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I. INTRODUCTION

It is two decades since the first edition of this volume was published. There now exists considerably more information regarding the various viral infections and diseases of leporids. Some viruses, covered previously in a general manner, can now be discussed specifically. As before, this review uses the most widely accepted viral terminology. The recommendations of the International Committee on Taxonomy of Viruses (1991) will be followed, but well-established common names for viruses will be used when appropriate.

The viral diseases of rabbits are discussed in a sequence based on the taxonomic groups to which the viruses belong. This sequence is 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. None of the viral infections of rabbits is known to be of
poxviruses of rabbits which produce distinct disease syndromes.

The major focus of this chapter is the naturally occurring viral diseases of rabbits (Tables I and II). Some viral infections of rabbits have provided fundamental information on basic mechanisms of virus–host interrelationships and have been useful as models for human diseases. Although the principal emphasis is on virus infections of domestic rabbits of the genus Oryctolagus, naturally occurring infections of other rabbits and hares are also discussed.

II. DNA VIRUS INFECTIONS

A. 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.

1. Myxoma Virus

a. 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 Tapeti or tropical forest rabbit (Sylvilagus brasiliensis) in which the virus causes relatively mild disease. Transmission from wild to domestic rabbits probably occurred via 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 of the virus (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). Although the virus was first introduced into Australia in 1926, for more than two decades it was 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, after a somewhat slow start, it became established and spread rapidly, decimating 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 a process of 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). The passage of time has resulted in further, often regional, increases in the 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 in nature (Fenner et al., 1957; Fenner and Woodroofe, 1965). 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 South and North America and in wild rabbits of the genus Oryctolagus in South America, Europe, Australia, and New Zealand.

b. ETIOLOGY. Myxomatosis is caused by any one of several strains of myxoma virus, a member of the genus Leporipoxvirus in the family Poxviridae (International Committee on Taxonomy of Viruses, 1991). Antigenic differences, demonstrated among different strains of the virus (Reisner et al., 1963; Fenner, 1965), have prompted some to consider the California
### TABLE I
DNA VIRUS INFECTIONS OF RABBITS

| Virus group       | Family         | Genus            | Virus Group | Host                                      | Geographic distribution                                      |
|------------------|----------------|------------------|-------------|-------------------------------------------|-------------------------------------------------------------|
| **Poxviridae**   | Leporipoxvirus | Myxoma           | Sylviagalus | Sylvilagus brasiliensis                   | South America                                               |
|                  |                |                  | bactrani    | Sylvilagus bactrani                       | North America                                               |
|                  |                |                  | virulans    | Sylvilagus virulans                       | South America, Europe, Australia, New Zealand               |
|                  |                |                  | (wild and domesticated) | Sylvilagus floridanus | North America                                               |
|                  |                | Rabbit (Shope) fibroma |          | Sylviagalus floridanus                   | North America                                               |
|                  | Orthopoxvirus  | Rabbit fibroma   | Orchothelaghus | Orchothelaghus conicus                | Europe                                                     |
| **Herpesviridae**| Gamma herpesvirus | Leperid herpesvirus 1 | Sylvilagus | Sylvilagus floridanus                   | United States                                               |
| Unclassified     |                | Leperid herpesvirus 2 | Orchothelaghus | Orchothelaghus conicus                | England, United States (laboratory colonies)                |
| **Bunyaviridae** | Pappilomavirus | Rabbit (Shope) papilloma | Sylvilagus floridanus | Sylvilagus floridanus                   | United States                                               |
|                  |                | Rabbit oral papilloma | Orchothelaghus | Orchothelaghus conicus                | United States, Mexico                                        |
| **Papoviridae**  | Mastadenovirus | Aderenavirus      | Orchothelaghus | Orchothelaghus conicus                | Hungary, Quebec                                             |
| **Adenoviridae** | Parvovirus     | Lapine parvovirus | Orchothelaghus | Orchothelaghus conicus                | Japan, United States                                        |

* Aberrant host.
* Subfamily.

### TABLE II
RNA VIRUS INFECTIONS OF RABBITS

| Virus group       | Family         | Genus            | Virus Group | Host                                      | Geographic distribution                                      |
|------------------|----------------|------------------|-------------|-------------------------------------------|-------------------------------------------------------------|
| **Reoviridae**   | Rotavirus      | Rotavirus        | Orchothelaghus | Orchothelaghus conicus                | North America, Japan, Europe                                 |
| **Coronaviridae**| Coronavirus     | Pleural effusion disease | Sylvilagus | Sylvilagus floridanus                   | Canada                                                     |
|                  |                | infectious cardiomyopathy | Orchothelaghus | Orchothelaghus conicus                | Europe, United States                                       |
|                  |                | Rabbit enteric   | Orchothelaghus | Orchothelaghus conicus                | Canada, Europe                                              |
| **Caliciviridae**| Calicivirus     | Rabbit (viral) hemorrhagic | Orchothelaghus | Orchothelaghus conicus                | China, Korea, Europe, India, Middle East, North Africa      |
|                  |                | disease | (wild and domesticated) | Orchothelaghus floridanus                | Europe                                                     |
|                  |                | European brown hare | Orchothelaghus | Orchothelaghus conicus                | North America                                               |
| **Paramyxoviridae** | Unclassified | Rabbit syncytium | Sylvilagus | Sylvilagus floridanus                   | United States                                               |
|                  | Paramyxovirus  | Sendai-like      | Orchothelaghus | Orchothelaghus conicus                | Japan                                                      |
| **Bunyaviridae** | Bunaviruses     | California encephalitis | Sylvilagus | Sylvilagus floridanus                   | North America                                               |
|                  |                | Snowshoe hare    | Lepus americanus | Lepus americanus                | North America                                               |
|                  |                | Tahyna           | Lepus europeaus | Lepus europeaus                | Europe                                                     |
|                  |                | Inkoo            | Lepus timidus | Lepus timidus                | Finland                                                    |
| **Togaviridae**  | Togaviruses     | Silverwater      | Lepus americanus | Lepus americanus                | Canada                                                     |
|                  | Alphavirus     | Western equine encephalitis | Sylvilagus | Sylvilagus floridanus                   | North America                                               |
|                  |                | Eastern equine encephalitis | Lepus americanus | Lepus americanus                | North America                                               |
| **Flaviridae**   | Flavivirus      | St. Louis encephalitis | Lepus americanus | Lepus americanus                | North America                                               |

* Serological evidence only.
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 discussed as strains of myxoma virus.

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 chemical and physical characteristics of myxoma virus have been described (Fenner, 1953; Fenner and Ratcliffe, 1965; Porterfield, 1989). Myxoma virus is readily propagated at 35°C on the chorioallantoic membrane of embryonated hens’ eggs, forming distinct poxks (Fenner and McIntyre, 1956). Different strains of virus cause poxks of various sizes, the variation being sufficiently distinct to allow tentative strain identification. The South American strains cause large poxks, 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 (Woodroffe and Fenner, 1965; Porterfield, 1989). 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 (Woodroffe 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).

c. Epidemiology. Myxomatosis is endemic on four continents: South America, North America, Europe, and Australia. In Brazil and Uruguay, the virus is endemic in wild rabbits of the genus Sylvilagus, particularly *S. 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 (Fenner and Ratcliffe, 1965). The California strains of myxoma virus, also known as the California rabbit fibroma virus (Porterfield, 1989), are endemic in wild rabbits of the genus Sylvilagus, especially *S. bachmani*, which serves as the principal source of infection for domestic rabbits (Marshall et al., 1963). In Australia, the myxoma virus has been endemic in wild European rabbits 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 (*O. cuniculus*) serving as the predominant host species.

