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REVIEW ARTICLE

Viral Infections in Domestic Animals as Models for Studies of Viral Immunology and Pathogenesis

BY H. BIELEFELDT OHMANN*† AND L. A. BABIUK
Department of Veterinary Microbiology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 0W0

INTRODUCTION

The interactions between viruses and the host immune system involve a complex series of events which often lead to activation of the immune response and clearance of the infectious agent. Alternatively, viruses can adversely affect the immune system resulting in chronic or persistent infections or immunopathology. The majority of information regarding viral infection and the host response to such infections has been obtained from laboratory animal models. Although these laboratory models have been very useful in helping us understand many virus–host interactions, they do have some limitations which natural animal models may overcome. The present review will attempt to focus on a few isolated animal models not often considered, as well as to review the most recent information regarding some viral diseases of domestic animals previously recognized as useful (Table 1). Using these models, we hope to focus on questions pertinent to how viruses may evade the immune response, resulting in viral persistence and immunopathology or cause immunosuppression, and demonstrate the value of these natural animal models in aiding the elucidation of virus–host interactions. In each of the instances attempts will be made at demonstrating the usefulness of these models for comparative studies.

Virus persistence

Congenital infection

A major challenge to the student of viral immunology and immunopathology is the disease complex caused by pestiviruses. Even though only one similar human disease is caused by a non-arthropod-borne togavirus, i.e. congenital rubella, the complex appears to present so many challenges to the general understanding of virus–cell and virus–host interactions that it deserves attention beyond the narrow field of veterinary medicine (Porter, 1971).

The genus Pestivirus comprises bovine viral diarrhoea virus (BVDV, also known as mucosal disease virus), hog cholera virus (HCV, synonym: classical or European swine fever) and border disease virus (BDV, synonym: hairy shaker disease virus), and constitute in conjunction with rubella virus (RV), equine arteritis virus and lactic dehydrogenase-elevating virus the ‘non-arbo’ togaviruses (Porterfield et al., 1978; Horzinek, 1981). A common feature of BVDV, BDV and HCV is their ability to cause acute, chronic or clinically inapparent infections in their respective hosts with similar clinical, pathological and immunological manifestations (Stober, 1984; van Oirschot, 1980; Barlow et al., 1983; Bielefeldt Ohmann, 1981). All three viruses, like RV, are capable of causing a wide variety of congenital abnormalities including abortion, stillbirth, intrauterine growth retardation and selective organ stunting, cerebral and cerebellar malformations (including hypoplasia, dysmyelination, skeletal defects and skin abnormalities; for reviews, see van Oirschot, 1983; also Barlow et al., 1979; Bielefeldt Ohmann, 1984). In addition, BVDV and RV can cause chorioretinopathy and cataracts (Bielefeldt Ohmann, 1984; Forrest & Menser, 1975; Dudgeon, 1976). Generally, multiple defects are present, but clinically

†Present address: Department of Veterinary Virology and Immunology, The Royal Veterinary and Agricultural University, 13 Bulowsvej, DK-1870 Copenhagen V, Denmark.
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Inapparent persistently infected individuals may also be born. They may remain clinically normal throughout life, or they may with time (weeks, months or years later) develop a clinical, inevitably fatal syndrome (BVDV, HCV, BDV), or other long-term sequelae including progressive panencephalitis (RV) (for review, see van Oirschot, 1983). Factors determining the outcome of a congenital infection include (i) the stage of foetal development at the time of infection, including both organogenetic and immunological aspects (Mims, 1968), (ii) virus strain (McClurkin et al., 1984; Barlow et al., 1979; Vantsis et al., 1980; Done et al., 1980; Brown et al., 1973, 1974; van Oirschot, 1980; Bielefeldt Ohmann, 1981) and (iii) host genotype (Barlow et al., 1979, 1980). The latter phenomenon has also been inferred to influence the outcome of RV infections in humans (Honeyman et al., 1975).

The teratological mechanisms involved in congenital infections with pestiviruses appear to be a neglected field of research (Derbyshire & Barlow, 1976; Barlow & Storey, 1977). More information is available for RV despite the necessary (for ethical reasons) limitations to in vitro studies and studies on aborted foetuses (examples: Plotkin et al., 1965; Rawls & Melnick, 1966; Tondury & Smith, 1966). Virus-induced congenital malformations and lesions are fraught with
pathogenic possibilities; thus, these naturally occurring infections in easily assessible species lend themselves as obvious tools for studies in teratology that have immediate relevance to both animal and human viral infections.

Of even greater interest are the disease manifestations encountered later on in postnatal life, notably in persistently viraemic animals lacking evidence of a virus-specific humoral immune response. In cattle, in which the relation between virus persistence and a clinical syndrome was first noted (Liess et al., 1974), the disease has long been known as mucosal disease (MD) (Ramsey & Chivers, 1953). Typically it is seen in animals 6 to 18 months old, often occurring in isolated cases (1 to 5%) in herds which generally contain a high percentage of BVDV-seropositive animals. Another characteristic feature is that within a particular affected herd, clinically acute MD is often seen in the same age group of animals. The course is acute, usually with a fatal outcome within 5 to 7 days. The animals show intercurrent fever and develop severe ulcerative lesions of the mucosa of the entire digestive tract. This is associated with a profuse watery diarrhoea, often mixed with blood and fibrin. Furthermore, dermatosis becomes evident (Pritchard, 1963; Bielefeldt Ohmann, 1981). In addition to the gross and histopathological lesions related to the above-mentioned signs, the most significant findings are severe atrophy of the thymus, depletion of lymphocytes in T cell-dependent areas in the peripheral lymphoid tissues, and fibroid replacement of cells in germinal centres (Bielefeldt Ohmann, 1981, 1983). The virus can be isolated from blood and most tissues. The animals thus affected invariably lack neutralizing antibodies to BVDV. In recent years another course of MD has been recognized. The opinion has been that the disease might have changed over the years, towards a less classical symptomatology; however, it is more likely that improved diagnostic procedures have led to the aetiological identification of previously unrecognized conditions (Horzinek, 1981; Stober, 1984). It affects cattle from 0.5 to 3 years of age, with a low incidence in affected herds similar to that seen with 'classical' acute MD. Animals become, over a course of weeks to months, emaciated with intermittent, exacerbated diarrhoea. Gross necrotic erosive lesions of the mucosa and dermatosis may be absent or insignificant, but histopathologically moderate changes are usually present, as are changes in the lymphoid tissues (atrophy and cell depletion) (Bielefeldt Ohmann, 1981). Virus can be isolated from blood and tissues before and during the prolonged clinical course. Nevertheless, neutralizing BVDV-specific antibodies are not detectable.

