cross-protection tests to be antigenically related to myxoma, rabbit fibroma, and squirrel fibroma viruses (Woodroofe and Fenner, 1962). Agar-gel diffusion microprecipitation techniques reveal that hare fibroma virus shares more common antigens with *Rabbit fibroma virus* than with *Myxoma virus* (Fenner, 1965). A considerable degree of cross-protection exists between hare fibroma and myxoma viruses. European rabbits immune to *Myxoma virus* are completely refractory to hare fibroma virus, whereas rabbits immunized with hare fibroma virus develop signs when infected with *Myxoma virus* but survive, indicating some protection (Woodroofe and Fenner, 1965).

EPIDEMIOLOGY

Hare fibromatosis has been recognized only in Europe, where under natural conditions it infects the European hare. However, dermal tumors were reported on Cape hares (*Lepus capensis*) in the Laikipia District of Kenya that had gross and histopathologic similarities to hare fibromatosis (Karstad et al., 1977). In 2001, an outbreak of fibromatosis occurred in farmed game European hares (*Lepus europaeus*) in Italy (Grilli et al., 2003). The European rabbit (*Oryctolagus cuniculus*) is susceptible to the virus, but natural outbreaks of disease in rabbits have not been reported. A seasonal occurrence of disease has been reported, with the peak incidence in late summer and autumn (Lafenetre et al., 1960; Leinati et al., 1959). The mode of transmission and interepidemic survival of the virus are unknown.

CLINICAL SIGNS

In European hares, the disease is characterized by development of numerous skin nodules, up to 2.5 cm in size, occurring especially on the face, eyelids, and around the ears. In farmed game European hares, fibromas also occurred on the legs (Grilli et al., 2003). The nodules closely resemble rabbit fibromas (Leinati et al., 1961). In adult European rabbits the virus causes formation of small fibromas, but newborn rabbits exhibit large fibromas resembling the lesions of rabbit fibromatosis (Fenner and Ratcliffe, 1965).

PATHOLOGY

The gross and microscopic appearance of the lesions of hare fibroma is similar to that of the lesions of rabbit fibroma (Lafenetre et al., 1960; Leinati et al., 1961).

DIAGNOSIS

The disease is usually diagnosed from clinicopathological features. The diagnosis can be confirmed by virus isolation in rabbit kidney cell cultures or on the chorioallantoic membrane of chicken embryos. Serological characterization of the virus can be achieved using the agar-gel diffusion technique (Fenner, 1965).

CONTROL

Because the disease is endemic and of little significance in hares, no control measures have been developed. Farmed game hares, used for stocking areas, should be free of infection to avoid dissemination of the virus (Grilli et al., 2003).

Rabbitpox

HISTORY

Rabbitpox was first diagnosed at the Rockefeller Institute in New York when a highly fatal disease occurred spontaneously in the European rabbit (*Oryctolagus cuniculus*) colony in 1932 (Greene, 1933, 1934a; Pearce et al., 1933; Rosahn and Hu, 1935). A smaller outbreak had occurred in 1930. Rabbits developed an erythematous rash followed by cutaneous eruptions closely resembling the pocks seen in human infection with variola virus (smallpox). The disease was extremely contagious and caused high mortality, especially in young rabbits and pregnant females. Belgian hares were also susceptible to the disease. The causative agent of the disease was a poxvirus (Pearce et al., 1936; Rosahn et al., 1936a).

A spontaneous outbreak of a similar disease in a laboratory rabbit colony in Holland was described by Jansen (1941). The disease was highly fatal and differed from the Rockefeller outbreak in that it was not exanthematous, giving rise to the name "pockless" rabbitpox (Jansen, 1947). This disease was also caused by a poxvirus closely related to vaccinia virus (Jansen, 1946). A second outbreak of the disease in Holland was reported by Verlinde and Wersinck (1951). The second

outbreak of rabbitpox reported in the United States occurred in New York (Christensen et al., 1967) and was also of the pockless type first observed by Jansen (1947) in Holland. Another serious outbreak of the disease, resulting in mortality of 95%, occurred following the introduction of supposedly inactivated rabbitpox virus of the Dutch (Utrecht) strain into the rabbit colony of a medical school (Christensen et al., 1967). Various aspects of the infection have been reviewed by Fenner et al. (1989). Rabbitpox virus infection in rabbits can serve as a model for human smallpox infection as a fatal systemic disease developed with a low inoculum and inoculated rabbits naturally transmitted the virus to susceptible rabbits by aerosol (Adams et al., 2007).

ETIOLOGY

Rabbitpox virus is an *Orthopoxvirus* in the family *Poxviridae* (Fauquet et al., 2005) and is antigenically related to vaccinia virus (Fenner, 1958; Hu et al., 1936; Jansen, 1946). The biological properties of the Utrecht (Jansen, 1941) and Rockefeller (Greene, 1934a) strains of rabbitpox viruses are indistinguishable from certain neurovaccinia strains (Fenner; 1958; Fenner et al., 1989). The close antigenic relationship between rabbitpox virus and vaccinia virus, taken together with the fact that all reported outbreaks of rabbitpox have occurred in laboratory colonies, suggests that rabbitpox may be a laboratory variant of vaccinia virus (Greene, 1935a; Verlinde and Wersinck, 1951). Wittek et al. (1977) used genome mapping to show that rabbitpox virus (Utrecht strain) was a strain of vaccinia virus. The viruses have been shown to exhibit over 95% sequence similarity (Li et al., 2005).

Rabbitpox virus can be propagated on the chorioallantoic membrane of chicken embryos with development of distinct pocks. The predominant pock type is hemorrhagic (Jansen, 1946), but white pock mutants have been described (Fenner and Sambrook, 1966; Fenner et al., 1989). Rabbitpox virus has been propagated in several cell lines, including HeLa, Chang Liver, L929 (mouse fibroblast), human heart, KB (human epithelial), FL (human amnion), AT (Chinese hamster epithelial), PK-2A (pig kidney), and FAF cells (Chinese hamster fibroblast) (Christensen et al., 1967). The Rockefeller strain of rabbitpox virus hemagglutinates chicken erythrocytes, but the Utrecht strain and the strain isolated from the first American outbreak of pockless rabbitpox do not (Christensen et al., 1967).

EPIDEMIOLOGY

Rabbitpox is relatively rare, and all reported outbreaks have occurred in laboratory colonies in the United States and Holland. The highest mortality occurs in rabbits and pregnant or lactating females (Greene, 1934a, 1935b). Differences in susceptibility by rabbit breed also occur (Greene, 1935b). Within infected colonies, the spread of disease is extremely rapid, and, in the outbreak of 1932, removal and isolation of infected rabbits failed to prevent the disease from spreading throughout the colony (Greene, 1934a). The virus appears to spread by nasal discharges, which usually appear on the third day after infection. Airborne droplets may be inhaled or ingested by susceptible rabbits (Bedson and Duckworth, 1963). Recovery from infection does not appear to result in establishment of a carrier state, as recovered rabbits can be safely mated with susceptible rabbits and clean colonies derived from recovered stock (Greene, 1934a). Arthropods have not been shown to play a role in the epidemiology of rabbitpox infection. In general, the primary sources of infection resulting in outbreaks of disease have not been determined, although the origin may have been rabbits inoculated with vaccinia virus (Greene, 1935a).

CLINICAL SIGNS

The clinical disease has been described in detail (Bedson and Duckworth, 1963; Christensen et al., 1967; Greene, 1934a). The virus initially infects and multiplies in the nasal mucosa and later in lymph nodes of the respiratory tract and in the lungs and spleen. Fever and a profuse nasal discharge usually occur 2–3 days after infection. Another early sign is enlargement and induration of the lymph nodes, especially the popliteal and inguinal nodes, which usually persist throughout the course of disease. Widely distributed skin lesions usually appear about 5 days after infection, initially as an erythematous macular rash which becomes papular and may progress to nodules up to 1 cm in size. These nodules eventually form dry, superficial crusts. Macules and papules may also occur on the mucous membranes of the oral and nasal cavities. Extensive edema of the face and oral cavity is often observed, as is focal necrosis of the hard palate and the gums. Hemorrhages in the skin may occur in severe cases.

Male rabbits frequently develop severe orchitis with extensive scrotal edema, and papules in the prepuce and urethra are observed. Similar lesions may also occur in the vulvae of females. If edema is extensive, urine retention may occur in either sex. Pregnant females usually abort. The eyes are almost invariably affected and exhibit blepharitis, purulent conjunctivitis, and acute keratitis with corneal ulceration. Death usually occurs 7–10 days after infection but may occur as early as 5 days, or rabbits may survive for several weeks before dying.

The generalized disease syndrome described above represents the findings of Greene (1934a) and Bedson and Duckworth (1963) with the Rockefeller strain of virus. This strain may occasionally result in peracute disease in which death is preceded only by fever, anorexia, and occasionally blepharitis. The peracute

form is unusual with the Rockefeller strain, but natural outbreaks of rabbitpox of the pockless type (Jansen, 1941, 1946, 1947; Christensen et al., 1967), without erythema or skin lesions, have occurred. In the first Dutch outbreak, some rabbits died within 1 week after infection, with only anorexia, fever, and lethargy (Jansen, 1941). In the first American outbreak of pockless disease, rabbits developed conjunctivitis and diarrhea and died 7–9 days after experimental infection (Christensen et al., 1967). Jansen (1941, 1946, 1947) and Christensen et al. (1967) described the occasional presence of scattered papules on the lips and tongues of rabbits with pockless rabbitpox. Experimentally, both the Utrecht and Rockefeller strains of virus produce skin lesions (Bedson and Duckworth, 1963).

PATHOLOGY

The gross and microscopic pathology of rabbitpox has been described in detail by Greene (1934b) for the Rockefeller Institute outbreak and by Christensen et al. (1967) for the first outbreak of pockless rabbitpox in the United States. The most distinctive gross lesions are the skin lesions, which may range in severity from a few localized papules to severe, almost confluent skin lesions with extensive necrosis and hemorrhage. Nodules occur in the mouth, upper respiratory tract, spleen, liver, and lungs but may also occur elsewhere in the body. Subcutaneous and oral submucosal edema and edema of other body orifices are common. Only rabbits with severe lesions of the mouth are emaciated at necropsy.

The liver is enlarged, yellowish, and has numerous small, gray nodules. Focal areas of hepatic necrosis may be seen. Small nodules may also occur in the gallbladder. The spleen is usually moderately enlarged with occasional focal nodules or areas of focal necrosis. Scattered diffusely throughout the lungs may be small white nodules and, in advanced cases, focal areas of necrosis. The testicles, ovaries, and uterus frequently exhibit diffuse white nodules and marked edema. Necrosis of the testes occurs frequently, and the uterus may contain focal abscesses. Focal nodules may be present in lymph nodes, adrenal glands, thyroid glands, parathyroid glands, peritoneum, omentum, and, rarely, the heart. Specific gross lesions are seldom observed in the central nervous system or kidneys. In the pockless form of the disease, a few pocks may be found in the mouth, and occasional skin lesions may be revealed by shaving the rabbit. The prominent gross lesions at necropsy are pleuritis, multifocal hepatic necrosis, splenomegaly, and edema and hemorrhage of the testes. The small white nodules, abundant in the more typical form of the disease, occur occasionally in the lungs and adrenal glands.

The predominant histological lesion in rabbitpox is the papule or nodule which occurs in the skin and many other organs. A typical nodule consists of a central zone of necrosis, surrounded by mononuclear cells. Adjacent tissues are frequently edematous and occasionally hemorrhagic. Diffuse lesions with massive mononuclear cell infiltration, necrosis, hemorrhage, and edema often occur. Typical variola-like vesicles and pustules are not characteristic of rabbitpox infection. Vascular occlusion from the pronounced swelling of the endothelium may result in necrotic lesions.

In the lungs, focal nodular lesions and diffuse pneumonitis, with perivascular mononuclear and polymorphonuclear cell infiltration occur. Focal to diffuse pulmonary necrosis may be found. There is severe congestion of the spleen, with marked distention of sinuses by mononuclear cells, edema of Malpighian corpuscles, and focal to diffuse necrosis. Lymph nodes are generally greatly enlarged, mainly from severe edema. Extensive necrosis of lymph nodes and other lymphoid tissues such as Peyer's patches may occur. Hemorrhage and necrosis of the bone marrow occur frequently, interspersed with areas of mononuclear cell infiltration. Degeneration and necrosis of hepatic parenchyma may be focal or diffuse and may involve the whole organ. Focal necrosis with edema is detected in the testes, as are necrotic foci in the adrenal glands, uterus, thyroid glands, thymus, and salivary glands. The characteristic cytoplasmic inclusions associated with poxvirus infections are seldom encountered in rabbitpox.

DIAGNOSIS

Rabbitpox can be diagnosed by the clinical signs and the characteristic gross and microscopic lesions. Confirmatory diagnosis can be made by detection of viral antigen in tissues by fluorescent antibody on tissue impression smears (Christensen et al., 1967) or by virus isolation and identification. A PCR assay, using four primers, followed by electrospray ionization mass spectrometry, has been described which identified and speciated orthopoxviruses (Eshoo et al., 2009). The virus can be isolated by chorioallantoic membrane inoculation of chicken embryos or by cell culture propagation of the virus on cells derived from rabbits, mice, or any of several animal species (Christensen et al., 1967). The virus may be identified by the fluorescent antibody procedure, hemagglutination inhibition (some strains), or cross-protection tests using vaccinia-immunized and susceptible rabbits. Vaccinia-immunized rabbits should be resistant, whereas severe disease with high mortality should occur in susceptible rabbits.

CONTROL

Because the natural source of virus causing outbreaks has not been determined, control measures to prevent the occurrence of disease have not been

developed. In outbreaks, preventing spread of the virus in the colony by isolation of sick rabbits has met with mixed success (Christensen et al., 1967; Greene, 1934a). Investigators using rabbitpox virus experimentally should take exceptional precautions to prevent the virus from reaching susceptible rabbit populations. In an outbreak in a large colony, vaccination with vaccinia virus can be used to protect uninfected rabbits (Appleyard and Westwood, 1964; Boulter et al., 1971; Rosahn et al., 1936b).

Herpesvirus Infections

Herpesviruses have long been recognized as the causative agents of respiratory and genital diseases in humans, cattle, horses, and swine. They are also the recognized causes of other disease syndromes in many species of animals, including neoplastic diseases in frogs, chickens, rabbits, monkeys, and humans. An important characteristic of the herpesviruses is the capacity to cause mild or subclinical disease after which viral persistence in a latent state may ensue. Stresses of various kinds may result in viral recrudescence even after prolonged periods of latency. The possible existence of latent virus infections may have an important influence on the quality of experimental animals and potentially on the validity of experimental findings. In addition, there are numerous examples of herpesviruses that cause severe disease when infecting an abnormal host as demonstrated when *Human herpesvirus 1* infects rabbits. The *Herpesviridae* of rabbits and hares can be subdivided into *Gammaherpesvirinae* and *Alphaherpesvirinae* (Fauquet et al., 2005). The *Gammaherpesvirinae* contain two tentative members of the genus *Rhadinovirus*, Leporid Herpesvirus 1 and Leporid Herpesvirus 2. Two members of the *Alphaherpesvirinae*, genus *Simplex virus*, are known to infect rabbits, Leporid Herpesvirus 4 and *Human herpesvirus 1*.

Leporid Herpesvirus 1

HISTORY

Leporid herpesvirus I (synonyms *Herpesvirus sylvilagus,* cottontail virus, Hinze herpesvirus lymphoma) was isolated from primary kidney cell cultures from apparently healthy weanling Eastern Cottontail rabbits (*Sylvilagus floridanus*) trapped in Wisconsin (Hinze, 1968, 1971a). The virus was detected when focal areas of cell destruction were observed in cell monolayers 14 days after incubation. The virus has since been propagated in kidney cells of both Eastern Cottontail and domestic rabbits. Another herpesvirus, apparently distinct from the original isolate of Hinze (1971a), was recovered from primary kidney cell cultures of *Sylvilagus floridanus* (Cebrian et al., 1989).