The naturally susceptible species are the European rabbit (*O. cuniculus*), the European hare (*Lepus europaeus*), the mountain hare (*Lepus timidus*), the Tapeti or tropical forest rabbit (*S. brasiliensis*), the brush rabbit (*S. 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 by arthropod vectors, mosquitoes and fleas being most often incriminated. Because transmission occurs by mechanical transport of virus on mouth parts, the species of mosquito is unimportant, and thus any mosquito which feeds on rabbits (Grohlaus et al., 1963), as well as biting flies and gnats (Mykytowycz, 1957), may serve as vectors. 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 Woodroffe, 1953), where surface-feeding arthropods such as mites and lice may obtain the virus and serve as mechanical vectors. Experimentally, virus can spread from infected to uninfected rabbits in the absence of arthropod vectors, and such contact transmission may occur under natural conditions in rabbit warrens (Mykytowycz, 1958, 1961). Windborne spread was suspected in France (Arthur and Louzis, 1988), and myxomatosis may have reached England from France in 1953 by this mode of transmission (Sellers, 1987). 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).

Arthropod transmission of myxoma virus in its original habitat in South America has not been investigated intensively although circumstantial evidence indicates that mosquitoes of the genus *Aedes* are important vectors. Experimentally, *Aedes aegypti* and *Aedes scapularis*, as well as the cat flea, *Ctenocephalides felis*, may transmit the virus (Chapple and Lewis, 1965). In California, it has been shown experimentally that *Anopheles freeborni*, *Aedes serriniens*, *A. aegypti*, *Caliseta incidenis*, and *Culex tarsalis* can transmit myxoma virus between *S. bachmani* (Grohlaus et al., 1963). The virus was isolated from wild-caught *A. freeborni* in an area of myxomatosis out-
breaks, further implicating it as a possible vector (Marshall and Regnery, 1960). In Australia, the disease spreads along river valleys, the main vector mosquitoes being *Culex annulirostris, Anopheles annulipes, Culex pipiens australicus*, and several *Aedes* species (Fenner and Ratcliffe, 1965). Although black flies (*Simulium* spp) are possible vectors in Australia, only *Simulium melatum* has been conclusively shown to be a vector (Mykytowycz, 1957). Stickfast fleas (*Echidnophaga* spp.) and the cat flea, *C. felis*, can transmit the virus, and the louse (*Haemodiphus ventricosus*) and fur mite (*Cheyletiella parasitivorax*) are also vectors (Mykytowycz, 1958).

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 (Sobey and Conolly, 1971; Shepherd and Edmonds, 1977). 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, *S. 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, *S. cuniculi*, which is less influenced by seasonal changes, is the major vector (Lockley, 1954; Armour and Thompson, 1955; Andrews et al., 1959; 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).

d. **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 South America, Europe, California, and Australia.

i. Signs in Sylvilagus Species. Rabbits of the genus *Sylvilagus*, the natural host of the virus, are relatively resistant to infection. Infection of the Tapeti or tropical forest rabbit (*S. brasiliensis*) with the South American virus under natural or experimental conditions results in development of skin tumors (fibromas) at the site of virus inoculation or mosquito bite. These nodules usually appear 4 to 8 days after exposure to the virus and may persist for up to 40 days. Young rabbits may succumb to generalized disease following infection with myxoma virus (Aragao, 1943). In the brush rabbit (*S. bachmani*), skin tumors, rarely more than 1 cm in diameter, develop at the base of one or both ears (Regnery and Miller, 1972). Experimental inoculation of *S. bachmani* with the South American and California strains results in development of local skin tumors, with the South American virus causing slightly more prominent tumors than the California virus (Marshall and Regnery, 1963). Cottontail rabbits (*S. floridanus, Sylvilagus nutalli, and Sylvilagus auduboni*) develop small lesions at the site of California virus inoculation, but in *S. nutalli* and *S. auduboni* the South American virus induces a larger lesion (Fenner and Ratcliffe, 1965).

ii. Signs in Lepus Species. The European hare (*L. europaeus*) is resistant to the myxoma virus under experimental conditions, and field experience supports this observation. Occasionally, however, individual hares (*L. europaeus and L. timidus*) with mild to severe generalized myxomatosis have been encountered (Fenner and Ratcliffe, 1965).

iii. 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 of clinical disease is largely determined by the strain of virus as well as the strain of rabbit (Sobey, 1969; Sobey et al., 1970). The varieties of clinical syndromes which can result from infection with various strains of virus in various strains of rabbits 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 (Kessel et al., 1931; Chapple and Bowen, 1963).

Signs which develop following infection with California strains of the virus in susceptible rabbits vary depending on the length of time the rabbit survives. Rabbits with the pustular 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 to 2 weeks, usually edema of the eyelids, resulting in a "droopy" appearance of the eyes, appears at 6 to 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 may develop purulent blepharoconjunctivitis and edema at the base of the ears, signs more often associated with other myxoma strains. 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 acute disease, which follows inoculation of rabbits with the original South American isolate of Moses (1911), results in a mean survival time of 11 days. From 3 to 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 (Fig. 1). 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 to 15 days after infection. Infection with the 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).

c. Pathology. The gross and microscopic pathology of myxomatosis has been comprehensively reviewed (Rivers, 1930; Hurst, 1937a; Fenner and Ratcliffe, 1965). 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 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 (Fig. 2). 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.
VIRAL DISEASES

characteristic of myxomatosis. Central necrosis of myxomas and inflammatory cells (Figs. 3 and 4). It is because of this characteristic of myxomatosis. Central necrosis of myxomas come large stellate (myxoma) cells surrounded by a homogeneous mucinous substance that the tumors are referred to as myxomas. Vascular endothelial proliferation with narrowing of the lumen and extrusion of stellate cells has been described by Hurst (1937a), who considered this lesion 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 basal layer of the skin (Rivers and Ward, 1937; Patton and Holmes, 1977).

Lesions in other organs, although not consistently present, reflect the 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).

Fig. 3. Subcutaneous myxoma in Oryctolagus cuniculus. Courtesy Dr. N. F. Cheville.

Depending on the strain of virus. The skin tumors result from proliferation of undifferentiated mesenchymal cells, which become large stellate (myxoma) cells surrounded by a homogeneous matrix of mucinous material interspersed with capillaries and inflammatory cells (Figs. 3 and 4). It is because of this mucinous substance that the tumors are referred to as myxomas and the disease myxomatosis. Vascular endothelial proliferation with narrowing of the lumen and extrusion of stellate cells has been described by Hurst (1937a), who considered this lesion characteristic of myxomatosis. 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 basal layer of the skin (Rivers and Ward, 1937; Patton and Holmes, 1977).

f. Diagnosis. Myxomatosis in European rabbits can usually be diagnosed by the clinicopathological features. 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. The technique of choice is intracutaneous inoculation of young susceptible rabbits with fresh tissue collected from lesions free of bacterial contamination. Lesions should develop at the site of inoculation within 1 week. The virus may be isolated by chorioallantoic membrane inoculation of 11- to 13-day-old embryonated chicken eggs followed by incubation at 35°C for 4 to 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 cell cultures or any one of several cell types can also be accomplished. The virus isolated can be identified as myxoma virus by a direct fluorescent antibody test (Takahashi et al., 1958, 1959), the plaque-neutralization test (Woodrooffe and Fenner, 1965), or the agar-gel diffusion microprecipitation test (Fenner, 1965). Infection of Sylvilagus rabbits with myxoma virus clinically resembles fibromatosis and should be differentiated from the latter disease by inoculation of young susceptible rabbits of the genus Oryctolagus. Myxomatosis causes severe to fatal disease, whereas fibromatosis causes a localized fibroma.

g. Control. Control of myxomatosis is of prime importance in areas where the virus is endemic in wild rabbit populations. In such areas, 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

Fig. 4. Center of myxoma nodule with homogeneous mucinous substance interspersed with inflammatory cells in Oryctolagus cuniculus. Courtesy Dr. N. F. Cheville.
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. Other attenuated strains have been used as vaccines in Europe with some success, and experiments with a live virus vaccine (SG-33) using a flea, *Xenopsylla cunicularis*, as the vector appear promising (Delobette, 1991).