A syndrome very similar to the chronic 'atypical' MD has now also been recognized in pigs (van Oirschot, 1980). This disease appears to be a consequence of an intrauterine infection of pregnant pigs with low-virulent HCV in mid-gestation (natural or experimental). The piglets born to these dams develop a runting-like syndrome at approximately 4 months of age. They become emaciated, develop conjunctivitis, dermatitis and locomotory disturbances, eventually leading to posterior lameness. Thymus atrophy and lymph node swelling are the most prominent pathological findings (van Oirschot, 1980). The pigs are viraemic from birth and fail to respond specifically to HCV after disappearance of maternal antibodies (van Oirschot, 1980, 1983).

Lambs that recover from typical congenital BD, i.e. hairy shaker disease in the postnatal period, may later in life develop intractable diarrhoea or respiratory distress and die. The clinical signs and pathological changes resemble those seen in MD-affected calves (Barlow et al., 1983). Moreover, affected sheep remain persistent virus excreters from birth and only rarely produce BD-specific neutralizing antibody (Barlow et al., 1983; Gardiner et al., 1983).

The common mechanism for viral persistence in cattle, sheep and pigs without development of antibody to the virus, has been suggested to occur as a result of congenital infection early in gestation, resulting in immunotolerance (Kendrick, 1971; Liess et al., 1974). However, the events that precipitated the disease in these immunotolerant animals remain an enigma. Recently, it was demonstrated that immunotolerant, persistently infected offspring could be produced experimentally by infecting the bovine foetus between days 40 and 125 of gestation (McClurkin et al., 1984). Similar results were obtained in sheep with BDV (Terpstra, 1981) and in pigs with HCV (van Oirschot, 1980). One difference is that the persistently infected pigs inevitably develop disease, whereas sheep and cattle can remain clinically normal throughout life (Terpstra, 1981; Coria & McClurkin, 1978; McClurkin et al., 1984; Liess et al., 1983).
Several theories have been proposed to explain the events which may precipitate the disease in some of these persistently infected animals. One possibility is that re-infection with the homologous virus strain to which the animal is tolerant (Barlow et al., 1983; Gardiner et al., 1983; Steck et al., 1980), a heterologous strain (Brownlie et al., 1984; Liess et al., 1983), or hormonal changes associated with puberty (Roeder & Drew, 1984) can induce clinical disease. However, several paradoxes have to be resolved. Persistently infected animals of all three species are immunocompetent, as evidenced by the presence of normal humoral and cellular responses to other microbial as well as inert antigens (Terpstra, 1981; van Oirschot, 1980; Steck et al., 1980; Liess et al., 1983; McClurkin et al., 1984). Furthermore, persistently infected cattle may develop a good antibody titre to a BVDV vaccine strain, but nevertheless die from acute or chronic MD (Steck et al., 1980; Liess et al., 1983), suggesting that tolerance is restricted to epitopes on the particular virus strain, or closely related strains, that caused in utero infection. Likewise, BDV-infected sheep may respond to BVDV (cross-reacting antibodies) or to a heterologous strain of BDV (Vantsis et al., 1980). Some sheep can, however, develop strain-specific antibodies later in life (Gardiner et al., 1983; Terpstra, 1981; Westbury et al., 1979). This suggests that the unresponsiveness of the immune system (tolerance) to specific epitopes is neither absolute nor invariably permanent, and consequently not the result of a clonal deletion of virus-reactive cells (Oldstone, 1979). However, until it is known which specific epitopes are involved in immunotolerance and which are involved in protection, and whether these are common epitopes among virus strains, it will not be possible to draw any major conclusions as to how immunotolerance to specific epitopes is established.

Unfortunately, the difficulties encountered in the study of the molecular structure and biology of pestiviruses may continue to hamper our efforts in this regard. Thus, they remain among the least characterized of animal viruses. In cell cultures the yields of pestiviruses are usually low, the macromolecular synthesis of the host cell is not shut off, and virus purification is difficult since they appear to remain intimately associated with host cell membrane components. Host cell-controlled modifications of the virion occur in cell culture systems, as demonstrated by changes in virion densities (Laude, 1979), are also likely to take place in vivo. This latter aspect will certainly hamper studies of serological similarity and diversity among strains of a particular virus, and among BVDV, HCV and BDV (Horzinek, 1981). Thus, it seems unlikely that a resolution of virus–host interactions can be obtained unless the biology of the pestiviruses is better understood, and the first objective in pestivirus research should perhaps be in this area. The development of specific monoclonal antibodies would be a definite asset with respect to identification of the important epitopes on the virus and their relationships among different isolates as well as the modifications caused by the host cell. This would help to establish whether the strains that induce disease in immunotolerant animals are indeed different from the persistent virus acquired in utero, as well as which epitopes are important in providing protection. Thus, these virus infections provide a unique, challenging model for the understanding of viral persistence following congenital infection and hopefully will allow us to ‘break’ tolerance to the appropriate epitopes and thereby lead to virus clearance.

**Role of the macrophage in virus persistence**

The mononuclear phagocytic system (MPS) (van Furth et al., 1972) is considered to be one of the primary non-specific defence mechanisms against foreign agents, including viruses. In addition, it is involved in induction, regulation and amplification of the immune system, thus playing a central role in eliminating viruses. Extensive evidence supporting the importance of the MPS in resistance to viral infections has recently been reviewed (Morahan et al., 1985) and will not be reiterated here. However, in addition to playing a role in eliminating viruses from the host, cells of the MPS can also play a major role in viral persistence.

