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Review

Important mammalian veterinary viral immunodiseases and their control

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ABSTRACT

This paper offers an overview of important veterinary viral diseases of mammals stemming from aberrant immune response. Diseases reviewed comprise those due to lentiviruses of equine infectious anaemia, visna/maedi and caprine arthritis encephalitis and feline immunodeficiency. Diseases caused by viruses of feline infectious peritonitis, feline leukaemia, canine distemper and aquatic counterparts, Aleutian disease and malignant catarrhal fever. We also consider prospects of immunoprophylaxis for the diseases and briefly other control measures. It should be realised that the outlook for effective vaccines for many of the diseases is remote. This paper describes the current status of vaccine research and the difficulties encountered during their development.

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1. Introduction

Viruses require living cells for their replication and survival. Virus infection of cells in vitro and in vivo may interfere with normal cell function in a way that is useful to the infecting virus. The interfering effects are sometimes subtle and complex in an organism. Virus infection may directly affect function of one or more organs leading to disease or may result in disease due to immune-pathological mechanisms. Some of notable examples of the former are those of reduced growth hormone production and growth retardation in mice with persistent lymphocytic choriomeningitis virus (LCMV) infection of the posterior pituitary gland without obvious evidence of cellular damage and the defect could be rectified by growth hormone administration [1]. Another example is that of small rubella babies due reduced foetal growth attributed to rubella virus induced production of mitotic inhibitor resulting in reduced cell division and cell numbers both in placenta and foetus without obvious pathology [2]. The complex nature of some viral infections is illustrated by the example of LCMV disease in immunocompetent and immunodeficient (lacking T cells or radiation or cytostatic drugs immunosuppressed) mice [3] (and references therein). There are likely to be other examples but in this review we focus on pathogenesis of some important viral diseases of companion animals and livestock involving pathology caused by host's dysfunctional and/or aberrant immune response, referred to here as viral immunodiseases. Viruses which significantly subvert the immune system will be considered here in greater detail and those viruses that have a lesser adverse effect on the immune system will be considered separately. Only some examples of the latter will be briefly mentioned under a separate heading 'Examples of some lesser immunosuppressive viruses'. We also cover the prospects of immunoprophylaxis against many of the diseases. In this review we introduce the term 'viral immunodiseases' to describe viruses which adversely affect host's immune system.

The purpose of this article is to provide an overview of the important diseases in animals impairing the immune systems and describe/highlight the underlying mechanisms of immune pathology. Moreover, we also attempt to review the current status of vaccine development against these diseases and difficulties blocking vaccine development and mention alternative control measures for some of the viral diseases.

2. Retroviruses

Of the family *Retroviridae*, the members of the genus lentivirus [4] are extensively and intensively studied [5] and occur worldwide [4], affecting primates, companion and farm animals. Lentivirus infections are characterised by immune system dysfunction as a consequence of their tropism for cells of the immune system. Members cause chronic, lifelong infections culminating in progressive

and degenerative diseases [5–8]. Lentiviruses have the unique ability among retroviruses to replicate in non-dividing cells and require activation and/or differentiation of the host cell for productive replication [4]. A further characteristic is virus persistence in immune cells such as cells of macrophage lineage. The latter play an important role in virus dissemination because they are present in inflammatory exudates and secretions such as milk and colostrum. Lentivirus infections result in primary disease due to the virus and often a secondary disease caused by opportunistic pathogens that proliferate unchecked as a result of loss of helper T lymphocyte function [4]. Lentiviruses have been developed as efficient gene delivery vectors. Recently, for instance a prototype human Chikungunya virus lenti-viral vector vaccine was shown to be highly efficacious in laboratory animals and non-human primates [9]. A common lentivirus characteristic is their tropism for cells of the monocyte/macrophage lineage which are neither destroyed by the replicating lentivirus nor by the infected host's immune response. The virus is able to hide inside the genome of these cells, without expression of viral genes and hence the absence of viral antigen(s) presentation by MHC-II molecules on the membrane of the cell. In the present review we restrict our account to lentiviruses of the ungulates and cats.

2.1. Equine infectious anaemia (EIA)

2.1.1. Disease

EIA is a chronic, relapsing virus disease of horses, first described in France in 1843 and shown to have viral (EIAV) aetiology in 1904 [4,10]. Mules and donkeys are also susceptible to the virus. EIAV is endemic in parts of the Americas including Canada, parts of Europe, Russia, the Middle and Far East and parts of Africa. Virus is transmitted mechanically by blood feeding mosquitoes and blood sucking horse flies, deer flies, stable flies (*Stomoxys* spp.) and possibly midges [4,11,12]. EIAV transmission has also occurred due to use of virus contaminated bloody syringes, needles and surgical instruments and also via ingestion of milk and/or colostrum. EIAV can cross placenta and infect developing foetus [13]. Horses worldwide are affected by EIAV and infection in horses is characterised by three phases namely acute, chronic and inapparent [14–17]. The acute disease typically is manifest by 2 months after exposure. The acute and chronic phases of EIA are defined by fever, jaundice, haemolytic anaemia, a significant decrease in erythrocytes and platelets count, immune complex glomerulonephritis, organ inflammation oedema and high titre viraemia. The acute stage progresses to chronic stage characterised by recurrent episodes of clinical signs and viraemia then to the inapparent carrier stage of disease until death [14–17]. In the inapparent stage, clinical signs are absent. In the acute stage, main site of virus replication is macrophages of liver and spleen whereas in asymptomatic animals viral DNA and RNA are present in many tissues but at very low levels indicative of immune control [18]. Horses with subclinical disease

remain infective to others. The disease is less severe in donkeys and mules.

In vivo, EIAV is primarily, if not exclusively, a macrophage-tropic virus and once it is introduced into the circulation of susceptible horses, virus infects and replicates in blood macrophages which disseminate progeny virus to other mononuclear phagocytes in lymph nodes and organs such as spleen, lung, brain, liver, kidney establishing secondary foci of infection. Thus virus replicates in many organs/tissues but evokes an ineffective immune response (see below). Interestingly, infected macrophages are neither destroyed by the replicating virus and nor by the emergent immune response but instead the shed virus and viral subcomponents complex with antibody and complexes become deposited on erythrocytes, vascular endothelium and kidney glomeruli where they activate complement. The latter causes inflammation and haemolysis.

2.1.2. Control

There is no known treatment that can eliminate EIAV from the body. However vaccines against EIA have been developed which are able to control the spread of the virus [19,20]. In the early 1970s, Shen et al. developed an attenuated EIAV vaccine. This vaccine strain, EIAV DLV120, was developed via a series of in vitro passages of the EIAV pathogenic strain EIAV D510, which was obtained through the in vivo passaging of a wild type strain, EIAV LN40, in donkeys [21,22]. EIAV DLV120 was used extensively in China between 1975 and 1990 for the vaccination of 61 million equines to control an EIA pandemic. This large-scale vaccination successfully controlled the spread of EIA in China; the outbreak at the time of vaccination had resulted in the deaths of 40 million equines due to the disease or to slaughter [19] (and references therein). The Chinese trial suggests that an EIAV attenuated vaccine can induce immune protection and can be safely used for vaccination [21–23]. Live attenuated vaccines against EIAV are also in development outside of China but the experience is different and difficult for us to explain. Much effort towards EIAV vaccine has been by Professor Montelaro's group [24–26]. In general development of an effective EIAV vaccine is hindered by the relatively rapid and continuing sequential mutation of viral glycoproteins (gp) 90 and 45 during persistent infection of a single host under selective immune pressure. The infected host produces virus neutralising (VN) antibody to the original virus which does not effectively neutralise the variant virus strain. An outcome of this is emergence of novel antigenic strains of virus which evade the host's immune surveillance and elimination; also the newly emergent strains are only marginally neutralised by the host's antibodies [26–30]. Interestingly, EIAV glycoproteins appear to be stable upon repeated passage in cell culture [30]. It is noteworthy that the internal EIAV proteins (p26, pp15, p9 and possibly p11), unlike the glycoproteins do not undergo change upon in vivo passage [30]. Thus viral glycoproteins' antigenic drift appears as playing a crucial role in establishment of EIAV persistence in vivo. As for the protective mechanisms, clearance of EIAV viraemia is associated with CTL response and not with neutralising antibody but the viral antigenic variants escape both CTL and neutralising antibody [31]. There is also a transient suppression of the lymphocyte proliferative responses temporally associated with recurrent episodes of fever and viraemia [32]. The immune response to the viral variant antigens result in the formation of antigen-antibody-C3 immune complexes, decrease in plasma C3 level, inflammation and deposition of the complexes in the kidneys and glomerulitis. Interestingly, a similar mechanism of antigenic drift in vivo visna virus infection was suggested [33,34]. EIAV antigenic drift in vivo, leading to immunogenic and antigenic variation, is the limiting factor against the development of broadly effective vaccines. Attenuated vaccines become less protective against challenge virus strains when they contain divergent gp90 protein [24–26].

