

## OCULAR VIRAL DISEASES OF VERTEBRATE ANIMALS

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**SUMMARY** – Several viruses are able to infect eyes and ocular adnexa of vertebrates. Considering the variety of cells and tissues comprising eyes and adnexa, viruses have multiple opportunities to colonize them and to induce a pathologic effect. This also varies depending on the animal species, age, immune status, virus species and type. Viruses may target conjunctival, glandular, corneal and/or retinal epithelium, endothelium, myocytes and pericytes, retinal and optic nerve neurons, fibers and glial cells, and lymphocytes, macrophages and dendritic cells of lymphoid follicles. Cell injury can be induced by direct cytopathic effect or via inflammatory mediator release and/or proteolytic enzymes released by inflammatory cells or the injury may result from the intraparietal vascular deposition of antigen antibody complexes and following complement activation. In fetuses and youngsters some agents are able to induce various degrees of ocular dysplasia. Immunodeficiency viruses favor the colonization and growth of other agents such as other viruses, bacteria, protozoa and mycetes. Leukemia oncornaviruses can cause neoplastic lymphocytic infiltration of eyes and adnexa. This review includes viruses able to affect multiple species of vertebrates, and others specific to ruminants, horses, pigs, marsupials, dogs, cats, minks, rabbits, rats, birds and fish. Herpesvirus, arterivirus, orbivirus, paramyxovirus, morbillivirus, nodavirus, pestivirus, asfivirus, orthomyxovirus, retrovirus, lentivirus, adenovirus, calcivirus, coronavirus, reovirus and prions are discussed. Zoonotic agents include influenza orthomyxoviruses, Newcastle disease paramyxovirus, rabies rhabdovirus, transmissible bovine spongiform encephalopathy prion, simian immunodeficiency lentivirus, cercopithecine herpesvirus 1 and perhaps Borna disease virus. Anthroozoonoses include human measles morbillivirus and herpes simplex virus.

**Key words:** *Eye diseases; Virus diseases; Animal*

### Introduction

Several viruses are able to infect eyes and ocular adnexa, of vertebrates. Considering the variety of cells and tissues comprising eyes and adnexa, viruses have multiple means of inducing a pathologic effect. This also varies depending on the animal species, age, immune status, virus species and type with consequent different cellular pantropism, polytropism or oligotropism. Viruses may target conjunctival, glandular, corneal and/or retinal epithe-

lium, endothelium, myocytes and pericytes, retinal and optic nerve neurons, fibers and glial cells, and lymphocytes, macrophages and dendritic cells of lymphoid follicles. Occasionally the skeletal muscle fibers of the ocular muscles can be also directly or indirectly affected. Cell injury can be induced by direct cytopathic effect or via inflammatory mediator release and/or proteolytic enzymes released by inflammatory cells or the injury may result from the intraparietal vascular deposition of antigen antibody complexes and following complement activation. In fetuses and youngsters some agents are able to induce various degrees of ocular dysplasia. Immunodeficiency viruses favor the colonization and growth of other agents such as other viruses, bacteria, protozoa and mycetes. Leukemia oncornaviruses can cause neoplastic lymphocytic infiltration of eyes and adnexa. The diagnosis *in vivo* can be

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achieved by clinical ophthalmologic examination, evaluation of seroconversion, conjunctival and corneal cytopathology, direct and indirect immunohistochemistry of conjunctival and corneal samples, virus isolation followed by identification of viruses using specific polyclonal and monoclonal antibodies and virus nucleic acid amplification using polymerase chain reaction. Following enucleation or post mortem examination, histopathology in combination with indirect immunohistochemistry, *in situ* hybridization and all the techniques mentioned above can be used. The ocular adnexa include eyelids, nictitating membrane, and lachrymal and accessory lachrymal glands and inflammatory changes caused by some viral and other agents can be observed in these tissues. The viral diseases affecting these structures are included in this review, with the exception of the outer lid surface, which is skin and may suffer any of the pathological conditions of that tissue. In particular the conjunctiva is a target of several viral agents such as canine distemper morbillivirus, equine viral arteritis arterivirus, bovine virus diarrhea pestivirus, malignant catarrhal fever herpesvirus, classical swine fever pestivirus, African swine fever asfivirus, rinderpest and peste des petites ruminants morbilliviruses, feline herpesvirus, equine herpesvirus 2 and others. All the agents here described are able to infect the conjunctiva. Acute conjunctival injury includes hyperemia, severe edema and lachrymation that can be serous to mucous to suppurative. Chronic injury includes epithelial hyperplasia, hyperplasia of goblet cells and lymphoid follicles and squamous metaplasia progressing to keratinization. Conjunctivitis may spread to the cornea and, uncommonly, to the orbit. Keratitis, uveitis and glaucoma may be associated with conjunctivitis. The vast majority of the viral diseases able to infect eyes, conjunctivae and adnexa of vertebrates, with the exception of the outer lid surface, are described in the following text. Zoonotic agents include influenza orthomyxoviruses, Newcastle disease paramyxovirus, rabies rhabdovirus, transmissible bovine spongiform encephalopathy prion, simian immunodeficiency lentivirus, cercopithecine herpesvirus 1 and perhaps Borna disease virus. Anthroponoses include human measles morbillivirus and herpes simplex virus.

### Viruses Crossing Species

#### *Influenza orthomyxoviruses*

*Introduction.* Influenza orthomyxovirus virions<sup>1</sup> have a complex construction and consist of an envelope, a matrix protein, a nucleoprotein complex, a nucleocapsid, and a

polymerase complex. Virions are enveloped, spherical to pleomorphic, filamentous forms occur the dimensions are 80–120 nm in diameter and 200–300(–3000) nm long. The surface projections are distinctive with about 500 spikes, evenly covering the surface, composed of one type of protein, or different types of proteins. The surface projections comprise hemagglutinin, or neuraminidase, or esterase-esterase. Surface projections are 10–14 nm long, 4–6 nm in diameter. Capsid-nucleocapsid is elongated and exhibits helical symmetry. The nucleocapsid is helical and segmented and segments have different size classes. The genome is segmented and consists of six segments of to eight segments of linear, negative-sense, single-stranded RNA. The complete genome is 10000–14600 nucleotides long. The multipartite genome is encapsidated, each segment in a separate nucleocapsid, and the nucleocapsids are surrounded by one envelope. It encodes structural proteins and non-structural proteins. Influenza A viruses contain genomes composed of eight separate segments of negative-sense RNA. Circulating human strains are notorious for their tendency to accumulate mutations from one year to the next and cause recurrent epidemics. However, the segmented nature of the genome also allows for the exchange of entire genes between different viral strains. These viruses are potentially able to infect many vertebrates<sup>2,3</sup>. The evolution of influenza viruses<sup>4</sup> results in recurrent annual epidemics of disease that are caused by progressive antigenic drift of influenza A and B viruses due to the mutability of the RNA genome and infrequent but severe pandemics caused by the emergence of novel influenza A subtypes to which the population has little immunity. The latter characteristic is a consequence of the wide antigenic diversity and peculiar host range of influenza A viruses and the ability of their segmented RNA genomes to undergo frequent genetic reassortment (recombination) during mixed infections. Contrasting features of the evolution of recently circulating influenza AH1N1, AH3N2 and B viruses include the rapid drift of AH3N2 viruses as a single lineage, the slow replacement of successive antigenic variants of AH1N1 viruses and the co-circulation over some 25 years of antigenically and genetically distinct lineages of influenza B viruses.

*Avian influenza orthomyxoviruses.* Highly pathogenic avian influenza (HPAI), also known as fowl plague, is caused by infection with influenza A viruses of the family *Orthomyxoviridae*. Influenza A viruses<sup>5,6</sup> are the only orthomyxoviruses known to affect birds. Many species of birds have been shown to be susceptible to infection with influenza A viruses and aquatic birds form a major reservoir of these

viruses, but the overwhelming majority of isolates have been of low pathogenicity for chickens and turkeys, the main birds of economic importance to be affected. Influenza A viruses have antigenically related nucleocapsid and antigenically related matrix proteins, but are classified into subtypes on the basis of their haemagglutinin (H) and neuraminidase (N) antigens. At the moment 15 H subtypes (H1-H15) and 9 neuraminidase subtypes (N1-N9) are recognized. The highly pathogenic disease may vary from one of sudden death with little or no overt signs a disease with respiratory signs, conjunctivitis and epiphora, sinusitis, head edema, cyanosis of the unfeathered skin. Lesions include multifocal necrosis of multiple organs where pancreas, intestine and lymphoid organs are major targets. The disease needs to be differentiated from other respiratory illnesses and in particular from Newcastle disease paramyxovirus. The H5N1 avian influenza outbreak in Hong Kong was associated to cases of human death. All influenza viruses should be considered potential zoonotic agents<sup>7</sup>. Chick embryos at Hamburger-Hamilton stage 9 infected by an *in ovo* injection under the blastoderm with influenza B virus (B/Taiwan/25/99) develop 48 h after infection gross malformations of the eye and brain, ranging from 25 to 58% of 168 infected embryos<sup>8</sup>. There was extensive cell death and heterotopia. Viral RNA was extensively present within the nucleus and cytoplasm of the cells in the head surface ectoderm and in the lung bud. In the developing brain, viral RNA was located in the anterior neural retina, habenular area, mid-thalamus, and rhombencephalon.

*Swine influenza orthomyxoviruses.* Swine influenza (SI)<sup>9</sup> is caused by type A orthomyxoviruses where pigs are the main host, but some strains can also be directly transmissible to humans, and reciprocally. SI was responsible for the human outbreak of influenza in 1918-1920 that led to the demise of more than 20 million people over the world. The influenza pandemic of 1918-1919 killed more people than World War I and it has been cited as the most devastating epidemic in recorded world history. More people died of influenza in a single year than in four-years of the Black Death Bubonic Plague from 1347 to 1351. Known as "Spanish Flu" or "La Grippe" the influenza of 1918-1919 was a global disaster. There is increasing evidence of interchange of influenza viruses between pigs, other terrestrial and marine mammalian and avian hosts, either directly or after a process of genetic reassortment or mutation. SI can be characterized by very high morbidity rate and most pigs in a herd get the disease almost simultaneously. SI may remain endemic. Young pigs are more severely affected.

Swine influenza is transmitted by direct contact between pigs and in the acute stages of the disease, high concentrations of virus are found in nasal secretions. Aerosols transmit virus over a short distance and the virus can be shed for 30 days after infection and has been recovered from clinically normal animals. Lesions include conjunctivitis with epiphora, rhinitis, tracheobronchitis, lymphadenitis and interstitial pneumonia, which characterizes the fatal cases. Bacteria often are responsible of complication leading to cranioventral bronchopneumonia and pleuropneumonia.

*Equine influenza orthomyxoviruses.* Equine influenza<sup>10,11</sup> is caused by two subtypes: subtype 1 (H7N7) and subtype 2 (H3N8) of influenza A viruses of the genus *Influenzavirus* A, B, of the family *Orthomyxoviridae*. Although these are not genuine human pathogens, humans can become infected with equine influenza virus subtypes. Such infections are unusual and subclinical, but may represent a potential biohazard to laboratory personnel. Lesions in horses include conjunctivitis with epiphora, rhinitis, tracheobronchitis, lymphadenitis and interstitial pneumonia. Bacteria often are responsible of complication leading to cranioventral bronchopneumonia and secondary necrotic sequestra that may lead to pleuropneumonia.