A number of viral diseases of domestic animals have in common an established or conjectural predilection for the MPS wherein virus replication, persistence and spread in the host occurs as a consequence of infection of these cells. Viruses capable of MPS infection are found in several different virus groups (Table 1).

Visna–maedi viruses (VMV) are the classical examples of conventional viruses capable of
causing slow virus disease (Gudnadottir, 1974; Sigurdsson, 1954). In addition, lentiviruses include progressive pneumonia virus (PPV) initially isolated from sheep in North America (Kennedy et al., 1968) and caprine arthritis–encephalitis virus (CAEV) (Crawford et al., 1980). The disease complex induced by these viruses includes progressive leukoencephalitis (visna), progressive pneumonia (maedi), chronic arthritis and mastitis. The lesions induced by PPV/VMV and CAEV have the same types of cellular infiltrates and progression although the organ distribution is frequently different. Whether this is due to differences in tissue tropism of the various virus strains or to host-related factors, or both, remains to be investigated. Nevertheless, in both natural and experimental infections with PPV and CAEV, the lesions are often indistinguishable (Oliver et al., 1981 a, b; Banks et al., 1983; Querat et al., 1984). Caprine arthritis has recently received much attention as a natural model for chronic connective tissue disease and a possible correlate to rheumatoid arthritis in man (Cork & Narayan, 1980; Adams et al., 1980; McGuire, 1984). Several excellent reviews regarding immunopathological aspects of these infections as well as of equine infectious anaemia are available (Crawford et al., 1978; Gudnadottir, 1974; Henson & McGuire, 1974; McGuire, 1984; McGuire & Crawford, 1979; Stroop & Baringer, 1982; Thormar et al., 1974). Therefore, only a brief account of the diseases will be given, highlighting some of the most recent findings and their implications with respect to their potential use as models for helping understand a number of immunopathological events.

One central question is how these viruses persist in the host in the face of a very active immune response. Another, and closely related, question concerns the identity of the host cell involved in viral persistence. Not surprisingly the monocyte–macrophage (Mφ) series has been implicated in the pathogenesis of these retrovirus infections, because viral antigens and/or virus replication can be detected in this population of cells in the infected animals and, furthermore, Mφ readily support viral replication in vitro (Adams et al., 1980; Anderson et al., 1983; Henson & McGuire, 1974; Kleijver-Anderson & Anderson, 1982; Narayan et al., 1982, 1983). However, neither the exact role of the Mφ in viral persistence nor the specific subpopulation of the MPS allowing virus replication is well characterized in most instances. In blood, only a minor fraction of the monocytes appear to be infected with CAEV or VMV, and the infection does not appear to be productive until after the cells differentiate and mature (Narayan et al., 1983). In addition to acting as a depot for virus replication Mφ may also be important in inducing virus production in other persistently infected, non-productive cells such as fibroblasts (Narayan et al., 1982), possibly by releasing macrophage secretory products (enzymes), which are taken up by the fibroblast and cleave virus precursor proteins required for virion assembly. This latter mechanism could also conceivably be involved in equine infectious anaemia virus (EIAV) disease, where Mφ are the only cells identified which harbour the virus and support viral replication (Stroop & Baringer, 1982) even though a persistent non-productive infection can be established in fibroblasts in vitro (Crawford et al., 1978). These recent observations demonstrate the various ways, both direct and indirect, in which Mφ may aid viral replication and persistence.

One mechanism whereby viruses can elude the antiviral immune response and persist is by emergence of antigenically new virus strains in the infected host due to mutational changes of the viral genome. EIAV is a highly mutable virus with point mutations occurring spontaneously, perhaps even independently of the immune response (Payne et al., 1984), producing new stable strains. These mutations occur most frequently in viral glycoproteins gp90 and gp45, which are the primary immunogens during a persistent infection (Payne et al., 1984). Once these mutations occur, the immune response acts as the selective force for the ensuing emergence of novel antigenic strains of EIAV (Payne et al., 1984). Thus, it is conceivable that each clinical episode is related to a Mφ-mediated production of a new mutant that will also infect Mφ, thereby amplifying virus production and spread. The ensuing antibody response will again cause formation of immune complexes promoting vascular lesions and clinical disease. Moreover, enhanced infection of Mφ may occur due to Fc receptor-mediated uptake of infectious complexes (Schlesinger & Brandriss, 1981). The viraemia is, however, eventually controlled and the infection becomes quiescent until a new virus mutant emerges, perhaps as a result of an intracellular event in the Mφ–virus interaction (Morahan et al., 1985).
The phenomenon of antigenic drift has also been observed with VMV (Narayan et al., 1977) but is not likely to play a major role in persistence of this virus group, as it does not occur until several months after the appearance of neutralizing antibodies (Narayan et al., 1978). With CAEV, antigenic drift does not seem to be important in persistence since no neutralizing antibodies are induced by the virus (Klevjer-Anderson & McGuire, 1982). Instead, virus characteristics such as the level of expression of particular viral components or the degree of integration of viral DNA into the host cell genome may be implicated in establishment of virus persistence and the fate of the host cell (Querat et al., 1984; Harris et al., 1984; Gonda et al., 1985). In addition, host genetic factors may be decisive in the outcome of an infection with ovine or caprine lentiviruses (Nathanson et al., 1976; Narayan et al., 1974, 1977).