2. Rabbit (Shope) Fibroma Virus

a. HISTORY. The transmissible tumor-inducing agent now known as rabbit or Shope fibroma virus was isolated from a cottontail rabbit (*Sylvilagus floridanus*) in 1932 (Shope, 1932a). The virus was transmissible to 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 (Shope, 1932b). He showed that it was antigenically related to myxoma virus. Similarities between fibroma and myxoma viruses 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), and micro-precipitation procedures (Fenner, 1965). The 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 cottontail rabbits (Yuill and Hanson, 1964). The disease is historically considered a benign endemic disease of wild cottontail rabbits, of little economic significance to commercial rabbit producers or laboratory investigators. However, an epidemic 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 rabbits (*O. cuniculus*) with experimentally induced Shope fibromas (Strayer *et al.*, 1983a). Although the virus was present in a stock of fibroma virus, its origin is unclear. The virus is antigenically similar to both fibroma and myxoma viruses 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 (Strayer *et al.*, 1983c; Corbel *et al.*, 1983; Strayer and Sell, 1983; Skaltsky *et al.*, 1984). The disease may be a useful model for the study of virus-induced immunologic impairment (Strayer *et al.*, 1985).

b. ETIOLOGY. The fibroma virus is a *Leporipoxvirus* of the family Poxviridae (International Committee on Taxonomy of Viruses, 1991) and is closely related to myxoma virus (Fenner, 1953) and the hare and squirrel fibroma viruses (Fenner, 1965). 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 cottontail and domestic rabbits (Constantin *et al.*, 1956; Kilham, 1956; Padgett *et al.*, 1962; Hinze and Walker, 1964; Kasza, 1974). 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).

c. EPIDEMIOLOGY. Since rabbit fibroma virus was first isolated from a 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 cottontail rabbits trapped in the Patuxent Wildlife Refuge in Maryland had fibroma virus or antibodies to fibroma virus. The virus has also been isolated from cottontail 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 than was formerly believed.

The natural transmission cycle of fibroma virus has not been completely elucidated. The virus may persist in the epidermis of experimentally infected cottontail rabbits for 5 to 10 months (Kilham and Fisher, 1954; Kilham and Dalmat, 1955), which would enhance the likelihood of mechanical arthropod transmission. Experimentally, several species of mosquitoes as well as triatomines, fleas, and bedbugs can serve as vectors (Kilham and Wake, 1953; Kilham and Dalmat, 1955; Dalmat, 1959). Infected mosquitoes are capable of infecting wild cottontail 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.

The natural host of fibroma virus is the eastern cottontail rabbit (*S. floridanus*). Three other species of *Sylvilagus* (*S. bachmani*, *S. nuttalli*, and *S. auduboni*) are refractory to fibroma virus (Fenner and Ratcliffe, 1965). A closely related virus, isolated from fibromas in *S. 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 (Porterfield, 1989). The European rabbit 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).
d. Clinical Signs. The clinical signs are largely those described by Shope (1932a,b, 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 they 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 Fisher, 1954; Dalmat and Stanton, 1959; 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 cottontail 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 cottontail 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 cottontail rabbits, but regression of the tumors occurs more rapidly.

The earliest microscopic lesions in cottontail 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 cottontail 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 (Fig. 6) 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.

e. Pathology. The gross and microscopic changes associated with fibroma virus infection in naturally and experimentally infected cottontail rabbits and in experimentally infected European rabbits have been described by several workers (Shope, 1932a; Andrewes, 1936; Ahlstrom, 1938; Fisher, 1953; Kilham and Fisher, 1954; Dalmat and Stanton, 1959; 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 cottontail 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 cottontail 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 cottontail rabbits, but regression of the tumors occurs more rapidly.

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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 fibroma inclusions are observed. Myxomatosis in cottontail rabbits may resemble fibromatosis but is differentiated by subcutaneous inoculation of young European rabbits with a tumor cell suspension. 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).

g. CONTROL. Because the disease is endemic and of little significance in cottontail 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.

3. Hare Fibroma Virus

a. HISTORY. Epidemics of a fibromatous disease in European hares (Lepus europaeus) occurred in France and Northern Italy in 1959 (Leinati et al., 1959; Lafenetre et al., 1960). 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).

b. ETIOLOGY. The causative agent of hare fibromatosis is a Leporipoxivirus in the family Poxviridae (International Committee on Taxonomy of Viruses, 1991), which has been shown by plaque-neutralization and cross-protection tests to be antigenically related to myxoma, rabbit fibroma, and squirrel fibroma viruses (Woodroofs 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 do survive, indicating some protection (Woodroofs and Fenner, 1965).

c. EPIDEMIOLOGY. Hare fibromatosis has been recognized only in Europe, where under natural conditions it infects the European hare. 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 (Leinati et al., 1959; Lafenetre et al., 1960). The mode of transmission and interepidemic survival of the virus are unknown.

d. 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. 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).

e. 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).

f. 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).

g. CONTROL. Because the disease is endemic and of little significance in hares, no control measures have been developed.

4. Rabbitpox

a. HISTORY. Rabbitpox was first diagnosed at the Rockefeller Institute in New York when a highly fatal disease occurred spontaneously in the 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 epidemic 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 epidemic 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).

b. Etiology. Rabbitpox virus is an Orthopoxivirus in the family Poxviridae (International Committee on Taxonomy of Viruses, 1991) and is antigenically related to vaccinia virus (Hu et al., 1936; Jansen, 1946; Fenner, 1958). The biological properties of the Utrecht strain (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. 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).

c. 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 young 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 via 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).

d. Clinical Signs. The clinical disease has been described in detail (Greene, 1934a; Bedson and Duckworth, 1963; Christensen et al., 1967). 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 to 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 to 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 to 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).

e. 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 in almost any part of the body. Subcutaneous edema and edema of the mouth and 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. Vesicles and pustules, as with human variola infection, are not characteristic of rabbitpox infection. Vascular occlusion from the pronounced swelling of the endothelium may result in necrotic lesions.

Focal nodular lesions and diffuse pneumonitis, with perivascular mononuclear and polymorphonuclear cell infiltration, occur in the lungs. Focal to diffuse pulmonary necrosis may be found. There is severe congestion of the spleen, with marked distension 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 monocellular 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.

f. 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 or tissue impression smears (Christensen et al., 1967) or by virus isolation and identification. 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.

g. 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 (Greene, 1934a; Christensen et al., 1967). Investigators using rabbitpox virus experimentally should take exceptional precautions to prevent the virus from reaching susceptible rabbit populations. In an epidemic in a large colony, vaccination with vaccinia virus can be used to protect uninfected rabbits (Rosahn et al., 1936b; Appleyard and Westwood, 1964; Boulter et al., 1971).

B. 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 laboratory rabbit is by definition an experimental animal and may frequently be exposed to stresses of various kinds. The possible existence of latent virus infections thus has an important influence on the quality of experimental animals and potentially on the validity of experimental findings. It is in this context that the two currently recognized herpesviruses of rabbits are discussed.