Furthermore, EIAV vaccines may enhance the severity of disease [35]. The challenge EIAV virologists face is similar to influenza virus vaccine development but it is in fact greater since the EIAV drift occurs, albeit to a varying extent, in each infected host and the virus continues to mutate under immune pressure. Recent studies suggest that engineering of *env* immunogens that elicit a broader and more effective recognition of variant *env* species, along with an efficient presentation system that allows for a rapid evolution of a protective response may be desirable instead of a single shot multivalent approach [26]. Clearly, EIAV vaccine is a challenge but it is important that it is pursued. In absence of an effective vaccine, in endemic areas the risk of transmission may be reduced by insect-proof stabling during summer and at risk periods along with use of effective insecticides to control EIAV vectors. An important and necessary measure to control EIA incidence is identification of infected horses, apparently free of clinical signs and horses with EIA, and their removal from virus-free herd. This would entail regular monitoring of the herd for virus by the Coggins' test. This later having a rather low sensitivity is recently replaced in most diagnostic institutes by a commercial ELISA test which identifies infected horses much sooner than the Coggins' test. Results of the ELISA were confirmed by PCR even in Coggins' negative horses [36].

2.2. Small ruminant lentiviruses

2.2.1. Disease

The visna/maedi virus (VMV) and the caprine arthritis encephalitis virus (CAEV) were considered to be specific pathogens of sheep and goats respectively. Over the last 10 years, phylogenetic reconstructions based on partial sequences of SRLV clearly established that they are in fact part of a viral continuum [37]. The finding that these viruses frequently cross the species barrier between sheep and goats and vice versa has led to review the epidemiology of these and related viruses and their classification as small ruminant lentiviruses (SRLV) [38–40]. SRLVs occur worldwide [4,41]. Isolates are either neurotropic or pneumotropic and cause chronic disease. Infected animals remain carriers. SRLV infection in sheep and goats may result in encephalitis, progressive pneumonia, arthritis and mastitis [4,37,41]. SRLV transmission was one of the topics discussed at the meeting of the 16 European countries' collaborative meeting [4,37,40,41]. Conclusions then were: virus spread via ingested colostrum/milk, virus aerosol, particularly in ovine as their lungs are a major target organ [38,40,42,43]. Vertical intrauterine infection is also possible but uncommon [44,45] and virus contaminated needles have been also a cause of transmission.

VMV and CAEV share the same target organs. Only about 30% of SRLV infected animals develop disease. However, lungs and brain are the major targets of VMV [4,46] while joints being the main target of CAEV [4]; mammary gland is similarly affected by the two SRLVs. Since SRLVs do not infect lymphocytes, immunodeficiency and immunosuppression is not a significant feature in SRLV disease [38,47–49]. An important determinant in SRLV pathogenesis is virus tropism for monocytes, macrophages and dendritic cells [49,50]. Monocytes harbouring SRLV provirus in their genomes show little or no viral transcription. Such latently infected cells are refractory to host's immune attack and being mobile disseminate the virus to target organs [51–53] This has been referred to as the 'Trojan horse' hypothesis. However the mechanism of immune evasion by SRLVs remains obscure. At the level of viral antibodies, responses to infection by CAEV and VMV or EIAV are different. Goats with persistent CAEV infection produce antibodies to all viral proteins but virus is intrinsically poor inducer of virus neutralising (VN) antibodies which are of low affinity and avidity [4] (and references therein). The sialic acids of CAEV glycoprotein were considered as the cause of reduced

avidity of binding between virus and the VN antibody [4]. In contrast, hosts infected by VMV or EIAV produce VN and other antibodies which efficiently bind infecting virus but result in emergence of variant viral mutants during the persistent infection and the variants escape neutralisation and elimination but instead get opsonised by the antibodies and infect further macrophages by the Fc receptor binding. Non-neutralising CAEV antibodies opsonise virus which infects further macrophages via Fc receptor binding [4] and infection persists. The importance of these antibody-mediated enhancement of macrophage infection in CAEV and VMV diseases are best ascertained when cell mediated immune responses are more clearly understood. After infection with VMV, sheep mount an antiviral immune response (both antibody and T cell) but viral replication and dissemination still occur. An explanation put forward for this defect in VMV immune response has been the induction CD8+ T lymphocytes in a defective maturation state as also observed in T-cell-tropic lentiviruses [54]. The defective phenotype of CD8+ T lymphocytes in VMV infection involves expression of MHC class II DR and DQ molecules but not interleukin-2 receptor (IL-2R) and hence lacks lymphoproliferative and cytolytic activities [54]. CD4+ T lymphocytes in VMV infected hosts also appear to be defective and exert a negative influence in the favour of the host. This conclusion was based on the finding of significantly reduced count of VMV-infected monocytes in sheep depleted of CD4+ T cells [55]. Maturation of latently infected monocytes to macrophages in target organs activates productive virus replication [4,50]. This occurs in selective population of macrophages in different tissues [4]. The viral LTR is inactive in monocytes and becomes activated following differentiation of these cells to macrophages. It has been suggested that SRLV infection may modulate the accessory functions of infected macrophages and induce cytokine production when activated into a productive cycle of infection [37]. The efficiency with which this happens may be breed, species or even virus dependent (see below). Viral LTR contains enhancer/promoter and regulatory sequences required for trans-activation of virus transcription by macrophage produced factors and is an essential determinant of the tropism and expression of SRLV disease pathogenesis [4,37] (and references therein). In VMV, the trigger involves cellular factors binding to LTR enhancer sequence AP-1 while in CAEV, LTR activation may involve interaction of TNF alpha and interferon gamma with the U3 region of the viral LTR [4,37,50,56–60]. The host's genetic factors may regulate the extent of viral gene expression in tissue macrophages and thus the disease. Icelandic sheep are much more susceptible to central nervous system (CNS) visna virus disease than are British sheep while the Border Leicester sheep in the USA and the Texel sheep in Holland seem more susceptible to maedi form of disease [4]. The disease episodes occur in bouts. The latter and associated inflammation occurs at intervals of 6 months to 2 years and infected organs become chronically inflamed. In visna inflammation results in demyelination with sub acute meningitis and chronic paresis. In maedi, lung septa become infiltrated by lymphocytes, macrophages and smooth muscle becomes hypertrophic, dyspnoea results followed by death [61]. SRLVs interact with but do not infect T cells, infected animals remain immunocompetent throughout the infection and there is no T-cell depletion and immunodeficiency and virus persists despite virus-specific B and T cell immune responses. CAEV causes encephalitis of kids and chronic polyarthritis of adults. The latter is from fluid and lymphocyte exudation into the joint capsule [61].

2.2.2. Control

Work towards SRLV vaccine(s) has been ongoing in several laboratories since the 1980s but results have been somewhat disappointing. Various approaches have been tried including attenuated viral vaccines [62], vector vaccines [41]. Recombinant plasmid DNA encoding viral env with and without plasmids encoding cytokines

[63,64]. A proviral CAEV DNA vaccine lacking tat gene when given to goats initiated a persistent infection but conferred significant protection against challenge infection [65]. SRLV vaccines have occasionally caused increased viraemia and more severe disease [66–68]. The reason(s) for vaccine failure, poor efficacy and the increased disease in some instances remain obscure. An explanation may be stimulation defective T cell responses by the vaccines as suggested to occur during virus infection [54,55]. We believe understanding and countering the defective T cell responses in SRLV infections is important and it may lead eventually to effective vaccines. The only possible prophylactic measure is to raise new herds with virus-free animals and following validated management and containment protocols along with regular serological viral antibody testing [41]. However only a proportion of sero-positive animals develop the disease but all sero-positive animals including clinically unaffected animals are killed. This is done because infected animals without clinical signs are still a potential source of infection for naive animals.