Not only does CAEV fail to induce neutralizing antibodies in its natural host or in sheep (Narayan et al., 1984), but only complement-dependent neutralizing antibodies are induced in a heterologous host (Klevjer-Anderson & McGuire, 1982). CAEV is distinct from VMV/PPV as measured by genome sequence homology (Roberson et al., 1982; Querat et al., 1984), but has protein patterns similar to ovine lentiviruses (Johnson et al., 1983). In CAEV-infected goats non-neutralizing antibodies are produced against four or five of the six major proteins, including the high molecular weight glycoprotein (Johnson et al., 1983). The latter corresponds to the VMV glycoprotein responsible for induction of neutralizing activity (Scott et al., 1979). Faced with this fact, two possibilities for the apparent failure to neutralize the virus must be considered. One is the lack of appropriate antigenic epitopes, either qualitatively or quantitatively, on the glycoprotein(s). The other concerns the host immune response, which may either be constitutively deficient in presenting and responding to this antigen, or may somehow be impaired due to the infection itself. These questions were approached by Narayan et al. (1984), who found that CAEV infection of the Mφ was not the only deciding factor in the failure of induction of neutralizing antibodies, and that the ability of the host to produce neutralizing antibodies to heterologous agents, including VMV, was not compromised by persistent infection with CAEV. Interestingly, production of neutralizing antibodies to CAEV could be induced by injecting the goats with large amounts of Mycobacterium tuberculosis at the time of virus inoculation. Activation of Mφ both in vivo and in vitro by M. tuberculosis is a well established phenomenon (Edelson & Erbs, 1978; Lodwell & Ewalt, 1978). The indications are, however, it was not merely an activation of the Mφ normally present in the host, but induction of a totally different Mφ subpopulation with a novel or enhanced capacity for antigen processing (Narayan et al., 1984). This possibility should be further investigated since it may yield useful information with respect to other hyporesponsive states observed in viral infections, and may contribute to the understanding of development and differentiation pathways within the MPS (Bursuker & Goldman, 1983; Morahan et al., 1985).

No coherent picture of lymphocyte reactivity and involvement in the pathobiology and immunology of the non-oncogenic retrovirus infections has yet emerged. It is clear that infected animals do not suffer from generalized immunosuppression, as they are fully immunocompetent to other antigens, and produce virus-specific antibodies. Moreover, the pathological changes characteristic of the diseases are those of non-malignant lymphoproliferation and cell infiltrations. The occasional reports of transient depression of lectin-induced lymphocyte proliferation and decreased interleukin-2 production (Ellis & DeMartini, 1985a, b; Kono et al., 1978) are difficult to reconcile in this context. Obviously, more research is needed to elucidate the significance of such phenomena and their possible involvement in immunological imbalance leading to unrestricted lymphoproliferation, in addition to what the continuous presence of viral antigen or virus-induced changes in tissue antigens will induce. The recent findings that human T-cell leukaemia virus type III (HTLV-III), the aetiological agent of the acquired immune deficiency syndrome (AIDS), shares genomic and morphological features with VMV (Gonda et al., 1985) and that HTLV-III can be detected in brain tissue of AIDS patients (Shaw et al., 1985), and shows antigenic cross-reactivity with EIAV (Montagnier et al. as cited in Thiry et al., 1985) and BLV (Thiry et al., 1985), may create an upsurge in research on the non-oncogenic retroviruses to the benefit of both human and veterinary medicine, as well as stimulating basic studies in virology, immunology and pathology.
The disease caused by African swine fever virus (ASFV) in domestic pigs has attracted much attention over the years, and its various aspects have been frequently reviewed in monographs and textbooks (Hotchin, 1971; Coggins, 1974; Maurer, 1975; Hess, 1981; Wardley et al., 1983). Therefore, we will only review aspects of the obscure immunological response that apply to pathogenesis. ASF may appear as a peracute, acute, subacute or chronic disease. Lesions encountered in peracute to subacute cases comprise haemorrhages in various organs, especially peripheral lymph nodes and fluid accumulation in body cavities. Extensive cell necrosis is usually present in lymphoid tissues (Maurer, 1975). Chronic ASF begins rather uncharacteristically with interstitial pneumonia, eventually progressing to lung necrosis (Moulton et al., 1975), arthritis, skin ulcers and emaciation (Hess, 1981). Such animals remain viraemic for extended periods. Neutralizing antibodies nevertheless fail to develop, even though high titres of precipitating, complement-fixing and haemadsorption-inhibiting antibodies develop. Chronically infected animals thus develop hypergammaglobulinaemia (Pan et al., 1970). The initial virus replication is thought to take place in Mφ in lymphoid tissues (tonsil) and from there to spread to lymphocytes and endothelial cells. As this infection is lytic it may account for the lesions in acute cases. However, as will be discussed later, a hypersensitivity reaction may also be involved. Macrophages are also thought to be the primary site of virus persistence (Wardley & Wilkinson, 1977). However, infection of Mφ by ASFV appears to imply some inherent contradictions, or alternatively to constitute a virus–cell interaction completely contrary to what is known about virus–Mφ relations in other virus infections (Allison, 1974). Thus, ASFV attenuated by in vitro cultivation (i.e. avirulent for swine) appears to be much more cytopathic for Mφ than virus strains highly virulent for pigs, when the comparison is based on the initial infection dose (multiplicity of infection). In addition, infection with this attenuated ASFV is established much more easily and gives rise to comparatively higher virus yields (Wardley et al., 1979), suggesting that factors other than the ease of infection of Mφ are important in determining the virulence of the virus for the animal host (Virelizier & Allison, 1976).

Following an acute infection with virulent ASFV, pigs develop lymphopenia. Conflicting results have been reported with respect to the differential effect on lymphocyte populations. Thus, Wardley & Wilkinson (1980) reported that B cells were predominantly affected. Curiously, the changes in total and relative lymphocyte numbers did not result in significant changes in lectin-stimulated lymphocyte proliferation. In contrast, Sanchez-Vizcaino et al. (1981) found that the T cell population was depleted, that lectin-stimulated T cell proliferation was correspondingly decreased, and that mitogenic responsiveness and antibody production reflected the chances of the animal surviving the disease. Their findings seem to correlate better with the finding that ASFV-infected animals can mount a normal humoral response to other microbial antigens (DeBoer, 1967).