#### *Borna disease virus*

Borna disease virus (BDV)<sup>12</sup> causes a fatal neurological disorder originally described in horses and sheep, but other animals species, such as rabbits, cattle cats, dogs and various zoo animals such as hippopotamus, sloths, monkeys and alpacas are also susceptible. BDV is the prototype of *Bornaviridae* within the order of *Mononegavirales*. The virus<sup>13,14</sup> has not been fully characterized morphologically. Virions have a complex construction, are spherical, and consist of an envelope and a core. The genome is not segmented and consists of a single molecule of linear, negative-sense, single-stranded RNA. Similarities of nucleotide sequence and open reading frame structure suggest a strong relationship to the family *Rhabdoviridae*. The total genome length is 8900 nucleotides. The tick *Amblyomma* spp. is involved in the transmission of BDV. The neural histological lesions<sup>12</sup> include T lymphocyte, often large, perivascular cuffing with gliosis mainly in olfactory areas, caudate nucleus, hippocampus and the periventricular regions of thalamus, hypothalamus, midbrain and medulla oblongata. Intranuclear eosinophilic inclusions (Joest-Degen bodies) can be sometimes identified within neurons. In horses abundant virus can be identified within the retinal neurons in absence of retinopathy. Prominent

changes can be observed in Lewis rat experimentally infected with highly neuronotropic strain of BDV<sup>15,16</sup>. The retinal thickness can be reduced up to one third of that of controls. Photoreceptor segments are completely extinguished and the number of neurons is greatly reduced. The typical laminar organization of the retina is largely dissolved. Ultrastructurally severe spongy degeneration is observed. Large numbers of activated microglia and macrophages performing phagocytosis can be observed. The microglial cells are characterized by large numbers of processes, with some of them penetrating the endfeet of Muller cells and others establishing highly complex interdigitations with vacuolized swellings and endings of neuronal processes. Muller cells are not reduced in number but display clear indications of gliosis such as alterations in the immunoreactivity for filament proteins and glutamine synthetase, and significantly thickened stem processes. In these rats the expression profile of proinflammatory cytokines and chemokines, as well as the immunohistochemical detection of alpha beta TCR-positive, CD4- and CD8-positive T-cells in the BDV-infected retinae, is similar to the situation observed in the brains of Lewis rats during the acute phase of Borna disease and this suggests that similar immunopathological mechanisms are operating in retinae and brains of infected rats, which is a T-cell-dependent process.

#### ***Rabies rhabdovirus***

The virus belongs to the genus *Lyssavirus*, family *Rhabdoviridae* order *Mononegavirales*. Virions<sup>17,18</sup> are enveloped, bullet shaped, 45-100 nm in diameter, 100-430 nm long. Surface projections of envelope are distinct with spikes, dispersed evenly over the surface, except for the quasiplanar end of bullet-shaped viruses. Nucleocapsids are filamentous, when uncoiled, cross-banded. The symmetry is helical. Virions contain one molecule of linear usually negative-sense single-stranded RNA. The characteristic lesions are nonsuppurative perivascular encephalomyelitis with ganglionitis and variable numbers, often numerous variously sized intracytoplasmic acidophilic round to oval inclusion bodies. In animals dying of rabies<sup>19</sup> there is moderate to severe lymphocytic perivascular inflammation in gray and white matter of cerebral hemispheres with mild lymphocytic leptomeningitis. In the basal nuclei, gray matter of thalamus and brain stem there is prominent inflammation with diffuse gliosis and presence of lymphocytes in the neuropil. The virus is mainly in neuronal cell bodies, axons and dendrites, which appear morphologically normal. There is prominent immunostaining<sup>19</sup> of cortical

neurons, pyramidal cells and neurons of gyrus dentatus, as well as nuclei of thalamus and brain stem. In the cerebellum the virus is primarily localized within the Purkinje cells and some neurons of the granular and molecular layers. The spinal cord often contains abundant virus in dorsal and ventral horns with sparing of the white matter. Virus is also observed in some astrocytes and oligodendrocytes, ganglion cells of the retina and trigeminal ganglia cells and other ganglia. Lesions associated with the ocular localization of rabies virus are minimal to mild. The virus can be also identified within the cytoplasm of corneal epithelial cells and corneal smears can be part of the routine antemortem work-up for presumptive rabies<sup>20</sup>.

#### ***Prions of transmissible spongiform encephalopathy***

Prions<sup>21</sup> are small, proteinaceous infectious particles that resist inactivation by procedures that affect nucleic acids. No detectable nucleic acids and no virus-like particles have been associated with prions. Prions cause spongiform encephalopathies of animals and humans. Microsomal membranes are visible in infected brain cells. Bovine spongiform encephalopathy (BSE), scrapie of sheep, and Creutzfeldt-Jakob disease (CJD) of humans are among the most notable prion diseases. The scrapie prions are contained also within the neural portion of eyes. Progressive retinal degeneration is described in experimentally scrapie-infected hamsters<sup>22</sup>. Scrapie infectivity rises progressively in the eye to maximal levels between 6 and 8 weeks after inoculation, and then it reaches a plateau. Ocular abnormalities are first visible 8 weeks after infection. The process begins with a gradual loss of rod outer segments, after which progressive loss of rod inner segments and photoreceptor nuclei occurs. By 10 weeks, only a vestige of the outer nuclear layer remains. Ultrastructurally, this destruction is associated with macrophages. Later Muller cells increase their pericellular investment of remaining photoreceptor cell nuclei.

#### **CATTLE, SMALL RUMINANT AND SYLVATIC RUMINANT VIRUSES**

##### ***Bovine herpesvirus 1***

*Bovine herpesvirus 1* (BoHV-1), a major pathogen of cattle, is mainly associated with two clinical syndromes designated infectious bovine rhinotracheitis (IBR) and infectious pustular vulvovaginitis. As with other members of the subfamily *Alphaherpesvirinae*, family *Herpesviridae* the BoHV-1 virion consists of an icosahedral nucleocapsid sur-



rounded by an electron-dense zone called the tegument, and by a bilayered envelope exhibiting spikes on its surface<sup>23</sup>. The viral genome is around 135000 nucleotides with linear double-strand DNA putatively encoding at least 70 proteins from which approximately 33 are virion structural components<sup>24,25</sup>. BoHV-1 is able to cause abortion, stillbirth, conjunctivitis, rhinitis, tracheitis, necrotizing bronchiolitis and vulvovaginitis. BoHV-1 also causes serous to neutrophilic conjunctivitis. Following instillation of BoHV-1 multifocal lymphoid follicle hyperplasia on palpebral or bulbar conjunctiva occurs with conjunctival ulceration<sup>26</sup>. The cornea is rarely involved, which is a feature of infectious bovine keratoconjunctivitis due to *Moraxella bovis*, where *Mycoplasma* spp. or BoHV-1 may enhance or hasten the disease process. The manifestations of infectious bovine keratoconjunctivitis may range from mild conjunctivitis to severe ulceration, corneal perforation, and blindness<sup>27</sup>.

#### ***Bovine virus diarrhea pestivirus (BVDV).***

Bovine virus diarrhea pestivirus (BVDV)<sup>28,29</sup> is a pestivirus of the family *Flaviviridae*, very close to border disease of sheep and classical swine fever (hog cholera) pestiviruses. Virions have a complex construction and consist of an envelope and a nucleocapsid, are spherical to pleomorphic and 40–60 nm in diameter. The surface projections are distinctive spikes surrounded by a prominent fringe. Surface projections form ring shaped subunits and patterns are 10 nm in size. Capsid-nucleocapsid is round and exhibits polyhedral symmetry. The core is isometric. The genome<sup>28-30</sup> is not segmented and consists of a single molecule of linear positive-sense single-stranded RNA. Six nonstructural proteins are encoded by the noncytopathic BVDV genome. Npro (p20) is the first protein produced from the open reading frame. It has papain-like protease activities. The next nonstructural protein produced is NS23 (p125). This protein has several unique characteristics that suggest its involvement in multiple functions. These characteristics include a very hydrophobic domain, a zinc-finger, a protease, and a helicase. **Cytopathic BVDV** strains have changes within the coding region for p125 that result in the production of the protein NS3 (p80). This protein is unique to the cytopathic BVDV biotype. The NS3 protein of cytopathic BVDV contains the protease and helicase activity of the NS23 protein. Other nonstructural proteins include NS4A (p10), NS4B (p32), and NS5A (p58) and they may play a role in viral replication. The final protein produced is NS5B (p75) that is thought to be the RNA-dependent-RNA polymerase needed to replicate the vi-

ral genome. Replication of BVDV begins with receptor-mediated endocytosis into a cell. The E2 glycoprotein appears to mediate this step. Once in the cell, the viral RNA is released into the cytosol. RNA translation then begins with the 5' untranslated region serving as an internal ribosomal entry site. Viral proteins can be detected as early as three hours after cell infection. Following gene translation, the large polyprotein product is processed by both cellular and viral enzymes into mature proteins. Once the RNA-dependent RNA polymerase is produced, new genomic RNA is produced to be incorporated into virus packages. Viral packaging occurs in either the Golgi apparatus or endoplasmic reticulum where they acquire their lipid envelope through budding into the vesicle lumen. Mature virus packages are then released from the cell exocytosis. New virus can be released as early as 10 hours post cell infection. BVDV has been subdivided into two genotypes, BVDV1 and BVDV2. BVDV is a pantropic virus<sup>31</sup> able to cause abortion, stillbirth, malformations, pneumonia, enteritis, and immunosuppression. In addition virulent strains of BVDV2 cause severe thrombocytopenia with hemorrhage and a severe acute disease resembling mucosal disease. Cattle of all ages are susceptible to infection with BVDV. Distribution of the virus is world-wide. The clinical signs range from subclinical to the fulminating fatal condition called mucosal disease<sup>32</sup>. Acute infections may result in transient diarrhea or pneumonia, usually in the form of group outbreaks. Most infections are mild and are unrecognized clinically. The virus spreads mainly by contact between cattle. Vertical transmission plays an important role in its epidemiology and pathogenesis. Fetal infection between 40<sup>th</sup> and 120<sup>th</sup> day of gestation with noncytopathic BVDV may result in persistently infected newborn calves. Persistently infected animals can be easily identified with indirect peroxidase immunohistochemistry on a skin biopsy sample where the viral antigen is easily identified within epidermis, adnexal, vessels and nerves. Infection of calves with BVDV between 79 and 150 gestation days is a thoroughly studied model of viral retinal dysplasia<sup>33-35</sup>. The initial ocular lesion is lymphocytic panuveitis and retinitis with multifocal retinal and choroidal necrosis. The acute inflammation progressively decreases over several weeks. Cornea, uvea and optic nerve, already well differentiated at the time of the endophthalmitis, may undergo atrophy and scarring or be left with no significant lesions. Other tissues such as retina are actively differentiating and exhibit a combination of this atrophy and scarring as well as abortive regeneration and arrested differentiation. Retinal pigment epithelium is infected and dam-

aged by viral cytopathic effect, which causes multifocal abortive retinal regeneration, hyperplastic pigment epithelium and post-necrotic glial scarring. The lesions are usually more severe in nontapetal retina and are bilateral.

#### *Malignant catarrhal fever herpesviruses*

Malignant catarrhal fever (MCF)<sup>36</sup> is an acute, generalized and usually fatal disease affecting many species of *Artiodactyla* caused by *Rhadinoviruses* of the subfamily *Gammaherpesvirinae* with double stranded DNA and about 130600 nucleotides<sup>37</sup>. The disease has been most often described as affecting species of the subfamily *Bovinae* and family *Cervidae*, but is also recognized in domestic pigs as well as giraffe and species of antelope belonging to the subfamily *Tragelaphinae*. The alcelaphine herpesvirus-1 (AIHV-1), the natural host of which the wildebeest (gnu, *Connochaetes taurinus*) is infected inapparently, causes the disease in cattle in regions of Africa and in a variety of ruminant species in zoological collections world-wide. Ovine herpesvirus-2 (OvHV-2), which is prevalent in all varieties of domestic sheep as a subclinical infection, is the cause of MCF in most regions of the world. This form of the disease was formerly referred to as sheep-associated MCF. In both forms of the disease, animals with clinical disease are not a source of infection as virus is only excreted by the natural hosts, wildebeest and sheep, respectively. Viral DNA has been detected in clinical material from MCF caused by both AIHV-1 and OvHV-2 using the polymerase chain reaction, and this is becoming the method of choice for diagnosing the OvHV-2 form of the disease<sup>38,39</sup>. Gross lesions include conjunctivitis, keratitis, erosive and ulcerative stomatitis, interdigital dermatitis, and lymphadenopathy. The microscopic pathology of MCF<sup>40</sup> is characterized by lymphoid proliferation and infiltration, necrotizing vasculitis and epithelial necrosis in various organs. The predominant infiltrating cell type in lesions is CD8 (+) T lymphocytes and large numbers of these cells are infected with ovine herpesvirus 2. Lesions also contain macrophages, but no detectable CD4 (+) or B-lymphocytes. Recovery is associated with the resolution of the acute lymphoid panarteritis that characterizes the acute phase of MCF and with the development of generalized chronic obliterative arteriosclerosis. Ocular findings<sup>41</sup> include: lymphocytic vasculitis of retinal, scleral, posterior ciliary, and uveal vessels; uveitis, especially involving ciliary processes, ciliary body, and iris; keratitis with corneal edema, neovascularization, and epithelial and endothelial degeneration. Lymphocytic ciliary neuritis and optic meningitis are found less frequently. Bilateral leucomata can de-

velop due in part to the focal destruction of corneal endothelium secondary to acute inflammation involving the endothelium<sup>42</sup>.