ETIOLOGY

The virus possessed the physical, chemical, and biological properties of a herpesvirus and was named *Herpesvirus sylvilagus* (Heine and Hinze, 1972; Hinze, 1971a). Although infectious virus could not be demonstrated in lymphocytes from infected *Sylvilagus* rabbits, it could be detected after in vitro cocultivation with rabbit kidney cells (Hinze and Wegner, 1973; Wegner and Hinze, 1974). The virus is strongly cell-associated (Ley and Burger, 1970), and both B and T lymphocytes are infected (Kramp et al., 1985). The virus can be propagated in cells of both Eastern Cottontail and domestic New Zealand White rabbits but not in cells from humans, monkeys, hamsters, mice, nor in chicken embryos. The highest concentrations of virus are obtained by the use of primary kidney cell lines established from newborn or juvenile Eastern Cottontail rabbits (Cohrs and Rouhandeh, 1982; Medveczky et al., 1984). The virus possesses no antigenic relationship to Leporid herpesvirus 2 or to four other Leporid herpesviruses (Hinze, 1971a). The genome of the virus is similar to those of *Herpesvirus saimiri* and Epstein-Barr virus, in that it contains a variable number of repetitive DNA elements at both ends (Heine and Hinze, 1972; Cohrs and Rouhandeh, 1987; Rouhandeh and Cohrs, 1987; Medveczky et al., 1989).

EPIDEMIOLOGY

A serological survey in Wisconsin revealed antibodies to the virus in six of 101 wild Eastern Cottontail rabbits (Spieker and Yuill, 1976). In experimentally infected Eastern Cottontail rabbits, herpesvirus was not recovered from feces, urine, milk, ejaculates, or conjunctival and genital secretions, but was isolated from the oral secretions of one of 15 infected rabbits (Spieker and Yuill, 1977a). Shedding of infectious virus in oral secretions, unrelated to age, sex, or season, was demonstrated in naturally infected Eastern Cottontail rabbits (Hinze and Lee, 1980). The tonsils are the likely site of persistent infection and virus is released into the oral cavity. Transplacental transmission of virus was not found (Spieker and Yuill, 1977a). Transmission by insect vectors was not detected (Spieker and Yuill, 1977b). Repeated attempts to infect domestic New Zealand White rabbits have met with failure (Hinze, 1971a). Only rabbits of the genus *Sylvilagus* appear to be susceptible.

CLINICAL SIGNS

Inoculation of Eastern Cottontail rabbits by various routes results in a chronic low-grade viremia that persists, in most instances, for the life of the rabbit (Hinze, 1971b; Hinze and Chipman, 1972; Hinze and Wegner, 1973). Persistently infected rabbits have a pronounced lymphocytosis, with differential lymphocyte counts of up to 95% compared to 50–60% in normal rabbits (Hinze, 1969).

PATHOLOGY

The lymphoproliferative lesions in Eastern Cottontail rabbits occur in the lymphoid and other organ systems (Hesselton et al., 1988; Hinze, 1969, 1971b; Hinze and Wegner, 1973). Extensive infiltration of various tissues, commonly the kidneys, liver, lungs, and myocardium, with immature, actively proliferating lymphocytes occurs 6–8 weeks after experimental inoculation. The experimentally induced lymphoproliferative disease varies from benign lymphoid hyperplasia to lesions consistent with malignant lymphoma. Juvenile rabbits are affected more frequently and severely than adult rabbits.

DIAGNOSIS

Natural infection with Leporid herpesvirus 1 in Eastern Cottontail rabbits may result in leukocytosis, splenomegaly, and lymphadenopathy. Virus can be isolated from the oral cavity and circulating lymphocytes of infected rabbits cocultured with rabbit kidney cells (Hinze and Lee, 1980). Antibodies can be detected by indirect immunofluorescence and plaque reduction assays (Spieker and Yuill, 1976; Yang et al., 1990).

Leporid Herpesvirus 2

HISTORY

Nesburn (1969) isolated Leporid herpesvirus 2 (synonyms *Herpesvirus cuniculi,* virus III of rabbits, Leporid herpesvirus 3) from primary kidney cell cultures from *Oryctolagus cuniculus* and named it *Herpesvirus cuniculi.* This may represent a reisolation of virus III of rabbits (Rivers and Tillett, 1923), but, as the original isolate was not available, a direct serological comparison could not be made. Comparison of the reported characteristics of virus III with *Herpesvirus cuniculi,* however, indicates that they are identical (Nesburn, 1969). Virus III was isolated during attempts to find the etiologic agent of varicella (chicken pox). When inoculated into rabbits, the agent induced fever, exanthema, skin vesicles, corneal lesions, and intranuclear inclusions reminiscent of varicella infection (Rivers and Tillett, 1923). Convalescent sera from human varicella patients failed to inactivate the virus (Rivers and Tillett, 1924a). A similar virus was isolated from serially passaged normal rabbit testicular tissue during investigations of the etiology of rheumatic fever (Miller et al., 1924). McCartney isolated the virus while working on scarlet fever in England (Topacio and Hyde, 1932), and the agent has also been isolated by Doerr in Switzerland (Andrewes, 1928).

ETIOLOGY

Nesburn (1969) showed that the viral isolate possesses the physical, chemical, cytopathic, histological, and electron microscopic characteristics of a herpesvirus. The virus can be propagated in primary or established cell lines of rabbit origin as well as in African green monkey kidney cells. The virus is now designated Leporid herpesvirus 2 (Roizman, 1982).

EPIDEMIOLOGY

Rivers and Tillett (1924a) found that four of 20 rabbits possessed antibodies to the virus and that 15% of 200 rabbits were immune to infection. Andrewes (1928), in England, found 98% of 377 experimental rabbits susceptible to the virus. He concluded that the virus was probably endemic in some rabbit colonies. Topacio and Hyde (1932), in Maryland, found that 17% of 76 rabbits were immune to infection. They suggested that older bucks, resistant to infection, were carriers of the virus. Neutralizing antibodies to the virus were detected in 6% of 196 rabbits from Connecticut and Maryland (Swack and Hsiung, 1972). Nesburn (1969) was unable to reisolate the virus from over 100 batches of primary rabbit kidney cell cultures prepared since initial isolation of the virus. Experimentally, virus was recovered from the blood of rabbits more than 100 days after inoculation (Swack and Hsiung, 1972). Appreciable titers of virus were detected in leukocytes, spleen, liver, lungs, and salivary glands, whereas the concentration of virus in kidneys was variable. However, transmission of the virus by direct contact or transplacentally failed to occur.

CLINICAL SIGNS

All reported isolations of virus have been from apparently normal rabbits, and no naturally occurring disease has been attributed to infection with the virus. However, a viral agent, presumably a herpesvirus, was recovered from the nares of rabbits with respiratory disease (Renquist and Soave, 1972). Experimentally, intradermal inoculation of rabbits with virus resulted in pronounced erythema at the site of inoculation after 4–7 days, which usually disappears within 2 weeks (Rivers and Tillett, 1924a). Occasionally, generalized reactions with anorexia, diarrhea, emaciation, fever, and skin vesicles have been reported. Intradermal inoculation may result in erythematous papules, whereas corneal scarification caused swelling and vesiculation of corneal cells (Topacio and Hyde, 1932). Intratesticular inoculation of rabbits results in acute orchitis and fever within 3–4 days (Andrewes, 1928). Intramuscular and subcutaneous inoculation of rabbits failed to induce clinical signs; however, corneal scarification with virus resulted in mild punctate keratitis (Nesburn, 1969). Similarly, intraperitoneal inoculation of virus did not induce clinical disease (Swack and Hsiung, 1972).

PATHOLOGY

No gross pathological changes have been observed in internal organs of experimentally infected rabbits.

Microscopically, testes, skin, and cornea show edema and an intense mononuclear leukocyte infiltration. Large eosinophilic intranuclear inclusions, typical of herpesviruses, characteristically occur in corneal epithelium, interstitial cells of the testicles, and in endothelial leukocytes of the skin (Rivers and Tillett, 1924b). Severe myocarditis with typical herpesviral inclusions occurred in rabbits inoculated intracardially with virus (Pearce, 1950, 1960). The absence of reported cases could be attributed to the relative rarity of disease or to lack of intensive etiologic investigation of cases which do occur.

DIAGNOSIS

Pathological findings described above including herpesviral inclusions in domestic rabbits (*Oryctolagus cuniculus*) are suggestive of Leporid Herpesvirus 2. PCR, in situ hybridization, and immunohistochemical labeling would be necessary to separate Leporid Herpesvirus 2 from the *Alphaherpesvirinae* described below (Gruber et al., 2009; Jin et al., 2008a; Weissenböck et al., 1997).

CONTROL

Both herpesvirus 1 of Eastern Cottontail rabbits and herpesvirus 2 of domestic rabbits possess the capacity to persist in infected hosts as a subclinical infection. Such infections, if not recognized, could result in considerable confounding in experimental studies, especially if conditions cause recrudescence of latent infections.

Leporid Herpesvirus 4

HISTORY

Leporid herpesvirus 4 (LHV 4) was isolated from a naturally occurring outbreak with high morbidity and mortality affecting miniature and crossbred domestic European rabbits (*Orcytolagus cunniculi*) in a rabbitry in Alaska (Jin et al., 2008a). Two other outbreaks, with similar clinical signs and pathology, have been reported in North America, although the virus was not identified (Onderka et al., 1992; Swan, 1991).

ETIOLOGY

Electron microscopy of LHV 4 demonstrated capsid and core particles similar in size and structure to *Human herpesvirus 1*. The genome of LHV 4 is 120–130 kbp and partial sequences compared to other *Alphaherpesvirinae* demonstrated the closest homology by nucleotide identity with *Bovine herpesvirus 2* (Jin et al., 2008b). *Bovine herpesvirus 2* was originally isolated from cattle in Africa, but has been found in a variety of domestic and wild ruminants (Borchers et al., 2002; Kálmán and Egyed, 2005). LHV 4 infects rabbit skin and Vero (monkey kidney) cells with cytopathic effects similar to *Human herpesvirus 1* (Jin et al., 2008a).

EPIDEMIOLOGY

LHV 4 was isolated from an outbreak of acute disease in an outdoor rabbitry in Alaska (Jin et al., 2008a). The mode of herpesvirus introduction in this outbreak was not determined as there had been no travel or introduction of new rabbits. However, feral domestic European rabbits (*Oryctolagus cuniculus*) and Snowshoe hares (*Lepus americanus*) were in the area. In addition, the outbreak occurred in July and August, when mosquito and biting fly activity is typically high. A second outbreak occurred in the same rabbitry the following year in the spring and summer, although it could not be determined if this was due to a re-introduction or reactivation of a chronic infection (Jin et al., 2008b). Two outbreaks of disease caused by herpes-like viruses that were not identified were reported in Canada (Onderka et al., 1992; Swan, 1991). The clinical signs and pathology of those outbreaks were similar to the Alaska outbreak and may suggest that there is an animal reservoir in northwestern North America of this Alpha herpesvirus.

CLINICAL SIGNS

Clinical signs reported in the naturally occurring outbreaks included conjunctivitis and periocular swelling with purulent ocular discharge, ulcerative dermatitis, progressive weakness, anorexia, respiratory distress, torticollis, ataxia, weight loss, diarrhea, bruxism, genital swelling, and abortion (Jin et al., 2008a). Morbidity was approximately 50%, with 29% mortality. Some rabbits died acutely with anorexia, the only sign observed prior to death. Recovered virus administered intranasally or by the cornea to New Zealand White rabbits caused severe acute disease within 4 days of inoculation with one out of four affected animals being euthanized due to severity of the disease. The remaining rabbits recovered. Acute mortality associated with unidentified herpesviruses was reported in four adult *Oryctolagus cuniculus* in two rabbitries in Canada (Onderka et al., 1992; Swan, 1991). Acute death without clinical signs occurred in some rabbits as well as conjunctivitis, nasal discharge, edematous eyes and faces. Herpesviruses were recovered on rabbit kidney cells and experimental inoculation of rabbits with the virus reproduced the disease syndrome (Onderka et al., 1992; Swan, 1991). However, it is unclear if the herpesviruses responsible for these outbreaks are Gamma herpesviruses or Alpha herpesviruses related to LHV 4.

PATHOLOGY

Lesions included severe dermal and subcutaneous hemorrhage, edema, and necrosis with vascular necrosis and thrombosis (Jin et al., 2008a, 2008b). There was a mixed infiltrate of macrophages, lymphocytes, plasma cells with fewer heterophils. Necrosis and hemorrhage

were found within the ventricular walls, spleen, lymph nodes, and lungs. Areas of fibrin deposition were present in the spleen and lung. Intranuclear inclusions were found within the affected skin, subcutis, and ventricular walls, but not in the spleen, lungs, or lymph nodes. Similar lesions were seen following experimental infection (Jin et al., 2008b).

DIAGNOSIS

Typical lesions in the skin, spleen, lymph nodes, lungs, and heart with demonstrative intranuclear inclusions are suggestive of LHV 4 infection. DNA extracted from most tissues, including appendix, sciatic nerve, kidney, adrenal gland, spleen, liver, lung, lymph node, salivary gland, tonsil, and brain from an inoculated rabbit that died in the acute phase of the disease was specific for LHV 4 ribonuclease reductase gene by PCR (Jin et al., 2008b). At 14 days after inoculation, the eye, trigeminal ganglion, and tonsil were positive for LHV 4 by PCR analysis. In the second outbreak at the rabbitry in Alaska, the eye of an affected rabbit was positive for LHV 4 by PCR.

CONTROL

As latent infection is typical of Alpha herpesviruses, control measures are difficult. The rabbitry involved in the Alaska outbreak was depopulated after the second outbreak (Jin et al., 2008).

Human Herpesvirus 1 (HHV-1)

Herpesviruses of other species, including HHV-1, can cause encephalitis in rabbits experimentally inoculated (Chowdhury et al., 2000; Seto et al., 1995) and horizontal transmission of HHV-1 between rabbits has been reported (Kaplan, 1969). Spontaneous cases of HHV-1 encephalitis presumably transmitted from humans to pet domestic European rabbits have also been reported (Grest et al., 2002; Gruber et al., 2009; Müller et al., 2009; Weissenböck, et al., 1997). In each of these reports, rabbits with HHV-1 encephalitis were in close contact with a person with herpes labialis before they developed illness. The rabbits presented with neurological signs including anorexia, tonic-clonic spasms, circling, incoordination, ataxia, seizures, and opisthotonus. One rabbit also had a history of epiphora of the left eye, conjunctivitis, bruxism, and hypersalivation (Müller et al., 2009). Pathological findings included non-suppurative meningoencephalitis and large, eosinophilic intranuclear inclusion bodies in the neurons and glial cells. Diagnosis was confirmed by immunohistochemical labeling with polyclonal antibodies specific for HHV-1 (Grest et al., 2002; Gruber et al., 2009; Weissenböck et al., 1997), in situ hybridization using a DNA probe for HHV-1 (Gruber et al., 2009; Müller et al., 2009; Weissenböck et al., 1997), or PCR specific for the UL42 gene of HHV-1 (Grest et al., 2002; Gruber et al., 2009; Weissenböck et al., 1997). Control measures would include preventing close contact between humans with active herpetic lesions and rabbits.

Papilloma and Polyoma Viruses

The family *Papillomaviridae* contains viruses in the genus *Kappapapillomavirus* which cause papillomas (warts) in various animals and includes two species of rabbit viruses, the *Cottontail rabbit papillomavirus* and the *Rabbit oral papillomavirus* (Fauquet et al., 2005). The family *Polyomaviridae* contains one genus, *Polyomavirus*, which includes the species *Rabbit kidney vacuolating virus*.

Cottontail Rabbit Papillomavirus

HISTORY

The Cottontail rabbit or Shope papillomavirus was recognized as a transmissible agent by Shope and Hurst (1933) while they were attempting to define the etiology of wart-like tumors on Eastern Cottontail rabbits (*Sylvilagus floridanus*) in the Midwestern United States. They demonstrated the filterability of the infectious agent, transmitted it to other Eastern Cottontail rabbits as well as domestic European rabbits, and described the histopathology of the disease (Shope, 1935). Rabbit papillomatosis was initially considered a natural benign disease of *Sylvilagus* rabbits only; however, spontaneous outbreaks of papillomatosis in *Oryctolagus cuniculus* indicate that the disease has greater relevance (Hagen, 1966). Soon after discovery of the virus, it was also shown to cause malignant neoplasms histologically resembling squamous cell carcinomas (Kidd and Rous, 1940; Rous and Beard, 1934, 1935). This was the first recognition of an oncogenic virus in mammals. The disease has served as a model system to elucidate the role of viruses in the pathogenesis of cancer in humans and animals (Evans and Thomsen, 1969; Evans et al., 1962a, 1962b; Georges et al., 1984; Kreider and Bartlett, 1981, 1985; Smith and Campo, 1985) and potential therapeutic interventions (Gambhira et al., 2007).