2.3. Feline immunodeficiency virus (FIV)

2.3.1. Disease

FIV was first isolated in 1986 from a group of cats in California [69] and virus can be isolated from blood, serum, plasma, cerebrospinal fluid and saliva of infected cats [70,71]. Since the initial recognition nearly two and half decades ago, FIV is now recognised as an endemic pathogen in domestic cats worldwide [72]. Additionally, there is serological evidence of FIV infection of wild felids such as snow leopards, lions, tigers, jaguars and bobcats. Prevalence varies from 1% to up to 44% depending on the health status of the cat population in a region. Well kept household cats tend to be less prone to FIV infection as their interaction with stray cats is low and also the density of cats in a household is generally low. Sick cats tend to have higher prevalence of FIV [73]. Commonly FIV transmission is via virus shed in saliva, occurring between biting cats. Free ranging male cats that co-habit and interact aggressively with others are most commonly infected and form a source of FIV. Sexual contact does not appear to be a significant mode of virus transmission although the virus may be shed in semen; transmission via colostrum and milk can occur as well and also importantly FIV can be vertically transmitted in chronically infected cats [74]. FIV infection in cats has three stages, just like HIV infection in humans [75]. The initial acute stage is characterised by fever, swollen lymph nodes, oral, respiratory, eye and intestinal clinical signs which may be recurrent or chronic in occurrence [70]. This stage is also characterised by rapidly increasing viral loads, weight loss, lymphadenopathy and neutropenia. The initial burst of viraemia is associated with infection of CD4+ and CD8+ T lymphocytes [76,77] and a marked decline of CD4+ lymphocytes in circulation. At this stage virus is found throughout the lymphoid tissues, replicating in thymus, regional lymph nodes and mucosa-associated lymphoid tissues [77,78]. Virus may also be shed in saliva, milk/colostrum and vaginal secretions. Viraemic cats also respond by producing VN antibodies and cytotoxic T cells [79,80]. FIV preferentially infects CD4+CD25+ T cells expressing cell surface co-receptor CXCR4 and also transcription factors required for FIV replication; infection of these cells activates their immunosuppressive activity and the cells lose their effector functions and develop immunodeficiency [81,82]. The emergence of the viral immune response corresponds with a sharp decline in viraemia which defines the end of the acute infection. In the second latent stage, often lasting for years, the immune system is slowly destroyed leading to immunodeficiency followed by the third AIDS-like stage when affected cats may suffer weight loss, anaemia, leucopenia in combination with thymic depletion, progressively declining CD4+ T cell numbers and rapidly increasing viral loads.

2.3.2. Control

Although FIV is a cause of significant disease in domestic cats worldwide, immunoprophylaxis against FIV disease is limited. To our knowledge, only one vaccine company offers a vaccine, approved in spring 2002 but its uptake may be limited while others are reportedly in development [83]. The licensed vaccine is a dual subtype inactivated whole virus preparation consisting of subtype A and subtype D virus strains and has been shown to induce protective immunity against challenge with various homologous and heterologous (other subtypes) strains at various times after the last vaccination [84–88]. Although these studies, carried out by the vaccine manufacturer, demonstrated significant differences between vaccinated and control groups, the vaccine can however not protect all vaccinated cats from presence of proviral DNA in peripheral blood mononuclear cells (PBMC's) or from decreased CD4/CD8 ratios when challenged with a heterologous strain 12 months after vaccination [88]. However there have been other studies reporting no protection against more distantly related strains [89] or high challenge inocula [90]. Some FIV vaccines may increase the severity of infection as was the case with a FIV envelope DNA vaccine [91]. The protocols for the measurement of efficacy between studies have varied; a uniform scheme is desirable and one such scheme has been described [88]. Hence caution is necessary in comparing studies. Like its human counterpart namely HIV, FIV presents a formidable challenge for vaccine development despite a vigorous host immune response to the virus. Firstly since there are many variants of the virus endemic in different parts of the world and secondly since the emergence of mutated variants due to immune pressure/selection in individual infections appears to be the main obstacles against development of an effective vaccine that would protect against all emergent variants. Despite this difficulty efforts have been made for an effective vaccine [83,92–95]. At best these investigations were only partially protective despite induction of both cellular and humoral responses. An important point to consider here is that the challenge dose and the vaccine administration route mimic the field situation in the assessment of vaccine efficacy. Under natural conditions, the infection dose is most likely to be low. In support of this consideration, laboratory studies with an inactivated whole virus vaccine demonstrated lack of heterologous efficacy whereas field studies demonstrated efficacy in a two-year observation period [87,96]. This vaccine is only available in the USA, Australia and New Zealand. Vaccination of sero-positive cats is controversial and the risk-benefit analysis should be made on a case by case basis [73]. In other parts of the world where no vaccine is available, hygienic measures and regular serological testing should be performed to monitor viral incidence and prevalence. Sero-positive cats should be isolated and cats coming into a population should be quarantined [see 73 for more detailed recommendation]. Treatment of FIV infected cats with human anti HIV drugs like AZT or AMD3100 was found to be effective (see [73] for details).

2.4. Feline leukaemia virus (FeLV)

2.4.1. Disease

Members in the genus *Gammaretrovirus* (subfamily *Orthoretrovirinae*) are mainly associated with neoplastic diseases and are not a cause of significant immune-mediated pathology. However Feline leukaemia virus (FeLV) is an exception in that, since it causes B and T cell tumours and also a number of immune response mediated diseases. FeLV infection of cats may result in immune complex glomerulonephritis, autoimmune haemolytic anaemia, thrombocytopenia and chronic progressive polyarthritis [97,98]. FeLV is a leading killer of cats and its prevalence is significantly influenced by the cat population density, being high in multiple-cat households but low in individually kept cats [99] and susceptibility of cats to FeLV infection decreases with cat's age. Currently four

subgroups (A, B, C, and AC) exist based on virus envelope and virus neutralisation tests [99,100]. Cats become infected through close contact with other cats and ingestion of virus containing saliva during mutual grooming. Virus replicates in the oropharynx and then spreads via the agency of leukocyte-associated viraemia to most tissues of the body notably the bone marrow (B cells, monocytes and macrophages), thymus (T cells), salivary gland and reproductive organs [97–99,101]. In 30–40% of infected cats, primary oropharynx replication adequately stimulates host's immune system and the cats develop viral neutralising antibodies and cellular immunity which often leads to virus clearance [99]. Some 30–40% of infected cats however fail to mount an adequate protective immune response [99]. In the latter cats, virus localises to bone marrow where it replicates unabated in the cells of the immune system resulting in chronic viraemia and further virus dissemination to other tissues including the salivary gland. The chronically infected cats produce viral antibodies that do not aid in virus clearance but instead contribute towards pathology and the antibodies have been referred to as pathogenic antibodies. The chronically infected cats may develop various tumours of lymphoid cells while some also develop immunopathologic diseases and generalised immunosuppression. The latter stems from lysis of lymphoid cells including macrophages in various lymphoid organs namely thymus, spleen, and bone marrow while surviving lymphoid cells become dysfunctional. Such affected cats however also produce antibodies to viral antigens (gp70, P15E, P27, P15, and P10) which are continuously produced along with whole virions and feline oncornavirus cell membrane antigen (FOCMA) in tumour bearing cats [98]. The viral antibodies bind respective antigens and form small and medium-sized nephrotoxic circulating immune complexes [102–105]. This is a continuous process over a long period depleting circulating complement and consequently adversely affecting beneficial antiviral complement requiring functions of immune cytolysis and cytotoxicity. More persistently infected cats die of chronic immunosuppressive diseases than due to FeLV tumours.

2.4.2. Control

The observation that cats can recover naturally from FeLV infection led to development of subunit (envelop P45, gp 70, gp70+FOCMA), live canary pox-vectored and killed FeLV vaccines (see Table 2, [95]). Although FeLV is considered a non-core part of cat vaccines, in most circumstances FeLV immunisation should be part of the routine vaccination programme for pet cats. It should be realised that current FeLV vaccines are not fully protective in all vaccinated cats as vaccine efficacy is expressed as the preventable fraction of a vaccinated group compared to the controls [106–109]. Nevertheless, the protection they provide in the protected vaccinated groups is good against this potentially life threatening disease [99], especially in view of the risk of infection for an individually kept cat. There is an ongoing effort to develop improved vaccines, target being prevention of viraemia, latent bone marrow infection and formation of various tumours. A variety of approaches towards improved immunoprophylaxis have been undertaken with variable success [95]. Hygiene measures, preventing exposure of susceptible young cats to excreta of potentially FeLV infected cats, prevention of grooming and limiting cat population size, can also contribute to reducing the spread of the disease.