#### *Rinderpest morbillivirus*

Rinderpest (cattle plague)<sup>43</sup> is a highly fatal disease of domestic cattle, buffaloes and yaks caused by a morbillivirus of the family *Paramyxoviridae* (see also canine distemper morbillivirus paragraph). The virus also affects sheep, goats and some breeds of pigs and a large variety of wild-life species within the order *Artiodactyla*, although not always in a clinically apparent form. Two lineages of the virus still occur in eastern Africa and a third lineage occurs in Asia. Except for part of the Arabian Peninsula, West Asia is probably rinderpest-free, but periodic outbreaks could continue to occur until the virus is eradicated from Pakistan, the only South Asian country in which the disease remains endemic. Lesions include mucopurulent rhinitis and conjunctivitis with sunken eye due to dehydration, erosive and ulcerative stomatitis, pharyngitis esophagitis and pillar ruminitis, necrotizing enterotyphlocolitis with Peyer's patch necrosis. Microscopic lesions include epithelial necrosis with erosions and ulcer, lymphoid depletion and formation intranuclear and intracytoplasmic acidophilic inclusion bodies and syncytia. Rinderpest viral antigen<sup>44</sup> is located mainly in the cytoplasm of the epithelial cells of the digestive, respiratory, and urinary tracts, as well as in the cells of endocrine glands (adrenal, thyroid) and exocrine glands (salivary glands, sebaceous glands, exocrine pancreas). Different types of cells in lymphatic organs contain rinderpest virus. The principal differential diagnoses are peste des petite ruminants in small ruminants, and bovine viral diarrhea-mucosal disease and malignant catarrhal fever in cattle. The virus can be identified<sup>45</sup> sampling base of tongue, eyelid, and retropharyngeal lymph node using virus isolation, indirect immunohistochemistry, in situ hybridization and polymerase chain reaction. In this samples histologic lesions are highly suggestive of rinderpest. Ocular shedding can be detected at the onset of viremia and before the onset of clinical signs whilst virus shedding in nasal, oral and rectal discharges appeared at the same time as lesions. It is suggested that virus isolation from ocular and nasal swabs should be considered in the diagnosis of rinderpest in addition to the other methods currently employed, as virus was isolated from swabs collected from dead animals<sup>46</sup>. Chromatographic strip-test has been developed as a pen-side test for the detection of rinderpest antigen in eye swabs taken from cattle in the field<sup>47</sup>.

### *Peste des petits ruminants morbillivirus*

Peste des petits ruminants (PPR), is an acute contagious disease caused by a morbillivirus in the family *Paramyxoviridae* antigenically similar to rinderpest morbillivirus of cattle, but also to measles and canine distemper morbilliviruses (see also canine distemper virus paragraph)<sup>48</sup>. The comparison of the nucleic acid sequences of different morbillivirus fusion (F) protein genes revealed that the 5'-end sequence of the mRNA is specific to each virus. It affects small ruminants, especially goats, which are highly susceptible, and occasionally wild animals. It occurs in Africa (south of the Sahara), the Arabian Peninsula, throughout most of the Middle Eastern countries, and south-west Asia. The clinical disease resembles rinderpest in cattle. It is usually acute and characterized by serous ocular and nasal serous and mucopurulent discharges, severe pyrexia, which can last for 3-5 days, erosive stomatitis, enterotyphlocolitis and bronchointerstitial pneumonia with syncytia sometimes complicated by bacteria<sup>49</sup>. Lesions and virus distribution<sup>50</sup> are similar to rinderpest. PPRV is detectable in conjunctival epithelial cells obtained from goats in the early or late stage of the disease using monoclonal antibodies with immunohistochemistry sometimes in association with syncytial cells<sup>51</sup>.

### *Bluetongue orbivirus*

Bluetongue orbivirus (BTV)<sup>52-54</sup> is a member of the *Orbivirus* genus, one of nine genera in the family *Reoviridae*. Family members are characterized by a segmented, double-stranded RNA genome and an icosahedral, double-shelled capsid. Orbiviruses differ from viruses in the other genera, except Coltiviruses, by virtue of the structure of their outer capsid layer, the number of genomic double-stranded RNA segments and the fact that they are insect borne. Within the *Orbivirus* genus, 14 groups are differentiated on serological grounds. Within the serogroups, individual members are differentiated on the basis of neutralization tests, and 24 serotypes of BTV have been described to date. The outer layer of BTV contains two proteins, VP2 and VP5. The former is the major determinant of serotype specificity and contains neutralizing epitopes and hemagglutination sites. The inner icosahedral core contains two major proteins - VP3 and VP7 - three minor proteins, and ten species of double-stranded RNA. Trimers of VP7 are arranged on the surface of the core particle. All of the double-stranded RNA segments code for a single protein with the exception of one segment, which has been shown to code for two small, closely related minor proteins. The replication phase of BTV infection cycle is

initiated when the virus core is delivered into the cytoplasm of a susceptible host cell. The 10 segments of the viral genome remain packaged within the core throughout the replication cycle, helping to prevent the activation of host defense mechanisms that would be caused by direct contact between the dsRNA and the host cell cytoplasm. However, the BTV core is a biochemically active "nanoscale" machine, that can simultaneously and repeatedly transcribe mRNA from each of the 10 genome segments, which are packaged as a liquid crystal array within a central cavity. These mRNAs, which are also capped and methylated within the core, are extruded into the cytoplasm through pores at the vertices of the icosahedral structure, where they are translated into viral proteins. One copy of each of the viral mRNAs is also assembled with these newly synthesized proteins to form nascent virus particles, which mature by a process that involves negative RNA strand synthesis on the positive strand template, thereby reforming dsRNA genome segments within progeny virus cores. The crystal structure of the BTV core has also an outer surface festooned with dsRNA. This may represent a further protective strategy adopted by the virus to prevent host cell shut-off, by sequestering any dsRNA that may be released from damaged particles. The vector of BTV is *Culicoides* spp., which is also the living laboratory where the virus mutates by independent gene rearrangement. *Culicoides sonorensis* is the principal vector of BTV in the USA. Its survival is inversely proportional to temperature and virogenesis is temperature dependent. Bluetongue<sup>55-57</sup> is an infectious, noncontagious disease of sheep and domestic and wild ruminants, such as goats, cattle, deer, bighorn sheep, most species of African antelope and various other *Artiodactyla*. The outcome of infection ranges from inapparent in the vast majority of infected animals to fatal in a proportion of infected sheep, deer and some wild ruminants. Overt disease in cattle is rare and the signs, when they occur, are much milder than those observed in sheep. In nondomestic ruminants, the disease can vary from an acute haemorrhagic disease with high mortality, as observed in white-tailed deer (*Odocoileus virginianus*), to an inapparent disease as seen in the North American elk (*Cervus canadensis*). Epizootic haemorrhagic disease orbivirus (EHDV) can produce a disease in wild ruminants with clinical manifestations identical to those observed in response to BTV infection. Ibaraki and Chuzan orbiviruses are also able to cause a disease very similar to bluetongue. BTV can be carried in red cell membrane invagination for weeks producing a long lasting viremia, but persistent infection is not a feature of this disease and BTV RNA can

be detected by nRT-PCR up to 200 days in absence of infectious virus. Clinical signs and lesions of in sheep include fever, face, eyelids and ear edema, hemorrhages, erosions and ulcerations of the mucous membranes. Extensive erosions can develop in the cheeks and on the tongue opposite molar teeth. The tongue may show intense hyperaemia and become swollen and edematous, protrude from the mouth and, in severe cases, become cyanotic. Hyperemia may extend to the groin, axilla and perineum. There is often severe muscle necrosis and in particular necrosis of the papillary muscles of the heart. Fatal cases are associated with severe pulmonary edema, hydrothorax and hydropericardium. Dermatitis may cause wool breaks. Coronitis with hemorrhage of the coronary band of the hoof is common and may cause lameness. Most cases show a distinctive haemorrhage near the base of the pulmonary artery. All these changes are associated to endothelial cell injury enough to release disruptive vasoactive mediators and vasculitis which associated with small quantity of intracytoplasmic BTV within endothelial cells and macrophages<sup>58</sup>. BTV infection of fetal ruminants<sup>57</sup> provides an excellent model for the study of virus-induced teratogenesis. This model has shown that only viruses modified by passage in cell culture, such as modified live virus vaccine strains, readily cross the ruminant placenta, and that the timing of fetal infection determines the outcome. Thus, cerebral malformations only occur after fetal infection at critical stages during development and the precise timing of fetal BTV infection determines the severity of the malformation present at birth. Fetal BTV infection also can result in fetal death, followed by abortion, growth retardation, or no obvious abnormalities, depending on age of the conceptus at infection. It is suspected that ocular abnormalities may also occur.

## EQUINE VIRUSES

### *Equine arteritis arterivirus*

Equine arteritis arterivirus (EAV) is an enveloped, spherical, positive-stranded RNA virus with a diameter of 50-70 nm. The virion is comprised of an isometric core surrounded by a lipid-containing envelope from which delicate spikes protrude. The viral genomic RNA, which is encapsidated by a single nucleocapsid protein, is contained within the core particle. Within the viral envelope at least 3 integral membrane proteins are incorporated. EAV is a non-arthropod-borne virus which has been classified as a member of the order *Nidovirales*, including also the bigeneric family *Coronaviridae*, within the family *Arterivir-*

*idae* with porcine respiratory and reproductive syndrome virus, simian hemorrhagic fever virus and lactate dehydrogenase elevating virus<sup>59,60</sup>. EAV is similar to coronaviruses genetically but with dissimilar viral structure, with a complement fixing antigen but no hemagglutinins<sup>61</sup>. Genetic diversity is recognized among field isolates<sup>62</sup>. Only one strain of EAV is recognized, the Bucyrus strain, however various isolates present different degrees of virulence<sup>63</sup>. Equine viral arteritis (EVA)<sup>64-66</sup> can cause prominent economic losses for the equine industry. The vascular system is the principal but not unique viral target of EAV. Clinical signs may be absent or may include pyrexia, depression and anorexia, leukopenia, limb edema, stiffness of gait, rhinorrhea and epiphora, conjunctivitis, rhinitis, periorbital and supraorbital edema, midventral edema involving the scrotum and prepuce of the sire and mammary gland of the mare, urticarial rash, and abortion in the mare. Less frequently severe respiratory distress, ataxia, mucosal papular eruptions, submaxillary lymphadenopathy, intermandibular and shoulder edema may be observed. Conjunctivitis and episcleritis with photophobia are the so-called "pink eye". EVA has variable pathological presentations, including interstitial pneumonia, panvasculitis with edema, thrombosis and hemorrhage, lymphoid necrosis, renal tubular necrosis, abortion, and inflammation of male accessory genital glands. EAV can be immunohistochemically demonstrated within the cytoplasm of epithelial cells such as alveolar pneumocytes, enterocytes, adrenal cortical cells, trophoblast, thymus stroma, renal tubular cells, and male accessory genital gland cells. It can be also demonstrated within endothelia, in vascular, myometrial, and cardiac myocytes, macrophages, dendritic cells of lymphoid organs, and chorionic mesenchymal stromal cells. In young and adult horses, following colonization of macrophages, the virus spreads systemically using circulating monocytes and enters the endothelium and tunica media of blood vessels, histiocytes, and dendritic cells. Eventually, the virus multiplies within renal tubular cells. Lesions are uncommon in the aborted fetus; if present, they are mild, and EAV is frequently not detectable within fetal tissues and placenta and evaluation of mare's seroconversion is necessary to obtain a diagnosis.

### *Equine herpesvirus 2*

Equine herpesvirus 2 (EHV-2) is a double-stranded DNA virus belonging to *Herpesviridae*, *Gammaherpesvirinae* with 184427 nucleotides<sup>67</sup>, which was also identified in twelve equine keratoconjunctivitis cases using nested PCR on ocular swabs<sup>68</sup>.