ETIOLOGY

The virus is the type species of the genus *Kappapapillomavirus* (formerly *Papillomavirus*) of the family *Papillomaviridae* (Fauquet et al., 2005) and possesses the characteristic circular DNA genome, icosahedral structure, and other chemical and physical properties of this family (Gross, 1983; Kass and Knight, 1965; Murphy et al., 1981). The complete genome contains 7863 nucleotides (Giri et al., 1985) and consists of ten genes. All of the papilloma viruses have two capsid proteins (major L1 and minor L2) and although the C terminus of L1 is

exposed on the surface of the viron, suggesting it may have an important role in immune responses, both proteins encode virus-neutralizing epitopes (Campo, 2003). The virus is antigenically distinct from other members of the genus *Kappapapillomavirus.* Nuclear (Yoshida and Ito, 1968) and cytoplasmic (Ishimoto et al., 1970) viral antigens have been demonstrated by immunofluorescence in virus-inoculated normal skin cells and virus-induced papillomas. However, the significance of these findings is difficult to interpret since controls for rabbit kidney vacuolating virus, a passenger virus (Hartley and Rowe, 1964), were usually not included (Kreider and Bartlett, 1981). The virus can be maintained by serial propagation in the skin of *Sylvilagus* rabbits, inoculated intracutaneously or scarified with virus (Shope and Hurst, 1933). Intramuscular inoculation does not result in clinical papillomatosis. Dogs, cats, pigs, goats, rats, mice, and guinea pigs are refractory to the virus. The skin of embryonic rats is susceptible to the virus, and typical papillomas develop following inoculation (Greene, 1953b); however, few papillomas develop, and they regress unless the host is immunosuppressed (Kreider et al., 1971). Cellular proliferation or neoplastic transformation by the virus has been reported in rabbit skin cell cultures (Coman, 1946), skin cultures derived from neonatal domestic European rabbits (DeMaeyer, 1962), and explants of embryonic rabbit skin (Greene, 1953a). Transplantation of transformed skin cultures into rabbits resulted in the formation of papillomas (Coman, 1946; Kreider, 1963). (see also Chapter 16).

EPIDEMIOLOGY

Papillomatosis occurs most frequently as a natural disease of *Sylvilagus* rabbits in the Midwestern United States extending from Minnesota and North Dakota to Texas (Gross, 1983; Hagen, 1966). The virus has apparently not become established in the eastern states. The only natural outbreaks of disease in domestic European rabbits were in southern California, suggesting that the virus is present in wild *Sylvilagus* rabbits of the area, and spreads to domestic European rabbits by arthropod vectors (Hagen, 1966). The disease in *Sylvilagus* rabbits also occurs on coastal islands in Washington, in a population of rabbits introduced from Kansas (Lancaster and Olson, 1982).

The *Sylvilagus* rabbit is the natural host, but the domestic European rabbit is also susceptible to the virus (Shope, 1935). Natural outbreaks have been reported in commercial rabbitries (Hagen, 1966). The Black-tailed jackrabbit (*Lepus californicus*) is also susceptible to the virus (Beard and Rous, 1935). Infection of the skin of domestic European rabbits results in the formation of papillomas essentially devoid of infectious virus (Shope, 1935). Papillomas, primary carcinomas, and metastases from domestic European rabbits have about 10–100 copies of viral DNA, whereas papillomas from *Sylvilagus* rabbits have 2400–8800 copies (Stevens and Wettstein, 1979). Papillomas from domestic European rabbits can be serially transferred, but only small amounts of infectious virus are typically demonstrated (Gross, 1983; Hu et al., 2007; Selbie and Robinson, 1947; Shope, 1935), indicating that domestic European rabbits are not a source of virus for arthropod vectors.

Infection of *Sylvilagus* rabbits, Black-tailed jackrabbits, and Snowshoe hares (*Lepus americanus*) induces lesions containing a high concentration of virus (Lancaster and Olson, 1982; Syverton et al., 1950). Contact transmission of papillomatosis may occur, but transmission of the virus by the rabbit tick (*Haemaphysalis leporis-palustris*) is probably the most common natural mode (Larson et al., 1936). Transmission by mosquitoes and reduviid bugs has been demonstrated experimentally (Dalmat, 1958). In commercial rabbitries, the mosquito may be the principal vector between wild *Sylvilagus* and domestic European rabbits (Hagen, 1966). This hypothesis is strengthened by the observation that in natural cases of disease in domestic European rabbits, lesions were confined to the relatively hairless parts of the body around the eyes, ears, and anus, areas where mosquitoes are more apt to feed. Nematodes may be involved in the natural transmission of virus (Rendtorff and Wilcox, 1957). Experimentally, papillomas were induced when papilloma virus and larvae of the nematode *Nippostrongylus muris* were applied to rabbit skin, but not by virus or nematode larvae alone. See Chapter 16 for further information.

CLINICAL SIGNS

Papillomatosis of wild *Sylvilagus* rabbits is characterized by the presence of horny warts, usually on the neck, shoulders, or abdomen. The warts begin as red raised areas at the site of infection, grow to become typical papillomas with rough rounded surfaces, and may later develop into large, keratinized horny growths (Shope and Hurst, 1933). The virus was initially believed to cause only transient papillomatosis, but it was later shown that in naturally infected *Sylvilagus* rabbits papillomas may become malignant squamous cell carcinomas (Syverton and Berry, 1935). This phenomenon was later shown to be a relatively frequent occurrence in both naturally and experimentally infected *Sylvilagus* rabbits, as 25% of infected rabbits developed carcinomatous lesions following infection (Syverton et al., 1950). In approximately 35% of naturally infected rabbits, papillomas regress within 6 months after infection. In natural outbreaks of papillomatosis of domestic European rabbits in southern California (Hagen, 1966), papillomas most commonly occurred on the eyelids and ears. Experimentally induced papillomas develop more slowly in domestic European rabbits than in *Sylvilagus* rabbits, reach a stationary phase, and then occasionally regress (Syverton, 1952).

Regression occurs depending on the interaction of the genotype of the virus and host immunity (Hu et al., 2002, 2005). A variant virus that contains the regressive E6 gene has a high rate of regression (Hu et al., 2002). Certain MHC haplotypes have been associated with regression or persistence in domestic European rabbits (Salmon et al., 2000). In one study, papillomas persisted when a regressive viral strain was used if rabbits were immunosuppressed with cyclosporine A treatment, but regression also varied with the strain of rabbit as more papillomas regressed in outbred New Zealand White rabbits than inbred EIII/JC rabbits (Hu et al., 2005). Once immunosuppression was removed, most papillomas regressed in outbred rabbits (67–89%), whereas only 13% regressed in inbred rabbits, highlighting the importance of multiple factors in persistence of papillomas. Rous and Beard (1934, 1935) recognized the malignant potential of rabbit papillomavirus when they demonstrated that intramuscular inoculation of papillomatous tissue into domestic European rabbits resulted in invasive squamous cell carcinomas. In experimentally infected domestic European rabbits, 75% developed carcinomas if kept longer than 6 months (Syverton, 1952). *Sylvilagus* rabbits have a three-fold lower incidence of carcinomas than European rabbits (Rous and Beard, 1935; Syverton et al., 1950).

PATHOLOGY

The warts which develop following infection in *Sylvilagus* and domestic European rabbits are typical papillomas. The malignant tumors which arise from papillomas are squamous cell carcinomas. Metastasis to regional lymph nodes, particularly the axillary nodes, is common (Kreider and Bartlet, 1981) and about 25% of rabbits that succumb have pulmonary metastases. In addition, amyloid deposition in renal glomeruli, hepatic sinusoids and splenic red pulp is present in the majority of rabbits.

DIAGNOSIS

Cottontail rabbit papillomatosis is diagnosed clinically by the characteristic skin tumors, which never occur in the mouth, and may be confirmed by histopathological examination. A survey of tumors in pet rabbits submitted to the surgical biopsy service of a veterinary school in Pennsylvania over a 16-year period revealed that Shope papilloma was diagnosed in two tumors, both on the ears, from 179 rabbits (von Bomhard et al., 2007). No cell culture system is available for routine isolation of virus (Lancaster and Olson, 1982).

CONTROL

The endemic disease of *Sylvilagus* rabbits is of little economic significance, and thus no prophylactic methods have been developed. Because natural infection occurs in domestic European rabbits (Hagen, 1966), the adoption of control methods may become necessary. In areas where the disease is endemic in wild *Sylvilagus* rabbits, where arthropod vectors are present, and where outdoor rabbit husbandry is practiced, arthropod control would appear to be a logical approach. Rabbits can be immunized by two intraperitoneal inoculations with glycerinated rabbit papilloma suspensions (Shope, 1937). Domestic rabbits with experimentally induced papillomas resist challenge with virus derived from papillomas of cottontail rabbits (Hagen, 1966). A tumor-specific vaccine composed of allogenic tumor cells increased the regression rate of papillomas (Evans et al., 1962a).

Rabbit Oral Papillomavirus

HISTORY

Oral papillomatosis of rabbits was recognized as a distinct viral disease of domestic European rabbits (*Oryctolagus cuniculus*) by Parsons and Kidd (1936). They found a 17% prevalence of small papillomas in the mouths of rabbits of several breeds in New York City. The lesions were usually confined to the ventral surface of the tongue. They transmitted the virus to both domestic European and *Sylvilagus* rabbits and by cross-immunity tests and tissue-susceptibility studies demonstrated that it was distinct from the Cottontail rabbit (Shope) papillomavirus. They also showed that virus is frequently present in the mouths of rabbits without lesions and that tattooing or licking of tar stimulated lesion development in such carrier rabbits (Parsons and Kidd, 1943). A spontaneous outbreak in New York of rabbit oral papillomatosis, involving several breeds of domestic European rabbits, was described (Weisbroth and Scher, 1970). New Zealand White rabbits with oral papillomas were reported in Illinois (Sundberg et al., 1985) and Mexico (Dominguez et al., 1981).

ETIOLOGY

The virus was partly characterized by Parsons and Kidd (1943) and was later included in the genus *Kappapillomavirus* of the family *Papillomaviridae* (Fauquet et al., 2005). The virus consists of 7565 nucleotides and has the greatest amino acid sequence identity to *Cottontail rabbit papillomavirus*, although the greatest area of homology was only 68% (Christensen et al., 2000). However, the virus is immunologically distinct from the *Cottontail rabbit papillomavirus* and naturally infects only leporids (Parsons and Kidd, 1936, 1943). Nuclear viral replication, characteristic of the *Papovaviridae*, has been demonstrated (Rdzok et al., 1966; Richter et al., 1964). Neonatal hamsters, inoculated subcutaneously with a tumor suspension from naturally infected rabbits, developed fibromas (Sundberg et al., 1985). The virus has not been propagated outside of susceptible host animals.

EPIDEMIOLOGY

The virus probably spreads by direct contact, and lesion development may require oral trauma for viral entry. Coarse feed, maloccluded teeth, or other oral irritants may serve as the inciting event (Parsons and Kidd, 1943; Weisbroth and Scher, 1970). Experimentally induced lesions appear 9–38 days after inoculation (Parsons and Kidd, 1936), but the incubation period of the natural disease is unknown. The disease generally occurs in rabbits 2–18 months old (Sundberg et al., 1985; Weisbroth and Scher, 1970).

CLINICAL SIGNS

Oral papillomatosis is a benign disease characterized clinically by small discrete whitish growths on the ventral surface of the tongue. The early lesions are sessile, later become rugose or pedunculated, and ultimately ulcerate (Parsons and Kidd, 1936; Sundberg et al., 1985; Weisbroth and Scher, 1970). The lesions are seldom more than 5 mm in size and 4 mm in thickness and usually substantially smaller. Papillomas have been known to persist for as long as 145 days, but usually disappear in weeks (Parsons and Kidd, 1936). Lesions rarely occur elsewhere in the mouth and never on the body. However, in a Flemish Giant pet rabbit in New Zealand, virus recovered from lesions on the nictitating membrane and lower eyelid had 99.3% homology with *Rabbit oral papillomavirus* (Munday et al., 2007).

PATHOLOGY

The lesions are microscopically typical papillomas (Parsons and Kidd, 1943; Rdzok et al., 1966; Richter et al., 1964; Sundberg et al., 1985; Weisbroth and Scher, 1970). Cells in the stratum spinosum contain basophilic intranuclear inclusions (Dominguez et al., 1981; Sundberg et al., 1985).

DIAGNOSIS

The disease is diagnosed by typical lesions occurring only in the mouth, in contrast to rabbit papillomatosis, in which lesions are observed only on the skin. The lesions are typical papillomas, and papillomavirus antigens can be detected in cells of the stratum spinosum by the peroxidase antiperoxidase technique (Sundberg et al., 1985).

CONTROL

Rabbits recovering from disease are resistant to reinfection but are susceptible to *Cottontail rabbit (Shope) papillomavirus*.

Rabbit Kidney Vacuolating Virus

The *Rabbit kidney vacuolating virus* was isolated in primary rabbit kidney cell cultures from papillomas of Eastern Cottontail rabbits (*Sylvilagus floridanus*) collected in Kansas (Hartley and Rowe, 1964). The virus causes vacuolar cytopathic effects in cell cultures. The virus resembles the *Cottontail rabbit papillomavirus* but is a distinct virus. It does not produce papillomas when inoculated into rabbits and does not immunize rabbits against *Cottontail rabbit papillomavirus*. The virus is slightly smaller than the viruses of the genus *Papillomavirus* and resembles *Polyomavirus* in size, morphology, and DNA composition (Crawford and Follett, 1967). The virus has been classified as a member of the genus *Polyomavirus* within the family *Polyomaviridae* (Fauquet et al., 2005). Ultrastructurally, the virus is a typical *Polyomavirus* in its replication pattern (Chambers et al., 1966). The virus is not pathogenic for either domestic European or Eastern Cottontail rabbits or any other animal species. Inoculation of both neonatal and adult domestic and Eastern Cottontail rabbits by several routes did not induce disease (Hartley and Rowe, 1964). Antibodies to the virus have been found in wild *Sylvilagus* rabbits in Kansas and Maryland, but not in domestic European rabbits (Hartley and Rowe, 1964). The virus thus appears to be a fairly common non-pathogenic virus of *Sylvilagus* rabbits, causing only latent infections. Intranuclear inclusions consistent with rabbit kidney vacuolating virus have been found as an incidental finding in New Zealand White rabbits (Percy and Barthold, 2007). Although a contaminant of rabbit papillomas, the virus appears to have no role in the pathogenesis of papillomatosis (Goldman et al., 1972; Ito et al., 1968; Kreider and Bartlett, 1981).

Adenovirus Infections

Adenovirus infections of rabbits, spontaneous and experimental, have been reported. While the taxonomy of the spontaneous adenoviruses found in rabbits has not been determined, the human, swine, and bovine adenoviruses described belong to the genus *Mastadenovirus*. An adenovirus was isolated in Hungary from the spleen, kidneys, lungs, and intestines of rabbits, 6–8 weeks old, with diarrhea (Bodon et al., 1979). The virus was detected in primary rabbit kidney cultures stained with acridine orange although no cytopathic effect was observed. The virus failed to replicate in pig kidney, calf kidney, calf testicle, or human embryonic lung cells. Antisera to several swine and bovine adenoviruses failed to neutralize the virus, whereas a partial antigenic relationship to human adenoviruses was demonstrated by complement fixation and immunodiffusion tests. The virus agglutinated rabbit but not human erythrocytes. A serological survey of 30 *Oryctolagus cuniculus* from four rabbitries in Quebec revealed that three rabbits from three colonies had antibodies to bovine adenovirus type 1 (Descoteaux et al., 1980).

Experimental inoculation of rabbits with human adenovirus type 5 resulted in no clinical response but induced a persistent viral infection in lymphoid tissues for as long as 1 year (Reddick and Lefkowitz, 1969). Human adenovirus type 5 infects rabbit corneas following either intrastromal

injection or topical application to damaged cornea resulting in acute blepharoconjunctivitis, iritis, and corneal edema which peaks at 13 days after infection (Gordon et al., 1992; Trousdale et al., 1995). Other serotypes of human adenovirus induce disease as well, although adenovirus type 5 is commonly used as an animal model to test therapeutic approaches to adenovirus-induced keratoconjunctivitis (Romanowski et al., 1998). Recombinant adenoviruses have been used successfully to infect rabbits in many gene transfer protocols (Kozarsky et al, 1996; Schneider et al., 1999).