3. Parvoviruses

3.1. Disease

The family *Parvoviridae* includes important pathogens of cats, dogs, pigs, mink and geese. Virus neutralisation test distinguishes member species. Members have been the cause of disease and

deaths extending to other species such as racoons and pandas. Parvovirus pathology and disease stems from viral tropism for rapidly dividing cells of the enteric epithelium in the crypts of ileum, bone marrow and foetus. Virus transmission and infection is frequently via fomites since the members are extremely resistant to environmental inactivation. Primary virus replication may be in the mucosa of the buccal cavity. Primary replication is followed by viraemia and dissemination of progeny virus to target organs and then a second round of replication in target organs including in rapidly dividing enteric epithelium crypts and virus being shed in faeces which forms an important source of virus transmission. Parvovirus-mediated dysfunction of the immune system is not a significant contributor to disease due to cat, dog, pig, and goose parvoviruses. In cat secondary virus replication in bone marrow, lymph nodes and spleen may result in transient leucocytosis followed by a marked leucopenia and anaemia while in infected dog leucopenia may result. Of interest for the present review is an economically important common disease due to a parvovirus causing chronic infection and disease in farm raised minks, first recognised in 1956 in minks homozygous for the Aleutian (blue) gene and hence the name Aleutian disease (AD). It was subsequently found that other genetic types of mink could develop AD but infection of non-Aleutian mink is not uniformly persistent [110–112]. The causative parvovirus (ADV) also infects other mustelids particularly skunks and ferrets; in pet ferrets AD is an emerging disease and the virus appears to have adapted to the species and a strain of virus (the ADV-F) is only pathogenic in ferrets. In Aleutian mink and pet ferrets ADV usually causes persistent progressive immune complex disease [113]. Infection of newborn mink kits results in acute disease characterised by virus replication in type II pneumocytes in the lung. The replication is permissive and cytopathic, leading to fulminant interstitial pneumonia and fatal respiratory distress [114]. In adult mink, following primary infection progeny virus is disseminated by macrophages to liver, spleen, bone marrow and other lymphoid organs [115]. Here secondary virus replication cycles take place in B or pre-B lymphocytes [116–119]. This results in an uncontrolled polyclonal B and plasma cell proliferation in lymphoid and non-lymphoid tissues followed by a dramatic plasma cell lysis, hypergammaglobulinaemia, and immune complex (IC) disease. Virus replication occurs in the lymph node macrophages and is restricted to virus DNA replication, RNA transcription, protein synthesis and low level of progeny virus production [114]. A considerable proportion (up to 80%) of the globulin in diseased mink is against viral structural and non-structural proteins [120]. Antibody binding to virus facilitates the entry of the complex into macrophages via antibody binding to cellular Fc-receptors [121] and this mode of entry has been referred to as antibody enhancement of disease [114]. This mechanism and the role of enhancing antibodies in conjunction with macrophages and the Fc receptor has been known since the early 1980s particularly with dengue haemorrhagic fever and the dengue shock syndrome due to dengue virus and other viruses [122,123]. This enhancement effect is demonstrable in vitro with sub-neutralising concentrations of homotypic and heterotypic antibodies [122] and antibody is known to modulate antigens and may have a role in viral persistence [123]. Macrophages are the target cells for persistent ADV infection via antibody binding to the Fc receptors and may therefore play a role in the genesis of the immune disorder [124]. In other viral infections ligation of Fc receptors leads to the production of IL10 [125,126] a cytokine which has a role in suppressing interferon gamma production. Interferons are responsible for the antiviral state of cells. IL10 promotes both the induction of antibody responses and the suppression of cytotoxic T-cells [126]. Therefore these IL-10-mediated events may have a role in the pathogenesis of ADV [114]. Continuous formation of IC eventually results in glomerulonephritis, necrotising arteritis and iridocyclitis. ADV is

transmitted horizontally and vertically and disease takes several months to develop [127].

3.2. Control

At the present time we are not aware of a commercial ADV vaccine. There may be a justification on commercial basis for a vaccine since AD is an economically important disease [111] but it would appear that the task is a major challenge. Hence attempts towards a vaccine were unsuccessful, at best conferring partial protection [128] but vaccines employing ADV capsid proteins VP1 and 2 worsen the disease while vaccine based on non-structural NS1 gene only induced partial protection from disease [129]. A possible reason for ADV's whole capsid's failure to elicit a protective response may lie in the fact that the capsid has epitopes that have activities for both virus neutralisation and virus infectivity enhancement [124]. Consequently removal of the enhancement sequences could aid in performance of the neutralisation response and hence the antiviral effect. This may be somewhat simplistic since the capsid gene is suspected of having epitopes involved in disease [124]. Effective capsid based vaccines are for instance available against another mink parvovirus, Mink enteritis virus, which is not defective and closely related to Feline panleucopenia virus. As is the case for all parvoviruses ADV can persist for a long time in infected premises causing continuous outbreaks of disease. Strict hygiene measures and containment and disease monitoring protocols of the stock animals and strict export /import policy should help in reducing the risk of infection.

4. Paramyxoviruses

4.1. Disease

Members of the family *Paramyxoviridae* cause a wide range of diseases including Newcastle disease, distemper, rinderpest, and respiratory diseases of varying severity. Members evoke a good immune response and vaccination against their diseases has been largely successful. Pathology and disease due to adverse immune response is not a significant feature in infections by most paramyxoviruses except in some cases of infection by some morbilliviruses. Until 1988 the genus *Morbivirus* comprised Measles virus (MV), Canine distemper virus (CDV), Rinderpest virus (RPV) and Pestides-petitis ruminants virus (PPRV). Between 1988 and 1990 aquatic morbilliviruses emerged and were found to be responsible for a mass die-off and/or severe disease in harbour seals (*Phocine distemper virus*, PDV), porpoises and striped dolphins (*Cetacean morbillivirus*, CMV) in coastal waters of Northern and Mediterranean Europe [130]. Minor PDV outbreaks have also occurred in USA and Canadian Atlantic coastal waters. CDV, MV, PDV, and CMV, in addition to respiratory pneumonic and gastrointestinal lesions, also cause central nervous system (CNS) lesions. The main mode of CDV and MV transmission is via oro-nasal route which is also likely to be the mode of transmission of the aquatic counterparts (PDV, PMV, and DMV). As in CDV, the important determinant in pathogenesis and disease by these viruses is their tropism for leukocytes and immune cells in general [131–133]. As in CDV, the lymphotropism is likely to be mediated via viral H protein binding to signalling lymphocyte activation molecule (SLAM) [134] or equivalent. The expression of SLAM appears to be up regulated in response to CDV infection. SLAM is also expressed on antigen presenting cells and infection of these cells has been hypothesized to be associated with impaired antigen presentation [135]. CDV causes a systemic disease in dogs involving several organs often after aerosol infection and primary replication in the upper respiratory tract or tonsil or both associated with primary pyrexia