### *Equine herpesvirus 1*

Equine herpesvirus 1 (EHV-1) is a double-stranded DNA virus *Varicellovirus* belonging to *Alphaherpesvirinae* with a genome of 150223 nucleotides<sup>69</sup> causes abortion with multifocal necrosis of fetal organs, respiratory disease, pulmonary vascular necrosis and myeloencephalopathy in horses<sup>70-74</sup>. Blindness characterized by dilated unresponsive pupils and fundoscopic evidence of varying degrees of vitritis, retinal vasculitis, retinitis, chorioretinitis, and optic neuritis developed in 21 alpacas and 1 llama within a 30-day period<sup>75</sup>. Four of the affected animals also had signs of neurologic dysfunction. A herpesvirus indistinguishable from equine herpesvirus 1 was isolated from four of the affected animals, and antibody titers diagnostic for equine herpesvirus 1 were demonstrated in the serum of all but one of the affected animals. We did not identify ocular lesions in cases of EHV-1 myeloencephalopathy in horses, excepting those associated with trauma of recumbency<sup>76</sup>.

### PORCINE VIRUSES

#### *Porcine reproductive and respiratory syndrome (PRRS) arterivirus.*

Porcine reproductive and respiratory syndrome (PRRS)<sup>77</sup> is characterized by reproductive failure of sows and pneumonia in piglets and growing pigs. The PRRS virus (PRRSV)<sup>78-80</sup> is classified as a member of the order of *Nidovirales*, family *Arteriviridae*, genus *Arterivirus* (see also equine arteritis virus paragraph). It has a predilection to grow in porcine alveolar macrophages, both *in vivo* and *in vitro*. The virus is an enveloped positive-stranded RNA virus with a diameter of 50-70 nm. The viral RNA is 15428 nucleotides long and encodes eight open reading frames. Three major structural proteins have been identified: a nucleocapsid protein (N; ORF 7) of 14-15 kDa, a membrane protein (M; ORF 6) of 18-19 kDa, and an envelope glycoprotein (E; ORF 5) of 24-25 kDa. Three other less abundant structural glycoproteins are encoded by ORFs 4, 3, and 2<sup>81</sup>. The European strains of the virus are antigenically closely related to each other, but distinct from American strains of the virus and the American strains are also antigenically closely related<sup>82</sup>. There is prolonged duration of viremia and subsequent transmission of the virus to contact animals in comparison with other viral infections. Lifelong persistence of the infection does not seem to occur. It seems that the virus may indeed cause some secondary infections to be more severe. Gross and microscopic lesions characteristic of PRRSV infection are mostly observed in neonatal and nursery pigs. In older pigs,

lesions may be similar but less severe. Gross lesions include cranioventral bronchopneumonia and lymphadenopathy with prominent lymphadenomegaly. Histologically there is multifocal interstitial pneumonia with alveolar septa infiltration by lymphocytes and macrophages, type 2 pneumocyte hypertrophy and hyperplasia, and prominent accumulation of inflammatory and necrotic alveolar exudate. Lymph nodes have follicular hyperplasia, foci of follicular necrosis. Vasculitis, myocarditis and encephalitis may be observed. Inconsistently observed fetal lesions are vasculitis, myocarditis and encephalitis. Rare but highly suggestive is the umbilical cord vasculitis.

#### *Classical swine fever (hog cholera) pestivirus*

Classical swine fever (hog cholera) pestivirus (CSFV)<sup>83</sup> is a lipid-enveloped agent belonging to the family *Flaviviridae*, genus *Pestivirus*. CSFV has a close antigenic relationship with the bovine viral diarrhoea virus (BVDV) and the border disease virus (BDV), as demonstrated in immunodiffusion and immunofluorescence tests and PCR can be also used to differentiate CSFV from other pestiviruses<sup>84,85</sup> (see also bovine viral diarrhoea pestivirus paragraph). CSFV possesses a positive sense, single-strand RNA genome about 12 300 nucleotides in length. Like other pestiviruses the genome contains a single large open reading frame encoding a polyprotein of about 4 000 amino acids. The polyprotein is co- and post-translationally processed by cellular and viral proteases to give rise to 11 or 12 structural and nonstructural viral proteins. Although minor antigenic variants of CSFV virus have been reported, there is only one serotype. CSFV is able to cause systemic vasculitis with edema, hemorrhage and infarcts, pneumonia, enterotyphlocolitis with Peyer's patch necrosis, abortion and malformations in pigs and one of the initial clinical signs is conjunctivitis with epiphora<sup>86,87</sup>. Regarding the virus localization via identification of the protein Gp55<sup>88</sup>, the first positive reactions are seen in lymphatic tissues, digestive tract and skin on postinoculation day (pid) 4, respiratory and urinary tissues on pid 5, nervous tissues on pid 6, and endocrine tissues on pid 7. These staining reactions persist until the last observation on pid 18. The highest levels of virus are found in tonsils, spleen, and pancreas, and the esophageal mucosa and skin epithelial cells are also intensely and widely stained. Vaccine viral strain and wild types of this pestivirus are able to induce malformations in piglets and retinitis<sup>89,90</sup>. Fetuses are susceptible to infection regardless the immune status of the sow. Piglets may be born persistently infected and are susceptible to infection and malformation at least from day 10 to 97 of

gestation with the most vulnerable period of infection for malformation at day 30. Malformations include cerebellar hypoplasia and dysplasia, hypomyelinogenesis, microencephaly, but also mummification, stillbirth, lung hypoplasia, nodular hepatopathy, ascites, anasarca, cutaneous purpura, arthrogryposis, and micrognathia<sup>90</sup>.

#### *African swine fever asfivirus*

African swine fever (ASF) virus is an *Asfivirus*, the only member of the family *Asfarviridae* and it is an double stranded-DNA virus with a genome 170101 nucleotides long<sup>91</sup>. Virions not enveloped, or enveloped in case of extracellular virus, spherical, 200-300 nm in diameter. Nucleocapsids are isometric without obvious regular surface structure, 80 nm in diameter. Symmetry is icosahedral. Nucleocapsids appear to be angular with 1892-2172 capsomers per nucleocapsid, with a diameter of 13 nm each and they are hexagonal prisms with a central hole with an intercapsomeric distance of 7.4-8.1 nm.

The virus mainly replicate within the cytoplasm of macrophages forming focal virus factories in megakaryocytes, some tubular epithelial cells of the kidneys, tonsillar epithelium, some hepatocytes, and in a few endothelial cells and neutrophils in the later stages of the infection<sup>92</sup>. ASF<sup>85,93</sup> is an infectious disease of domestic and wild pigs, which affects animals of all breeds and ages, caused by a virus that produces a range of syndromes. Acute disease is characterized by high fever, hemorrhages in the lymphoid tissue and high mortality. Hemorrhages, associated with platelet activation, degranulation and consumption, mainly involve the gastrohepatic lymphnode and then the renal lymph nodes and the others. Splenic infarction may be observed. Conjunctivitis and epiphora, like in classical swine fever, can be signs of ASF. Infectious virus can survive for several months in fresh and salted dried-meat products. ASF cannot be differentiated from classical swine fever (hog cholera) by either clinical or postmortem examination, and both diseases should be considered in the differential diagnosis of any acute febrile haemorrhagic syndrome of pigs. Bacterial septicemias may also be confused with ASF and classical swine fever. Laboratory tests are essential to distinguish between these diseases.

#### *Aujeszky's disease (pseudorabies) suid herpesvirus 1*

The suid herpesvirus 1 (SHV-1) genome<sup>94</sup> sequence comprises 143,461 nucleotides and more than 70 open reading frames are identified with homologs in related alphaherpesviruses (see also canine herpesvirus 1 paragraph). The transcriptional control architecture is charac-

terized by three key features: core transcription elements shared between genes, yielding divergent transcripts and a large number of coterminal transcripts; bifunctional transcriptional elements, yielding head-to-tail transcripts; short repetitive sequences that could function as insulators against improperly terminated transcripts. SHV-1 causes Aujeszky's disease also called pseudorabies, mad itch, and infectious bulbar paralysis. The common domestic animal species are naturally susceptible, but there are a few reports in horses and goats. Progressive infections do not occur in humans. Outbreaks in pigs are sporadic. Natural infection has been identified in rats, mice, and various species of wildlife and on fur farms. The rabbit is very sensitive and develops intense focal pruritus in the inoculation site. The virus spreads centripetally from the site of inoculation or from ingestion toward the central nervous system and then centrifugally from the CNS. Lesions include dermatitis at the level of the inoculation site, encephalomyelitis with a few neutrophils and sporadic intranuclear eosinophilic inclusion bodies, abortion and natimortality with multifocal necrosis and pneumonia in fetuses and piglets<sup>95-97</sup>. SHV-1 with his polytropism and in particular epitheliotropism and endotheliotropism is also able to cause keratoconjunctivitis in pigs and retinitis<sup>98,99</sup>.

#### *Porcine rubulavirus*

This rubulavirus belongs to the subfamily *Paramyxovirinae*, family *Paramyxoviridae*, *Mononegavirales* (see also canine distemper paragraph). It causes "blue eye" disease of pigs<sup>100</sup>, which is characterized by infertility in sows and boars, nervous signs in young pigs, and corneal opacity in pigs of all ages. The changes are mainly microscopic and characterized by a lymphocytic encephalomyelitis, interstitial pneumonia and anterior uveitis with corneal edema.

#### *Teschovirus porcine enterovirus serotype 1*

The genomic sequence<sup>101</sup> of the *Teschovirus porcine enterovirus* serotype 1 (PEV-1) contains a large open reading frame that encodes a leader protein prior to the capsid protein region. This shows no sequence identity to other picornavirus leader regions and the sequence data suggested that it does not possess proteolytic activity. The 2A protease is small and shows considerable sequence identity to the aphthoviruses and to equine rhinovirus serotype 2. The 2A/2B junction possesses the typical cleavage site (NPG/P) exhibited by these viruses. The other proteins share less than 40% sequence identity with equivalent proteins from other picornavirus genera. Phylogenetic analyses of the P1 and 3D sequences indicated that this

virus forms a distinct branch of the family *Picornaviridae*. PEV-1 causes a virulent manifestation of porcine polioencephalomyelitis<sup>102</sup> with a high morbidity and high mortality. In addition further porcine enteroviruses from the serotype 1 cause porcine polioencephalomyelitis, including Talfan virus and benign enzootic paresis, which cause a milder, more sporadic and less contagious disease. There are 11 serotypes of porcine enterovirus potentially causing encephalomyelitis (PEV 1-7 and PEV 11-13), which have been grouped under enterovirus encephalomyelitis. Central and Eastern Europe, Madagascar and Uganda have the highly virulent strain of PEV1 (Teschén disease). Talfan disease is more widely distributed; it is present in Australia as well as PEV2, PEV5 and PEV8. The highly virulent strain of PEV1 (Teschén disease) can occur in pigs of all ages, with the highest incidence in piglets up to 3 months. The lower virulent viruses cause a milder disease. They usually affect piglets and do not cause a total paralysis. No characteristic gross lesions. Histologically, lesions are confined to the central nervous system and retinitis can be observed.

#### CANINE VIRUSES

##### *Canine adenovirus 1*

The mastadenovirus Canine adenovirus 1 (CAV-1) is characterized by a genome that is not segmented and consists of a single molecule of linear double-stranded DNA that is 30536 nucleotides long<sup>103</sup>. Virions<sup>104,105</sup> have a simple construction and consist of a capsid, fibers, a core, associated proteins and are not enveloped. Capsid is round and exhibits icosahedral symmetry. The capsid is isometric, has a diameter of 70–90 nm and appears hexagonal in outline. CAV-1 is the etiologic agent of infectious canine hepatitis (*Hepatitis contagiosa canis*, Rubarth hepatitis)<sup>106</sup> characterized by necrotizing periportal hepatitis with intranuclear amphophilic or basophilic large viral inclusions with chromatin margination. Diffuse clouding of the cornea (“corneal edema”, “blue eye”) of sudden onset and usually transient duration and with accompanying anterior uveitis, may be attributable to natural infection with CAV-1 or to vaccination with live modified virus<sup>107</sup>. The keratouveitis is a manifestation of type III hypersensitivity in which immune complex formation resulting from the release of virus, especially from infected corneal endothelial cells, brings about corneal endothelial damage and hence corneal edema. A proportion of cases fail to resolve. At least one breed, the Afghan hound, appears to be particularly susceptible. The incidence of ocular lesions re-

sulting from vaccination has stimulated the development of new vaccines incorporating canine adenovirus type 2 (CAV-2), a serotype that does not cause ocular disease<sup>108</sup>.