Parvovirus Infections

A virus that induced cytopathic effects in primary rabbit kidney cell cultures was isolated from the feces of a rabbit (*Oryctolagus cuniculus*) inoculated with *Herpesvirus cuniculi* in a laboratory in Japan (Matsunaga et al., 1977). The virus had the morphological, physical, and chemical properties of a parvovirus. The various proteins of the virus have been characterized (Matsunaga and Matsuno, 1983). Subsequently, parvovirus was recovered from kidney cells of neonatal rabbits in the United States (Metcalf et al., 1989). These viruses are of the species *Lapine parvovirus*, genus *Parvovirus*, family *Parvoviridae* (Fauquet et al., 2005).

Serological surveys have identified positive rabbitries in Japan, the United States, and Europe. Among 90 rabbits from a commercial source in Japan, 42 (47%) had hemagglutination-inhibiting antibody to the virus (Matsunaga et al., 1977). Of 46 rabbit sera, collected from various sources in the United States, 75% had antibodies detected by immunofluorescence or hemagglutination inhibition assays (Metcalf et al., 1989). In Switzerland, over 70% of 132 rabbit sera from various commercial breeding colonies had antibodies in the hemagglutination inhibition test (Metcalf et al., 1989). Experimental inoculation, orally or intravenously, induced anorexia, listlessness, and catarrhal enteritis in 1-month-old rabbits (*Oryctolagus cuniculus*) (Matsunaga and Chino, 1981). Pathologic changes included catarrhal enteritis with hyperemia, exfoliation of the small intestinal epithelial cells, and increased secretion of intestinal mucus. Virus was detected in feces, small intestine, liver, pancreas, spleen, appendix, and mesenteric lymph node. Rabbits developed hemagglutination-inhibiting antibodies.

RNA VIRUS INFECTIONS

Rotavirus Infections

Rotavirus

HISTORY

Rotavirus was initially isolated from rabbits with diarrhea by Bryden et al. (1976) in England. Virus was recovered from both sporadic cases and outbreaks of diarrhea in weanling rabbits as well as from healthy rabbits. Subsequently, rotavirus was isolated from young rabbits with diarrhea in Japan (Sato et al., 1982), Europe (Castrucci et al., 1985; Eaton, 1984; Peeters et al., 1982, 1984), and the United States (DiGiacomo and Thouless, 1986; Schoeb et al., 1986). Various serological surveys have since revealed that rotavirus infection is widespread in domesticated European rabbits (*Oryctolagus cuniculus*).

ETIOLOGY

Rabbit rotaviruses belong to the family *Reoviridae*, genus *Rotavirus* (Estes and Kapikian, 2007; Fauquet et al., 2005). They are 75-nm icosahedral viruses with a triple-layered protein capsid that contains 11 segments of double-stranded RNA, each of which codes for a protein. The sixth gene (VP6) codes for an inner capsid protein which contains the subgroup specificity. The fourth (VP4) and seventh genes (VP7), code for outer capsid proteins that are the viral neutralization antigens. VP4 is the viral hemagglutin and must be cleaved by a protease, e.g., trypsin, to yield VP5 and VP8 before the virus can infect cells (Matsui et al., 1989; Ramig and Ward, 1991).

The rotaviruses are classified serologically into seven groups (A to G). Groups A to C are found in animals and humans, whereas groups D to G are found only in animals. The rabbit rotaviruses described belong to group A (Tanaka et al., 1988; Thouless et al., 1986). Within each serogroup, rotaviruses are classified into serotypes, defined by reactivity against the outer capsid proteins VP4 (P type) and VP7 (G type). Since the glycoprotein VP7 appears to be immunodominant, classification of VP7 serotypes is more advanced and within group A, 15 serotypes (1–15) have been identified. All rabbit rotaviruses recovered to date have been serotype 3 (G3) (Tanaka et al., 1988; Thouless et al., 1986). Serotype 3 contains the largest and most diverse number of rotaviruses and is common to humans and several other animals. This reflects the genetic reassortment that occurs when different viruses of the same group simultaneously infect susceptible hosts.

Some rotavirus isolates from rabbits induce a cytopathic effect in MA104 rhesus monkey kidney cells in about 3 days (Castrucci et al., 1985; Sato et al., 1982; Thouless et al., 1986), whereas other isolates demonstrate cytopathic effect only after additional passages. Physicochemical studies reveal that rotaviruses are stable from pH 3.0 to 9.0 (Fauquet et al., 2000). Virus remains infectious for months at room temperature on porous and non-porous environmental surfaces, in fecal material, or if stabilized with $CaCl_2$. Rotaviruses can be inactivated when heated at 50°C for 30 min and by treatment with chlorine, formalin, phenols, and

betapropriolactone. Ethanol, 95%, is the most effective disinfectant as it renders the rotavirus non-infectious by removing the outer capsid layer.

EPIDEMIOLOGY

Serological studies indicate that rotavirus infection is widespread in domesticated European rabbits (*Oryctolagus cuniculus*). Of 91 adult rabbits from two commercial rabbitries in Ontario, Canada, 98% had antibodies to rotavirus (Petrie et al., 1978). Sera collected from fryer rabbits at two abattoirs in Ontario, Canada, revealed that 60% of 200 rabbits had antibodies (Percy et al., 1993). A survey in Tokyo prefecture, Japan, of 39 adult rabbits revealed that 82% had antibodies (Takahashi et al., 1979). A more extensive survey of ten breeding and 13 laboratory colonies in metropolitan Tokyo and Ibaragi, Saitama, Kanagawa, Shizuoka, and Nagano prefectures in Japan revealed antibodies to rotavirus in 83% of the 23 colonies and in 81% of 160 sera (Iwai et al., 1986). In Hungary, 74% of 112 sera from five large-scale rabbit farms had rotavirus antibodies (Kudron et al., 1982). In the United States, 95% of 149 sera from rabbits more than 2 months old in a commercial colony in Washington had antibodies (DiGiacomo and Thouless, 1984). Rotavirus was detected in fecal samples from rabbits in three other colonies in the state (DiGiacomo and Thouless, 1986). Antibodies against rotavirus have also been detected in 29% of 17 sera from Eastern Cottontail rabbits *(Sylvilagus floridanus)* in Ontario, 52% of 27 sera from Snowshoe hares (*Lepus americanus*) in the Yukon, and 6% of 48 sera from Snowshoe hares in Nova Scotia (Petrie et al., 1978).

In colonies with endemic rotavirus infection, nearly all adult rabbits have serological evidence of rotavirus infection (DiGiacomo and Thouless, 1984, 1986). Litters in such colonies have transplacentally acquired maternal antibodies to rotavirus at birth. In the absence of rotavirus infection, the antibodies fall to undetectable levels by 60 days of age. In colonies with endemic infection, shedding of rotavirus in the feces is detected in rabbits 4–7 weeks old (Peeters et al., 1984), followed by the appearance of naturally acquired antibodies in rabbits greater than 6 weeks old (DiGiacomo and Thouless, 1986). Subsequently, infected rabbits demonstrate antibodies for long periods. Hence, in infected colonies, rabbits usually acquire infection when maternal antibodies have declined to low concentrations, which usually coincides with weaning. Both sexes appear equally susceptible. Rotavirus infection in domesticated European rabbits has been reported in New Zealand White, Dutch, and Californian rabbits, suggesting no difference in breed susceptibility (Bryden et al., 1976).

Rotavirus is shed in the feces of infected rabbits. In a survey of 187 rabbits of mixed ages, rotavirus was detected in 4% of fecal samples (Petric et al., 1978). In another study, 11% of 18 fecal samples contained virus (Kudron et al., 1982). Rotavirus was detected in 9% of 106 fecal samples from healthy rabbits, 1–2 months old, from four rabbitries (DiGiacomo and Thouless, 1986). Hence, transmission probably occurs by fecal–oral spread. Rabbits inoculated orally with rotavirus shed virus in the feces for 6–8 days, beginning 2–5 days after inoculation (Blutt et al., 2003; Castrucci et al., 1984; Conner et al., 1988; Hambraeus et al., 1989; Petrie et al., 1978; Thouless et al., 1988). Furthermore, uninoculated control rabbits maintained in the same room with inoculated rabbits also acquired rotavirus infection (Conner et al., 1988; Thouless et al., 1988). As fomite transmission appeared unlikely because of the handling of uninoculated rabbits first, it was concluded that rabbits were infected by airborne transmission of virus. In gastrically inoculated rabbits, rotavirus RNA was also detected in sera 4 days after inoculation (Blutt et al., 2003). Experimentally, rabbits were also infected with simian rhesus rotavirus (Ciarlet et al., 2000b).

Recent reports suggest that rabbits may be a source of rotaviruses for humans. Comparison of the sequence analysis of several rotavirus genes of rabbit and human origin revealed a close relationship with clustering of strains in phylogenetic analyses (De Leener et al., 2004; Matthijnssens et al., 2006, 2009). However, the molecular similarity of strains should not infer interspecies transmission without supporting epidemiologic evidence of spread.

CLINICAL SIGNS

Rotavirus was initially detected and recovered from rabbits with diarrhea by Bryden et al. (1976). That report included both sporadic cases and outbreaks in 5-week-old rabbits. A spectrum in the severity of disease associated with rotavirus infection has been reported, which is probably influenced by a synergy among various microorganisms responsible for diarrheal diseases in rabbits. In outbreaks of diarrhea associated with rotavirus infection, rabbits 30–80 days old are usually affected (Castrucci et al., 1985; Peeters et al., 1984; Sato et al., 1982). Rabbits exhibit severe mucoid or watery diarrhea, anorexia, and dehydration, with mortality of 60–80%. In one outbreak, rabbits 8–12 days old had a greenish-yellow watery diarrhea (Peeters et al., 1982). About 20% of litters were affected, with 98% mortality within 1–2 days after onset of signs. A similar disease was reported in a specific pathogen-free colony in which litters 7–21 days old exhibited watery diarrhea and lethargy (Schoeb et al., 1986). Approximately 40% of affected litters died within 2 days after onset of signs. That preweanling rabbits were affected in both outbreaks suggests that rotavirus had been recently introduced into the colonies.

In a comprehensive study of various infectious agents (parasites, bacteria, and viruses) associated with

diarrhea in 21 rabbitries, Peeters et al. (1984) detected rotavirus in 35% of 130 affected rabbits. However, the clinical signs associated with rotavirus infection consisted of watery diarrhea for 2–3 days, with low mortality. Hence, in endemically infected colonies, other factors, including other infectious agents, may enhance the pathogenicity of rotavirus (Peeters et al., 1984). That rotavirus may be only mildly pathogenic is supported by experimental studies. In general, orogastric inoculation of rabbits, 1–22 weeks old, with rotavirus did not result in diarrhea, although some rabbits developed soft or fluid feces for 2–4 days (Conner et al., 1988; Hambraeus et al., 1989; Petric et al., 1978; Thouless et al., 1988). Whereas inoculation of one rotavirus strain induced diarrhea, depression, anorexia, and mortality in rabbits (Castrucci et al., 1984), this could not be repeated (Hambraeus et al., 1989). Inoculation of rabbits of various ages revealed that partially formed to liquid stools developed in 1-week-old rabbits but not in rabbits ≥2 weeks old (Ciarlet et al., 1998). Thus, in nonendemically infected rabbits, rotaviral disease may be age-restricted, occurring only in neonatal rabbits.

PATHOLOGY

In weanling rabbits infected with rotavirus, the intestines are markedly congested and distended, and petechiae are found in the colon (Sato et al., 1982). In addition to congestion, there are mucosal hemorrhages in the small intestine and distention of the cecum with fluid (Castrucci et al., 1985). However, in both of the reports, the presence of other infectious agents was not examined. Peeters et al. (1984) reported that, in pure rotavirus infection, gross lesions are limited to fluid cecal contents and swollen mesenteric lymph nodes. Histologically, the small intestine shows moderate to severe villous atrophy, more marked in the ileum. Apical enterocytes on the tips of villi are swollen, rounded, and desquamating; occasionally tips are denuded. The lamina propria is usually infiltrated with lymphocytes and occasional neutrophils. Lesions in the cecum are limited to focal areas of enterocyte desquamation. In outbreaks involving preweanling rabbits, gross lesions are most pronounced in the ileum (Peeters et al., 1982). Microscopically, there is villous atrophy and attenuation or desquamation of epithelial cells at the apical tips of jejunal or ileal villi (Peeters et al., 1982; Schoeb et al., 1986). In some areas, the submucosa is edematous (Schoeb et al., 1986).

Experimentally, rabbits inoculated orally with rotavirus have markedly congested and distended intestines with accumulation of fluid and gas in the small intestine, cecum, and colon from 2–9 days after inoculation (Castrucci et al., 1984; Ciarlet et al., 1998; Petric et al., 1978; Thouless et at., 1988). Microscopically, villi are shortened with villus blunting, fusion, and vacuolation, low to moderate numbers of lymphocytes and plasma cells infiltrate the villi and lamina propria of the small intestine. There is mild lymphoid reactivity in mesenteric lymph nodes. Lesions are not observed in the cecum or colon. The pathologic changes are considered to be mediated by enterotoxin (Ciarlet et al., 2000a).

DIAGNOSIS

Diarrhea caused by rotavirus is diagnosed from clinical signs, histopathology, detection of the virus, and demonstration of antibodies. Clinical signs and pathological findings alone are not diagnostic, although villous atrophy and degeneration and desquamation of enterocytes at the tips of villi in the small intestine are characteristic features. Rotaviral diarrhea must be differentiated from other diarrheal diseases of rabbits such as coccidiosis, salmonellosis, Tyzzer disease, clostridial enterotoxemia, enteric coronaviral enteritis, and colibacillosis. In weanling rabbits with severe disease, the possibility of dual infections should be considered, since rotavirus infections are usually mild. Electron microscopy (Ciarlet et al., 1998; Peeters et al., 1984; Schoeb et al., 1986) or a capture enzyme-linked immunosorbent assay can be used to detect rotavirus in feces (Blutt et al., 2003; Conner et al., 1988; De Leener et al., 2004; Hambraeus et al., 1989; Thouless et al., 1986, 1988). A commercial human rotavirus detection kit, utilizing immunochromatography, tested with fecal samples from rabbits with diarrhea was shown to be applicable, as positive results were confirmed by reverse transcription-polymerase chain reaction (RT-PCR) and restriction endonuclease analysis (Fushuku and Fukuda, 2006). The electropherotype of rotaviruses can be determined by extraction of nucleic acid from feces and electrophoresis in polyacrylamide gel (De Leener et al., 2004; Herring et al., 1982). Cytoplasmic fluorescence can be observed at the tips of ileal villi using indirect immunofluorescence (Petric et al., 1978). Reverse transcription-polymerase chain reaction (RT-PCR), immunohistochemistry, and in situ hybridization can be used to detect rotavirus in formalin-fixed tissues (Tatti et al., 2002). Serum antibodies to rotavirus can be detected by enzyme immunoassay (Conner et al., 1991; Hambraeus et al., 1989; Kelkar et al., 2004; Thouless et al., 1988). Rabbits with rotaviral diarrhea usually have no or low concentrations of antibody to rotavirus, with a subsequent rise 2–4 weeks after onset of signs (Bryden et al., 1976; Sato et al., 1982). Unaffected littermates develop high antibody concentrations, reflecting concurrent subclinical infections.

CONTROL

Rotavirus is highly infectious and is transmitted by fecal–oral spread; however, fomites cannot be excluded. Transplacental transmission has not been demonstrated. Infection appears to be acute and self-limiting. Experimentally, virus is shed in the feces for about

1 week following inoculation (Castrucci et al., 1984; Conner et at., 1988; Hambraeus et al., 1989; Petric et al., 1978; Thouless et al., 1988). Recovered rabbits are refractory to challenge with homologous (Castrucci et al., 1984; Ciarlet et al., 1998; Conner et al., 1988, 1991; Hambraeus et al., 1989) or heterologous rotaviruses (Hambraeus et al., 1989). Hence, cessation of breeding or quarantine of the colony for 4–6 weeks, to prevent the introduction of susceptible rabbits, should permit the infection to run its course. As seropositive dams are not infectious, their offspring should remain free of infection after maternal antibodies disappear. Early weaning of rabbits with high concentrations of passively acquired maternal antibodies and removal to isolated facilities offer the possibility of rederiving rabbits free of infection. Prevention of rotavirus infection depends on barrier maintenance of rabbits.