[136,137]. Uptake of virus by macrophages leads to infection of lymphocytes and macrophages and dissemination throughout the body. The leucotropism induces a leucopenia and lymphadenitis and secondary pyrexia. Leucopenia is a consequence of lysis of lymphocytes, mainly of the CD4+ T cells in blood, tonsils, thymus, spleen, lymph nodes, mucosal lymphoid tissues and macrophages. Another consequence of leucotropism is viraemia and progeny virus dissemination to intestines, CNS and other tissues and there is a widespread and rapid generalisation of virus infection within the body of the host if unchecked by the host's immune response; in some cases the immune response halts the virus spread and eliminates foci of infection and the lesions heal. Transmission of virus to: (i) bronchial, conjunctival and nasal epithelia and lung macrophages causes nasal and ocular discharges concurrent with bronchopneumonia and (ii) intestinal epithelium lymphoid tissues gives rise to vomiting and diarrhoea [136,137]. The mechanism of CDV transmission to CNS is poorly understood but two modes are considered likely. One route is leukocyte-associated haematogenous spread via the choroid plexus and cerebral blood vessels and the second via the olfactory nerve [138]. The CNS infection gives rise to inco-ordination, muscle tremors, myelitis, ataxia and seizures and other symptoms [139]. Relevant to present account is the lesions and disease due to deleterious immune response in infections by CDV and other animal morbilliviruses. Such lesions occur, albeit at low incidence, in CDV [140] and aquatic morbilliviruses [130] but the pathogenesis is intensively investigated as models towards a better understanding of multiple sclerosis (MS) [130]. In some dogs with acute distemper, immunosuppression occurs and such dogs are lymphopenic, have minimal or no viral neutralising antibodies and cell mediated activity; such dogs are poorly responsive to other antigenic stimuli [141]. Immunosuppression is suggested to arise from virus-mediated and virus-independent destruction of lymphocytes as well as impaired output of infected and uninfected lymphoid cells [133]. Perhaps of greater interest is the tissue damage in chronic CDV demyelinating encephalomyelitis [137]. A brief description of CNS organisation at this juncture may aid description of CDV CNS lesions. The CNS consists of neurones in the cortex/grey matter with their myelin-wrapped axons traversing the white matter made up of four types of CNS-function supportive neuroglial cells (ependymal cells, oligodendrocytes, microglia, and astrocytes). Oligodendrocytes form and maintain myelin sheaths, ependymal cells line the ventricles and their beating cilia circulate cerebrospinal fluid (CSF), microglia cells function as CNS macrophages while astrocytes provide nutrients, energy and electrolyte balance. Further details on CNS organisation can be found elsewhere [130]. The CDV demyelinating encephalomyelitis is a biphasic process consisting of an initial acute phase virus-mediated pathology [130,133,139] followed by chronic process mediated by immune response. The mechanisms leading to the CNS CDV lesions are complex and poorly understood [130,133,137,139]. The target cells for CDV in the brain white matter are astrocytes and microglia while oligodendrocytes appear to be rarely infected but only non-productively [139]. A common view at present for the acute phase CDV pathology is that the white matter infection leads to metabolic oligodendroglial changes culminating in demyelination [130]. As for the chronic phase demyelination, at least three mechanisms have been proposed [130,133]. A first theory suggests destruction of oligodendrocytes via bystander effect resulting from stimulation of microglia (CNS macrophages) by anti viral antibodies binding to virus infected cells in close proximity. The second theory proposes virus stimulated anti myelin antibodies as the cause of myelin destruction [130,142,143]. Thirdly, virus persistence and recurrent immune response and reaction have been suggested as a contributory factor in chronic phase demyelination [137] CNS lesions including myelin destruction has also been in infections by the aquatic morbilliviruses but the

available literature is somewhat limited [see 130]. Although CDV and MV CNS lesions have been a subject of intensive investigations, the causative pathogenesis mechanisms are not clearly understood and currently there is no general consensus as to the mechanism(s).

4.2. Control

CDV is a cause of fatal disease in many species of carnivores. CDV related viruses have been identified in seal, dolphins, whales and porpoises [144,145]. Currently available live CDV vaccines are suitable for immunising domestic dogs and mink [95]. A CDV vaccine based on Onderstepoort strain is safe and efficacious in lions [146]. In a first pilot study, the same vaccine seemed effective in otters and seals (MSD Animal Health, unpublished). Other companies also offer CDV vaccines [95]. However, the live vaccine safety concern and the global CDV distribution involving a wide variety of susceptible species, require new safe and effective vaccines for the protection of wild as well as domestic species along with CDV eradication. Most CDV vaccines contain live attenuated virus strain and the vaccine is given parenterally. The choice of live as opposed to a killed vaccine is probably because the strain is leucotropic and vaccine virus undergoes several rounds of replication in leukocytes without causing overt disease. An outcome of this is a rapid stimulation of immunity starting with a small amount of virus possibly of the order of 5–5.5 log₁₀ median tissue culture infectious dose per vaccine dose. For a killed vaccine several thousand fold more virus would be required to stimulate immunity with the help of an adjuvant and after booster vaccination.

5. Herpesviruses

5.1. Disease caused malignant catarrhal fever (MCF) virus

MCF is a fatal lymphoproliferative disease of cattle and other ungulates namely deer, bison and pigs caused by alcelaphine herpesvirus 1 (AIHV-1) and ovine herpesvirus 2 (OvHV-2) [147–150]. Other less characterised MCF gammaherpesviruses include hippotragine herpesvirus 1 [151], virus from white-tailed deer [152], caprine herpesvirus 2 (CapHV-2 [153–155]). An intriguing feature of MCF is that in the natural reservoir hosts, wildebeest for AIHV-1 and sheep for OvHV-2, respective viruses cause inapparent infection without disease and hosts shed virus in nasal mucus, tears and possibly other sites and form the source of virus transmission between individuals of reservoir hosts and from reservoir hosts to secondary susceptible hosts (cattle, bison and deer [156–159]). The secondary species are regarded as dead-end hosts as they apparently do not transmit virus to other susceptible secondary hosts [160]. Experimentally, transmission is possible with nasal mucus containing AIHV-1 [161] or OvHV-2 genome copies [162,163]. However exceptions have been recorded as was the case for deer [164]. The reservoir carrier hosts of MCF appear to govern the prevalence of MCF viruses. AIHV-1 is a particular problem where wildebeests are found namely Eastern and Southern Africa [156,160,165,166]. In a marked contrast, the sheep MCF virus (OvHV-2) since its first recognition in Europe has been the cause of MCF worldwide wherever sheep and cattle or bison or deer are present [160].

As for the pathogenesis of MCF in secondary host species due to AIHV-1, OvHV-2 and possibly other MCF viruses such as Hippotragine herpesvirus-1 (HipHV-1), the mechanism inducing mainly T cell hyperplasia and necrotic lesions is not fully understood [160,167–169]. MCF lesions are characterised by accumulation of mainly CD8+ T lymphocytes in various organs, often

associated with tissue necrosis [156,160,169]. The latter is suggested to arise from indiscriminate activity of MHC-unrestricted cytotoxic T/natural killer cells. Studies have been in cattle but mostly in rabbits [156,166–171]. Based on earlier findings of the paucity of virus infected cells [172,173] led to the suggestion that MCF necrotic lesions resulted from auto-immune response involving uninfected cytotoxic cells [167,168]. Subsequent *in situ* PCR study of vascular brain lesions in MCF affected cattle bison recorded a higher incidence of OvHV-2 infected CD8+ lymphocytes [169]. Preliminary unpublished *in situ* hybridisation analysis of various tissues from OvHV-2 infected rabbits also found viral gene sequences in many more lymphocytes [160]. These recent findings raise the possibility that the MCF lesions arise from the direct action of virus infected, dysregulated cytotoxic T cells. The invading CD8+ T lymphocytes in vascular lesions of American bison with experimental sheep-associated (SA-MCF) caused by OvHV-2 have been further defined [174]. This lymphocyte immunotyping study predominantly found CD8+/perforin+/wc- γ/δ and not CD8+ α/β cells. However the cytokine profiles of the invading T lymphocytes remains to be defined [174]. These authors concluded that the predominant CD8+ T lymphocytes invading vascular lesions of bison with SA-MCF are cytotoxic MHC-unrestricted lymphocytes of innate immune system and that MCF is essentially a disease of immune dysregulation. A new model for the pathogenesis of wildebeest-MCF in rabbits experimentally infected with AIHV-1 was proposed and it relies on the proliferation of dysregulated CD8- T cell as a result of their latent infection by the virus [175,176]. Still more work is needed, particularly definition of the phenotype of CD8+ T lymphocytes in MCF lesions in secondary hosts (cattle, bison and deer) with AIHV-1 and OvHV-2. Importantly, we are nowhere close to understanding the mechanism causing T cell hyperplasia in MCF.