1. Leporid Herpesvirus 1

a. HISTORY. Leporid herpesvirus 1 (synonyms Herpesvirus sylvilagus, cottontail virus, Hinze herpesvirus lymphoma) was isolated from primary kidney cell cultures from apparently healthy weanling 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 cottontail and domestic rabbits. Another herpesvirus, apparently distinct from the original isolate of Hinze (1971a), was recovered from primary kidney cell cultures of S. floridanus (Cebrian et al., 1989).

b. ETIOLOGY. The virus possessed the physical, chemical, and biological properties of a herpesvirus and was named Herpesvirus sylvilagus (Hinze, 1971a; Heine and Hinze, 1972). Although infectious virus could not be demonstrated in lymphocytes from infected cottontail 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 cottontail and domestic rabbits but not in cells from humans, monkeys, hamsters, and 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 cottontail rabbits (Fig. 7) (Cohrs and Rouhandeh, 1982; Medveczky et al., 1984). The virus possesses no antigenic relationship to Leporid herpesvirus 2 or to four other mammalian herpesviruses (Hinze, 1971a). The virus is a gamma herpesvirus (Cohrs and Rouhandeh, 1987; Rouhandeh and Cohrs, 1987), in the family Herpesviridae (International Committee on Taxonomy of Viruses, 1991). 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; Medveczky et al., 1989).

c. EPIDEMIOLOGY. A serological survey in Wisconsin revealed antibodies to the virus in 6 of 101 wild cottontail rabbits (Spieker and Yuill, 1976). In experimentally infected cottontail rabbits, herpesvirus was not recovered from feces, urine, milk, ejaculates, or conjunctival and genital secretions, but virus was isolated from the oral secretions of 1 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 rabbits (Hinze and Lee, 1980). The tonsils are the likely site of persistent infection and virus release 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).

d. CLINICAL SIGNS. Inoculation of 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 to 60% in normal rabbits (Hinze, 1969). Repeated attempts to infect domestic New Zealand White rabbits have met with failure. Only rabbits of the genus Sylvilagus appear to be susceptible.

e. PATHOLOGY. The lymphoproliferative lesions in cottontail rabbits occur in the lymphoid and other organ systems (Hinze, 1969, 1971b; Hinze and Wegner, 1973; Hesselton et al., 1988). Extensive infiltration of various tissues, commonly the kidneys, liver, lungs, and myocardium, with immature, actively proliferating lymphocytes occurs 6 to 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.

2. Leporid Herpesvirus 2

a. HISTORY. Nesburn (1969) isolated Leporid herpesvirus 2 (synonyms Herpesvirus cuniculi, virus III of rabbits) 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 compari-
son 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).

b. 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). The virus is an unclassified member of the family Herpesviridae (International Committee on Taxonomy of Viruses, 1991).

c. Epidemiology. Rivers and Tillett (1924a) found that 4 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 for 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 transplacently failed to occur.

d. 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). More recently, acute mortality associated with an unidentified herpesvirus was reported in four adult *O. cuniculus* in two rabbitries (Onderka et al., 1992). Herpesvirus was recovered on rabbit kidney cells, and experimental inoculation of rabbits with the virus reproduced the disease syndrome. In both reports, further characterization of the virus is indicated. Experimentally, intradermal inoculation of rabbits with virus resulted in pronounced erythema at the site of inoculation after 4 to 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 scarring caused swelling and vascularization of corneal cells (Topacio and Hyde, 1932). Intratricular inoculation of rabbits results in acute orchitis and fever within 3 to 4 days (Andrewes, 1928). Intramuscular and subcutaneous inoculation of rabbits failed to induce clinical signs; however, corneal scarring with virus resulted in mild punctate keratitis (Nesburn, 1969). Similarly, intraperitoneal inoculation of virus did not induce clinical disease (Swack and Hsiung, 1972).

e. Pathology. No gross pathological changes have been observed in internal organs of experimentally infected rabbits. Microscopically, testes, skin, or 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.

f. Diagnosis. Natural infection with herpesvirus 1 in cottontail rabbits may result in leukocytosis, splenomegaly, and lymphadenopathy. Virus can be isolated from the nasal cavity and circulating lymphocytes of infected rabbits in rabbit kidney cells (Hinze and Lee, 1980). Antibodies can be detected by indirect immunofluorescence and plaque reduction assays (Spike and Yuill, 1976; Yang et al., 1990). Although a herpesvirus has been recovered from European rabbits with respiratory disease (Renquist and Soave, 1972), infection has not been definitively linked to disease. However, an unidentified herpesvirus has been recovered from an acute fatal disease in domestic rabbits (Onderka et al., 1992).

g. Control. Both herpesvirus 1 of 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 confusion in experimental studies, especially if conditions cause recrudescence of latent infections.

C. Papovavirus Infections

The family Papovaviridae has two subfamilies, the Papillomavirinae, with a single genus *Papillomavirus*, and the Polyomavirinae, also with a single genus *Polyomavirus* (Porterfield,
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1989). Viruses of the genus *Papillomavirus* cause papillomas (warts) in various animal species and includes two rabbit viruses, the cottontail rabbit (Shope) papillomavirus and the rabbit oral papillomavirus. The genus *Polyomavirus* contains one virus of rabbits, the rabbit kidney vacuolating virus.

1. Cottontail Rabbit (Shope) Papillomavirus

   a. 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 wartlike tumors on cottontail rabbits (*Sylvilagus floridanus*) in the midwestern United States. They demonstrated the filterability of the infectious agent, transmitted it to other cottontail rabbits as well as domestic rabbits (Shope, 1935), and described the histopathology of the disease. Rabbit papillomatosis was initially considered a natural benign disease of cottontail rabbits only; however, spontaneous outbreaks of papillomatosis in *Oryctolagus cuniculus* (Hagen, 1966) indicates that the disease has greater relevance. Soon after discovery of the virus, it was also shown to cause malignant neoplasms histologically resembling squamous cell carcinomas (Rous and Beard, 1934; 1935; Kidd and Rous, 1940). This was the first recognition of an oncogenic virus in mammals. The disease has served as a model system in numerous investigations aimed at elucidation of the role of viruses in the etiology of cancer in humans and animals (Evans et al., 1962a,b; Evans and Thomsen, 1969; Kreider and Bartlett, 1981, 1985; Georges et al., 1984; Smith and Campo, 1985).

   b. ETIOLOGY. The virus is the type species of the genus *Papillomavirus* of the Papovaviridae (Porterfield, 1989) and possesses the characteristic circular DNA genome, icosahedral structure, and other chemical and physical properties of this family (Kass and Knight, 1965; Murphy et al., 1981; Gross, 1983). The virus is antigenically distinct from other members of the genus *Papillomavirus*. 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 cottontail 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).

   Neoplastic transformation only occurs in epidermis-bearing hair follicles (Kidd and Parsons, 1936). Cellular proliferation or neoplastic transformation by the virus has been reported in rabbit skin cell cultures (Coman, 1946), skin cultures derived from neonatal domestic 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). Papillomas, primary carcinomas, and metastases from domestic rabbits have about 10-100 copies of viral DNA, whereas papillomas from cottontail rabbits have 2400 to 8800 copies (Stevens and Wettstein, 1979).

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

   The cottontail rabbit is the natural host, but the domestic rabbit is also susceptible to the virus (Shope, 1935). Natural outbreaks have been reported in commercial rabbitries (Hagen, 1966). The jackrabbit (*Lepus californicus*) is also susceptible to the virus (Beard and Rous, 1935). Infection of the skin of domestic rabbits results in the formation of papillomas essentially devoid of infectious virus (Shope, 1935). Papillomas can be serially transferred in rabbits, but infectious virus is seldom demonstrated (Shope, 1935; Selbie and Robinson, 1947), indicating that domestic rabbits are not a source of virus for arthropod vectors. However, Nartsisssov, working with virus obtained from Shope, serially passaged the virus in domestic rabbits and demonstrated infectious virus in experimentally produced tumors (Gross, 1983). Cottontail rabbits have a 3-fold lower incidence of carcinomas than domestic rabbits (Rous and Beard, 1935; Syvertson et al., 1950).