Chronic ASF is characterized by lymphocytosis accompanied by fluctuations in the numbers of T and B cells in the blood; but the only significant changes appear to be a marked increase in the number of 'null' lymphocytes at various times during the course of the infection and a rise in B cell numbers corresponding to the appearance of precipitating serum antibodies. The significance of the 'null' cells is not known (Pan et al. as cited in Hess, 1981).

It has been suggested that the lesions seen in pigs with chronic ASF are caused by an autoimmune phenomenon (Pan et al., 1975; Wardley, 1982; Wardley et al., 1983). However, data were not presented to substantiate this. The hypergammaglobulinaemia seen after infection in vivo and in vitro with virulent ASFV strains (Wardley, 1982) may be due to a large extent to non-specific activation of 'bystander' cells (Ahmed & Oldstone, 1984). So far, there is no evidence for production of auto-antibodies or activation of auto-aggressive cells. There seems to be more support for the theory of a hypersensitivity reaction being central in the pathogenesis of lesions, as proposed by Slauson & Sanchez-Vizcaino (1981). During ASFV infection virus-specific IgE is produced, as is precipitating IgG. Blood basophils armed with this IgE then become activated upon encounter with antigen (viraemia) and release platelet-activating factor, causing platelets to aggregate and release vasoactive amines. This mechanism, designated the anaphylactic trigger for immune complex (IC) deposition (Henson & Pinchard, 1977), provokes leakage of circulating IC into the tissues. Upon deposition, the IC may bind complement (Slauson &
Sanchez-Vizcaino, 1981) and IC disease ensues. Whether the latter occurs depends on how long
the animal survives. Nevertheless, deposition can be detected in the kidneys of pigs in the acute
phase of the infection. It is not inconceivable that deposition also occurs in the lungs and
vascular bed of the skin, and can thus account for the lesions in chronic ASF. In agreement with
this proposal, it has also been found that eosinophils occur constantly in chronic lung lesions
(Moulton et al., 1975). Eosinophils appear to be an important constituent of an anaphylactic
reaction. It remains to be shown that this mechanism, proposed by Slauson & Sanchez-Vizcaino
(1981), can eventually lead to the pathological lesions seen in chronic ASF. In the same context it
may be speculated whether the anaphylactic trigger is also involved in the substantial extra-
vasation in acute ASF. In addition to its usefulness as a model for virus-induced IC disease, ASF
provides an opportunity for exploring how a virus may bypass the development of neutralizing
antibodies.

Immunopathological phenomena similar to those of ASF may prove central to another viral
disease, feline infectious peritonitis (FIP). The infection appears to occur worldwide in the cat
population (Horzinek & Osterhaus, 1979a), but is usually subclinical or has transient mild and
uncharacteristic symptoms of an upper respiratory tract or gastrointestinal tract infection
(Pedersen, 1976a; Horzinek & Osterhaus, 1979b). In a small percentage of cats, a secondary
fatal disease occurs weeks to years later, characterized by fibrinous serositis (i.e. inflammation
of serosal membranes with fibrin deposited) and/or disseminated perivascular pyogranulomatous
(i.e. focal, chronic inflammation of purulent character) (Pedersen, 1976a; Horzinek &
Osterhaus, 1979b). Experimentally, it has been found that seropositive cats develop cardinal
symptoms and die faster than seronegative cats (Hayashi et al., 1982a, b, 1983; Weiss & Scott,
1981; Weiss et al., 1980a). Thus, a comparison has been drawn to the dengue shock syndrome in
humans (Horzinek & Osterhaus, 1979b; Weiss et al., 1980a). This may apply as far as the first
part of the immunological enhancement hypothesis (Halstead, 1980) is concerned, which
proposes that in the presence of virus-specific opsonizing, non-neutralizing antibodies, virus
uptake by mononuclear phagocytes is enhanced. This is followed by a rapid and upgraded
replication in these cells, and spread of the infection to various tissues, mainly intracellularly in
infected monocytes. A similar step in the pathogenesis has been proposed for FIP (Pedersen,
1976b; Jacobse-Geels et al., 1982; Weiss & Scott, 1981). The hypothesis further states that an
immune elimination response directed against virus-infected monocytes, probably involving T-
killer lymphocytes, is responsible for activating the monocytes to release various substances
such as C3b, thromboplastin and vascular permeability factor (Halstead, 1980). In contrast, an
Arthus-like reaction has been suggested as the basis for the lesions in classical FIP (Hayashi et
al., 1982a, 1983; Jacobse-Geels et al., 1980; Pedersen & Boyle, 1980). This was supported by the
observation that a decrease in total haemolytic activity (CH50) and the third component of
complement (C3) occurred at the same time as an increase in anti-coronavirus antibodies and in
circulating immune complexes (Jacobse-Geels et al., 1982). However, appearance of clinical
FIP and pathological lesions, most notably disseminated intravascular coagulation, was
accompanied by increased quantities of fibrin–fibrinogen degradation products and decreased
quantities of various coagulation factors (Weiss et al., 1980b). It was proposed that this occurred
as a consequence of systemic complex deposition (Weiss et al., 1980b; Jacobse-Geels et al.,
1982). In this context, it was suggested that the preclinical increase in CH50 might be explained
by virus activation of Mφ, which then releases complement factors (Brade & Bentley, 1980), or,
alternatively, release of such factors may be the result of leakage from virus-damaged Mφ
(Jacobse-Geels et al., 1982). Apart from being a component of an inflammatory response in FIP,
especially in the pyogranulomatous lesions, polymorphonuclear neutrophils (PMNs) have also
been implicated as being virus carriers either passively or as infected cells (Hayashi et al., 1984;
Horzinek & Osterhaus, 1979b; Ward et al., 1971).