5.2. Control

The fact that reservoir hosts and the secondary ruminant species develop antibody responses to MCF viruses [177,178] is indicative of immune recognition and therefore raises the possibility of immunoprophylaxis. Experimental live and killed AIHV-1 vaccines have been investigated in cattle or rabbits since early 1950s [179–184]. Findings from these studies were mixed comprising no protection, short-lived protection, partial protection and ambiguous results. No firm conclusion could be reached from these studies as to best formulation and vaccination/challenge regimes. We believe that MCF vaccine should aim to protect secondary hosts (cattle, bison and deer) from oro-nasal infection. A promising AIHV-1 vaccine study in cattle (OvHV-2 sero-negative) was reported recently [185]. The study analysed different vaccine formulations (live or killed with different adjuvants) and different challenge routes (intranasal or intravenous). The pre-titrated intranasal challenge inoculum was uniformly pathogenic and was significantly resisted by 9 of 10 calves twice vaccinated four weeks apart with live virus in Freund's adjuvant; killed virus in the adjuvant was unprotective. An important issue the study did not investigate was the vaccine's performance in calves with maternal viral antibodies. We suggest this, despite MCF being a sporadic disease with cattle generally dying within a short period of infection, to simply ascertain if vaccine takes in calves in face of maternal antibodies. There will be some calves with maternal MCFV antibodies and we maintain that it is important to ask if such animals are protected following intramuscular vaccination. A carefully planned and executed field trial is likely to address the efficacy to a natural challenge in calves without maternal antibodies and also calves with maternal viral antibodies.

6. Coronaviruses

6.1. Disease induced by feline infectious peritonitis virus

Feline coronaviruses (FCoV) occur as two serotypes with different serological and biological characteristics [186]. Most FCoVs cause mild enteric disease but could give rise to highly pathogenic variants in individual infections causing peritonitis (FIP). Both serotypes of FCoV mutate to virulent FIP virus (FIPV) variants. Their relative prevalence in nature of FCoV varies but serotype I FIPV and FCoV strains are dominant in the field [187]. FCoVs are transmitted via the faecal-oral route and virus's site of primary replication is gut enterocytes [188,189] from where the progeny virus disseminates to internal organs via monocyte-associated viraemia. Although FCoVs occur commonly the incidence of FIP disease is relatively low, rarely exceeding 5% of FCoV infected cats [188,189]. FIP is a progressive debilitating disease. A characteristic feature of FIP is widespread occurrence of pyogranulomatous lesions in lungs, liver, spleen, omentum and brain. Other features of FIP involve a marked T-cell depletion, particularly in end-stage FIP [190] and hypergammaglobulinemia [191]; B-cell leucopenia is also a feature in FIP [192]. The T-cell depletion is apparently not the result of virus infection since T-cells appear not to support virus replication [190]. Other important determinants in FIP pathogenesis seems to be (i) spread inside infected cat of mutant progeny FIPV by activated macrophages and monocytes [193] and (ii) types of viral S protein neutralising antibodies at suboptimal concentration which opsonise the virus and enhance its infectivity for target cells via FC receptor mediated attachment [194–196]. There is also complement activation with resultant platelet aggregation, intravascular coagulation, necrotising lesions and exudation of fluid into the abdomen and thoracic cavity in the so-called wet form of FIP. Wet FIP is most common in kittens under one year of age and the incidence declines by 5 year of age when dry form is more common. While there is no protective immunity in wet FIP, the dry form is a result of partial immunological protection [196,197]. Some of the pathogenic features of FIP, notably the T-cell lymphopenia, multiphasic disease course and virus persistence were seen in severe acute respiratory syndrome (SARS) corona virus cases. Both these diseases are an enigma possibly stemming from virus-induced immune dysregulation.

6.2. Control

Many attempts have been made to develop an FIP vaccine, most of which failed, with antibody-dependent enhancement of infection observed experimentally and resulting in more vaccinated than control cats developing FIP [195]. Currently, there is only one live temperature sensitive vaccine based on subtype II FCoV rather than on subtype I [198] licensed in some countries [199,200] but its efficacy has been a subject of debate [201,202]. A live attenuated oro-nasal experimental vaccine derived by site directed mutagenesis of a lethal FIPV strain to remove group specific gene cluster 3abc proved innocuous and efficacious [203]. Thus the outlook is promising for FIP disease should the 3abc deletion mutant or equivalent be licensed.

7. Examples of some lesser immunosuppressive viruses

Some viruses, to a varying degree, modulate the host's immune system for their own advantage; immunosuppression, often transient, is one consequence of an infection for instance. Upon gaining entry into host's body, viruses encounter dendritic cells (DCs) which are permissive to infection by some viruses and in some cases the encounter subverts normal DC function. The latter are

a heterogeneous collection of leukocytes broadly falling into two groups: conventional DC (cDC) and plasmacytoid DC (pDC, natural interferon producing cells) and are omnipresent in the body (in most organs, tissues and skin). DCs recognise and process invading pathogens and present their processed antigens to B and T lymphocytes and are therefore central to development of an effective immune response. The subversion of the normal immune response by viruses via action on DC is not known for many viruses as the field is quite new because dendritic cell markers of the various species are being characterised and antisera/reagents to them being raised but some examples exist [204]. Classical swine fever virus (CSFV), a pestivirus of pig, infects and replicates in pig DC cells when viral NP^{pro} protein inhibits dsRNA induced type I interferon synthesis [205]. This modulation of DC function and its possible role in CSFV leucopenia and haemorrhagic immunopathology see review by McCullough and others [204]. These authors also describe infection of pDC cells of pigs by porcine circovirus 2 and the resultant immunosuppressive effect.

7.1. African swine fever (ASF)

ASF is a highly contagious acute haemorrhagic disease of domestic pigs and also European wild boar (*Sus scrofa*) caused by a large double stranded DNA virus, an only member of Asfarviridae family (ASFV). Since the original description of ASF in Kenya in 1921 [206], the disease has been recorded in most African countries south of the Sahara and has spread to Portugal, Spain, Sardinia, the Caribbean (Cuba, Dominican Republic and Haiti), Brazil, west African countries and Madagascar). ASF has now moved into northern Asia and Russia and threatens China. This is an important extension of the disease. Field isolates range in virulence for the domestic pig from highly, moderately virulent to avirulent [207]. However in natural reservoir hosts namely warthogs (*Phacochoerus aethiopicus*), bush pigs (*Potamochoerus porcus*) and the soft ticks (*Ornithodoros moubata*) ASFV is not pathogenic but causes persistent infection with sufficiently high viraemia to allow vector bite transmission. Virulent and haemorrhagic domestic pig isolates are apathogenic in reservoir hosts. Domestic pigs primarily acquire ASFV via the bite of infected tick [208]. Other modes of ASFV transmission may also occur. An example is that of after a meal of infectious warthog tissues or whole infectious ticks [209]. Experimental oral infection with attenuated ASFV suspension was also recorded [210].

ASFV and poxviruses replicate in cell cytoplasm and are examples of DNA viruses that do not require the host RNA polymerase to transcribe their genes. An advantage this replication strategy bestows to the viruses is an ability to interfere with host cell gene transcription without affecting their own. An important determinant in ASFV pathogenesis is its tropism for macrophages in domestic pigs, warthogs and bush pigs. In domestic pigs the characteristic lesions are haemorrhages, leucopenia and apoptosis of lymphocytes in lymphoid tissues. In a study in domestic pigs, initial virus replication was detected in spleen and then in other organs [211]. Based on this study, it is likely that in natural infection following a bite, virus initially infects macrophages which then localise in lymphoid organs and progeny virus initiates secondary foci of infection. Another noteworthy observation is the occurrence of haemorrhages in lymphoid organs without obvious infection of endothelial cells; thus cause of ASFV haemorrhages remains unestablished [211]. Our understanding of ASFV infection in the reservoir hosts is limited and may differ from the pathogenesis in domestic pigs. In the former spleen appears to be the main site of virus replication while other lymphoid organs are minimally affected [212]. A significant difference in ASFV pathogenesis between domestic pigs and wild reservoir pigs is the massive apoptotic destruction of lymphocytes in the former but stimulation in the reservoir hosts. It is generally accepted that a

better understanding of lymphoid cell apoptosis and its regulation is required to aid planning of prophylactic control of ASF. ASFV modulates signalling pathways in infected macrophages, thus interfering with the expression of many immunomodulatory genes. For a detailed account and associated literature we direct interested readers to the review by Dixon and others [213]. The evasive mechanisms used by ASFV are complex and not fully understood [213]. ASFV A238L, a potent immunosuppressive protein, is considered to inhibit two key signalling pathways namely NFκB activation and calcineurin phosphatase in infected macrophages. This single protein may therefore inhibit transcription of many immunomodulatory genes and pathways and thus interfere with initiation of both the innate and the adaptive immune responses. It is now generally accepted that the massive apoptosis of B and T lymphocytes in domestic pig infection by hot ASFV isolates, is not due to virus infection of lymphocytes and it is a result of some unknown by-stander mechanism generated by macrophages [211,213,214]. There are other viral proteins that modulate macrophage function in order to evade host defences [213].