   Infection of cottontail rabbits, jackrabbits, and snowshoe hares (*Lepus americanus*) induces lesions containing a high concentration of virus (Syvertson et al., 1950; Lancaster and Olson, 1982). 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), but, in view of the low frequency of ticks and bugs in commercial rabbitries, the mosquito may be the principal vector between wild cottontail and domestic rabbits (Hagen, 1966). This hypothesis is strengthened by the observation that in natural cases of disease in domestic 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 bite. Nematodes may be involved in the natural transmission of virus (Rendtorff and Wilcox, 1957). Experimentally, papillomas were...
induced when papillomavirus and larvae of the nematode *Nippostrongylus muris* were applied to rabbit skin, but not by virus or nematode larvae alone.

d. CLINICAL SIGNS. Papillomatosis of wild cottontail 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 cottontail rabbits papillomas may become malignant, being replaced by squamous cell carcinomas (Syverton and Berry, 1935). This phenomenon was later shown to be a relatively frequent occurrence in both naturally and experimentally infected cottontail rabbits, as 25% of infected rabbits developed carcinomatosus lesions following infection (Syverton et al., 1950). In approximately 35% of naturally infected rabbits, papillomas disappeared within 6 months after infection.

In natural outbreaks of papillomatosis of domestic rabbits in southern California (Hagen, 1966), papillomas most commonly occurred on the eyelids and ears (Fig. 8). Experimentally induced papillomas develop more slowly in domestic rabbits than in cottontail rabbits, reach a stationary phase, and then occasionally regress. Rous and Beard (1934, 1935) recognized the malignant potential of rabbit papillomavirus when they demonstrated that intramuscular inoculation of papillomatous tissue into domestic rabbits resulted in invasive squamous cell carcinomas. In experimentally infected domestic rabbits, 75% developed carcinomas if kept longer than 6 months (Syverton, 1952). Thus, regression of papillomas occurred less frequently in domestic rabbits than in cottontail rabbits.

e. PATHOLOGY. The warts which develop following infection in cottontail and domestic 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 Bartlett, 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 many rabbits.

f. 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. No cell culture system is available for routine isolation of virus (Lancaster and Olson, 1982).

g. CONTROL. The endemic disease of cottontail rabbits is of little economic significance, and thus no prophylactic methods have been developed. Because natural infection occurs in domestic rabbits (Hagen, 1966), the adoption of control methods may become necessary. In areas where the disease is endemic in wild cottontail 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 resisted 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).

2. Rabbit Oral Papillomavirus

a. HISTORY. Oral papillomatosis of rabbits was recognized as a distinct viral disease of domestic 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 and cottontail 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 rabbits, was described (Weisbroth and Scher, 1970). New Zealand

![Fig. 8. Papilloma on ear of *Oryctolagus cuniculus*. Courtesy Dr. K. W. Hagen.](image-url)
White rabbits with oral papillomas were reported in Illinois (Sundberg et al., 1985) and Mexico (Dominguez et al., 1981).

b. ETIOLOGY. The virus was partly characterized by Parsons and Kidd (1943) and was later included in the genus Papillomavirus of the family Papovaviridae (Smith and Campo, 1985). The virus is immunologically distinct from the cottontail rabbit (Shope) papillomavirus and infects only leporids (Parsons and Kidd, 1936, 1943). Nuclear viral replication, characteristic of the papovavirus group, has been demonstrated (Richter et al., 1964; Rdzok et al., 1966). 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.

c. 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 to 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 to 18 months old (Weisbroth and Scher, 1970; Sundberg et al., 1985).

d. CLINICAL SIGNS. Oral papillomatosis is a benign disease characterized clinically by small discrete whitish growths on the ventral surface of the tongue (Fig. 9). The early lesions are sessile, later become rugose or pedunculated, and ultimately ulcerate (Parsons and Kidd, 1936; Weisbroth and Scher, 1970; Sundberg et al., 1985). 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.

e. PATHOLOGY. The lesions are microscopically typical papillomas (Parsons and Kidd, 1943; Richter et al., 1964; Rdzok et al., 1966; Weisbroth and Scher, 1970; Sundberg et al., 1985). Cells in the stratum spinosum contain basophilic intranuclear inclusions (Fig. 10) (Dominguez et al., 1981; Sundberg et al., 1985).

f. 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).

g. CONTROL. Rabbits recovering from disease are resistant to reinfection but are susceptible to the unrelated cottontail rabbit (Shope) papillomavirus.

3. Rabbit Kidney Vacuolating Virus

The rabbit kidney vacuolating virus was isolated in primary rabbit kidney cell cultures from papillomas of 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 (Shope) papillomavirus but is a distinct virus. It does not produce papillomas when inoculated into rabbits and does not immunize rabbits against 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 Polymavirus within the family Papovaviridae (Porterfield, 1989). Ultrastructurally, the virus is a typical papovavirus in its replication pattern (Chambers et al., 1966). The virus is not pathogenic for either domestic or cottontail rabbits or any other animal species. Inoculation of both neonatal and adult domestic and cottontail rabbits by several routes did not induce disease (Hartley and Rowe, 1964). Antibodies to the virus have been found in wild cottontail rabbits in Kansas and Maryland, but not in domestic rabbits (Hartley and Rowe, 1964). The virus thus appears to be a fairly common nonpathogenic virus of cottontail rabbits, causing only latent infections. Although a contaminant of rabbit papillomas, the virus appears to have no role in the pathogenesis of papillomatosis (Ito et al., 1968; Goldman et al., 1972; Kreider and Bartlett, 1981).

D. Adenovirus Infections

An adenovirus was isolated in Hungary from the spleen, kidneys, lungs, and intestines of rabbits, 6–8 weeks old, with diarrhea (Bodón et al., 1979). The virus was detected in primary rabbit kidney cultures stained with acridine orange, as 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).

E. Parovirus Infections

A virus that produced 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 parovirus. The various proteins of the virus have been characterized (Matsunaga and Matsuno, 1983). Subsequently, parovirus was recovered from kidney cells of neonatal rabbits in the United States (Metcalf et al., 1989). 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 (Matsunaga and Chino, 1981). Virus was detected in feces, small intestine, liver, pancreas, spleen, appendix, and mesenteric lymph node. Rabbits developed hemagglutination-inhibiting antibodies.

III. RNA VIRUS INFECTIONS

A. Rotavirus Infections

1. 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 (Peeters et al., 1982, 1984; Eaton, 1984; Castrucci et al., 1985), 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 rabbits (Oryctolagus cuniculus).

2. Etiology

Rotaviruses belong to the family Reoviridae (International Committee on Taxonomy of Viruses, 1991). They are icosahedral viruses with a double capsid shell which contains 11 segments of double-stranded RNA, each of which codes for a protein. The sixth gene codes for a structural protein which contains the subgroup specificity. The product of the fourth and seventh, eighth, or ninth genes are the viral neutralization antigens, VP4 and VP7. VP4 is the viral hemagglutinin and must be cleaved to yield VP5 and VP8 before the virus can infect cells (Matis et al., 1989; Ramig and Ward, 1991).

The five groups of rotaviruses, identified as A, B, C, D, and E (Pedley et al., 1986), are divided into two subgroups, I and II (Greenberg et al., 1983). The rabbit rotaviruses described belong to group A, subgroups I and II (Thouless et al., 1986; Tanaka et al., 1988). Although group A rotaviruses comprise 14 serotypes (Estes and Cohen, 1989), only serotype 3 is found in rabbits (Thouless et al., 1986; Tanaka et al., 1988). Serotype 3 is common to humans and several other animals and is defined by more than one epitope (Hoshino et al., 1984; Thouless et al., 1986). Some rotavirus isolates from rabbits induce a cytopathic effect in MA104 rhesus monkey kidney cells in about 3 days (Sato et al., 1982; Castrucci et al., 1985; Thouless et al., 1986), whereas other isolates demonstrate cytopathic effect only after additional passages. Physicochemical studies reveal that isolates are resistant to pH 3 and 20% ether and are partially sensitive to 10% chloroform (Castrucci et al., 1985). Additionally, they are inactivated when heated at 50°C for 30 min, even in
the presence of MgCl₂. Electron microscopy of negatively stained preparations reveal virus particles of 75-80 nm in diameter.