Coronavirus Infections

Pleural Effusion Disease/Infectious Cardiomyopathy Virus

HISTORY

During the 1960s in Scandinavia, increased mortality in European rabbits (*Oryctolagus cuniculus*) inoculated with the Nichols strain of *Treponema pallidum* (Jorgensen, 1968) was attributed to a virus, named the Stockholm agent, present in rabbit testicular emulsions (Gudjonsson et al., 1970). As the principal necropsy finding was pleural effusion, the name pleural effusion disease was suggested (Fennestad et al., 1975). Later, it was shown that the major target organ was the heart, and the name infectious cardiomyopathy was suggested, since the etiologic agent appeared to be a coronavirus (Small et al., 1979). The resemblance of the clinicopathological features to feline infectious peritonitis, a systemic coronavirus infection of cats, was noted (Osterhaus et al., 1982). The failure to propagate the agent in vitro has precluded more definitive characterization. It is unclear whether the agent is a naturally occurring pathogen of rabbits or a virus from another species adapted to rabbits in contaminated treponemal stocks. However, the disease may be useful as a model for virus-induced cardiomyopathy (Alexander et al., 1992, 1993; Baric et al., 1990; Edwards et al., 1992).

ETIOLOGY

The disease, initially described in 1968, occurred in rabbits inoculated with suspensions of rabbit testes containing the Nichols strain of *T. pallidum* (Gudjonsson and Skog, 1970; Jorgensen, 1968). Rabbits developed fever, circulatory insufficiency with pulmonary edema, and pleural effusion and had high mortality (Gudjonsson and Skog, 1970; Gudjonsson et al., 1970). Subsequent inoculation of rabbits with pulmonary tissue and pleural fluid from dead rabbits, previously inoculated with treponemes, resulted in a similar syndrome (Gudjonsson et al., 1970). Differential filtration of pleural fluid and serum from rabbits revealed an infectious particle size of 25–50 nm, which is ether-sensitive and inactivated at temperatures of 65°C or above but not at 56°C (Fennestad and MacNaughton, 1983; Gudjonsson et al., 1972; Small et al., 1979). Sera from rabbits contained pleomorphic virus particles, round or elliptic, 75–100 nm in diameter, bearing club-shaped projections 15–20 nm long (Small et al., 1979), whereas plasma from rabbits contained high concentrations of pleomorphic virus-like particles measuring 51–98 nm in diameter with projections 8–13 nm long (Osterhaus et al., 1982). Infectious sera, passed in various cell lines, produced a cytopathic effect in primary rabbit kidney and newborn human intestine cells (Small et al., 1979). However, the cellular pathogenic effect was lost after two passages. Disease was not induced in mice, hamsters, or guinea pigs (Gudjonsson et al., 1970; Small et al., 1979).

In a complement fixation test, antigens in infectious sera cross-reacted with antisera to the 229E (two-way cross) and OC43 (one-way cross) strains of human coronavirus (Small et al., 1979). Antisera to the rabbit cardiomyopathy agent cross-reacted with feline infectious peritonitis virus (FIPV), canine coronavirus (CCV), and porcine transmissible gastroenteritis virus (TGEV) by radioimmunoassay (Small and Woods, 1987). Prior incubation of the agent with antisera to CCV, FIPV, TGEV, or 229E virus reduced mortality in rabbits following inoculation. However, prior immunization of rabbits with CCV, FIV, or TGEV had little effect on survival. Immunofluorescent staining of cardiac tissue from diseased rabbits with antisera to 229E virus revealed antigen in myocardial interstitial tissue, and rabbits surviving infection developed antibodies to the virus in a complement fixation assay (Small et al., 1979). In another study, however, surviving rabbits failed to demonstrate antibodies against 229E virus in an enzyme immunoassay and neutralization test, and against OC43 virus in a complement fixation test (Fennestad and MacNaughton, 1983).

EPIDEMIOLOGY

When the disease was recognized in 1961, rabbits used in the serial propagation of *T. pallidum* had a mortality rate of 2%. By the end of the 1960s, however, mortality had increased to 35–40% owing to contamination of treponemal stocks with virus (Fennestad, 1985; Jorgensen, 1968). There is no difference in disease among breeds (Gudjonsson and Skog, 1970) or between rabbits in the United States and Sweden (Gudjonsson et al., 1970). The agent was detected in *T. pallidum*-infected rabbit tissues from Europe, the United States, and Japan (Fennestad et al., 1980). Nine isolates, obtained from treponema-infected rabbits in various countries,

exhibited a wide range in pathogenicity when inoculated into rabbits (Fennestad et al., 1986). Whereas virtually all rabbits had fever, mortality ranged from 0 to 88%, and all surviving rabbits resisted challenge with a virulent strain. Two of four dams from litters inoculated at 6–9 days of age became infected, whereas uninoculated littermates or introduced cagemates failed to develop infection after exposure for several months (Fennestad et al., 1981). Hence, transmission by direct contact occurs rarely.

CLINICAL SIGNS

Whereas clinical features vary by strain and passage of the agent, inoculated rabbits generally develop a fever in 1–4 days which persists for 5–10 days. During this early phase, acute deaths can occur without clinical signs of illness (Alexander et al., 1999). Clinical signs are often consistent with those of congestive heart failure including anorexia, weight loss, atony, tachypnea, and dyspnea. Iridocyclitis has been reported. With virulent strains, a third of infected rabbits die 3–5 days after inoculation, although deaths can occur until 14 days (Baric et al., 1990; Fennestad, 1985; Fennestad and MacNaughton, 1983; Fennestad et al., 1975, 1986; Fledelius et al., 1978; Gudjónsson and Skog, 1970; Gudjonsson et al., 1970; Small et al., 1979). Generalized or hindquarter muscular weakness was also reported in rabbits surviving the acute phase of infection (Gudjonsson et al., 1970; Small et al., 1979). During the acute phase of infection, rabbits have a transient lymphopenia, followed by heterophilia (Fennestad et al., 1975). Red cell indices were also reduced but returned to normal by 6 weeks after inoculation. There was a transient hypoalbuminemia; however γ-globulin increased significantly (Fennestad et al., 1975). Serum potassium and lactate dehydrogenase were elevated transiently. ECG abnormalities have been reported during the acute phase (days 3–5) including tachycardia in 74% of the infected rabbits, depressed R wave voltages (16%), reduced T wave voltages (45%) and QT (corrected) prolongation (32–42%) and correlated positively with mortality (Alexander et al., 1995, 1999). Ninety percent of rabbits had persistent tachycardia in the subacute phase (days 6–12 after infection), ECG changes persisted, and echocardiographic changes in the subacute phase correlated positively with mortality. Surviving rabbits usually returned to normal in 3–4 weeks. However, ECG abnormalities persisted after day 30 in some rabbits, reflecting the development of dilated cardiomyopathy (Alexander et al., 1999). Reinoculation of surviving rabbits was without effect, indicating development of resistance to the agent (Fennestad, 1985; Fennestad and MacNaughton, 1983; Fennestad et al., 1986; Gudjonsson et al., 1970).

PATHOLOGY

Rabbits dying during the acute phase of disease have pulmonary edema, pleural effusion, and dilation of the right ventricle (Alexander et al., 1992, 1993; Baric et al., 1990; Christensen et al., 1978; Edwards et al., 1992; Fennestad et al., 1975; Small et al., 1979). The pleural cavities contain 2–50 ml of fluid, with or without fibrin, and few cells; ascites may also occur in rabbits dying after the first week. There are subepicardial and subendocardial hemorrhages. Other findings may include hepatosplenomegaly and congested lymph nodes. The heart weight is increased, and there is dilation of the right ventricle followed by dilation of the left ventricle. The cause of death appears to be congestive heart failure (Alexander et al., 1992, 1993; Baric et al., 1990; Edwards et al., 1992; Small et al., 1979). In fatal cases, there is lymphoid depletion of the splenic follicles, focal degenerative changes of the thymus and lymph nodes, and mild proliferative changes of renal glomeruli (Christensen et al., 1978; Small et al., 1979). In rabbits that survive the acute phase, there is multifocal to diffuse myocardial degeneration and necrosis, focal hepatic necrosis, and proliferative changes in the spleen, lymph nodes, interstitial pulmonary tissue, and renal glomeruli. Lesions similar to those in the heart can occur in the diaphragm (Small et al., 1979). A mild non-suppurative, non-granulomatous anterior uveitis develops during the acute phase of infection and regresses within 4 weeks (Fledelius et al., 1978). At 65 days after infection, myocarditis is evident, and about one-third of rabbits had evidence of right- and/or left-sided cardiac dilation (Baric et al. 1990). After 2 years, rabbits had pulmonary lymphoid hyperplasia, lymphoid hyperplasia of lymph nodes and spleen, siderosis in the spleen, necrosis and periportal inflammation in the liver and interstitial fibrosis of the myocardium (Fennestad et al., 1986). No evidence of circulating or tissue immune complexes was found (Fennestad et al., 1981, 1986).

DIAGNOSIS

It remains to be determined whether the agent is a naturally occurring pathogen of rabbits or perhaps a human virus adapted to rabbits in contaminated stocks of the Nichols strain of *T. pallidum*. The syndrome has only been reported in experimentally inoculated rabbits. The clinical course is characterized by onset of fever 1–3 days after inoculation. Deaths may occur from 2–17 days after inoculation, and mortality may exceed 75%. Other major signs include ocular disease, anorexia, weight loss, tachypnea, and atony. The gross and histological lesions are highly characteristic of the disease. Antibodies to the virus cross-react with the human coronavirus 229E and other members of the group I mammalian coronaviruses (FIPV, CCV, and TGEV) (Small and Woods, 1987; Small et al., 1979).

CONTROL

Because continued serial propagation of *T. pallidum* in rabbits coincided with emergence of disease associated with this agent, the possibility of contaminated stocks

should be considered (Fennestad, 1985; Fennestad et al., 1975; Gudjonsson et al., 1970). Rabbits inoculated with virus-contaminated *T. pallidum* stocks that elicited no or mild disease without mortality were protected from disease when challenged with stocks contaminated with more pathogenic virus (Fennestad, 1985; Fennestad and MacNaughton, 1983; Fennestad et al., 1980, 1986; Gudjonsson et al., 1970). This indicated that some *T. pallidum* stocks were contaminated with a non-pathogenic variant of the virus, which was able to confer protection. Furthermore, isolates decreased in pathogenicity, as a function of time, in rabbits that survived acute infection (Fennestad, 1985; Fennestad et al., 1986). Convalescent sera from rabbits that survived infection partially protected challenged rabbits against mortality but not disease (Fennestad et al., 1981; Gudjonsson et al., 1970; Small et al., 1979). Passage of contaminated *T. pallidum* stocks through hamsters removed the agent responsible for disease (Fennestad et al., 1980; Skovgaard Jensen, 1971). Subsequent reintroduction of these *T. pallidum* stocks in rabbits was without effect. Similarly, inoculation of rabbits, with popliteal lymph nodes from surviving rabbits, transferred treponemes but not the agent (Gudjonsson et al., 1970).

Rabbit Enteric Coronavirus

HISTORY

A coronavirus was detected in the feces of rabbits with diarrhea by LaPierre et al. (1980) in Canada. Rabbits were 6–10 weeks old and from several colonies. Subsequently, coronavirus was detected in young rabbits with diarrhea in several European countries (Eaton, 1984; Osterhaus et al., 1982; Peeters et al., 1984). Although the virus appears to be readily detected in rabbits by workers in Canada (Descoteaux et al., 1985; LaPierre et al., 1980), the failure to propagate the agent in vitro has hampered investigations of its prevalence in European rabbit (*Oryctolagus cuniculus*) populations.

ETIOLOGY

Feces of rabbits with diarrhea exhibit hemagglutination activity with rabbit erythrocytes, particularly with a peak of 1.18 g/cm^3 from a sucrose density gradient (Descoteaux et al., 1985; LaPierre et al., 1980). Electron microscopy of fecal samples revealed pleomorphic particles with an inner diameter of 60–220 nm and surface projections of 20 nm (Eaton, 1984; LaPierre et al., 1980). Particles obtained from a Percoll gradient appeared as spherical enveloped particles 40–50 nm in size with projections of 10–12 nm (Descoteaux et al., 1985). In rabbits inoculated orally, pleomorphic particles 60–90 nm, with surface projections of 10 nm, were detected in the feces (Osterhaus et al., 1982). Electron microscopy of fecal samples using antisera to rabbit coronavirus revealed immune aggregates of viral particles with morphological features of coronaviruses (Descoteaux et al., 1985). Analysis of structural polypeptides by immunoblotting revealed that antisera to avian infectious bronchitis virus (AIBV) and TGEV detected many of the same epitopes as antisera to the rabbit coronavirus (Descoteaux et al., 1985). Immune sera to 229E, but not AIBV nor porcine hemagglutinating encephalitis virus, inhibited the hemagglutination activity of the rabbit coronavirus. No cytopathic effect occurred following inoculation of various cell lines with fecal samples (Eaton, 1984; LaPierre et al., 1980).

EPIDEMIOLOGY

In a survey of 130 diarrheic rabbits from 21 rabbitries, coronavirus was detected in the cecal contents of one rabbit in association with *Escherichia coli* infection (Peeters et al., 1984). Rabbits with diarrheal disease associated with coronavirus infection are usually 3–10 weeks old (Eaton, 1984; La Pierre et al., 1980). Virus has also been detected in the feces of apparently healthy rabbits (Descoteaux et al., 1985). Experimentally, orally inoculated rabbits shed virus for up to 29 days (Descoteaux and Lussier, 1990). A serological survey of 238 *Oryctolagus cuniculus* from six rabbitries in Washington state revealed that 23 (10%) had antibodies to canine coronavirus (Deeb et al., 1993).

CLINICAL SIGNS

In an outbreak of enteric disease in 3–8-week-old rabbits in a barrier-maintained breeding colony, rabbits exhibited lethargy, diarrhea, and swollen abdomens (Eaton, 1984). Between 40 and 60% of rabbits were affected, and virtually all died within 24 h after onset of signs. LaPierre et al. (1980) also reported rapid death following the onset of clinical signs in the majority of affected rabbits. Experimentally, rabbits developed soft feces (Osterhaus et al., 1982) and transient watery diarrhea (Descoteaux and Lussier, 1990) after inoculation. None of the rabbits died (Descoteaux and Lussier, 1990).

PATHOLOGY

In rabbits with diarrhea, the perianal region is soiled with feces (Eaton, 1984). Rabbits appear cachectic and dehydrated. Although the stomach and intestines are unaffected, the cecum is distended with watery fluid (Eaton, 1984; Peeters et al., 1984). Histologically, in the small and large intestines there is a diffuse infiltration of inflammatory cells and mucosal edema (Eaton, 1984). In an experimental study, the small intestines were congested and the cecal contents watery (Descoteaux and Lussier, 1990). Microscopically, at 6 hours after inoculation, there was necrosis of enterocytes at the tips of intestinal villi. Villous atrophy and hypertrophic crypts

were present 2–3 days after inoculation. However, by 6 days, microscopic lesions were absent.

DIAGNOSIS

Rabbits with diarrheal disease are usually recently weaned and 3–10 weeks old (Eaton, 1984; LaPierre et al., 1980). Because the rabbit coronavirus agglutinates erythrocytes, the hemagglutination activity of the feces provides an indication of the presence of virus (LaPierre et al., 1980). Coronavirus particles can be demonstrated in the feces by electron (Eaton, 1984; LaPierre et al., 1980; Osterhaus et al., 1982; Peeters et al., 1984) and immunoelectron (Descoteaux and Lussier, 1990; Descoteaux et al., 1985) microscopy. The latter technique is more sensitive in detecting virus particles (Descoteaux et al., 1985). At necropsy, the cecal contents are fluid (Descoteaux and Lussier, 1990; Eaton, 1984); histologically, there is intestinal villous atrophy (Descoteaux and Lussier, 1990). Adult rabbits may have antibodies in the hemaglutination inhibition assay (LaPierre et al., 1980). As experimental inoculation of rabbits with coronavirus failed to mimic the field disease with its high morbidity and mortality, consideration should be given to the existence of co-pathogens (Descoteaux and Lussier, 1990; Osterhaus et al., 1982). In two studies where other agents were considered, coronavirus was associated with *Escherichia coli* and *Clostridium perfringens* infections (Eaton, 1984; Peeters, et al., 1984).

CONTROL

Because only one naturally occurring outbreak of diarrheal disease associated with coronavirus has been reported (Eaton, 1984), there is scant information on control of the disease. The feeding of hay, delay in weaning, and administration of coccidiostats and antibiotics were ineffective in preventing mortality.