##### *Canine herpesvirus 1*

The global structure of canine herpesvirus 1 (CHV-1) closely resembles that of the totally sequenced genomes of varicella-zoster virus and equine herpesvirus 1 and belongs to the genus *Varicellovirus* of *Herpesviridae*, *Alphaherpesvirinae*<sup>109</sup>. The hallmark of this family of herpesviruses is latency that develops after primary infection. Within the genus, CHV-1 appears to be most closely related to EHV-1, pseudorabies virus and feline herpesvirus. Varicelloviruses are enveloped, slightly pleomorphic, spherical, 120-200 nm in diameter. Surface projections are dispersed evenly over the entire surface. Nucleocapsids are isometric and surrounded by the tegument that consists of globular material, frequently asymmetrically, 100-110 nm in diameter. The symmetry is icosahedral. Surface capsomer arrangement is obvious with 162 capsomers per nucleocapsid. The core consists of a fibrillar spool on which the DNA is wrapped. The ends of the fibers are anchored to the underside of the capsid shell. Incomplete virus particles often present and they are capsids lacking the envelope. Virions contain one molecule of linear double stranded DNA. The total genome length of varicella virus is 125000 nucleotides and the sequence has terminal repeated sequences, reiterated internally in inverted form, repeated at one end. Each virion contains multiple isomeric forms of genome (i.e. 2 isomeric forms). CHV-1<sup>110-113</sup> is able to cause natimortality and perhaps abortion with multifocal acute necrosis of kidneys, liver, lungs, intestine and other organs with intranuclear acidophilic inclusions. Lesions also include encephalitis, and cerebellar renal and retinal dysplasia. Experimental infection in puppies<sup>114</sup> has been associated with panuveitis with the presence of intranuclear inclusion bodies, usually observed by the fourth day after infection. Eyes affected by severe inflammation had peripheral anterior synechiae, cataract, and keratitis. Developmental anomalies following the infection included retinal dysplasia with fold and tube formation of the neural retina, retardation of retinal maturation, and areas of necrosis and reorganization. The retinal pigment epithelium had initially patchy depigmentation and vacuolization and, subsequently, folding hypertrophy and duplication as well as areas of widespread atrophy and patchy loss. In some animals ectopic retina was observed within cystic spaces of the optic nerve.

### *Canine distemper morbillivirus*

Canine distemper virus (CDV) is a member of the genus *Morbillivirus* in the family *Paramyxoviridae*. *Paramyxoviridae* virions have a complex construction<sup>115</sup> and consist of an envelope, a nucleocapsid, and a matrix protein and during their life cycle, have an extracellular phase and mature naturally by budding through the membrane of the host cell. Virions are spherical to pleomorphic: filamentous and other forms are common and (60–)150–200 nm in diameter and 1000–10000 nm long. The envelope surface projections are distinctive spikes of hemagglutinin-neuraminidase (HN) and fusion (F) glycoproteins evenly covering the surface. The surface projections are embedded in a lipid bilayer. Capsid-nucleocapsid is elongated and exhibits helical symmetry, the nucleocapsid is filamentous and flexuous with varying length of 600–800(–1000) nm depending on the genus, 13–18 nm in diameter. The genome<sup>116</sup>, non infectious by itself, is usually monomeric, or sometimes multiploid, not segmented and consists of a single molecule of linear, negative-sense, single-stranded RNA. Virions may also contain occasionally a positive sense single-stranded copy of the genome. The complete genome is 15200–15900 nucleotides long. Envelope protein F is a fusion protein. Some others structural proteins are envelope protein G (*Pneumovirus*), H (*Morbillivirus*), HN (*Paramyxovirus*). CDV has been reported in all families of terrestrial carnivores: *Canidae*, *Felidae*, *Hyaenidae*, *Mustelidae*, *Procyonidae*, *Ursidae*, and *Viverridae*<sup>117,118</sup>. This pantropic virus causes bronchointerstitial pneumonia, lymphoid tissue necrosis and atrophy, dermatitis with hyperkeratosis, enterotyphlocolitis, myocardial necrosis, osteopathy, enamel hypoplasia, dacryoadenitis, chorioretinitis and encephalomyelitis. CDV targets retina and optic nerve causing degeneration, necrosis and inflammation<sup>119</sup>. Acute lymphocytic and plasmacytic chorioretinitis and optic neuritis with perivascular cuffing, edema, focal exudative retinal separation and hypertrophy of retinal pigment epithelium can be observed, as well as eosinophilic and pathognomonic intranuclear inclusion bodies in ganglion cells and astrocytes. Prevalent are full thickness retinal degeneration and scarring, secondary to retinitis with melanomacrophages gathering the retinal epithelium pigment. Occasionally lesions can be limited to the outer nuclear layer and photoreceptors. The optic nerve lesions resemble encephalitic changes and include lymphocytic perivascular neuritis, astrocyte scarring and demyelination.

### FELINE VIRUSES

#### *Feline herpesvirus 1*

Feline herpesvirus-1 (FHV-1)<sup>120,121</sup> is maintained within the feline population by ready transmission from cat to cat, ensuring continued exposure of kittens and adults. The virus is similar in structure and pathogenicity to herpes simplex virus in humans and both viruses are members of the family *Herpesviridae* and subfamily *Alphaherpesviridae*. FHV-1 DNA is approximately 134000 nucleotides in length and is composed of a long (L) and a short (S) segment. The long segment (U1) is 104 kb in size and is composed of unique DNA<sup>122</sup>. The adjacent S segment is approximately 30000 nucleotides in size and contains a central portion of unique DNA (Us), which is approximately 8000 nucleotides in size. The Us region is bounded by inverted repeat sequences which are 11000 nucleotides in size. FHV-1 causes conjunctivitis, keratitis, rhinotracheitis and, in neonates, systemic disease with encephalitis and multifocal necrosis in multiple organs. In adolescent cats FHV-1 causes bilateral erosive conjunctivitis, in adult cats causes keratitis, which is often unilateral. Intraepithelial intranuclear herpetic viral inclusions can be identified; the immunohistochemical virus distribution is intraepithelial, intranuclear and intracytoplasmic. A large percentage of cats that do not have clinical signs of ocular disease have detectable FHV-1 DNA in their corneas<sup>123</sup>.

#### *Feline calicivirus*

*Vesiviruses* of the family *Caliciviridae* virions have a simple construction and consist of a capsid with no envelope. Capsid-nucleocapsid is round and exhibits icosahedral symmetry, capsid is isometric has a diameter of 35–39 nm and appear round to hexagonal in outline. The capsomer arrangement is clearly visible and capsid appears with 32 cup-shaped depressions. The genome is not segmented and consists of a single molecule of linear positive-sense single-stranded RNA. The virus genome<sup>124,125</sup> is 7683 bases long and contains two large open reading frames. Proteins specified by these have similarity to those encoded in the corresponding regions of a candidate calicivirus rabbit hemorrhagic disease virus, but are distinctly different from those specified by another such virus, hepatitis E virus. A third, small open reading frame at the 3' end of the genome is present in both feline and rabbit viruses but is absent from hepatitis E. Lesions produced by feline calicivirus (FCV)<sup>126</sup> are usually confined to the oral mucosa, tonsils, and lungs. The more virulent FCV causes vesicles, or ulcers of the tongue and ulceration of the hard palate and



nostrils, but also pneumonia. Conjunctivitis may be observed. The FCV of low virulence causes similar lesions of the tongue, palate, and nostrils and not serious systemic involvement. FCVs are increasingly reported as a cause of a highly contagious febrile hemorrhagic syndrome<sup>127</sup>. Strains causing this syndrome are genetically different from the vaccine strain and other nonhemorrhagic FCV isolates. They apparently differ from one outbreak to another. The syndrome is characterized variably by fever, cutaneous edema, ulcerative dermatitis, upper respiratory tract signs, anorexia, occasionally icterus, vomiting, and diarrhea, and a mortality that approaches 50%. Adult cats tend to be more severely affected than kittens, and vaccination does not appear to have a significant protective effect.

#### *Feline reovirus*

The reovirus<sup>128</sup> genome has a double-stranded RNA, which makes it unlike any other RNA virus. This genome is linear and segmented. The number of segments seen in a virus depends on the genera the particular virus belongs to. Replication occurs within a mostly intact virion particle within the cell cytoplasm: there is no virion disassembling and uncoating. They are non-enveloped and spherical. The capsid shape is icosahedral with three layers: two concentric icosahedral capsids at the center of which is an icosahedral inner core. The reoviruses cause inclusion body formation. Feline reovirus<sup>129-131</sup> has been associated with natural and experimental disease in cats, inoculation of newborn kittens with reovirus type 1 results in acute fatal pneumonia, inoculation of kittens with reovirus type 2 causes mild diarrhea, and inoculation of kittens with reovirus type 3 induces mild conjunctivitis and respiratory signs.

#### *Feline leukemia retrovirus*

Retroviruses<sup>132</sup> are plus-sense RNA viruses. The virion contains a nucleocapsid, which is icosahedral in the C-type retroviruses, but cone-shaped in the lentiviruses. The capsid is surrounded by an envelope that contains spikes formed by a virus-encoded glycoprotein. The capsid is composed of three to four proteins, the three common to all retroviruses are known as CA (capsid), MA (membrane matrix), and NC, a nucleoprotein that binds the viral RNA. Feline leukemia retrovirus (FeLV) is 8448 nucleotides long. Upon entering the infected cell, the virion-associated polymerase or reverse transcriptase transcribes a DNA copy of the RNA genome. The DNA integrates into the cell genome mediated by the viral integrase protein, which has both nuclease and ligase activities, creating a stable

“provirus” in the cell’s genome which is replicated along with the cell’s DNA. The site of integration is not specific with respect to the cell genome but occurs at sequences not tightly complexed into nucleosomes. Usually an infected cell will have several proviruses. Retroviruses establish persistent infections in their hosts which often lead to serious and fatal diseases after a long incubation period. FeLV<sup>133,134</sup> has a simple genomic structure and survives in its host by suppressing the immune response to the virus. As a result, this virus is antigenically highly conserved. Persistently viremic FeLV cats are subject to development of a number of diseases that are either directly or indirectly caused by FeLV. Those directly caused by FeLV include lymphosarcoma (lymphoma), myeloproliferative disorders, anemia, a syndrome similar to parvovirus panleukopenia, thymic atrophy, glomerulonephritis, uveitis and reproductive disorders. Diseases indirectly caused by FeLV include a myriad of conditions that develop secondary to FeLV-induced immunosuppression. The prognosis for survival of persistently viremic cats is poor and approximately 50 percent die within six months of infection, while over 80 percent die within three years of infection. In the developing retinas of experimentally infected kittens<sup>135</sup> progressive disorganization and necrosis were documented, with subsequent reorganization into cell clumps and dysplastic rosettes. The retinal pigment epithelium presents proliferation and intraretinal migration. The mature retina exhibits full-thickness folds and tubes associated with infoldings of the retinal pigment epithelium. Ophthalmic manifestations of FeLV or FIV infection<sup>136</sup> can occur in all ocular tissues. The manifestations of common feline ocular pathogens may be more severe and poorly responsive to therapy because of the immunosuppressive effects of FeLV or FIV infection. FeLV antigens and proviral DNA are present in corneal tissues of some FeLV-infected cats and screening corneal donors for FeLV infection is suggested<sup>137</sup>. FeLV lymphoma follows feline infectious peritonitis in the causes of ocular diseases in cats<sup>138</sup>. The FeLV-induced tumors are considered to be caused, at least in part, by somatically acquired insertional mutagenesis in which the integrated provirus may activate a proto-oncogene or disrupt a tumor suppressor gene<sup>139</sup>.