3. Epidemiology

Serological studies indicate that rotavirus infection is widespread in domesticated rabbits (O. cuniculus). Of 91 adult rabbits from two commercial rabbitries in Ontario, Canada, 98% had antibodies to rotavirus (Petric et al., 1978). A survey in Tokyo prefecture, Japan, of 39 adult rabbits revealed that 82% had antibodies (Takahashi et al., 1979). A more extensive survey of 10 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% (range 40-100%) 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 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 (Petric 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 to 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 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 to 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 to 8 days, beginning 2 to 5 days after inoculation (Petric et al., 1978; Castrucci et al., 1984; Thouless et al., 1988; Conner et al., 1988; Hambraeus et al., 1989). Furthermore, unoinoculated control rabbits maintained in the same room with inoculated rabbits also acquired rotavirus infection (Thouless et al., 1988; Conner 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.

4. 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 (Sato et al., 1982; Castrucci et al., 1985; Peeters et al., 1984). Rabbits exhibit severe mucous or watery diarrhea, anorexia, and dehydration, with mortality of 60-80%. In one outbreak, rabbits 8 to 12 days old had a greenish-yellow watery diarrhea (Peeters et al., 1982). About 20% of litters were affected, with 98% mortality within 1 to 2 days after onset of signs. A similar disease was reported in a specific pathogen-free colony in which litters 7 to 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 preweaning 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 to 3 days, with low mortality. That rotavirus may be only mildly pathogenic is supported by experimental studies. In general, oro gastric inoculation of rabbits, 1 to 22 weeks old, with rotavirus did not result in diarrhea, although some rabbits developed soft or fluid feces for 2 to 4 days (Petric et al., 1978; Thouless et al., 1988; Conner et al., 1988; Hambraeus et al., 1989). 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). Hence, in endemically infected colonies, other factors, including other infectious agents, may enhance the pathogenicity of rotavirus (Peeters et al., 1984).

5. 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 preweaning 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 to 9 days after inoculation (Petric et al., 1978; Castrucci et al., 1984; Thouless et al., 1988). Microscopically, low to moderate numbers of lymphocytes and plasma cells infiltrate the villi and lamina propria of the small intestine (Thouless et al., 1988). Occasionally, villous atrophy is observed in the ileum. There is mild lymphoid reactivity in mesenteric lymph nodes. Lesions are not observed in the cecum or colon.

6. 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’s disease, clostridial enterotoxemia, and colibacillosis. In weanling rabbits with severe disease, the possibility of dual infections should be considered, since rotavirus infections are usually mild. Electron microscopy (Peeters et al., 1984; Schoeb et al., 1986) or a capture enzyme-linked immunosorbent assay can be used to detect rotavirus in feces (Thouless et al., 1986; 1988; Conner et al., 1988; Hambraeus et al., 1989). Cytoplasmic fluorescence can be observed at the tips of ileal villi using indirect immunofluorescence (Petric et al., 1978). Serum antibodies to rotavirus can be detected by enzyme immunoassay (Thouless et al. 1988; Hambraeus et al., 1989; Conner et al., 1991). Rabbits with rotaviral diarrhea usually have no or low concentrations of antibody to rotavirus, with a subsequent rise 2 to 4 weeks after onset of signs (Bryden et al., 1976; Sato et al., 1982). Nonaffected littermates develop high antibody concentrations, reflecting concurrent subclinical infections.

7. 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 (Petric et al., 1978; Castrucci et al., 1984; Thouless et al., 1988; Conner et al., 1988; Hambraeus et al., 1989). Recovered rabbits are refractory to challenge with homologous (Castrucci et al., 1984; Conner et al., 1988, 1991; Hambraeus et al., 1989) or heterologous viruses (Hambraeus et al., 1989). Hence, cessation of breeding or quarantine of the colony for 4 to 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.

B. Coronavirus Infections

1. Pleural Effusion Disease/Infectious Cardiomyopathy Virus

a. History. During the 1960s in Scandinavia, increased mortality in 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 (Baric et al., 1990; Edwards et al., 1992; Alexander et al., 1992, 1993).

b. Etiology. The disease, initially described in 1968, occurred in rabbits inoculated with suspensions of rabbit testes containing the Nichols strain of T. pallidum (Jorgensen, 1968; Gudjonsson and Skog, 1970). 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 either sensitive and inactivated at temperatures of 65°C or above but not at 56°C (Gudjonsson et al., 1972; Small et al., 1979; Fennestad and MacNaughton, 1983). Sera from rabbits contained pleomorphic virus particles, round or elliptic, 75 to 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 viruslike particles measuring 51 to 98 nm in diameter with projections 8–13 nm long (Osterhaus et al., 1982). Infectious sera, passed on 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 cardiomypathy 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, FIPV, 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).

c. 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 treponema stocks with virus (Jorgensen, 1968; Fennestad, 1985). 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 to 9 days of age became infected, whereas un inoculated litters or introduced cage-mates failed to develop infection after exposure for several months (Fennestad et al., 1981). Hence, transmission by direct contact occurs rarely.

d. CLINICAL SIGNS. Whereas clinical features vary by strain and passage of the agent, inoculated rabbits generally develop a fever in 1 to 4 days which persists for 5 to 10 days. Other clinical signs include anorexia, weight loss, atony, tachypnea, and iridocyclitis. With virulent strains, many rabbits die 3 to 5 days after inoculation, although deaths can occur until 14 days (Gudjonsson and Skog, 1970; Gudjonsson et al., 1970; Fennestad et al., 1975, 1986; Fledelius et al., 1978; Small et al., 1979; Fennestad and MacNaughton, 1983; Fennestad, 1985; Baric et al., 1990). 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. Surviving rabbits usually returned to normal in 3 to 4 weeks. Reinoculation of surviving rabbits was without effect, indicating development of resistance to the agent (Gudjonsson et al., 1970; Fennestad and MacNaughton, 1983; Fennestad, 1985; Fennestad et al., 1986).

e. PATHOLOGY. Rabbits dying during the acute phase of disease have pulmonary edema, pleural effusion, and dilation of the right ventricle (Fennestad et al., 1975; Christensen et al., 1978; Small et al., 1979; Baric et al., 1990; Edwards et al., 1992; Alexander et al., 1992, 1993). 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 (Small et al., 1979; Baric et al., 1990; Edwards et al., 1992; Alexander et al., 1992, 1993). In fatal cases, there is a uniform reduction of splenic white pulp, 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 nonsuppurative, nongranulomatous 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).

f. 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 2 to 3 days after inoculation. Deaths may occur from 2 to 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).

g. 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 (Gudjonsson et al., 1970; Fennestad et al., 1975; Fennestad, 1985). Rabbits inoculated with virus-contaminated T. pallidum stocks that elicited no or mild disease without mortality were protected from disease when rechallenged with stocks contaminated with more pathogenic virus (Gudjonsson et al., 1970; Fennestad et al., 1980, 1986; Fennestad and MacNaughton, 1983; Fennestad, 1985). This indicated that some T. pallidum stocks were contaminated with a nonpathogenic 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 (Gudjonsson et al., 1970; Small et al., 1979; Fennestad et al., 1981). Passage of contaminated T. pallidum stocks through hamsters removed the agent responsible for disease (Skovgaard Jensen, 1971; Fennestad et al., 1980). 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).