At present there is no vaccine for ASF. Observations of a protective immune response support the view that a vaccine is possible. These observations are: (i) the resistance of natural reservoir porcine hosts, (ii) domestic pigs subsequent to attenuated ASFV infection resist virulent ASFV challenge [215–217] and (iii) experimental subunit vaccine studies [218,219]. ASFV vaccine studies have focused on the identification of the protective immune response of the pig; ASFV neutralising antibodies to viral structural proteins P30, P54, and P72 were not protective [220] but a previous study with P30 and P54 recorded protection [219]. An in vivo CD8⁺ T lymphocyte depletion study in out bred pigs concluded that secondary viral antibodies did not contribute towards protection against virulent challenge [217]. Instead, these authors recorded a significant protective role for CD8⁺ T lymphocytes but the subset of the cytotoxic T cell remains to be identified [217].

7.2. Bovine viral diarrhoea virus (BVDV)

BVDV in genus *Pestivirus* within the family *Flaviviridae* is a common acute infection of cattle with a high prevalence (60–80%) globally but infection in cattle is generally inapparent, transient signs being pyrexia and a leucopenia 3–7 days post infection. Other pestiviruses are classical swine fever virus, border disease virus and a forth distinct species, BVDV-2 [221]. BVDV-1 species has at least 5 serologically distinct subspecies, 1a–1e which appears to vary in their geographical prevalence. The BVDV-2 viruses are largely restricted to the USA with some European isolations. The original description of BVDV disease was of transmissible profuse diarrhoea in adult cattle [222]. Although in most instances BVDV infection of barren adult cattle is mild and inapparent, cases of severe fatal disease have been described [223,224]. BVDV isolates occur as two distinct biotypes, non-cytopathic (NCPV) and cytopathic (CPV), if their growth in cell cultures results in death (CPV) or no death (NCPV) of infected virus producing cells. In nature, NCPV biotype predominates (mainly in persistently infected calves and adult cattle) and thereafter gives rise to CPV biotype through a variety of spontaneous mutations (insertion of host protein sequences, duplication of viral genes or point mutations). The latter results in cleavage of non-structural NS2-3 protein and expression of NS3.

The important aspect of BVDV infection of cattle, both epidemiologically and from the prospective of reproductive loss, is virus's ability to cross the placenta and infect the foetus. BVDV rarely infects the foetuses of sero-positive cattle. In acutely or persistently (see below) infected sero-negative cattle, virus invades the placentome replicating in the trophoblast damaging it and may cause placentitis. Then virus crosses to the foetus. How the latter occurs is unclear but ingestion of maternal cellular debris by foetal

trophoblast is a likely mechanism. An outcome of foetal infection is abortion which may occur as early as 10 days to several months after infection although NCPV viraemia is established 1–2 days following in-contact natural infection [225]. About up to 30% of foetuses are aborted while the majority of surviving foetuses go to full term and are born persistently infected (PI) with lifelong viraemia. Foetal infection is by NCPV; experimental *in utero* infection with CPV does not cause abortion or PI calves. Most foetuses born of PI dams are also PI and this near 100% vertical transmission from dam to foetus is the main mode of BVDV survival in the field. Thus PI calves and adult cattle readily infect susceptible cattle upon close contact via virus aerosol. This in sero-negative cattle results in infection of the upper respiratory tract (URT) and associated lymphoid tissues followed by leukocyte and serum viraemia while transmission to sero-positive cattle is limited to URT with no or transient leukocyte viraemia [225]. The other important clinical consequence of BVDV is mucosal disease (MD). This fatal condition of cattle, first described in 1953, is characterised by severe erosive lesions of the oral and intestinal mucosa [226] was not attributed to BVDV at its first recognition. It was several decades before the aetiology of MD was identified as due to BVDV and the causative MD pathogenesis established. The generally accepted premise leading to MD lesion is transplacentally infected PI calves with lifelong persistent NCPV viraemia upon super infection by a 'homologous' CPV develops MD [227]. Another clinical effect of BVDV infection is transient leucopenia and immunosuppression which may allow infection by other bovine pathogens.

Acute BVDV infections are always accompanied by immune suppression due, at least in part, to the death of immune cells within lymph nodes and gut-associated lymphoid tissue and reduction of numbers of circulating white blood cells. The suppression of the immune system leaves infected animals vulnerable to secondary infections [228]. A number of studies have demonstrated a synergistic role of BVDV in bovine respiratory disease by increasing pathogenicity of both viral and bacterial concomitant infection; this has been attributed to immunosuppressive effects of BVDV on the host [229]. There is evidence that cattle with persistent and primary postnatal infections with BVDV undergo immunosuppression, which increases the susceptibility of these animals to secondary infection [230].

However the economic impact of BVDV immunosuppression and co-infection by other bovine viruses and bacteria is not fully assessed. Also the mechanism causing lymphocyte death and leucopenia due to NCPV biotype of BVDV has to our knowledge not been reported but that hypothesized for CSFV may also apply to BVDV [204]. This aside, BVDV is an important bovine pathogen primarily due to the reproductive loss to the cattle industry and hence there is much interest and the need for vaccines against BVDV diseases, particularly prevention of transplacental infection. Vaccines are available and work is ongoing towards better vaccines, a subject recently reviewed by us [231,232].

7.3. Bovine leukaemia virus (BLV)

BLV in genus *Deltaretrovirus* of family *Retroviridae* causes persistent infection of cattle worldwide; currently 7 virus strains (envelope gene genotypes) are prevalent and sheep are also susceptible to the virus. BLV transmission in cattle occurs horizontally via contact, insect bite (mechanically), blood transfusion, contaminated needles; virus is shed in milk and colostrum but we are not aware if they are a source of transmission or not. BLV infection of cattle results in asymptomatic carrier state (in about 60% of cattle), a benign polyclonal proliferation of circulating lymphocytes known as persistent lymphocytosis (PL, in about 30% of cattle) or fatal, monoclonal lymphoid neoplasia known as enzootic bovine leukosis (EBL, in about 5% of cattle). Irrespective of clinical outcome,

the virus exists as provirus (integrated but not transcribed) in the genome of lymphocytes [233]. Infected cattle mount a high-titred antibody response against viral structural proteins and antibody tests have been a common means of BLV detection which is now increasingly backed up with virus gene PCR tests. With respect to effect on the host's immune function, BLV, unlike other mammalian retroviruses, appears to have a minimal effect. However some BLV virologists have concluded that BLV infection in cattle and sheep does not result in a significant immunosuppression [234,235].

8. Final comments

A noteworthy feature in the pathogenesis of the selected viral immunodiseases described here is the variation in the tropism of the viruses for the immune cell types and the mechanisms viruses use to suppress and/or subvert host's immune antiviral response. Examples for instance involve disruption of normal effector function of macrophages, B lymphocytes, CD4+ T lymphocyte, CD8+ T lymphocytes and dendritic cells. In almost all of the diseases the immunity disruptive mechanisms are not fully understood.