#### *Feline immunodeficiency virus*

Feline immunodeficiency virus (FIV)<sup>136</sup> belongs to the serogroup Feline lentivirus, genus *Lentivirus*, family *Retroviridae*. Virions are enveloped, slightly pleomorphic, 80-100 nm in diameter. Surface appears rough sometimes with spikes dispersed evenly over the entire surface. The nu-

cleocapsid core is isometric and the nucleoid is concentric and rod-shaped, or shaped like a truncated cone. The genome<sup>140-142</sup> consists of a dimer and virions contain one molecule of each linear positive-sense single stranded RNA and the total length is of one monomer 9200 nucleotides. Five structural major virion proteins are identified: Gp120, Gp41, P24, P17. FIV infection in cats is considered a model for human HIV infection. Well-developed areas of the FIV model include: transmission of cell-associated as well as cell-free virus, mucosal infectivity and immunopathogenesis, vertical transmission, acquired immunodeficiency including defects of the innate immune system, thymic dysfunction, neurotropism and neuropathogenesis, host-virus interactions and the role of specific gene products, efficacy of antiviral therapy, and efficacy and immune correlates of experimental vaccines<sup>143</sup>. Following experimental infection with FIV<sup>144</sup> cats become febrile with conjunctivitis and anterior uveitis. Other findings include generalized lymphadenopathy involving peripheral and visceral lymph nodes with concurrent hyperplasia of splenic white matter and mucosal lymphoid tissue of the digestive tract and conjunctiva. Within the lymph nodes there is a reactive follicular hyperplasia accompanied by a paracortical hyperplasia. Unusual features are the presence of lymphoid follicles in the bone marrow, thymus and parathyroid tissue. In addition, aggregates of lymphoid infiltrate salivary glands, kidneys, sclera and choroid of the eye.

#### *Feline infectious peritonitis coronavirus*

Feline infectious peritonitis coronavirus (FIPCoV)<sup>145</sup> belongs to the genus *Coronavirus*, family *Coronaviridae*, order *Nidovirales*. Coronavirus virions<sup>146,147</sup> are enveloped, slightly pleomorphic, spherical, (60-)120-160(-200) nm in diameter. Surface projections of envelope are distinct, club-shaped, 12-24 nm in length, spaced widely apart and dispersed evenly over the entire surface. Nucleocapsids are filamentous, 9-13 nm in diameter, the symmetry is helical. Virions contain one molecule of linear positive-sense single stranded RNA. The spike (S) glycoprotein of coronaviruses mediates viral entry into host cells. Feline infectious peritonitis<sup>145</sup> is a non curable viral disease affecting cats worldwide. It is suggested that the FIPCoV has evolved as a deletion mutation of the less pathogenic feline coronavirus occasionally associated with enteritis<sup>148</sup>. Immune complex deposition and vasculitis with pyogranulomatous lesions are the hallmark of FIP, which can be grossly characterized by an exudative form, and a pyogranulomatous ("dry") form. The only definitive *ante mortem* diagnostic test for FIP is histopathologic examination of

tissue better if associated to indirect immunohistochemistry for the detection of the viral structural antigen. Ocular manifestations occur commonly with noneffusive FIP. The most common clinical sign is a bilateral granulomatous or pyogranulomatous anterior uveitis often accompanied by chorioretinitis. Histopathologic findings in 158 globes obtained from 139 cats by enucleation or at necropsy<sup>138</sup>, with histopathologic diagnosis of uveitis, were compared, and morphology was correlated with clinical and/or histopathologic diagnosis. The most common morphologic feature was a lymphocytic-plasmacytic anterior uveal infiltrate that was either diffuse or nodular; specific cause could not be associated with this nongranulomatous anterior uveitis. In decreasing order of frequency, other common causes of uveitis in cats included feline infectious peritonitis, FeLV-associated lymphoma, trauma and lens-induced uveitis.

#### MUSTELIDAE VIRUSES

##### *Aleutian mink disease parvovirus*

Aleutian mink disease parvovirus (ADV) is a single-stranded DNA virus belonging to *Parvovirinae* and *Parvoviridae*. The nonpathogenic ADV-G strain of ADV<sup>149,150</sup> has a DNA sequence of 4,592 nucleotides. The 3'(left) end of the virion strand contains a 117-nucleotide palindrome that could assume a Y-shaped configuration similar to, but less stable than, that of other parvoviruses. Two regions in the right open reading frame allegedly conserved among the parvoviruses are not present in ADV. There is a short heterogeneous region at 64 to 65 map units in which 8 out of 11 residues diverge and this hypervariable segment may be analogous to short amino acid regions in other parvoviruses that determine host range and pathogenicity. Regarding the pathological changes caused by ADV<sup>151,152</sup>, splenomegaly, lymphadenomegaly are the most common gross lesions sometimes associated with nephromegaly and pallor. Splenic infarction as a result of marked splenomegaly may be observed. In terminal cases, clotting abnormalities associated with vasculitis and the marked hypergammaglobulinemia may result in petechial hemorrhage and hematuria. Histologically, prominent plasmacytic infiltrates are seen in numerous organs, most prominently in the renal interstitium, hepatic portal areas, and in the splenic red pulp, which is expanded by an almost pure population of plasma cells. Additionally, there may be marked plasmacytosis of numerous lymph nodes and the bone marrow. Interstitial pneumonia can be observed. In most cases, there is severe membranous glomerulonephritis and nu-

merous ectatic protein-filled tubules as a result. Vasculitis can be seen in almost any organ. Uveitis, characterized by infiltrates of lymphocytes and plasma cells, was the principal ocular lesion in 122 sapphire and pastel mink affected with experimental Aleutian disease<sup>153</sup>. It was present to various degrees in all but five mink examined five to 164 weeks after intraperitoneal or intranasal inoculation with any of four North American strains of Aleutian disease virus. The uveitis, mostly iridocyclitis, was accompanied often by protein-rich fluid in the anterior chamber and less often by fibrin and cells in the vitreous body. Cellular infiltration of the limbus, seldom pronounced, also occurred in about 20% of the mink. In 11 mink with moderate or severe uveitis, the retina was detached by pools of protein-rich fluid. Infiltrates of lymphocytes, plasma cells, and a few histiocytes often were found in the orbital soft tissues, occasionally in association with retrobulbar arteritis. In general, the ocular lesions were more severe in sapphire than in pastel mink. The uveitis accompanies glomerulonephritis, the principal lesion of Aleutian disease, much more regularly than do several other lesions of the disease. Like the glomerulonephritis, it could probably result from the deposition of circulating immune complexes. Development of AD<sup>152</sup> depends on both host and viral factors, and mink of certain genotypes fail to develop progressive disease when inoculated with low-virulence strains of virus. In newborn mink kits, ADV causes a fatal, acute interstitial pneumonitis associated with permissive viral replication in alveolar type 2 cells, but treatment of newborn kits with anti-viral antibody aborts the acute disease and converts into one resembling the persistent infection observed in adults. In infected adult mink, ADV is sequestered as immune complexes in lymphoid organs, but actual viral replication is restricted at the level of the individual cell and can be detected in only a small population of macrophages and follicular dendritic cells. ADV infection of mink primary macrophages and the human macrophage cell line U937 is antibody dependent and leads to the production of the cytokine interleukin-6. Furthermore, levels of interleukin-6 are increased in lymph node culture supernatants from infected mink. Chronic production of interleukin-6 may promote development of the immune disorder characteristic of AD.

#### KANGAROO VIRUSES

##### *Wallal orbivirus*

Wallal virus infects vertebrates and *Culicoides* spp. and belongs to the genus *Orbivirus*, family *Reoviridae*<sup>154</sup> (see also

bluetongue orbivirus paragraph). Virions are not enveloped, nucleocapsids are isometric, and capsid shells of virion are composed of two layers. Nucleocapsids are round, 80 nm in diameter, symmetry is icosahedral and the core is about 60 nm wide. Virions contain 10 segments of linear double stranded RNA and the total genome length is 19200 nucleotides. Wallal orbivirus<sup>155,156</sup> is able to cause chorioretinitis and encephalitis in kangaroos.

#### LAGOMORPHA VIRUSES

##### *Myxoma leporipox virus*

Myxomatosis is a viral disease of the European rabbit (*Oryctolagus cuniculus*) caused by the *leporipox myxoma virus*, a member of the *Chordopoxvirinae* of *Poxviridae*. Originating in the South American rabbit *Sylvilagus* spp., where it causes a relatively localized fibroma, myxoma virus is a classic example of a virus that has crossed species to produce a disease that coevolved with its new host. A total of 171 open reading frames are assigned to cover the 161.800 nucleotides genome<sup>157,158</sup>, including two copies each of the 12 genes that map within the 11.5-kb terminal inverted repeats. There is a central core of approximately 120 kb that encodes more than 100 genes that exhibit close relationships to the conserved genes of members of other poxvirus genera. Genes encode several novel, potentially immunomodulatory, proteins including a family with multiple ankyrin-repeat domains, an OX-2 like member of the neural cell adhesion molecule family, a third myxoma serpin, a putative chemokine receptor fragment, two natural killer receptor-like species, and a variety of species with domains closely related to diverse host immune regulatory proteins. The M150R myxoma virus gene encodes a nuclear factor (MNF) which interferes with NF-kappa B of the proinflammatory pathway, decreasing inflammation<sup>159,160</sup>. MNF has homologs in other poxviruses, such as vaccinia, cowpox, and variola viruses, and this protein is probably part of a key mechanism that contributes to the immunogenic and pathogenic properties of these viruses. Myxoma virus has a characteristic tropism for skin, causing a nodular skin form, or has an oculo-respiratory tract tropism, the nonmyxomatous form. Myxomatosis<sup>161</sup> affects rabbits of all ages and breeds, and strains, which vary in virulence, give rise to inflammatory skin lesions, systemic distribution and, sometimes, death by secondary bacterial infections or through inanition. The virus is transmitted to susceptible rabbits by biting insects, such as fleas and mosquitoes. Limited transmission from rabbit to rabbit is possible if they are closely confined. A primary myx-

oma lesion arises at the site of infection after 2-5 days, followed by conjunctivitis, infection of the anogenital region, and the formation of secondary skin lesions at various other sites. In the oculo-respiratory form, the primary lesion is usually an inflammatory pink macule followed by oculo-nasal catarrhal epiphora which becomes purulent and eyelid edema. Virulent strains can kill rabbits within 10-15 days. The virus needs to be distinguished from the Shope's fibroma virus<sup>162</sup>.

#### RODENTS VIRUSES

##### *Rat sialodacryoadenitis coronavirus*

Rat sialodacryoadenitis coronavirus (SDA) is commonly found in laboratory rats and that causes sialodacryoadenitis and respiratory illness. The cloning and sequencing of the 3' terminal 9.8 kb of the genomic RNA and analysis of the structure of the viral genome<sup>163</sup> revealed that SDAV genome, as with mouse hepatitis coronaviruses, is able to code for a spike protein, a small membrane protein, a membrane-associated protein, and a nucleocapsid protein. In addition, the hemagglutinin-esterase gene is capable of encoding a protein of 439 amino acids. A sequential study<sup>164</sup> of lesions of the nasal cavity associated with SDAV infection was made in the laboratory rat. Wistar rats were intranasally inoculated with approximately 10(3) TCID<sub>50</sub> of the coronavirus SDAV. Transverse sections of four regions of the nasal cavity from inoculated and control animals were examined by light microscopy and immunohistochemistry at 2, 4, 6, 8, 10, and 14 days postinoculation (PI). Lesions were observed in the following regions of the upper respiratory tract: respiratory epithelium, transitional epithelium, olfactory epithelium, nasolacrimal duct, vomeronasal organ, and the submucosal glands of the nasal passages. In general, in structures lined by ciliated epithelial cells, there was focal to segmental necrosis with exfoliation of affected cells and polymorphonuclear cell infiltration during the acute stages, progressing to squamous metaplasia during the reparative stages. Repair in these regions was essentially complete by 14 days PI. In the olfactory epithelium and the vomeronasal organ, there was interstitial edema with necrosis and exfoliation of epithelial cells and minimal to moderate inflammatory cell response during the acute stages. Residual reparative lesions were still evident in the olfactory epithelium, the columnar epithelium and neuroepithelium of the vomeronasal organ, and the nasolacrimal duct at 14 days PI. Viral antigen was demonstrated by immunohistochemistry in all regions during the acute stages of the disease, with the

exception of the vomeronasal organ. Viral challenge<sup>165</sup> results in a significant, time-dependent increase in SDAV titers that are primarily cell-associated and greatly exceed amounts contained in the original inoculum. SDAV infection does not compromise lachrymal acinar cell viability or prevent the cellular secretory component response to androgens but viral presence often attenuate the magnitude of this hormone action. SDAV infects salivary acinar cells, but the kinetics and magnitude of viral replication in lachrymal, submandibular and parotid cells are characterized by considerable variation.