Calicivirus Infections

The etiologic agents of necrotic hepatitis of leporids have profoundly affected world rabbit populations since 1984. They are classified as members of the family, *Caliciviridae*, and the genus, *Lagovirus*. This genus contains two distinct species which cause clinical disease denoted as *Rabbit hemorrhagic disease virus* (RHDV) and *European brown hare syndrome virus* (EBHSV) (Green et al., 2000). These diseases were first recognized in the mid-1980s. RHD was reported in China in 1984 and subsequently in other countries. EBHS was observed in Europe several years before RHD was diagnosed in domestic European rabbits. Antibodies to RHDV were in archived serum from 1961 in the Czech Republic and Austria (Nowotny et al., 1997) and viral RNA in serum samples from Britain stored in 1955 (Moss et al., 2002). Antibodies to EBHSV were found as early as 1962 (Frölich and Lavazza, 2008) in serum in England and viral RNA in tissues collected in the 1970s in Sweden (Bascunana et al., 1997).

A third member of the genus *Lagovirus* was identified in domestic rabbits in Italy in 1996 and was named rabbit calicivirus (RCV) (Capucci et al., 1996). No clinical signs were associated with RCV infection although seroconversion resulted in protection from RHDV (Capucci et al., 1997). A closely related strain, denoted rabbit calicivirus, Australia 1 (RCV-A1) was recently isolated from wild European rabbits in Australia and partially sequenced (Strive et al., 2009). Whether antibodies which recognize RHDV epitopes in retrospective studies are associated with RCV and its variants rather than RHDV is unknown. Another closely related virus, denoted Michigan Rabbit Calicivirus (MRCV) was isolated from an outbreak of hemorrhagic disease in the United States in 2001 (Bergin et al., 2009). One member of the genus *Vesivirus*, family *Caliciviridae* has been described as a potential intestinal pathogen of rabbits (Martín-Alonso et al., 2005).

Rabbit Hemorrhagic Disease Virus (RHDV)

HISTORY

In early 1984, an acute fatal disease of rabbits was reported from many regions of China (Xu and Chen, 1989; Xu et al., 1988). The disease was unlike any previously reported syndrome and may have originated in rabbits imported from Europe. Tests of rabbit sera stored in Czechoslovakia in 1978 revealed antibodies to the virus (Rodak et al., 1990a). Although the syndrome was initially variously named, it came to be known as RHD. Subsequently, the disease was reported in several European countries in 1987 and 1988 (Gregg and House, 1989; Parra and Prieto, 1990; Patton, 1989). The negative impact of this disease on wild rabbit populations in Europe has been significant (Calvete et al., 2002; Marchandeau et al., 1998). Currently, it is endemic in most of Europe, Asia, Africa, Australia, and New Zealand.

By late 1988, the virus reached North America and was reported from many locations in Mexico (Gregg and House, 1989; Gutierrez, 1990; Patton, 1989). Mexico mounted an eradication campaign and has since remained free of the virus (McIntosh et al., 2007). Four outbreaks of RHDV were reported in the United States between 2000 and 2007 (Anonymous, 2000; Campagnolo et al., 2003; U.S.D.A., 2005; McIntosh et al., 2007). Each time the virus was contained, but how it was introduced was not determined (McIntosh et al., 2007).

In 1995, a laboratory strain of RHDV was being tested in field experiments under quarantine conditions at Wardang Island, Australia, to evaluate the virulence,

transmissibility, and persistence of RHDV (McColl et al., 2002). It was also being considered as a potential biological control agent for rabbits. The virus escaped and spread, first to other rabbits on Wardang Island, and then to the mainland. It resulted in significant mortality immediately, reducing rabbit populations in some areas by 95% (Mutze et al., 1998). It is currently endemic throughout Australia. In 1996, the New Zealand government was asked to consider the use of RHDV as a biological control agent (Thompson and Clark, 1997). The government denied these requests; however, RHDV was introduced to New Zealand illegally by farmers hoping to reduce local rabbit populations and is now widely distributed in both the North and South Islands of New Zealand (O'Keefe et al., 1999; Thompson and Clark, 1997).

ETIOLOGY

A virus has been consistently purified from the liver and spleen of affected rabbits, the characteristics of which have been described by several investigators (Du, 1990, 1991; Du et al., 1986; Liebermann et al., 1992; Ohlinger and Theil, 1991; Sihid et al., 1989; Smid et al., 1989; Xu, 1991; Xu and Chen, 1989; Xu et al., 1988). The virus is non-enveloped, spherical, and 28–34 nm in diameter and has a buoyant density of 1.32–1.38 g/cm^3. The icosahedral capsid has 32 cylindrical capsomeres, 5–6 nm in diameter, comprised of four structural polypeptides. The virus is a member of the family, *Caliciviridae*, and is the type virus of the genus, *Lagovirus* (Green et al., 2000). RHDV was completely sequenced and has a positive strand RNA genome of 7437 kb (Meyers et al., 1991a). The genomic organization is similar to EBHSV with two open reading frames (ORF) rather than the three ORFs found in other caliciviruses (Wirblich et al., 1996). The first ORF encodes non-structural proteins as well as the large capsid protein and the second ORF encodes an additional capsid protein. One subgenomic RNA (2.2 kb) is present (Ohlinger et al., 1990; Parra and Prieto, 1990). Amino acid identity between RHDV and EBHSV is approximately 76% (Wirblich et al., 1994). The virus agglutinates erythrocytes of humans and guinea pigs, but not rabbits. Non-hemagglutinating strains of RHDV have been identified (Tian et al., 2007). While the majority of strains of RHDV have a high level of amino acid identity, antigenic variants have been described (Capucci et al., 1998; Asgari et al., 1999; Shirrmaier et al., 1999).

The virus is highly stable in the environment and sufficient infectious RNA is present to infect rabbits from liver samples stored for 20 days at 22°C (McColl et al., 2002). In a separate study, infectious virus was injected into bovine liver and then the liver was exposed outdoors to ambient temperatures (2–34°C) (Henning et al., 2005). Sufficient viral particles were present at the longest time point studied, 91 days, to infect rabbits when inoculated undiluted. Viral infectivity is unaffected by treatment with ether, chloroform, exposure to pH 3, or heating at 50°C. However, the virus is inactivated by 1% sodium hydroxide or 0.4% formaldehyde at ambient temperature, 4°C or 37°C. The virus fails to grow in many primary and established cell lines but has been adapted to a transformed rabbit kidney cell line (Ji et al., 1991; Xu, 1991). Rabbits may be the only species susceptible to infection, as inoculation of guinea pigs, hamsters, rats, or mice failed to induce disease. Experimentally, inoculation of European hares (*Lepus europaeus*) failed to induce disease (Lavazza et al., 1996; Smid et al., 1991).

EPIDEMIOLOGY

Since the report of the first outbreak of RHDV in China in 1984, RHDV has rapidly spread throughout the world. The disease has been reported from China, Korea, most European countries, Asia, Africa, North America, Australia. and New Zealand (Chasey et al., 1997; McIntosh et al., 2007; Morisse et al., 1991). Countries experiencing epidemics with high morbidity and mortality include China (Xu and Chen, 1989), Korea (Lee and Park, 1987), Italy (Cancellotti and Renzi, 1991; Patton, 1989), Spain (Parra and Prieto, 1990; Villafuerte et al., 1994); France (Morisse et al., 1991), Germany (Loliger and Eskens, 1991), Mexico (Gregg and House, 1989; Gutierrez, 1990), Taiwan (Shien et al., 1998), Cuba (Farnós et al., 2007), Saudi Arabia (Abu Elzein and Al-Afaleqand, 1999), Bahrain (Forrester et al., 2006), Tunisia (Bouslama et al., 1996), the United Kingdom (White et al., 2004), and the United States (McIntosh et al., 2007). The disease has also been reported from India (Sundaram et al., 1991) and the Middle East (Kuttin et al., 1991). Viruses from China, Korea, and Europe appear to be similar (Du, 1990; Gregg et al., 1991), although evolution of viruses in restricted geographic areas has occurred (Muller et al., 2009). Recently, a virus isolated in the Netherlands was demonstrated to be 99% identical to RHDV from France (van de Bildt, et al., 2006).

There have been four outbreaks of RHDV in the US; in Iowa in 2000 (Anonymous, 2000), in Utah in 2001, which was transferred to Illinois by shipment of infected rabbits (Campagnolo et al., 2003), in a zoo in New York in 2001 (McIntosh et al., 2007), and in Indiana in 2005 (McIntosh et al., 2007; U.S.D.A., 2005). Isolates from these outbreaks were shown by comparative genomic analysis to be closely related to isolates from China, but to have separate origins (McIntosh et al., 2007).

There is evidence that RHDV was present in wild and domesticated populations of rabbits in Europe (Moss et al., 2002; Rodak et al., 1990a), Australia (Cooke et al., 2000; Nagesha et al., 2000), and New Zealand (O'Keefe et al., 1999) prior to the recognition of RHDV. Studies in

England demonstrated serological evidence as well as partial RNA sequences recovered from tissues or serum of apparently healthy rabbits (Moss et al., 2002; White et al., 2004). These partial sequences were more closely related to RHDV than RCV, suggesting that non-pathogenic RHDV viruses have circulated in parts of the world for some time.

No apparent difference in susceptibility to infection among breeds of *Oryctolagus cuniculus* has been reported (Xu and Chen, 1989; Xu et al., 1988). Outbreaks of disease have occurred mainly in rabbits 2 months of age and older, whereas younger rabbits were clinically unaffected. Of the rabbits that survived the infection, viral RNA has been detected in various organs including the spleen, liver, mesenteric lymph node, and bile for 15 weeks after infection suggesting that a chronic carrier state can occur (Gall et al., 2007).

Transmission of virus is horizontal, primarily by direct contact with secretions and excretions of infected rabbits and fecal–oral spread may be the major mode of transmission. Contaminated fomites, such as feed, water, utensils, and animal attendants, may be important in transmission as well. Transmission by insects has been suggested as an explanation for the spread of RHDV from Wardang Island to the mainland. Laboratory experiments demonstrated that RHDV can be transmitted by blowflies (*Phormia* sp.), bushflies (*Musca vetustissima*) and mosquitoes (Gould et al., 1997; McColl et al., 2002). Transmission by the lesser brown blowfly, *Calliphora dubia* was suggested by evidence that RHDV RNA was detected in fly feces after flies were fed a meal from a RHDV-infected liver (Asgari et al., 1998). There is no evidence of vertical transmission. Fecal shedding by carnivores after ingestion of RHDV-infected carcasses has been suggested as a potential mode of spread. Serological evidence of infection in foxes has been demonstrated in several studies, although no infectious particles have been demonstrated (Frölich et al., 1998; Leighton et al., 1995; Philbey et al., 2005). Experimentally, the routes of entry, in order of importance, are oral, conjunctival, nasal, and skin trauma. In China and Europe, epidemics of disease usually begin in November and end in March. Although *Oryctolagus cuniculus* appears to be the only species susceptible to disease, hares in China also appear to be infected and capable of transmitting the virus to rabbits experimentally (Xu, 1991).

A serological survey of 1461 rabbits from 43 farms, apparently free of viral hemorrhagic disease in Czechoslovakia revealed that 283 rabbits (19%) from 33 farms had anti-RHDV antibodies (Rodak et al., 1990a). Using another set of sera, collected between 1975 and 1987 from laboratory-maintained rabbits, antibodies were detected in 32 of 42 sera (76%). This suggests that rabbit colonies in Czechoslovakia harbored a viral agent with characteristics similar to those of *Rabbit* hemorrhagic disease virus, but with lower pathogenicity, several years before the syndrome was recognized in China.

RHDV has been shown to bind to histo-blood group antigens expressed on the surface of respiratory and digestive tract epithelial cells (Ruvoën-Clouet et al., 2000). This binding may partially explain the differential susceptibility of young versus older rabbits (Rademacher et al, 2008; Ruvoën-Clouet et al., 2000). In addition, polymorphisms of these antigens in wild rabbits in France have been linked to differential survival from RHDV infection (Guillon et al., 2009).

CLINICAL SIGNS

In general, the disease is acute and highly infectious, with high morbidity and mortality (Marcato et al., 1991; Xu and Chen, 1989; Xu et al., 1988). The incubation period ranges from 1–2 days. Morbidity is 70–80%, and mortality approaches 100%. During outbreaks, the number of rabbits affected usually peaks in 2–3 days and lasts 7–13 days. After viral introduction, rabbits die suddenly with few clinical signs. Rabbits become febrile and exhibit depression, lethargy, and anorexia. Other clinical signs include tachypnea, cyanosis, abdominal distention, and constipation or diarrhea. Because the disease is acute, clinical signs may be brief and often are unnoticed. In the terminal stage, rabbits become hypothermic, recumbent, and have convulsions and epistaxis. Surviving rabbits exhibit depression, anorexia, and fever which usually abates in 2–3 days. In endemic areas, the form of disease observed in surviving rabbits is more common. Hematologic evaluation usually reveals a lymphopenia, a gradual decline in thrombocytes, and prolonged prothrombin and thrombin times. A paracoagulation test with protamine sulfate gives a strong positive reaction. Fibrin degradation products can be detected in most moribund rabbits.

In young rabbits, clinical signs of infection are typically absent (Ferreira et al., 2004, 2006; Mikami et al., 1999). However, liver inflammation as evidenced by increase in hepatic transaminases and increase in heterophil liver infiltrate occurs, although there is little hepatocyte damage (Ferreira et al., 2004, 2006; Mikami et al., 1999; Prieto et al., 2000) and less replication of the virus within hepatocytes than adults as evidenced by immunochemical staining (Preito et al., 2000). Elevation of transaminases persists for at least 3 weeks after infection (Ferreira et al., 2004). Young rabbits infected with RHDV develop a protective antibody response that persists and protects them from infection as adults (Ferreira et al., 2008). However, these rabbits may serve as healthy carriers of the virus (Ferreira et al., 2004, 2008).

PATHOLOGY

The pathological changes apparently result from viremia, with death attributable to an acute disseminated

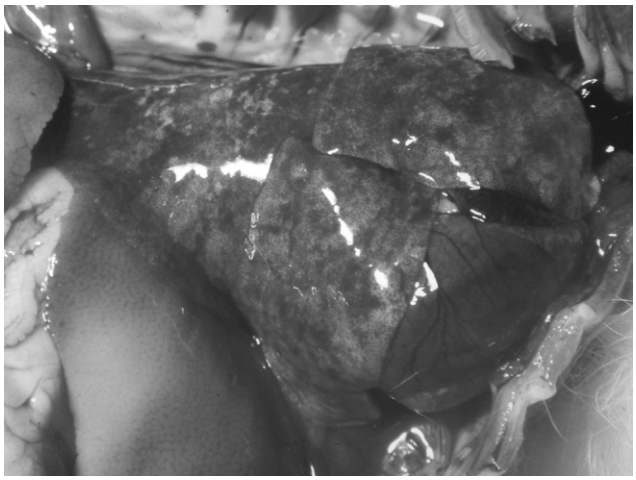

FIGURE 14.3 Diffusely congested lungs from rabbit found dead with RHD. *Courtesy of Dr. D. Gregg.*

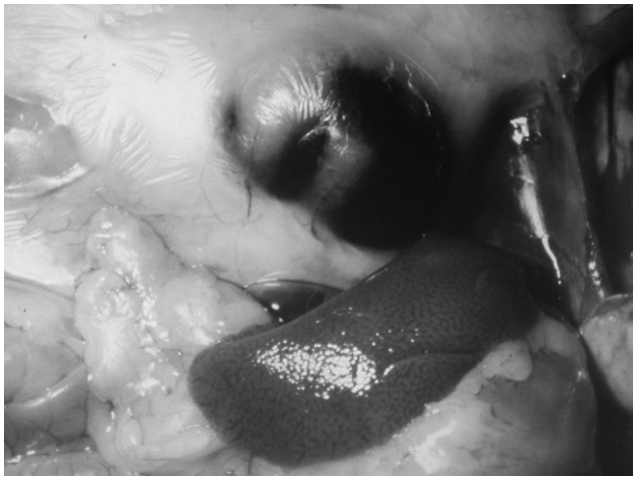

FIGURE 14.4 Reticular pattern of liver (bottom, center) consistent with periportal necrosis in a rabbit found dead with RHD. The kidney (top, center) is diffusely congested. *Courtesy of Dr. D. Gregg.*

coagulopathy with deep venous thrombosis (Gregg and House, 1989; Gregg et al., 1991; Marcato et al., 1991; Xu and Chen, 1989; Xu et al., 1986, 1988). Grossly, congestion and hemorrhage occur in most organs but are most pronounced in the lungs (Figure 14.3). The liver is pale and has a fine reticular pattern of periportal necrosis, the most consistent finding in the disease (Figure 14.4). The spleen and kidneys may be dark and swollen owing to acute infarction (Figure 14.4). Lymph nodes are edematous and may contain petechial hemorrhages. There is often segmental catarrhal enteritis.