The initial event(s) precipitating development of clinical FIP still remain to be elucidated.
Epidemiological observations indicate that other immunosuppressive infections, such as feline
leukaemia (Olsen et al., 1984), may play a role. Alternatively, an acute secondary infection with
a different FIP virus serotype may induce non-neutralizing antibodies in an anamnestic
response, and thereby initiate the pathogenic cascade (Weiss & Scott, 1981). Once the virus–host
balance is disturbed, one may envisage a sequence of events wherein the virus replicates in the intestinal (Hayashi et al., 1982b; Horzinek & Osterhaus, 1979b) and/or the respiratory tract epithelium (Weiss & Scott, 1981) of the FIP virus-immune host. Subsequently, IC are formed with non-neutralizing antibodies, and these are taken up by Mφ (Jacobse-Geesl et al., 1982; Weiss & Scott, 1981). This is next followed by a replication phase in the Mφ, and simultaneously the virus is transported intracellularly to local lymph nodes. Further spread to other monocytes and development of a cell-associated viraemia results in virus spread to the spleen and liver where local lesions may ensue. Concomitantly, renewed virus replication is likely to boost virus-specific immunoglobulin production, including that of IgE. Thereby, the scene is set for IC deposition (Henson & Pinchard, 1977). Moreover ICs formed in antibody excess and in the presence of complement will directly activate platelets, causing aggregation and release of vasoactive amines. Extravasation and deposition of ICs attract inflammatory cells, especially PMNs. The process now continues to escalate, with vascular lesions, complement activation, activation of the coagulation cascade, deposition of further ICs, extravasation of plasma constituents and cells (Jacobse-Geesl et al., 1982). The Mφ may contribute to this not only by being the site of viral replication and viral dissemination, but also by producing and releasing procoagulant (Rothenberger et al., 1977) and complement components, as well as taking part in antibody-dependent cellular cytotoxicity against other virus-infected cells. Whether the dominant feature of any particular case is polyserositis or pyogranulomata may depend on the animal's initial immune status and general immunological responsiveness, the site of initial virus replication, and perhaps its genotype (Virelizier & Allison, 1976) and the virus strain (Taguchi et al., 1981). Thus, the picture emerging is that of a very complex and multifarious pathogenesis, with obvious possibilities for studies of mechanisms involved in virus-induced immunopathology.

Aleutian disease (AD), a naturally occurring virus infection in mink, is caused by a non-defective parvovirus, ADV (Bloom et al., 1982; 1983). The main features of the chronic, progressive form of AD, caused by virulent virus strains, are virus persistence, hyperglobulinemia, circulating infectious ICs, and fatal IC disease (for reviews, see Porter & Cho, 1980; Stroop & Baringer, 1982). All types of mink become infected by ADV and virus may or may not persist (Larsen & Porter, 1975; An & Ingram, 1977). However, development of clinical progressive AD is strongly dependent on the genotype of the mink, and on the virus strain (Lodwell & Portis, 1981; Stroop & Baringer, 1982). Although differences in the structural proteins of virulent and non-virulent virus strains have been identified (Aasted et al., 1984) it is unlikely that the mere size of the virion proteins accounts for the differences in virulence. Breeding experiments show that no single gene is responsible for host resistance (An & Ingram, 1977). Differences in the antibody response, qualitative and quantitative, may explain, at least in part, differences in host susceptibility to virus persistence and development of IC disease. Thus, only mink with a strong antibody response to the ADV-induced non-structural polypeptide, p71, succumb to ADV (Bloom et al., 1982). It remains to be determined at what cellular level (Mφ, T cells, B cells) of the immune response such differences are controlled and regulated (Sherman et al., 1983; Howard & Paul, 1983; Singer & Hodes, 1983; Green et al., 1983).

Initially, it was suggested that ADV persisted and replicated in the Mφ (Porter et al., 1969); however, this has not been substantiated (Roth et al., 1984) and therefore the virus-producing target cell(s) remains unknown. Recent findings suggest a new and rather different role of the Mφ in the pathogenesis of AD. ADV undergoes proteolytic degradation during an in vivo infection (Aasted et al., 1984), and it was suggested that this may take place intracellularly in the Mφ after uptake of virus–antibody complexes (Aasted, 1980; Aasted et al., 1984). Moreover, the degradation products, low molecular weight proteins, are highly antigenic and react with antibody raised against ADV structural proteins (Aasted et al., 1984). The small immune complexes (9S and 25S) previously demonstrated in the blood and tissue deposits (Porter et al., 1965; Cochrane & Hawkins, 1968) may consist of these virus-specific low mol. wt. proteins and ADV-specific antibody (Aasted et al., 1984; Race et al., 1983). The contribution of other types of immune complexes such as p71–anti-P71 (Bloom et al., 1982) and DNA–anti-DNA antibody complexes (Hahn & Kenyon, 1980) also cannot be excluded. Furthermore, the low mol. wt.
degradation products and/or the 'modified' virus may play an important role in development of an ADV-specific T lymphocyte response. Thus, it was found that only mink developing clinically progressive AD acquire an ADV-specific T cell response, and that this is temporally correlated with development of IC lesions (Race et al., 1983). Therefore, not only may the Mφ degrade the ADV, but in addition they could also contribute to the lymphocyte response (T and/or B cells) by presenting the stimulating antigen (i.e. low mol. wt. proteins or ADV) in immunogenic complexes with major histocompatibility complex antigens (Sherman et al., 1983). It remains to be elucidated whether the antiviral lymphocyte response represents a normal antigen response or disordered immunoregulation in ADV infection. In this context it is noteworthy that pastel mink inoculated with a low-virulent ADV strain, such as Pullman ADV, develop a virus-specific humoral response and infectious virus persists. Nevertheless, they remain clinically normal and do not develop an ADV-specific lymphocyte proliferative response (Race et al., 1983). It might therefore be speculated that the lymphocytes specifically responding to ADV in vitro represent a subpopulation of T cells with helper function or suppressor cells, that in vivo deregulate normal immunoregulatory circuits, the consequence being unconstrained B cell proliferation (Green et al., 1983). As indicated above perhaps not all of the drastically elevated antibody is specific for viral antigen, but also includes one or more auto-antibodies (Hahn & Kenyon, 1980) which may add an autoimmunity aspect to the pathogenesis of ADV-induced lesions (Notkins et al., 1984).