#### NONHUMAN PRIMATES' VIRUSES

##### *Cercopithecine herpesvirus 1 (herpesvirus simiae, B Virus)*

Cercopithecine herpesvirus 1 (herpesvirus simiae, B Virus) is a double stranded DNA *Simplexvirus* belonging to *Herpesviridae*, *Alphaherpesvirinae*. The total genome<sup>166</sup> length is 156,789 nucleotides. Seventy-four genes are identified, and sequence homology to proteins known in herpes simplex viruses (HSVs) is observed. Unexpectedly, B virus lacks a homolog of the HSV gamma (1)34.5 gene, which encodes a neurovirulence factor. This dangerous zoonotic agent causes vesicles and ulcers in oral cavity and lips and conjunctivitis in macaques<sup>167,168</sup>. Disseminated infections with multifocal necrosis in various organs if generalized occur rarely, especially in young and debilitated animals. B virus can infect and cause fatal disease in owl monkeys, marmosets, African green monkeys, gibbons, and patas monkeys<sup>169</sup>. In humans vesicles develop at site of inoculation, conjunctivitis and often encephalomyelitis with fatality in 80% of the cases<sup>170</sup>.

##### *Herpes simplex herpesvirus*

The herpes simplex herpesvirus (HSV-1) virion<sup>171</sup> consists of a capsid into which the single stranded DNA is packaged, a tegument and an external envelope. The genome<sup>172</sup> length is 152261 nucleotides. Seven capsid proteins are identified, and two of them are mainly present in precursors of mature DNA-containing capsids. There are 150 hexamers and 12 pentamers in the icosahedral capsid. These capsomers all have a central channel and are connected by Y-shaped triplexes. In contrast to the capsid, the tegument has a less defined structure in which 11 proteins have been identified so far. Most of them are phosphorylated. Eleven virus-encoded glycoproteins are present in the envelope, and there may be a few more. Functions of these glycoproteins include attachment to and penetration



of the cellular membrane. There is latent or productive infection in many humans, which are the natural reservoir and the transmission occurs human to monkey and monkey to monkey from productive infection<sup>173-177</sup>. Lesions may be local or generalized including oral vesicles and ulcers, conjunctivitis, encephalitis, death. Owl monkey, tree shrew, lemur, marmosets, tamarins are susceptible to generalized disease. Chimpanzees and gibbons can be infected, but usually remains confined to skin, oral cavity, external genitalia, and conjunctiva. Inflammation and necrosis can be associated with multinucleated syncytial cells and intranuclear acidophilic inclusion bodies.

#### *Human measles morbillivirus*

Human measles morbillivirus<sup>178,179</sup> is a rubulavirus of the *Paramyxovirinae*, *Paramyxoviridae* family (see also canine distemper virus paragraph). The viral genomic RNA is single-stranded, nonsegmented, and of negative polarity and encodes six major structural proteins with a length of 15384 nucleotides. The two viral transmembrane glycoproteins, the hemagglutinin and fusion proteins, are both required for virus-host cell membrane fusion, while attachment to host cells is mediated by the hemagglutinin. The human CD46 molecule has been identified as a cellular receptor for measles virus. Antibodies raised against either viral glycoprotein neutralize measles virus *in vitro* and protect against infection. Although measles virus remains a single serotype (monotypic), nucleotide sequence analyses have identified distinct lineages among recent wild type isolates. These genetic changes are manifested by detectable antigenic variation between vaccine and wild type viruses. Transmission is respiratory and humans are the reservoir. Measles is not a natural disease of nonhuman primates but is acquired through contact with humans. It affects apes, macaques, baboons, African green monkeys, marmosets and squirrel monkeys with maculopapular rash, conjunctivitis, facial erythema, interstitial pneumonia, necrosis on oral mucous membranes, syncytial cells in skin, lymph nodes, lung, and intranuclear and intracytoplasmic acidophilic inclusion bodies<sup>180-184</sup>. In marmosets and owl monkeys measles is an often fatal gastroenterocolitis rather than a predominantly respiratory infection<sup>185</sup>.

#### *Simian adenoviruses*

The family *Adenoviridae* (see also canine adenovirus paragraph) comprises over 100 members, and is divided into two genera: *Mastadenovirus*, affecting mammals and marsupials, and *Aviadenovirus*, which infect birds. Adenoviruses are nonenveloped, and contain linear, double-strand-

ed DNA that is contained within an icosahedral protein capsid ranging between 70-100 nm in diameter. Human adenovirus genomes have a 34-36000 nucleotides length<sup>186</sup>. At least 27 strains are recognized to infect nonhuman primates<sup>187</sup> and were studied extensively for their ability to immortalize cells *in vitro* and induce neoplasms in experimentally inoculated hamsters. Simian adenoviruses are frequently isolated from intestine and lung of healthy animals. In rhesus monkeys conjunctivitis, necrotizing alveolitis and bronchiolitis, pneumonia, necrotizing pancreatitis, and enteritis with intranuclear amphophilic inclusions have been observed<sup>188-191</sup>. Immunosuppressed animals appear to be more susceptible<sup>192</sup>.

#### *Simian immunodeficiency viruses*

Simian immunodeficiency virus (SIV) is a lentivirus of the *primate lentivirus group*, belonging to *Retroviridae* and *Retroid viruses* (see also feline immunodeficiency virus paragraph) with a genome length of 10000 nucleotides. Previously named Simian T-lymphotropic virus type III (STLV-III), are comprised of four groups (HIV-2/SIVSMM/SIVMAC/SIVSTM/SIVMNE; HIV-1/SIVCPZ; SIVAGM/SIVWCM; SIVMND) of related viruses<sup>193-204</sup> that occur naturally and are indigenous in some African primates including *Cercopithecus* sp. (African green monkeys, vervets, grivets, tanzalus monkeys, Sykes monkeys), *Papio* sp. (mandrills and anubis), *Cercocebus* sp. (sooty and white crowned mangabeys), and *Pan troglodytes* (chimpanzee). These animals are persistently infected, but appear to remain asymptomatic for life. SIVAGM is the most genetically diverse group and has coevolved with the 4 geographically separate subspecies of African green monkeys (vervet, grivets, tanzalus, sabaeus). Viral load in African green monkeys is comparable to that in asymptomatic HIV-1 infected people, while sooty mangabeys carry higher viral loads<sup>205,206</sup>. SIV has also been isolated from several species of macaques (*M. mulatta*, *M. nemestrina*, *fascicularis*, *M. arctoides*) housed in laboratories. SIV does not infect Asian monkeys in the wild. The immunodeficiency disease produced in macaques by SIV from sooty mangabeys or macaques has many features similar to human AIDS. SIV has tropism to CD4+ lymphocyte and macrophage, causing depletion of CD4+ CD29+ T-cells, which are helper/inducer cells. Some isolates (SIVSMM(PBj)) are highly pathogenic, causing death within days, while others (SIVSMM(Delta/D915)) are attenuated<sup>207,208</sup>. Most isolates commonly used in laboratories cause fatal immunodeficiency within a few months to a few years in most inoculated animals. Experimentally infected macaques initial-

ly have a rash and develop lymphadenopathy<sup>209</sup> for a variable time, followed by significant lymphoid tissue depletion and opportunistic infections, which may also involve conjunctivae, eyes and adnexa. Such infectious agents include cytomegalovirus, adenovirus, rhesus Epstein Barr herpesvirus (rhEBV), and simian polyomavirus SV40 but also *Candida* spp., *Mycobacterium* spp., *Cryptosporidium* spp., *Pneumocystis carinii*, *Trichomonas* spp.<sup>210,211</sup>. Lesions thought to be directly caused by SIV include cutaneous rash, lymphoid hyperplasia, lymphoid depletion, anemia and thrombocytopenia, pneumonia, encephalitis, giant cell disease, and glomerulosclerosis<sup>212-214</sup>. Regarding SIV cellular colonization and distribution<sup>215,216</sup>, numbers of SIV-infected cells are rare during follicular hyperplasia, numerous during follicular and paracortical expansion, and rare during follicular and paracortical depletion; the splenic morphology reflects that of the lymph nodes, however, the numbers of SIV-positive cells are uniformly lower. SIV RNA is frequently restricted to a single nucleus within multinucleate syncytial cells in some cases of granulomatous lymphadenitis; there is evidence for antigen trapping in SIV-infected hyperplastic lymph nodes and for widespread viral infection of macrophages and lymphocytes during paracortical expansion. SIV is not oncogenic, but lymphoid neoplasms are common and have been associated with rhEBV and STLV-1. A few laboratory workers have seroconverted to SIV and virus (SIVHU) has been isolated from one for this SIV is considered a zoonotic agent<sup>217</sup>. Rubeosis in the anterior segment, and retinitis, optic neuritis, choroiditis and panophthalmitis in the posterior segment of the eye have been associated to a dual infection SIV and rhesus cytomegalovirus<sup>218</sup>.

#### *Rhesus cytomegalovirus*

The rhesus cytomegalovirus (RhCMV) strain 68-1 genome<sup>219</sup> is 221,459 nucleotides in length and possesses 230 potential open reading frames (ORFs) of 100 or more codons that are arranged colinearly with counterparts of previously sequenced betaherpesviruses such as human cytomegalovirus (HCMV). Of the 230 RhCMV ORFs, 138 (60%) are homologous to known HCMV proteins. The conserved ORFs include the structural, replicative, and transcriptional regulatory proteins, immune evasion elements, G protein-coupled receptors, and immunoglobulin homologues. The RhCMV genome also contains sequences with homology to cyclooxygenase-2, an enzyme associated with inflammatory processes. Closer examination identified a series of candidate exons with the capacity to encode a full-length cyclooxygenase-2 protein. Coun-

terparts of cyclooxygenase-2 have not been found in other sequenced herpesviruses. In SIV infected monkeys, RhCMV antigen can be identified in the gastrointestinal tract, the hepatobiliary system, the lungs, and the testicles, infection generally produces characteristic karyomegalic cells with prominent intranuclear inclusions often surrounded by a clear halo ("owl's eye cells") and rarely, smaller granular intracytoplasmic inclusions may be found<sup>220</sup>. Rubeosis in the anterior segment, and retinitis, optic neuritis, choroiditis and panophthalmitis in the posterior segment of the eye have been associated to a dual infection SIV and rhesus cytomegalovirus<sup>218</sup>.

#### AVIAN VIRUSES

##### *Newcastle disease paramyxovirus*

Newcastle disease (ND)<sup>221,222</sup> is caused by a virus member of the genus *Rubulavirus* of the family *Paramyxoviridae*. The paramyxoviruses isolated from avian species have been classified by serological testing into nine serotypes designated APMV-1 to APMV-9 and ND virus has been designated APMV-1<sup>223,224</sup>. ND virus pathogenicity for chickens greatly varies. Strains of ND virus have been grouped into five pathotypes on the basis of the clinical signs seen in infected chickens: 1) viscerotropic velogenic: a highly pathogenic form in which hemorrhagic intestinal lesions are frequently observed; 2) neurotropic velogenic: a form with high mortality, usually following respiratory and nervous signs; 3) mesogenic: a form that presents with respiratory signs, occasional nervous signs, but low mortality; 4) lentogenic or respiratory: a form that presents with mild or subclinical respiratory infection; and 5) asymptomatic enteric: a form that usually consists of a subclinical enteric infection. Pathotype groupings are rarely clear-cut and considerable overlapping may be seen. In addition, exacerbation of the clinical signs induced by the milder strains may occur in superimposed infections by other organisms or when adverse environmental conditions are present. This is a zoonotic agent which is able to cause painful transient conjunctivitis in humans.

##### *Marek's disease gallid herpesvirus 2*

Gallid herpesvirus 2 (MDV) is a double-stranded DNA virus belonging to *Alphaherpesvirinae*. The entire GA-MDV genome<sup>225</sup> is predicted to be about 174000 nucleotides in size, with an organization of TRL-UL-IRL-IRS-US-TRS, typical of an alpha-herpesvirus. The unique long region (UL) sequence contains 113,508 nucleotides with a total of 67 open reading frames and of these 55 are homologous

to genes encoded by herpes simplex virus-1. Twelve of them are unique with presently unknown functions. An additional unique feature of MDV is the presence of long terminal repeat remnant sequences of avian retrovirus reticuloendotheliosis virus. These remnant sequences are derived from the U3-enhancer region through ancestral insertions by reticuloendotheliosis virus proviruses. Marek's disease (MD) is a lymphomatous and neuropathic disease of chickens turkeys and quails<sup>226</sup> characterized by a nervous form and a visceral form with proliferation of neoplastic lymphocytes, resulting in death or severe production loss in both layer and meat chickens. Young birds are the most susceptible to infection. Most deaths from MD occur between 10 and 24 weeks of age, although in some cases the disease may not appear until later in life. Vaccination will reduce the losses. However, in recent years there has been an increase in MD, due to new strains of virus and faster growing, more susceptible birds. Tumors can also occur in the iris causing blindness. The differential diagnosis of MD is lymphoid leucosis, caused by an avian retrovirus, which generally develop in older birds.