In most fatal cases, rabbits die from a severe and massive intravascular coagulopathy (Gregg et al., 1991). The disease consistently causes acute hepatic necrosis, which may be the only lesion found. Hepatic necrosis is periportal and diffuse, and when severe, may bridge acini and cause dissociation of hepatic cords (Gregg et al., 1991; Percy and Barthold, 2007). Small single or multiple intranuclear inclusion bodies can be found in degenerate hepatocytes. There is often little inflammation in necrotic areas. Many tissues, especially the lungs, spleen, and kidneys, may have varying degrees of congestion and hemorrhage due to microinfarction or major venous thrombi. Acute coagulative necrosis due to microinfarction may be found in any organ. Microinfarcts in the brain account for the terminal neurological signs. Pulmonary venous thrombosis accounts for the frothy serosanguinous discharge from the nares seen terminally. A segmental necrotizing enteritis with severe crypt necrosis and villous atrophy can be found (Gregg et al., 1991). Lymphoid tissues may have varying degrees of degeneration and karyorrhexis of lymphocytes. The spleen and thymus are more often affected than lymph nodes.

DIAGNOSIS

A presumptive diagnosis can be made on the basis of the epidemiological features, clinical signs, and pathological findings (Xu and Chen, 1989). Virus can be detected with RT-PCR using multiple tissues including blood (Gall et al., 2007; Guittré et al., 1995; Shien et al., 2000; Vende et al., 1995; Wang et al., 2008; Yang et al., 2008). No satisfactory in vitro isolation methods have been described, and rabbit inoculation is the only method available to isolate or propagate a new strain of virus (O. I. E. 2008). Immunocapture RT-PCR was developed to simplify the tissue processing required to analyze numerous samples (Le Gall-Reculé et al., 2001). By electron microscopy, viral particles, 28–34nm in diameter, are frequently found in hepatocytes (Valicek et al., 1990; Xu and Chen, 1989). The hemagglutination test, with type O human erythrocytes, is useful for detection of virus in suspensions of liver, lungs, spleen, and kidneys, from infected rabbits (Shien et al., 2000; Xu and Chen, 1989). Antisera or monoclonal antibodies to the virus can detect virus in hepatocytes in infected rabbits by immunoenzyme and immunofluorescence tests (Berninger and House, 1995; Capucci et al., 1991; Carrasco et al., 1991; Gregg and House, 1989; Gregg et al., 1991; Park and Itakura, 1992; Rodak et al., 1990b, 1991; Stoerckle-Berger et al., 1992). Serological tests include the hemagglutination inhibition test and the enzyme-linked immunosorbent assay, the latter being preferable because of increased sensitivity and specificity (Chasey et al., 1995; Cooke et al., 2000; Rodak et al., 1990b). Both indirect sandwich ELISAs and competitive-ELISAs have been developed for detection of antibodies (Guittré et al., 1995). Seroconversion to RHDV without clinical signs of disease is suggestive of RCV infection and should be interpreted with caution (Capucci et al., 1997).

CONTROL

Measures to prevent introduction of the virus include restricted access and disinfection of all equipment entering or leaving a facility (Xu and Chen, 1989). Cages and equipment can be disinfected with 0.5% sodium hypochlorite or 1% formalin. Rabbits from endemic areas should not be introduced directly into the colony, but quarantined for at least 1 month and tested serologically for anti-RHDV antibodies. Similarly, colonies with disease should be quarantined and depopulated, since surviving rabbits shed virus for at least a month and possibly longer (Gregg and House, 1989; Gregg et al., 1991). Antiserum has been shown to be protective (Du, 1990; Huang, 1991). Tissue-derived vaccines, inactivated with formaldehyde (Du, 1990; Du et al., 1986; Huang, 1991; Xu and Chen, 1989) or β-propiolactone (Arguello Villares, 1991; Smid et al., 1991), have been shown to be safe and efficacious in preventing disease. Resistance develops within 1–2 weeks after vaccination and lasts for 5–15 months. Although disease may be prevented in vaccinated rabbits, persistent infection may develop on exposure to the virus (House et al., 1990). Thus, vaccinated rabbits infected with virus should be considered infectious and should not be introduced into previously unexposed rabbitries. Additional vaccines have been developed, including those combining protection against both RHDV and myxomatosis (Bertagnoli et al., 1996; Calvete et al., 2004; Fernández-Fernández et al., 2001; Torres et al., 2001). Since the decline of rabbit populations in southern France and the Iberian peninsula has affected the survival of rabbit-prey species (Marchandeau et al,. 2000), vaccination of free-living rabbits has been undertaken in a field trial on an island off Spain and subsequently on the mainland (Calvete et al., 2004; Torres et al., 2001).

European Brown Hare Syndrome Virus (EBHSV)

HISTORY

A disease, characterized by hemorrhages in the trachea and lungs, pulmonary edema, and necrotic hepatitis, with high mortality, has been observed since 1980–1985 in European hares (*Lepus europaeus*) and Mountain hares (*Lepus timidus*) in many European countries (Billinis et al., 2005; Duff et al., 1994; Frölich 1996; Frölich et al., 2001, 2003a, 2007; Gavier-Widen and Morner, 1991; Le Gall-Reculé et al., 2006; Morisse et al., 1990, 1991; Syrjälä et al., 2005). The virus has also been detected in European hares translocated to Argentina (Frölich et al., 2003b). The disease, named European brown hare syndrome (EBHS), is similar to RHD, but affects hares.

ETIOLOGY

Electron microscopy of hepatocytes from affected hares reveals non-enveloped, icosahedral particles about 30 m in diameter (Chasey and Duff, 1990; Marcato et al., 1991). Immunoblotting of the virus reveals a major structural protein of about 60 kDa, similar to RHDV; however, other proteins of the latter virus are absent, suggesting that the viruses are similar but not identical (Capucci et al., 1991; Ohlinger and Thiel, 1991). Sequencing of the genome (Gould et al., 1997; Le Gall et al., 1996; Meyers et al., 1991b; Nowotny et al., 1997; Parra et al., 1993; Rasschaert et al., 1995; Wirblich et al., 1994) revealed that RHDV and EBHSV have similar genomic organization and are both members of the family, *Caliciviridae*, and the genus, *Lagovirus*, however they represent two distinct species (Green et al., 2000). EBHSV and RHDV have been shown to have approximately 76% amino acid identity (Wirblich et al., 1994).

EBHSV fails to grow in primary hare and rabbit cell lines (Gavier-Widen and Morner, 1991; Henriksen et al., 1989), and inoculation of mice and guinea pigs failed to induce disease (Henriksen et al., 1989). In general, inoculation of rabbits (*Oryctolagus cuniculus*) with EBHSV, or tissues from infected hares, has not resulted in clinical disease in rabbits (Capucci et al., 1991; Chasey et al., 1992; Eskens and Volmer, 1989; Nauwynck et al., 1993) or cross-protective immunity (Nauwynck et al., 1993), although clinical disease similar to RHD was induced by Morrise et al. (1990) following inoculation of liver homogenates from affected hares in France.

EPIDEMIOLOGY

The disease has been reported in wild hares from several European countries, including England (Chasey and Duff, 1990), the Czech Republic (Nowotny et al., 1997), Greece (Billinis et al., 2005), Finland (Syrjälä et al., 2005), Slovakia (Frölich et al., 2007), Switzerland (Frölich et al., 2001), France (Le Gall-Reculé et al., 2006), Poland (Frölich et al., 1996, 2003a), as well as South America (Frölich et al., 2003b). EBHSV has also been reported from breeding farms for hares in Denmark (Henriksen et al., 1989) and Sweden (Gavier-Widen and Morner, 1991). In France, Germany, and Italy, the geographic distribution of EBHS coincides with RHD in wild and domesticated rabbits (Cancellotti and Renzi, 1991; Loliger and Eskens, 1991; Morisse et al., 1991). Seroprevalence has been determined in many countries. Thirty-eight percent of hares tested in Poland were positive for EBHSV antibodies (Frölich et al, 1996), 29% in Germany (Frölich et al., 2003) while 73% of hares shot by hunters in Slovakia had anti-EBHSV antibodies, suggesting some variation in the prevalence of infection.

Similar to RHDV, young hares are resistant to the virus (Morisse et al., 1991). The major mode of transmission appears to be fecal–oral (Morisse et al., 1991). Contamination of feed and water with excreta from infected hares is probably a common mode of transmission (Gavier-Widen and Morner, 1991). Among wild

and farmed hares in Denmark and Sweden, mortality is seasonal, beginning in October and continuing through March (Gavier-Widen and Morner, 1991; Henriksen et al., 1989), presumably as there are more young susceptible hares at the end of the breeding season. Recent evidence from Finland indicates that the majority of the cases occurred in the spring and summer, with a minor peak in October and November (Syrjälä et al., 2005). The hare population in Finland was lowest in winter and this may influence transmission. In England, excess mortality in wild hares was reported in September through November (Chasey and Duff, 1990).

CLINICAL SIGNS

In general, the disease is acute and highly infectious, with high morbidity and mortality (Henriksen et al., 1989; Marcato et al., 1991). Clinical signs include depression, anorexia, muscular tremors, incoordination, paralysis, convulsions, and occasionally epistaxis. Death occurs 5–24h after onset of signs, and affected hares rarely recover. The reported morbidity is 75%, and mortality approaches 100% (Gavier-Widen and Morner, 1991; Henriksen et al., 1989). In Argentina (Frölich et al., 2003b) and Slovakia (Frölich et al., 2007) evidence of a chronic, less pathogenic form of EBHSV has been demonstrated. In Argentina, no clinical signs suggestive of EBHSV were reported; however 11% of 80 spleen samples were positive for EBHSV antigen (Frölich et al., 2003b) whereas antibodies to EBHSV were present in only one sample. In Slovakia, antibodies against EBHSV were found in 73% of 86 sera tested although hare populations were reported to be stable with no increase in mortality noted before or during the sampling period (Frölich et al., 2007).

PATHOLOGY

Death is attributable to multiple organ failure resulting in pulmonary edema and hemorrhage, adrenocortical necrosis, renal circulatory disorders, and hepatic necrosis (Henriksen et al., 1989; Marcato et al., 1991). Gross examination of hares reveals marked pulmonary congestion and edema, as well as hepatic congestion and hemorrhages. Moderate splenomegaly and gastric ulceration are detected in some hares. A catarrhal to necrotizing conjunctivitis may be present. Microscopically, there is diffuse acute coagulation necrosis of hepatic periportal and midzonal areas, accompanied by formation of acidophilic bodies (GavierWiden and Morner, 1991; Henriksen et al., 1989). In many hares, there is basophilic stippling in the cytoplasm of hepatocytes in periportal areas, representing granular calcification. Many livers have microvacuolar fatty degeneration. About one-fourth of affected hares have splenic cellular depletion and hyaline-like changes in the sinuses and cords, and about one-third have renal tubular necrosis and calcification. In the brain, cerebral neurons and cerebellar Purkinje cells exhibit granulovacuolar degeneration. In apparently healthy hares with antibodies to the virus, hepatic vacuolar degeneration, tracheitis, and hyperplasia of splenic follicles are observed (Marcato et al., 1991).

DIAGNOSIS

Diagnosis is similar to that for RHD. RT-PCR has been used to detect virus in tissues (Bascunana et al., 1997; Gould et al., 1997). The hemagglutination test for detection of virus in tissue specimens is less sensitive (Capucci et al., 1991). Use of two ELISAs, in series, employing monoclonal antibodies, in which the first test detects group antigen and the second virus-specific antigen, has also been used to detect virus (Capucci et al., 1991). The ELISA is preferred for detection of antibodies (Capucci et al., 1991).

CONTROL

Methods of control in breeding farms for hares are similar to those for rabbit hemorrhagic disease. Preventive measures include restricted access, disinfection of equipment, and quarantine of newly acquired hares. As subclinically infected hares may shed virus, serological screening of quarantined hares may be advisable. Only seronegative hares should be permitted entry into the colony. Colonies with the disease should be quarantined and depopulated. No vaccine has been developed for use in hares.

Rabbit Calicivirus (RCV)

HISTORY

Non-pathogenic rabbit caliciviruses were first isolated from rabbits (*Oryctolagus cuniculus*) in a rabbitry in Italy that seroconverted to RHDV without exhibiting clinical signs of disease (Capucci et al., 1996). Serological studies revealed rabbit populations in Europe with serological evidence of RHDV, but no clinical evidence of disease (Capucci et al., 1996, 1997; Forrester et al., 1997; Rodak, 1990). In addition, retrospective studies demonstrated serological evidence of anti-RHDV antibodies prior to the spread of RHDV virus in Europe (Moss et al., 2002; Rodak, 1990a), Australia, and New Zealand (Bruce and Twigg, 2004; Nagesha et al., 2000; Robinson et al., 2002). Investigators in Italy isolated a non-pathogenic calicivirus, rabbit calicivirus (RCV), from domestic rabbits (Capucci et al., 1996). Partial sequences of apparently non-pathogenic caliciviruses were detected in rabbits (*Oryctolagus cuniculus*) from Lambay Island, Eire in 2007 (Forrester et al., 2007). In 2009, another apparently non-pathogenic calicivirus, RCV-A1, was isolated from wild rabbits (*Oryctolagus cuniculus*) in Australia (Strive et al., 2009).

ETIOLOGY

RCV is considered a strain of RHDV (Fauquet et al., 2005). Currently, similar viruses have been isolated from

Italy (RCV), Eire (Lambay Island strain), and Australia (RCV-A1) (Capucci et al., 1996; Forrester et al., 2007; Strive et al., 2009). Genome organization is similar to RHDV and EBHSV in that there are two open reading frames as opposed to three which are found in other caliciviruses (Capucci et al., 1996; Strive et al., 2009). RCV is most closely related to RHDV with an amino acid identity of 91% of the capsid protein, VP60. The amino acid identity to EBHSV was 75% in the same study (Capucci et al., 1996). The average identity of the full-length sequence of RCV-A1 when compared to RHDV was 87%. Phylogenetic analysis of RCV, the Lambay Island strain, and the Ashington strain (England) suggests that these isolates are more closely related to each other than to other strains of RHDV (Capucci et al., 1996; Forrester et al., 2007; Strive et al., 2009). Interestingly, the Ashington strain was isolated from a rabbit (*Oryctolagus cuniculus*) with typical signs of RHDV. Antigenically, sera from rabbits infected with RCV cross-reacted with anti-RHDV antibodies, but not anti-EBHSV antibodies (Capucci et al., 1996). Sera from ten of 11 healthy rabbits on Lambay Island, Eire, also cross-reacted with antibody to RHDV (Forrester et al., 2007) and RT-PCR detected virus sequences shown to be closely related to RCV from two serum samples.

EPIDEMIOLOGY

RCV-A1 RNA was recovered from the small and large intestines of wild Eurpean rabbits (*Oryctolagus cuniculus*) as well as the fecal pellets from the distal colon, suggesting a fecal–oral method of transmission similar to RHDV (Strive et al., 2009). Viral RNA was detected in Peyer's patches, spleen, and less frequently in liver. Experimental inoculation of *Oryctolagus cuniculus* with RCV by oronasal route resulted in seroconversion by day 6 after inoculation (Capucci et al., 1996). Uninoculated cagemates of infected rabbits were seropositive 1–2 days later, presumably from contact. Rabbits housed in the same room that had no contact with the infected rabbits did not seroconvert. RT-PCR detected viral antigens from the intestine of infected rabbits 3, 5, 6, and 7 days after inoculation but not from the liver or spleen. Western blot analyses of intestinal extracts were also positive. Infection with RCV provided complete protection from challenge with RHDV. Inoculation of hares with RCV resulted in no seroconversion and 5 days after inoculation all organs were negative for RCV by RT-PCR. Hares previously inoculated with RCV and then challenged with EBHSV were not protected from disease.

CLINICAL SIGNS

Experimental inoculation of *Oryctolagus cuniculus* with RCV resulted in no clinical signs of disease (Capucci et al., 1996) and no clinical signs of disease were observed in rabbitries with positive serology (Capucci et al., 1997). No clinical signs were observed in wild rabbits (*Oryctolagus cuniculus*) positive for the Lambay Island strain (Forrester et al., 2007) or RCV-A1 (Strive et al., 2009).

PATHOLOGY

Gross or histopathologic lesions have not been described.

DIAGNOSIS

Seroconversion to RHDV without clinical signs of disease is suggestive of RCV infection (Capucci et al., 1997). The virus can be detected by RT-PCR of intestinal contents or feces (Capucci et al., 1996; Forrester et al., 2007; Strive et al., 2009).