Much still remains to be learned before the pathogenesis of AD is unravelled. Recent developments clearly indicate that this will only be achieved by combined efforts from the areas of molecular virology and all aspects of immunology (Aasted et al., 1984; Bloom et al., 1982; Race et al., 1983). Thus, not only is AD a favourable model for persistent virus infections (Porter & Cho, 1980), but these studies could also provide new insights into directions of research with other virus diseases.

The recent availability of Mφ cell lines from a number of the species discussed, the ability to use primary Mφ cultures as well as molecular biological techniques and monoclonal antibodies to identify subpopulations of Mφ capable of being infected with specific viruses should greatly increase our understanding of virus–Mφ interactions. If these in vitro studies are combined with in vivo studies in the natural host, considerable progress will be possible in helping to elucidate the role of Mφ in persistence as well as in induction of immunity to a wide variety of viral infections.

Other virus infections characterized by immunopathology

Although the immune response evolved primarily to aid the host to ward off infections, in many instances during recovery the immune system can over-respond and produce more damage than is often caused by the virus itself. This is especially true in many persistent non-cytopathic or poorly cytopathic virus infections. These immunopathological events may occur as a result of direct killing of infected cells by cytotoxic T cells, natural killer (NK) cells or Mφ (for reviews, see Doherty, 1985; Morahan et al., 1985; Rager-Zisman & Bloom, 1982; Sissons & Borysiwecz, 1985). Alternatively, the immunopathology may occur as a result of virus infection of certain subpopulations of lymphoid/Mφ cells which leads to altered functions of these cells. These latter interactions are proving to be much more common than was previously thought. Two excellent models for deciphering virus–lymphocyte interactions are malignant catarrhal fever (MCF) and Marek's disease.

MCF is a benign lymphoproliferative disease of domestic cattle, deer and buffalo (Plowright, 1968; Reid et al., 1984) with a peracute to slightly protracted, but invariably fatal course. In Africa the aetiological agent has been identified as alcelaphine herpesvirus type 1 (Plowright et al., 1960; Reid et al., 1975), with the wildebeest (Connochaetes taurinus albojubatus) acting as the reservoir of this virus. Outside Africa no aetiological agent has so far been identified, but it is widely accepted that sheep are the natural host, hence the designation sheep-associated MCF (Plowright, 1968). The clinical and pathological changes that follow natural or experimental infection with either alcelaphine herpesvirus type 1 or the sheep-associated agent are very similar, and do not provide a basis for differentiation (Reid et al., 1984). The clinical signs are
those of generalized lymph node swelling, severe vasculitis, rhinotracheitis, eye inflammation, pansystemic involvement of the gastrointestinal tract and exanthema (Plowright, 1968). The most significant histopathological findings are widespread mononuclear cell infiltration and proliferation, generalized lymphoid vasculitis and epithelial lesions (Liggitt et al., 1978; Plowright, 1968; Selman et al., 1974). Both agents can be experimentally transmitted to rabbits, causing both symptoms and pathological lesions which rather closely resemble those in cattle (Buxton & Reid, 1980; Edington et al., 1979). The mononuclear cell infiltrates are dominated by small, medium and blast-like lymphocytes (Edington et al., 1979; Liggitt & DeMartini, 1980a, b), with variable numbers of monocytes and Mφ. Plasma cells and neutrophilic granulocytes are rare (Liggitt et al., 1978; Liggitt & DeMartini, 1980a, b; Selman et al., 1974), although in one report they seemed to occur more prominently, especially in relation to vessel involvement (Rweyemamu et al., 1976). It is notable that the overall architecture of the lymphoid tissues usually is largely preserved, but the thymus-dependent areas are markedly enlarged. In contrast, follicles and germinal centres are absent or inconspicuous (Selman et al., 1974). The pathogenesis remains unknown, but recent data open up new avenues for the use of this disease as a model not only to explore mechanisms of viral immunopathology but also to gain insights into some basic regulatory mechanisms of the immune system. Early suggestions that hypersensitivity is involved in the pathogenesis (Plowright, 1968) were based on the detection of viraemia in cattle with African MCF up to 10 days prior to the onset of clinical disease, hyperglobulinaemia and vascular lesions with neutrophil infiltration and thrombosis (Rweyemamu et al., 1976). Subsequent studies did not support this; rather, it was argued that cell infiltrations as well as vascular and epithelial lesions bore resemblance to a graft-versus-host reaction and other conditions with purported or established delayed hypersensitivity involvement in the pathogenesis (Liggitt & DeMartini, 1980a, b; Liggitt et al., 1978).

Alternatively, it was suggested that viral infection of a lymphocyte subpopulation might cause proliferation and activation of auto-aggressive T lymphocytes (Liggitt et al., 1978). Although the agent is cell-associated and can be transferred withuffy coat cells (Plowright, 1968), negligible numbers of blood lymphocytes or tissue-infiltrating cells appear to contain viral antigen (Rossiter, 1980; Edington et al., 1979; Patel & Edington, 1980, 1981; Edington & Patel, 1981). It remains to be seen whether some or all lymphocytes contain an integrated viral genome, such as has now been demonstrated in Marek's disease (Reid et al., 1984; Sharma, 1977). The most recent development in the studies of MCF pathogenesis is the isolation and propagation of a lymphoid cell type derived from lymphoid or infiltrated tissues of rabbits, deer or cattle with experimental sheep-associated MCF (Reid et al., 1983, 1984). The cells have been characterized morphologically as large granular lymphocytes (LGL) with T lymphocyte surface antigens, and possess cytotoxic activity against a range of normal and transformed cells (Reid et al., 1983). They do not contain viral antigen detectable by conventional methods (Reid et al., 1983), and they have so far not been identified within tissue by histological methods (Buxton et al., 1984). The results nevertheless led the authors to propose that these LGL are the actual virus targets, and that virus may persist as episomal DNA. The presence of viral DNA disrupts normal cellular functions, i.e. T cell suppression (Herberman, 1982), resulting in a non-specific, benign polyclonal proliferation of T lymphocytes. In addition, the infected LGL may now engage in non-discriminatory natural killing, leading to tissue destruction (Buxton et al., 1984; Reid et al., 1984). The proposal is highly conjectural, but both in the interest of resolving the enigmas of MCF as well as learning more about the consequences of deranged control mechanisms in the immune system, the proposal deserves to be pursued. This is not to say that the hypotheses for autoimmune and delayed hypersensitivity should therefore be completely ruled out.