2. Rabbit Enteric Coronavirus

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

b. Etiology. Feces of rabbits with diarrhea exhibit hemagglutination activity with rabbit erythrocytes, particularly with a peak of 1.18 g/cm³ from a sucrose density gradient (LaPierre et al., 1980; Descoteaux et al., 1985). Electron microscopy of fecal samples revealed pleomorphic particles with an inner diameter of 60–220 nm and surface projections of 20 nm (LaPierre et al., 1980; Eaton, 1984). 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 (AlbV) and TGEV detected many of the same epitopes as antisera to the rabbit coronavirus (Descoteaux et al., 1985). Immune sera to 229E, but not AlbV and 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 (LaPierre et al., 1980; Eaton, 1984).

c. 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 to 10 weeks old (LaPierre et al., 1980; Eaton, 1984). 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 O. cuniculus from six rabbitries revealed that 23 (10%) had antibodies to canine coronavirus (Deeb et al., 1993).

d. Clinical Signs. In an outbreak of enteric disease in 3- to 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 hr 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) or watery diarrhea (Descoteaux and Lussier, 1990) of brief duration after inoculation. However, none of the rabbits died (Descoteaux and Lussier, 1990).

e. Pathology. In rabbits with diarrhea, the perianal region is soiled with feces (Eaton, 1984). Rabbits appear cachectic and
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dehydrated. Although the stomach and intestines are unaffected, the cecum is distended with watery fluid (Peeters et al., 1984; Eaton, 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 hr after inoculation, there was necrosis of enterocytes at the tips of intestinal villi. Villous atrophy and hypertrophic crypts were present 2 to 3 days after inoculation. However, by 6 days microscopic lesions were absent.

f. Diagnosis. Rabbits with diarrheal disease are usually recently weaned and 3 to 10 weeks old (LaPierre et al., 1980; Eaton, 1984). 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 (LaPierre et al., 1980; Osterhaus et al., 1982; Peeters et al., 1984; Eaton, 1984) and immunoelectron (Descoteaux et al., 1985; Descoteaux and Lussier, 1990) microscopy. The latter technique is more sensitive in detecting virus particles (Descoteaux et al., 1985). At necropsy, the cecal contents are fluid (Eaton, 1984; Descoteaux and Lussier, 1990); histologically, there is intestinal villous atrophy (Descoteaux and Lussier, 1990). Adult rabbits may have antibodies in the hemagglutination 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 copathogens (Osterhaus et al., 1982; Descoteaux and Lussier, 1990). In two studies where other agents were considered, coronavirus was associated with E. coli and Clostridium perfringens infections (Peeters et al., 1984; Eaton, 1984).

g. 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.

C. Calicivirus Infections

The etiologic agents of necrotic hepatitis of leporids are the most recent viruses to be described. They have been classified tentatively as caliciviruses. The diseases caused by these viruses appeared in the mid 1980s. Rabbit or viral hemorrhagic disease was reported in China in 1984 and subsequently in other countries. European brown hare syndrome was observed in Europe several years before viral hemorrhagic disease was diagnosed in domestic rabbits. The diseases are similar and appear to be caused by related viruses. Because the first recognized outbreak in China occurred in rabbits imported from Europe and since reports of a similar disease in European hares predates the outbreak in China, the original source of the agent of viral hemorrhagic disease may have been wild Leporidae (Lepus europaeus and Oryctolagus cuniculus) in Europe (Loliger and Eskens, 1991).

1. Rabbit Hemorrhagic Disease Virus

a. History. In early 1984, an acute fatal disease of rabbits was reported from many regions of China (Xu et al., 1988; Xu and Chen, 1989). 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 rabbit or viral hemorrhagic disease. Subsequently, the disease was reported in several European countries in 1987 and 1988 (Patton, 1989; Gregg and House, 1989; Parra and Prieto, 1990). By late 1988, the disease was reported from many locations in Mexico (Patton, 1989; Gregg and House, 1989, Gutierrez, 1990).

b. 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 et al., 1986, 1990, 1991; Xu et al., 1988; Xu and Chen, 1989; Smid et al., 1989; Ohlinger and Theil, 1991; Xu, 1991; Liebermann et al., 1992). The virus is nonenveloped, spherical, and 28–34 nm in diameter and has a buoyant density of 1.32–1.38 g/cm3. The icosahedral capsid has 32 cylindrical capsomeres, 5–6 nm in diameter. The capsid is comprised of four structural polypeptides: VP1, 60–61 kDa; VP2, 54.7 kDa; VP3, 52 kDa; and VP4, 26–28 kDa. The virus has been reported to be a picornavirus (Xu and Chen, 1989), calicivirus (Smid et al., 1989; Valicke et al., 1990; Rodak et al., 1990b; Ohlinger et al., 1990; Parra and Prieto, 1990; Ohlinger and Theil, 1991; Liebermann et al., 1992), or parvovirus (Xu et al., 1988; Gregg and House, 1989; House et al., 1990; Du, 1990, 1991; Xu, 1991; Greg et al., 1991). Hence, the current classification must be considered provisional. Immunoblotting of the virus reveals three major proteins of 38, 52, and 61 kDa, with the latter being dominant (Rodak et al., 1990a; Ohlinger et al., 1990; Parra and Prieto, 1990). Comparison of nucleic acid sequences reveals significant homology with feline calicivirus (Meyers et al., 1991a,b). The virus agglutinates erythrocytes of humans and guinea pigs, but not rabbits.

The virus is highly stable in the environment; 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 hares (*Lepus eu-
ropaeus*) failed to induce disease (Smid et al., 1991).

c. EPIDEMIOLOGY. The disease has been reported from China, Korea, most European countries, and Mexico (Morisse et al., 1991). Countries experiencing epidemics with high morbidity and mortality include China (Xu and Chen, 1989), Korea (Lee and Park, 1987), Italy (Patton, 1989; Cancellotti and Renzi, 1991), Spain (Parra and Prieto, 1990), France (Morisse et al., 1991), Germany (Loliger and Eskens, 1991), and Mexico (Gregg and House, 1989; Gutierrez, 1990). 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 identical (Du, 1990; Gregg et al., 1991).

No apparent difference in susceptibility to infection among breeds of *Oryctolagus cuniculus* has been reported (Xu et al., 1988; Xu and Chen, 1989). Outbreaks of disease have occurred mainly in rabbits 2 months of age and older, whereas younger rabbits were clinically unaffected. Transmission of virus is horizontal, by direct contact with secretions and excretions of infected rabbits. Fecal–oral spread may be the major mode of transmission, but contaminated fomites, including feed, water, utensils, and animal attendants, may also be important modes. There is no evidence of vertical transmission or biological vectors. 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 *O. cuniculus* appears to be the only species susceptible to disease, hares in China also appear to be infected and capable of transmitting the disease 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 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.

d. CLINICAL SIGNS. In general, the disease is acute and highly infectious, with high morbidity and mortality (Xu et al., 1988; Xu and Chen, 1989; Marcato et al., 1991). The incubation period ranges from 1 to 2 days. The morbidity rate is 70–80%, and the mortality rate approaches 100%. During outbreaks, the number of rabbits affected usually peaks in 2 to 3 days and lasts 7 to 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 distension, 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 to 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.

e. PATHOLOGY. The pathological changes apparently result from viremia, with death attributable to an acute disseminated coagulopathy with deep venous thrombosis (Xu et al., 1986, 1988; Xu and Chen, 1989; Gregg and House, 1989; Gregg...
et al., 1991; Marcato et al., 1991). Grossly, congestion and hemorrhage occur in most organs but are most pronounced in the lungs (Fig. 11). The liver is pale and has a fine reticular pattern of periportal necrosis (Fig. 12), the most consistent finding in the disease. The spleen and kidneys may be dark and swollen owing to acute infarction. Lymph nodes are edematous and may contain petechial hemorrhages. There is often a 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. 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 similar to that seen with canine or feline parvoviral infections can be found (Gregg et al., 1991). Lymphoid tissues may have varying degrees of degeneration and karyorhexis of lymphocytes. The spleen and thymus are more often affected than lymph nodes.