8.1. Tropism for cells of monocyte/macrophage lineage

EIAV, SRLV, FIPV, ADV and ASFV infect and persist in cells of monocyte/macrophage lineage; in domestic pig, ASFV causes an acute infection but virus persists subclinically in the natural reservoir hosts namely bush pigs, warthogs and ticks. Interestingly, the latter namely acute disease in the secondary host but persistent, subclinical infection in the reservoir hosts is also the case for T lymphocyte-tropic MCF viruses. In all five viral diseases there is virus-mediated immune evasion via disruption of macrophage function possibly involving different mechanisms. In four (EIAV, SRLV, FIPV and ADV) infection is chronic despite a strong humoral and cellular immune response. The two SRLVs elicit significantly different antibody responses [4] (and references therein). CAEV is intrinsically poor inducer of VN antibodies and goats with persistent CAEV infection produce antibodies to all viral proteins but non-neutralising whereas VMV induces VN antibodies which give rise to mutant viral strains during the persistent infection [4] (and references therein). The viral long terminal repeat (LTR) region contains sequences for transcription initiation and mRNA capping sequences important in the regulation and control of viral mRNA synthesis. For VMV at least, the trigger involves cellular factors binding to AP-1 promoter while in CAEV, LTR activation may involve interaction of TNF alpha and interferon gamma with the U3 region of the viral LTR [4,37,50,56–60]. In VMV CD4+ T cells are required to establish infection in macrophages but not in dendritic cells [55]. The LTRs have been shown to be important in determining cell tropism and pathogenic phenotype of EIAV and the virus acquires env and LTR mutations during persistent infection *in vivo* [12,236,237]. Sheep's dendritic cells become productively infected following subcutaneous plus intradermal inoculation with VMV [49]. The role of dendritic cells in SRLV disease remains poorly investigated due to the lack of markers for ovine dendritic cell [49]. This would seem to be an important shortcoming in view of their central role in antigen presentation and the initiation of the immune response. Modulation of dendritic cell by viruses is at an early stage of investigation because of the lack of markers and reagents for dendritic cells generally. We however expect increased interest and progress in the understanding of disease pathogenesis as markers for dendritic cells are identified for the various species and antibodies raised against them. The switching over of latent to productive cycle of SRLV infection in monocyte/macrophage is analogous to the situation in HIV/SIV infection of T lymphocytes namely latently infected lymphocytes must be activated by cellular factors to induce productive virus infection [238].

Antibody-mediated enhancement infection of macrophages via Fc receptor binding has also been recorded for HIV [239]. In contrast to the lentiviruses, ASFV modulates signalling pathways in infected macrophages of domestic pigs through the agency of immunosuppressive proteins [213].

8.2. Viral immune complex disease and pathogenic antibodies

In EIAV, VMV, ADV and FIPV there is, as a consequence of the persistent monocyte and macrophage infection, the emergence of viral variants which the immune response fails to clear [4] (and 26–30 (EIAV) and 33–34 (SRLV)). In visna/maedi SRLV disease induction of CD8+ T lymphocytes in a defective maturation state (expressing MHC class II DR and DQ molecules but not interleukin-2 receptors) and hence lack lymphoproliferative and cytolytic activities as also observed in infections by primate T lymphocyte-tropic viruses (HIV and SIV) [54] merits further investigation; CD4+ T lymphocytes in SRLV infected hosts also appear to be defective [55]. In monocyte, SRLV infection is latent in that there is no virus transcription and the infected monocyte is neither killed by the virus nor by the host's immune response. SRLVs do not infect T cells and there is no T cell depletion and immunodeficiency. The strong immune responses in both persistent FIPV and ADV diseases are also defective in that infection is not cleared but instead antibody opsonises the virus and the complexes (IC) bind to uninfected monocyte/macrophages via the cellular Fc receptor and initiate replication adding to the virus burden of the host. In all four viral infections there is chronic antigenic stimulation and an ineffective immune response by the host. This ongoing scenario results in deposition of IC in various tissues, inflammation and activation of complement. For SRLVs an important distinction is the lack of VN antibodies in persistent CAEV infection of goats whereas sheep with persistent VMV infection produce VN antibodies and result in emergence of mutant viruses not efficiently removed by the prevalent VN antibodies. Notwithstanding this difference, in both cases infectious virus is opsonised to be taken up by and infecting further macrophages via the Fc receptor binding. Ineffective antibodies and IC formation is also a feature in chronic infection of cats by FeLV which infect B and T lymphocyte as well as monocytes/macrophages and virus also causes other immune pathology. In all cases there is widespread inflammation in many tissues along with exudation of fluid. In chronically FeLV infected cats, viral antibodies, the so-called pathogenic antibodies, do not aid virus clearance but instead contribute towards pathology.

8.3. Virus dissemination

The progeny virus produced by infected macrophages is the main mode of virus dissemination to target tissues in infections by EIAV, SRLVs, FIPV, ADV and AFSV; dendritic cells in VMV may also be important.

Viral tropism for both the macrophage and lymphocyte is important in diseases due to CDV and FeLV. This is with respect to establishing the infection following the oro-nasal exposure, primary replication in the respiratory tract including the macrophages, then infection of lymphocytes followed by virus dissemination to target tissues by mobile infected macrophages and lymphocytes. CDV infection of dogs often results in multi-organ diseases including the brain but relevant for the present account is the myelin destruction in the brain (see Section 8.5 below). In FeLV disease, effects of infection of bone marrow macrophages and B lymphocytes, thymus T cells, in chronically infected cats is immunosuppression, immunodeficiency, dysfunctional lymphoid cells resulting in abnormal humoral, cellular and phagocytic immunity; viral antibodies in such cats do not aid in virus clearance but instead contribute towards pathology and have therefore been

called pathogenic antibodies and are a cause of nephrotoxic IC lesions, complement activation and depletion.

8.4. Lymphocyte-tropic viruses

The lymphocyte-tropic viruses causing immune pathology include FIV, BLV, BVDV and MCFV. The pathology due to FIV and the disease pathogenesis is similar to other T cell tropic lentiviruses (HIV/AIDS and SIV). In vivo, FIV infects CD4+ and CD8+ lymphocytes causing a persistent infection, leucopenia (depletion of CD4+ and CD8+ T lymphocytes) and immunodeficiency due to disrupted T cell effector functions but mechanisms involved remain to be fully elucidated. The mechanisms causing transient immunosuppression and lymphocyte killing and leucopenia (decrease in numbers of T and B lymphocytes and neutrophils) in BVDV infection of cattle have to our knowledge not been reported and it is possible that BVDV, like the related CSFV [204] infects and replicates in dendritic cell and causes leucopenia [204]. BLV infection of lymphocytes may result in a carrier state or neoplasia or persistent lymphocytosis. Upon infection there is an immune response to BLV structural proteins. However the opinion is divided regarding the effect of BLV infection on host's immune response. The MCF viruses of AIHV-1 and OvHV-2 cause subclinical, persistent infection in the natural reservoir hosts, wildebeest and sheep respectively but trigger a severe and generally a fatal lymphoproliferative systemic disease in secondary hosts such as cattle, bison, pigs and various species of deer [147–153,160]. In the secondary hosts the immunotype of T lymphocyte that infiltrate the lesions (lymphoproliferation, lymphocytic vasculitis and mucosal ulceration) still remains undefined. The most recent immunotyping data of vascular lesions from bison with sheep-associated OvHV-2 MCF have concluded that the predominant CD8+ T cells in these lesions were cytotoxic, MHC-unrestricted lymphocytes of the innate immune system and not CD8+ $\alpha\beta$ T cells but the cytokine profiles of these invading cells remains to be defined [174]. These authors further conclude that MCF is essentially a disease of immune dysregulation. However the causative mechanism remains to be defined and so is the immunotypes of T cells in MCF lesions in cattle, bison and deer due to AIHV-1 and OvHV-2 in cattle and deer.

An interesting, much studied lesion in acute ASFV disease in domestic pig is the massive apoptotic destruction of B and T lymphocytes which is in a marked contrast to the situation in the reservoir host namely the bush pig. The apoptotic damage of lymphocytes in domestic pigs due to ASFV infection is currently and generally accepted to result from some unknown by-stander mechanism (see Section 8.5 below).

8.5. By-stander damage and demyelination

For CDV demyelination there is no general consensus regarding the exact causative mechanism for the lesion as is also the case for measles virus demyelination in human infections. However ideas put forward comprise: (i) virus infection mediated metabolic disruption of white matter cells; (ii) antiviral inflammatory and T cell cytotoxicity triggering a by-stander damage; (iii) virus-induced autoimmunity and; (iv) viral persistence and recurrent immune activation/responses resulting in damage. Although CTL killing is a specific and often a directed response, the release of cytotoxic molecules and cytokines such as tumour necrosis factor, particularly at the peak of immune response, when CTL numbers can reach high levels, may result in by-stander killing of uninfected cells. This may be relevant in CDV demyelination and possibly in ASFV apoptosis of lymphocytes in domestic pigs. Demyelination has been described in visna/maedi disease. Once more, chronic stimulation of the immune system in VMV infection may cause the myelin destruction via a bystander mechanism.

8.6. Immunoprophylaxis

The prospects of vaccines against some of the diseases described above remain distant at present; some EIAV, SRLV and FIV vaccines have caused increased immune pathology. Hence these diseases pose a major challenge for vaccine development. Notwithstanding the difficulties, we believe a better understanding of the aberrant defective immune responses of the diseases described here may aid in the development of effective vaccines.

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