#### *Fowlpox poxvirus*

Fowlpox<sup>227,228</sup> is a disease of chickens and turkeys caused by a double-stranded DNA virus of the genus *Avipoxvirus* of *Chordopoxvirinae* of the family *Poxviridae*. Avipoxviruses include *Canarypox virus*, *Fowlpox virus*, *Juncopox virus*, *Mynahpox virus*, *Pigeonpox virus*, *Psittacinepox virus*, *Quailpox virus*, *Sparrowpox virus*, *Starlingpox virus*, *Turkeypox virus*, *Crowpox virus*, *Peacockpox virus*, *Penguinpox virus*. The 288000 nucleotides FPV genome<sup>229</sup> consists of a central coding region bounded by identical 9.5-kbp inverted terminal repeats and contains 260 open reading frames. Fowlpox distribution is world-wide. It is slow-spreading and characterized by the formation of proliferative lesions and scabs on the skin, and diphtheritic lesions in the upper parts of the digestive and respiratory tracts. In the case of the cutaneous form the mortality rate is usually low. If the lesions are around the eyes with conjunctivitis and blepharitis, then swelling may occur with impairment of eyesight and possibly blindness in severe cases. In the majority of the cases the eyeball remains unaffected and, once lesions are resolved, eyesight should return to normal. Birds are more likely to recover from these lesions than those with the diphtheritic form. In the diphtheritic form, proliferative lesions involving the nasal passages, larynx or trachea can result in respiratory distress and death from suffocation. Fowl pox virus multiplies in the cytoplasm of epithelial cells with the formation of large intracytoplas-

mic inclusion bodies (Bollinger bodies) that contain smaller elementary bodies (Borrel bodies). The inclusions can be demonstrated in sections of cutaneous and diphtheritic lesions by the use of hematoxylin and eosin, acridine orange or Giemsa stains. The elementary bodies can be detected in smears from lesions, for example by the Gimenez method. Electron microscopy can be used to demonstrate viral particles of typical poxvirus morphology by negative staining or in ultrathin sections of infected tissues. Electron microscopy of thin sections of canarypox poxvirus pocks produced on the chorioallantoic membranes<sup>230</sup> reveals a variety of developmental forms: viral factories, immature, undifferentiated virions partially enclosed by membranes, completely enclosed nondifferentiated spherical or oval virions, immature virions with discrete nucleoids and the more compact brick-shaped mature virions. Two types of A-type inclusions are noted: those with virions around the periphery, and those filled with virus particles. The appearance of mature viruses within the inclusion bodies and different stages of viruses outside the inclusion indicate that in a course of development, maturing poxvirus may enter the inclusion bodies as they acquire surface tubules on their envelopes. Mature virions can also be seen budding out of the cell membrane, apparently enveloped in a portion of the membrane.

#### *Avian infectious laryngotracheitis gallid herpesvirus 1*

Gallid herpesvirus 1, an alphaherpesvirus, causes avian infectious laryngotracheitis (ILT)<sup>231</sup>. It can also affect pheasants, partridges and peafowl. In the acute form, the history, clinical signs and very severe tracheal lesions are highly suggestive, but the mild form may be indistinguishable from other mild respiratory diseases. Clinically, the disease may appear in three forms: peracute, subacute, and chronic or mild. The peracute form is characterized by high morbidity and mortality with severe necrohemorrhagic tracheitis. In the subacute form the morbidity is high but the mortality is lower than in the peracute form and the lesions are less severe with necrotizing or caseous and fibrinous tracheitis. Chronic or mild ILT may be seen among survivors of either of the above forms of the disease, although some outbreaks themselves may be entirely mild. Gross lesions are less severe and tend to be fibrinous. Histologically is possible to observe various degrees of necrosis, ulceration, lamina propria lymphocytic, plasmacytic and histiocytic infiltration and multifocal intranuclear acidophilic inclusion bodies with chromatin margination and frequent formation of syncytia. Conjunctivitis, rhinitis, sinusitis can be also observed. The viral DNA can be de-

tected performing polymerase chain reaction of material collected from the conjunctiva of affected birds<sup>232</sup>.

#### REPTILIAN VIRUSES

##### *Chelonian herpesviruses*

Herpesviruses<sup>233</sup> have surfaced as important pathogens of the oral cavity and respiratory tract in Hermann's tortoise (*Testudo hermanni*), spur-thighed tortoise (*Testudo graeca*), and other tortoises in Europe and the United States. Herpesvirus-associated respiratory diseases also have been reported in the green turtle, *Chelonia mydas*, in mariculture in the Cayman Islands. Experimental transmission of tortoise herpesvirus in Greek tortoises (*Testudo graeca*) caused conjunctivitis, diphtheritic stomatitis, and rhinitis<sup>234</sup>. Conjunctivitis, tracheitis, and pneumonia associated with herpesvirus infection has been identified in green sea turtles (*Chelonia mydas*)<sup>235</sup>. Macroscopically, lesions included periglottal necrosis, tracheitis with intraluminal caseous and laminated necrotic debris, and severe pneumonia. Several turtles had caseous conjunctival exudate covering the eyes. Microscopically, the turtles had fibrinonecrotic inflammation around the glottal opening, tracheitis, and severe bronchopneumonia and interstitial pneumonia. In multifocal areas, periglottal and tracheal epithelial cells adjacent to areas of necrosis had expanded euchromatic nuclei with amphophilic intranuclear inclusions. A mixed population of primarily gram-negative microorganisms was isolated from the tracheal and glottal lesions. Attempts at viral isolation in cultures of green sea turtle kidney cells resulted in the development of cytopathic effects characterized by giant cell formation and development of intranuclear inclusions. Using electron microscopy, intranuclear viral particles (88 to 99 nm in diameter) were seen in inclusion-containing tracheal and glottal epithelial cells and infected green sea turtle kidney cells; particles were consistently seen enveloping from nuclear membranes, and mature particles (132 to 147 nm) were found in the cytoplasm. On the basis of size, conformation, location, and presence of an envelope, the particles most closely resembled those of herpesviruses. An alpha-herpesvirus has been associated recently with green turtle fibropapilloma<sup>236</sup>. Histologic evaluation<sup>237</sup> of four eyes from three stranded juvenile green turtles (*Chelonia mydas*) from Florida, USA revealed ocular fibropapillomas composed of an overlying hyperplastic epithelium, various amounts of a thickened, well vascularized, collagenous stroma, and reactive fibroblasts. The histologic morphology of the ocular fibropapillomas varied depending on whether the

eyelid, conjunctiva, limbus, or cornea was the primary site of tumor origin. Fibropapillomas arising from the limbus, conjunctiva, or eyelid tended to be polypoid or pedunculated with a high degree of arborization. They often filled the conjunctival fornices and extended externally to be ulcerated on the distal aspects. Corneal fibropapillomas were more sessile and multinodular with less arborization. Some corneal tumors consisted primarily of a broad fibrovascular stroma and mild epithelial hyperplasia, whereas others had a markedly hyperplastic epithelium supported by stalks of fibrovascular stromal tissue. In green turtles ocular fibropapillomas may be locally invasive and associated with severe blindness and systemic debilitation.

#### PISCINE VIRUSES

##### *Nodaviruses of fish*

All the nodaviruses<sup>238-241</sup> in general, consists of a bipartite genome made up of RNA1 and RNA2. RNA1 (3.1 kb) codes for RNA-dependent RNA-polymerase, while RNA2 (1.4 kb) encodes the capsid protein subunit alpha. One-hundredandeighty copies of the capsid protein subunit rapidly and selectively packages RNA1 and RNA2 into a single particle to form provirion, which is meta-stable state of the virus. The provirion spontaneously undergoes maturation upon the cleavage of the capsid protein subunit to form stable and the infectious particle. Virions are not enveloped, nucleocapsid is isometric, 30 nm in diameter, symmetry is icosahedral. These viruses infect insects, mammals and fish. Nodaviruses have been found in over 30 species of marine fish and have caused a problem in the farming of several species worldwide. Viral encephalopathy and retinopathy, also known as fish encephalitis or viral nervous necrosis is caused by a nodavirus, and affects several farmed marine fish species in various geographic areas all over the world. Heavy losses affecting mainly juvenile and adult sea bass (*Dicentrarchus labrax*) have been observed in several on-growing facilities in Italy<sup>242</sup>. Histologic lesions include vacuolization brain and spinal cord gray matter and in the granular layers of the retina. In absence of clinical signs and lesions in the Atlantic halibut (*Hippoglossus hippoglossus*), nodavirus propagates invading central nervous tissue, retina within the circumferential germinal zone at the ciliary margin towards the iris<sup>243</sup>. The betanodavirus sevenband grouper nervous necrosis virus (SGNNV), can be used as a transneuronal tracer using the freshwater angelfish (*Pterophyllum scalare*)<sup>244</sup>. Intravitreal injections of SGNNV into the right eye results first in the labelings of neuronal cell bodies in the ganglion cell



layers of the retina and then those in the inner and outer nuclear layers in sequence. Labeled neurons were found also in the stratum periventriculare of the contralateral optic tectum, the ventrolateral and ventromedial thalamic nuclei, and the periventricular nucleus of posterior tuberculum in the brain, then the periventricular pretectal nucleus pars dorsalis and pars ventralis.

### *Eel rhabdovirus*

A virus belonging to *Rhabdovirus anguilla* is able to induce cutaneous ocular and tissue hemorrhages and celomitis in *Anguilla* spp.<sup>245</sup>.

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## Sažetak

## OČNE VIRUSNE BOLESTI U KRALJEŠNJAKA

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Više virusa može izazvati infekciju oka i očnih adneksa kod kralješnjaka. S obzirom na raznolikost stanica i tkiva koja sačinjavaju oči i adneksa virusi imaju mnogostruke prilike za njihovo koloniziranje i izazivanje patološkog učinka. Tu postoje razlike ovisno o životinjskoj vrsti, dobi, imunom statusu, te vrsti i tipu virusa. Virus mogu ciljati konjunktivni, žlijezdani, rožnični i/ili mrežnični epitel, endotel, miocite i pericite, neurone mrežnice i očnog živca, vlakna i glijalne stanice, te limfocite, makrofage i dendritske stanice limfoidnih folikula. Stanično oštećenje može biti izazvano izravnim citopatskim učinkom ili putem oslobađanja upalnih posrednika i/ili proteolitskih enzima što ih oslobađaju upalne stanice, ili pak oštećenje može biti posljedica intraparijetalnog vaskularnog odlaganja kompleksa antigena protutijela i susljednog aktiviranja komplementa. Kod fetusa i mladunčadi neki uzročnici mogu izazvati različit stupanj očne displazije. Virus imunodeficijencije potiču kolonizaciju i rast drugih uzročnika, kao što su drugi virusi, bakterije, protozoe i micete. Onkornavirusi leukemije mogu uzrokovati neoplastičnu limfocitičnu infiltraciju očiju i adneksa. Ovaj pregledni članak obuhvaća viruse koji mogu zahvatiti više vrsta kralješnjaka, kao i one specifične za preživače, konje, svinje, tobočare, pse, mačke, kune, kuniće, štakore, ptice i ribe. Rasprava obuhvaća herpesvirus, arterivirus, orbivirus, paramiksovirus, morbilivirus, nodavirus, pestivirus, asfivirus, ortomiksovirus, retrovirus, lentivirus, adenovirus, kalicivirus, koronavirus, reovirus i prione. Zoonotski uzročnici uključuju ortomiksovirus gripe, paramiksovirus newcastleske bolesti, rabdovirus bjesnoće, prion prenosive goveđe spongiformne encefalopatije, lentivirus majmunske imunodeficijencije, herpesvirus 1 cerkopitekusa i možda virus Borna bolesti. Antropozoonoze uključuju humani morbilivirus ospica i virus herpes simpleks.

Ključne riječi: *Očne bolesti; Virusne bolesti; Životinja*