CONTROL

Serologically, RCV is difficult to definitively distinguish from RHDV. RCV may represent an older nonpathogenic lagovirus that provides protection from RHDV and thus explains why in some areas seroreactivity to RHDV occurs without evidence of disease.

Michigan Rabbit Calicivirus (MRCV)

In January, 2001, an outbreak of hemorrhagic disease with a 32.5% case fatality rate occurred in a private New Zealand White rabbitry in Michigan (Bergin et al., 2009). Clnical signs consisted of acute fatality, inappetance, vulvar hemorrhage, conjunctival congestion, opisthotonus, and cyanosis of the lips and ear tips. On gross necropsy, evidence of icterus, gastric petechiae and ecchymoses, colonic serosal hemorrhage, and multifocal hemorrhage in the caudal lung lobes was observed. Histopathology revealed multifocal random or periportal hepatocellular necrosis and inflammation, pulmonary and uterine hemorrhages with fibrin clots, bile duct proliferation, and periductal fibrosis. RT-PCR of tissue samples ruled out RHDV, however, positive hepatocytes were detected by immunohistochemistry utilizing RHDV-specific antibodies.

Further amplification of sequences from pooled liver samples demonstrated a calicivirus with capsid sequences that most closely aligned to RCV (91.7% similarity) but were also closely related to RHDV (89.8–91.3% similarity). When ORF-1 polypepetide genomic sequence was aligned, excluding the capsid sequences, MRCV was 77.9–78.5% identical to RHDV, although other strains of RHDV share similarities of 87.9–98.1% in these same comparisons. These sequences of RCV have not been determined (Bergin et al., 2009).

Inoculation of homogenized liver from infected rabbits into naïve, SPF (free of *Pasteurella* sp.) rabbits did not induce disease after 7 days, although inoculated rabbits had viral RNA in the liver detected by RT-PCR and in situ hybridization. This short time course did not allow for determination of seroconversion (Bergin et al., 2009).

Clinical signs of disease resolved and rabbits were depopulated approximately 2 months after the initial outbreak. Antibody against MRCV was detected in depopulated rabbits and 20% had gross and non-specific histopathological changes in their livers consisting of biliary hyperplasia and periductal to bridging portal to portal fibrosis. How the virus was introduced into the colony was not determined (Bergin et al., 2009).

Rabbit Vesivirus

A novel member of the family Caliciviridae was isolated from pooled intestinal contents of five European rabbits (*Oryctolagus cuniculus*) that died with intestinal disease in Oregon (Martín-Alonso et al., 2005). Coccidia were detected in two rabbits and *Escherichia coli* was cultured from the pooled intestinal contents. Calicivirus particles were observed by electron microscopy and a calicivirus was isolated on porcine kidney cell lines and partially sequenced. The virus was not neutralized with anti-calicivirus antibodies (from 40 different antisera) and sequence analysis indicated it is a novel member of the Vesivirus genus. The genome consists of a single-stranded positive sense RNA of 8295 nucleotides and contains a 2.6-kb subgenomic RNA. Its genomic organization is unlike lagoviruses, as it contains three ORFs, rather than two. Phylogenic analysis grouped it in a clade containing marine caliciviruses and non-human primate calicivirus, Pan 1.

Paramyxovirus Infections

Rabbit syncytium virus was isolated in chicken embryos inoculated with extracts of liver and spleen from a wild Eastern Cottontail rabbit (*Sylvilagus floridanus*) in Virginia (Morris et al., 1965). The agent causes a cytopathic effect and syncytia in monkey and hamster kidney cell cultures. Experimentally, suckling mice are susceptible to the virus, but weaned mice, guinea pigs, domestic European and Eastern Cottontail rabbits failed to develop signs or lesions, although antibodies developed, following inoculation. Sera from eight of 25 (32%) Eastern Cottontail rabbits trapped in the same area as the original rabbit had antibodies to the virus. Antibodies to the virus were not detected in sera from seven other species trapped in the same area, *Oryctolagus cuniculus*, or humans. The virus resembles the paramyxoviruses in size, nucleic acid type, and in ether and heat sensitivity. Neither hemagglutination nor hemadsorption were observed, and the ultrastructure of the virus has not been described. The virus is serologically distinct from the known paramyxoviruses.

Evidence of another paramyxovirus, *Sendai virus*, has been found in domestic European rabbits (*Oryctolagus cuniculus*). *Sendai virus* is the type species of the genus *Respirovirus*, family *Paramyxoviridae* (Fauquet et al., 2005) and a primary pathogen of mice (Percy and Barthold, 2007). A serological survey of 23 breeding and laboratory colonies, in metropolitan Tokyo and Ibaragi, Chiba, Saitama, Kanagawa, Shizuoka, and Nagano prefectures, revealed that 85 of 160 (53%) Japanese White or New Zealand White rabbits had antibodies to *Sendai virus* (Iwai et al., 1986). Ito et al. (1987) also detected antibodies to *Sendai virus* in rabbit sera in studies comparing antigenic relationships among paramyxoviruses. Intranasal inoculation of *Oryctolagus cuniculus* with *Sendai virus* resulted in infection as rabbits shed virus for 3–7 days after inoculation, and viral antigen was detected by immunofluorescence in the nasal cavities (Machii et al., 1989). Although rabbits showed no clinical signs and had only a moderate increase of goblet cells in the nasal epithelium, antibodies to the virus developed. One of three uninoculated rabbits exposed to inoculated rabbits acquired infection. These studies suggest that *Oryctolagus cuniculus* is susceptible to *Sendai virus* and that this or a related virus may be endemic in rabbit colonies. Experimentally, genetically modified Sendai viruses have been used in gene therapy in rabbits (Nakamura et al., 1998).

Bunyavirus Infections

Evidence of infection with several viruses of the genus *Orthobunyavirus* in the family *Bunyaviridae* has been detected in leporids. Strains of *California encephalitis virus* found to infect rabbits or hares include California encephalitis, Snowshoe hare, Tahyna, and Inkoo viruses (Fauquet et al., 2005). Similar evidence of infection has been found with viruses of the genus *Bunyamwera virus* including cache valley virus, Tensaw virus, and Northway virus. One other member of the *Bunyaviridae* that infects rabbits and is not assigned to a genus is the Silverwater virus.

Antibodies to California encephalitis virus were initially detected in Eastern Cottontail rabbits (*Sylvilagus floridanus*) and Black-tailed jackrabbits (*Lepus californicus*) in California (Hammon and Reeves, 1952). The first virus of the group to be recovered from leporids was the Snowshoe hare virus, isolated in 1959 from the blood of a sick Snowshoe hare (*Lepus americanus*) in western Montana (Burgdorfer et al., 1961). The virus is widespread in Snowshoe hare populations of North America, as serological surveys revealed prevalences of 40–97% in adult hares (Hoff et al., 1969; McLean et al., 1975; Mean, 1983; Newhouse et al., 1963; Yuill et al., 1969). The virus has been isolated from seven species of boreal forest mosquitoes, including 0.04% of *Aedes communis* (McLean, 1983), and also from the rabbit tick, *Haemaphysalis leporis-palustris* (Newhouse et al., 1963).

The European hare (*Lepus europeaus*) and wild European rabbit (*Oryctolagus cuniculus*) appear to be the major reservoirs of Tahyna virus in Europe (Bardos,

1965, 1975; Danielova et al., 1969; Hannoun et al., 1969; Simkova, 1963). Clinical disease in infected hares has not been reported. Experimental infection of European rabbits results in viremia and antibody formation without clinical disease (Hammon and Sather, 1966; Simkova, 1962). Thus, domestic European rabbits are useful as sentinels of viral activity since they develop antibodies and can serve as a source for recovery of virus (Kolman et al., 1966; McKiel et al., 1966). A serological survey in Finland revealed that 5% of Mountain hares (*Lepus timidus*) and none of the *Lepus europeaus* tested had antibodies against Inkoo virus (Brummer-Korvenkontio, 1973). Similar viruses have been isolated from mosquitoes and humans in Russia (Vanlandingham et al., 2002).

Cache valley virus, Tensaw virus, and Northway virus are mosquito-borne viruses of North America. Cache valley virus has a wide geographic distribution in North America (Blackmore and Grimstad, 2008), whereas Tensaw virus is found predominantly in the Southeastern United States (Bigler et al., 1975) and Northway virus in Alaska and California (Campbell et al., 1990, 1991; Walters et al., 1999; Zarnke et al., 1983). Recent evidence suggests these host ranges may not be as restrictive as earlier thought (Sahu et al., 2002). The amplifying hosts for all of these viruses are unclear, however antibodies recognizing Cache valley virus have been found in Desert cottontails (*Sylvilagus audubonii*), Eastern cottontails (*Sylvilagus floridanus*), and Black-tailed jackrabbits (*Lepus californicus*) (Blackmore and Grimstad, 2008). Antibodies to Tensaw virus have been found in the Swamp rabbit (*Sylvilagus acquaticus*) (Calisher et al., 1986), Marsh rabbit (*Sylvilagus palustris*) (Bigler et al., 1975), and New England cottontail rabbit (*Sylvilagus transitionalis*) (Sudia et al., 1969) and those to Northway virus in the Snowshoe hare (*Lepus americanus*) (Zarnke et al., 1983). Experimental infection of Eastern cottontail rabbits with Cache valley virus resulted in transient viremia of insufficient magnitude to infect mosquitoes (*Coquillettidia perturbans*) suggesting that this species may not be an important vertebrate host for this virus (Blackmore and Grimstad, 2008). In contrast, rabbits and hares may be important hosts for Tensaw and Northway viruses as experimental infection of New England cottontail rabbits (*Sylvilagus transitionalis*) with Tensaw virus resulted in viremia of sufficient magnitude to infect mosquitoes (*Anopheles quadrimaculatus*) (Sudia et al., 1969). Living near Snowshoe hares (*Lepus americanus*) was found to be a significant risk factor for human serologic reactivity to Northway virus (Walters et al., 1999).

Silverwater virus has been isolated from Snowshoe hares (*Lepus americanus*) and from rabbit ticks (*H. leporis palustris*) from Snowshoe hares in Ontario and Alberta, Canada (McLean and Larke, 1963; Yuill et al., 1969). Although no disease has been reported in infected hares, they appear to play a central role in the natural cycle of the virus.

Togavirus Infections

Serological evidence of infection with *Western* (WEE), *Eastern* (EEE), and *Venezuelan* (VEE) *equine encephalitis viruses*, members of the genus *Alphavirus*, in the family *Togaviridae* (Fauquet et al., 2005) has been found in rabbits and hares. Wild *Sylvilagus* as well as hares (*Lepus californicus* and *Lepus americanus*) have antibodies to WEE (Bowers et al., 1969; Yuill et al., 1969). Infection studies of *Oryctolagus cuniculus* with strains of WEE isolated from South America and North America demonstrated virus strain variation in clinical signs and mortality (Bianchi et al., 1997). A South American strain (AG80-646) resulted in early onset of anorexia and rear limb paralysis with rabbits dying 6 days after inoculation. The North American strain caused no detectable clinical signs, but the rabbits seroconverted. Antibodies to EEE (Yuill et al., 1969) and VEE (Hoff et al., 1970) have been detected in Snowshoe hares (*Lepus americanus*) and antibodies to VEE have been detected in Eastern cottontail rabbits (*Sylvilagus floridanus*) (Smart and Trainer, 1975).

Complement fixation, hemagglutination-inhibition, ELISA, and plaque reduction neutralization tests are commonly used for diagnosis of these infections in humans and animals, although cross-reactivity between different viruses is problematic with all of these tests (O. I. E., 2008). An epitope-blocking assay was developed and tested on rabbit sera to better separate the individual virus groups (Pässler and Pfeffer, 2003). The infectious agent can be identified by viral isolation or PCR (O. I. E., 2008; Vodkin et al., 1993).

Flavivirus Infections

Two members of the Japanese encephalitis group in the family *Flaviviridae*, genus *Flavivirus* have been shown to infect rabbits or hares, *St. Louis encephalitis virus* and *West Nile virus* (WNV) and one member of the mammalian tick-borne virus group of the genus *Flavivirus* has been shown to infect hares, *Powassan virus* (Fauquet et al., 2005). Antibodies to St. Louis encephalitis virus have been detected in Snowshoe hares (*Lepus americanus*) (Yuill et al., 1969). Experimentally, Eastern cottontail rabbits (*Sylvilagus floridanus*) have been shown to be susceptible to WNV infection (Tiawsirisup et al., 2005). WNV is a mosquito-transmitted pathogen of significant public health importance (Hayes et al., 2005). The major route of infection of humans is by the bite of a mosquito infected by ingesting a blood meal from an infected bird. In general, mammalian hosts of WNV are dead-end hosts and do not develop viremia of sufficient magnitude to infect mosquitoes (Bowen and Nemeth, 2007). However, certain species, including Eastern cottontail rabbits (*Sylvilagus floridanus*), develop viremia which infects mosquitoes (*Culex pipiens* and

Culex salinarius) and therefore, may contribute to the endemic cycle of WNV in North America (Tiawsirisup et al., 2005). Infection in rabbits occurs without clinical signs. *Powassan virus* is a tick-borne virus of emerging public health concern in the United States, Canada, and Russia (Ebel, 2010). Antibodies to *Powassan virus* have been found in Snowshoe hares (*Lepus americanus*) (McLean et al., 1961; Zarnke and Yuill, 1981). Snowshoe hares experimentally infected with the virus develop no clinical symptoms, but become viremic for 1–3 days. Other vertebrates, including red squirrels (*Tamiasciurus hudsonicus*), chipmunks (*Tamias amoenus*), groundhogs (*Marmota monax*), and white-footed mice (*Peromyscus leucopus*) may be more important in perpetuating the virus than Snowshoe hares (Ebel, 2010).

Picobirnavirus Infections

A rabbit *Picobirnavirus*, a member of the *Picobirnaviridae* family, was detected in rabbit feces in a study in which rabbits were inoculated with human *Picobirnavirus* (Fregolente et al., 2009; Gallimore et al., 1993). Picobirnaviruses are non-enveloped bisegmented, double-stranded RNA viruses of 35–40 nm in diameter. Members of this family of viruses have been found in the feces of many different hosts, including humans, pigs, rabbits, dogs, rats, snakes, and birds (Fregolente et al., 2009). They are thought to be opportunistic gastrointestinal pathogens associated with clinical disease in humans (Giordano et al., 1999). These viruses have been associated with gastrointestinal disease in HIV-infected humans (Giordano et al., 1999; Grohmann et al., 1993) and may be important pathogens or co-pathogens in immunosuppressed rabbits. The *picobirnavirus* genome detected in rabbits consisted of two segments; 2.3 kbp and 1.85 kbp (Gallimore et al., 1993). The first segment contains one major ORF and two smaller ORFs and has been partially sequenced (Green et al., 1999). This segment is thought to encode a capsid protein while the second segment appears to encode an RNA-dependent RNA polymerase (Rosen et al., 2000). Picobirnaviruses do not replicate in tissue culture, although they were successfully detected in the feces of rabbits inoculated orally with rabbit *Picobirnavirus* (Gallimore et al., 1993; Ludert et al., 1995). No clinical signs of disease resulted, however, anti-*Picobirnavirus* antibodies developed (Gallimore et al., 1993).

Rabies Virus Infections

Rabies virus, the type species of the genus *Lyssavirus* and family *Rhabdoviridae* (Fauquet et al., 2005), is a neurotropic virus that infects mammals resulting in a generally fatal, progressive encephalomyelitis (Manning et al., 2008). It is found in high titers in the saliva of clinically ill animals and is typically transmitted through a bite. Rabies virus infections in rabbits and hares are rare, as these species often do not survive encounters with rabid animals. From 1971 to 1984, seven rabid rabbits were reported to the CDC, including four Eastern cottontails (*Sylvilagus floridanus*) (Fishbein et al., 1986), while in the next 9 years, 17 cases of rabies in rabbits were reported to the CDC (Childs et al., 1997). Of these 17, 11 were domestic European rabbits (*Oryctolagus cuniculus*) and the others were unknown. Four viruses were typed and shown to be either raccoon or skunk variants of rabies virus. In 1995, raccoon-variant rabies was reported in seven domestic European rabbits in New York State (Eidson et al., 2005). Rabies is typically diagnosed by fluorescent antibody test on brain tissue, however, strains may be further identified using monoclonal antibodies or genetic means such as nucleic acid probes, PCR, and DNA sequencing (O. I. E., 2008).

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