f. Diagnosis. A presumptive diagnosis can be made on the basis of the epidemiological features, clinical signs, and pathological findings (Xu and Chen, 1989). By electron microscopy, viral particles, 28–34 nm in diameter, frequently are found in hepatocytes (Xu and Chen, 1989; Valicek et al., 1990). 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. Antiserum or monoclonal antibodies to the virus are useful in detecting virus in hepatocytes (Xu and Chen, 1989; Valicek et al., 1990). By electron microscopy, viral particles, 28–34 nm in diameter, frequently are found in hepatocytes (Xu and Chen, 1989; Valicek et al., 1990). 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. Antiserum or monoclonal antibodies to the virus are useful in detecting virus in hepatocytes (Xu and Chen, 1989; Valicek et al., 1990). Immunoblotting of the virus reveals a major structural protein of about 60 kDa, similar to rabbit hemorrhagic disease virus; however, other proteins of the latter virus are absent, suggesting that the viruses are similar but not identical (Ohlinger and Thiel, 1991; Capucci et al., 1991). The European brown hare virus fails to grow in primary hare and rabbit cell lines (Henriksen et al., 1989; Gavier-Widen and Morner, 1991), and inoculation of mice and guinea pigs failed to induce disease (Henriksen et al., 1989). Inoculation of liver homogenates from affected hares into rabbits resulted in a clinical syndrome similar to rabbit hemorrhagic disease. Tissues from inoculated rabbits exhibited hemagglutination with human type O erythrocytes, and similar viral particles were detected by electron microscopy. Antiserum against rabbit hemorrhagic disease virus protected rabbits from mortality, and surviving rabbits had antibodies in the hemagglutination inhibition assay (Morisse et al., 1990). However, other investigators have failed to induce disease in rabbits with the European brown hare virus (Ohlinger and Thiel, 1991; Capucci et al., 1991).

g. 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 areas with the disease should not be introduced directly into the colony but should be quarantined for at least 1 month. Similarly, colonies with the disease should be quarantined and depopulated, since surviving rabbits shed virus for at least a month (Gregg and House, 1989; Gregg et al., 1991). Tissue-derived vaccines, inactivated with formaldehyde (Du et al., 1986; Xu and Chen, 1989; Du, 1990; Huang, 1991) or ß-propiolactone (Smid et al., 1991; Arguello Villares, 1991), have been shown to be safe and efficacious in preventing disease. Resistance develops within 1 to 2 weeks after vaccination and lasts for 5 to 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. Antiserum is also protective (Du, 1990; Huang, 1991).

2. European Brown Hare Virus

a. 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 brown hares (Lepus europaeus) and mountain hares (Lepus timidus) in several European countries (Morisse et al., 1990, 1991; Gavier-Widen and Morner, 1991). The disease, named European brown hare syndrome, is similar to rabbit hemorrhagic disease.

b. Etiology. Electron microscopy of hepatocytes from affected hares reveals nonenveloped,icosahedral particles about 30 nm 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 rabbit hemorrhagic disease virus; however, other proteins of the latter virus are absent, suggesting that the viruses are similar but not identical (Ohlinger and Thiel, 1991; Capucci et al., 1991). The European brown hare virus fails to grow in primary hare and rabbit cell lines (Henriksen et al., 1989; Gavier-Widen and Morner, 1991), and inoculation of mice and guinea pigs failed to induce disease (Henriksen et al., 1989). Inoculation of liver homogenates from infected hares into rabbits resulted in a clinical syndrome similar to rabbit hemorrhagic disease. Tissues from inoculated rabbits exhibited hemagglutination with human type O erythrocytes, and similar viral particles were detected by electron microscopy. Antiserum against rabbit hemorrhagic disease virus protected rabbits from mortality, and surviving rabbits had antibodies in the hemagglutination inhibition assay (Morisse et al., 1990). However, other investigators have failed to induce disease in rabbits with the European brown hare virus (Ohlinger and Thiel, 1991; Capucci et al., 1991).

c. Epidemiology. The disease has been reported in wild hares from several European countries, including England (Chasey and Duff, 1990), and 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 European brown hare syndrome coincides with viral hemorrhagic disease in wild and domesticated rabbits (Morisse et al., 1991; Loliger and Eskens, 1991; Can-
d. 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 to 24 hr after onset of signs, and affected hares rarely recover. The reported morbidity is 75%, and mortality approaches 100% (Henriksen et al., 1989; Gavier-Widen and Morner, 1991).

e. Pathology. Death is attributable to multiple organ failure resulting from 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 perportal and midzonal areas, accompanied by formation of acidophilic bodies (Henriksen et al., 1989; Gavier-Widen and Morner, 1991). In many hares, there is basophilic stippling in the cytoplasm of hepatocytes in perportal areas, representing granular calcification. Many livers have microvascular 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 granulovacular 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).

f. Diagnosis. Diagnosis is similar to that for rabbit hemorrhagic disease. The hemagglutination test for detection of virus in tissue specimens is less sensitive, possibly owing to the presence of lower concentrations of virus in comparison with rabbit hemorrhagic disease virus (Capucci et al., 1991). Use of two enzyme-linked immunosorbent assays (ELISAs), in series, employing monoclonal antibodies, in which the first test detects group antigen and the second virus-specific antigen, has permitted the detection of European brown hare virus (Capucci et al., 1991). The ELISA is preferred for detection of antibodies (Capucci et al., 1991).

g. 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.

D. Paramyxovirus Infections

Rabbit syncytium virus was isolated in chicken embryos inoculated with extracts of liver and spleen from a wild 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 and cottontail rabbits failed to develop signs or lesions, although antibodies developed, following inoculation. Sera from 8 of 25 (32%) 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. Hemagglutination or hemadsorption was not 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 rabbits (O. cuniculus). 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 O. cuniculus with Sendai virus resulted in infection; rabbits shed virus for 3 to 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 O. cuniculus is susceptible to Sendai virus and that this or a related virus may be endemic in rabbit colonies.
E. Bunyavirus Infections

Evidence of infection with several viruses of the genus *Bunyavirus* in the family Bunyaviridae has been detected in leporids. The viruses (California encephalitis, snowshoe hare, Tahyna, and Inkoo virus) are grouped in the California antigenic group (International Committee on Taxonomy of Viruses, 1991). Antibodies to California encephalitis virus were initially detected in cottontail rabbits (*Sylvilagus floridanus*) and 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 to 97% in adult hares (Newhouse et al., 1963; Yuill et al., 1969; Hoff et al., 1969; McLean et al., 1975). 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 europaeus*) and wild European rabbit (*Oryctolagus cuniculus*) appear to be the major reservoirs of Tahyna virus in Europe (Simkova, 1963; Bardos, 1965, 1975; Danielova et al., 1969; Hannoun et al., 1969). Clinical disease in infected hares has not been reported. Experimental infection of European rabbits results in viremia and antibody formation without clinical disease (Simkova, 1962; Hammon and Sather, 1966). Thus, domestic 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 snow hares (*Lepus timidus*) and none of the *L. europaeus* tested had antibodies against Inkoo virus (Brummer-Korvenkontio, 1973).

Silverwater virus, a *Tospovirus* in the family Bunyaviridae, has been isolated from snowshoe hares and from *H. leporis-palustris* ticks from snowshoe hares in Ontario and Alberta (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.

F. Togavirus Infections

Serological evidence of infection with western and eastern equine encephalitis viruses, aphavirus in the family Togaviridae (International Committee on Taxonomy of Viruses, 1991) has been found in rabbits and hares. Wild *Sylvilagus* as well as hares (*Lepus californicus* and *Lepus americanus*) have antibodies to western equine encephalitis virus (Bowers et al., 1969; Yuill et al., 1969). Antibodies to eastern equine encephalitis virus have also been detected in snowshoe hares (Yuill et al., 1969).

G. Flavivirus Infections

Antibodies to St. Louis encephalitis virus, a member of the Japanese encephalitis subgroup in the family Flaviviridae (International Committee on Taxonomy of Viruses, 1991), have been detected in snowshoe hares (*Lepus americanus*) (Yuill et al., 1969).

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