Firmer progress has been made with another herpesvirus-induced lymphoproliferative disease, Marek's disease in chickens. The virus (MDV) replicates only in epithelial cells of the feather follicles (Purchase, 1974), but infects lymphocytes also. Here the viral genome either becomes integrated or the virus undergoes an abortive replication cycle. The virus transforms the lymphocytes and induces a tumour antigen, designated MATSA (Marek's disease tumour-associated surface antigen; Witter et al., 1975). The transformed cells proliferate and infiltrate most tissues, most notably peripheral nerves (Purchase, 1974). The latter feature may be the
direct cause of clinical disease, i.e. paralysis and death, although direct viral infection of Schwann cells and satellite cells with subsequent demyelination due to a specific immune response probably also contributes to the disease (Pepose et al., 1981). The recognition of MATSA as a marker for cellular transformation by MDV has generated interest in the possible role this antigen may play in the pathogenesis of the disease. Thus, it was found that chickens infected with MDV develop a cell-mediated immune response to MATSA as revealed by the presence of antigen-specific cytotoxic cells in the spleen and peripheral blood, albeit in very low numbers (Powell, 1976; Sharma & Coulson, 1977). Interestingly enough, the indications are that it is T cells which become both transformed by MDV (Hudson & Payne, 1973; Rouse et al., 1973; Sharma et al., 1977) and express anti-MATSA cytotoxicity (Sharma, 1977). Lymphomas may thus consist of at least two different T cell subpopulations, i.e. target cells and effector cells. This circumstance may account for the necrosis and atrophy in some lymphoid organs (Purchase, 1974).

In contrast to T cell involvement in the specific immune response and pathogenesis of Marek’s disease, NK cells have been implicated in the resistance-susceptibility phenomenon of the disease (Lam & Linna, 1980; Sharma, 1981). Susceptibility to MDV appears to be, in part, genetically determined and is strongly correlated to the level of NK activity (Sharma, 1981). The lower NK activity in susceptible chicks may be due either to induction of a suppressor mechanism by MDV (Lee et al., 1978) or to a lack of responsiveness to natural NK cell enhancers such as interferon (Sharma, 1981; Santoli & Koprowsky, 1979). Alternatively, responsiveness to interferon induction may be absent. Thus, the interferon response appears also to be genetically determined (DeMaeyer & DeMaeyer-Guignard, 1969). It is therefore obvious that Marek’s disease in chickens is a useful model for studies of ‘natural’ resistance and defence against tumour development and progression (Gorelik et al., 1979). Other aspects such as the importance of antibody in the early pathogenesis of virus-induced oncogenesis (Calnek, 1972) also deserve further attention.

The possibility that the pathogenesis of MCF in cattle and Marek’s disease in chickens are similar deserves investigation, i.e. that transformation of a lymphocyte subpopulation and its subsequent infiltration of various tissues is followed by recruitment of other, normal lymphoid cells which react against the transformed cells, and perhaps against normal cells with cross-reacting surface antigens or innocent bystanders. The outcome would be similar to an auto-aggressive reaction, and could result in the animal’s death before lymphomatous disease develops. These models may help to clarify how disruption of one subset of lymphocytes alters production of regulatory factors which can lead to immunopathology.

**Virus-induced neurological disease**

Virus infections that have as a prominent component neurological lesions in domestic animals, include several examples already treated in other contexts in this review. These are visna and caprine encephalitis-arthritis in sheep and goats respectively, and Marek’s disease in chickens (for reviews, see also Dal Canto & Rabinowitz, 1982; Pepose et al., 1981; Lampert, 1978; Johnson, 1982). They will not be discussed further. The questions and problems surrounding rabies have recently been reviewed by Koprowski (1984). Here we shall restrict the discussion to canine distemper virus (CDV)-induced encephalitides.

Demyelinating disease caused by CDV may develop weeks or months after the initial systemic disease, or after several years in which case it is called chronic distemper meningoencephalitis (CDE) (Appel & Gillespie, 1972; Koestner & Krakowska, 1977). In addition, CDV has been implicated in old dog encephalitis (ODE), a demyelinating encephalitis occurring in aged and CDV-immune dogs without any preceding clinical illness (Lincoln et al., 1971; Imagawa et al., 1980). Because of the relatedness of CDV to measles virus, and its involvement in central nervous system (CNS) lesions with a similarity to demyelinating diseases in humans (Adams et al., 1975), CDV infections have on several occasions been considered as a model for subacute sclerosing panencephalitis (SSPE) and multiple sclerosis (Dal Canto & Rabinowitz, 1982; Lampert, 1978; Adams et al., 1975; Koestner & Krakowska, 1977). CDV has
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even been suggested to be the causative agent of the latter; however, this has since been disproved (for review, see ter Meulen & Carter, 1982). The usefulness of this model has been hampered by the difficulties in consistently reproducing demyelinating disease by CDV; there also appear to be some essential differences in the virological aspect as well as humoral immune responses during measles in man and distemper in dogs (Dal Canto & Rabinowitz, 1982; ter Meulen & Carter, 1982). Despite these dissimilarities the two agents induce CNS disorders with extensive similarities in clinical features and neuropathological changes (Adams et al., 1975; ter Meulen & Carter, 1982). The recent finding that CDV strains more likely to cause persistent infection and demyelinating disease can be distinguished by peptide mapping of the nucleocapsid (NP) protein (Shapshak et al., 1982) may help overcome some of the difficulties in establishing a reproducible animal model with CDV. It should then be possible to pursue studies on the temporal relation between the virus-induced immunosuppression and immunological recovery with the development of CNS lesions (Summers et al., 1979; Vandervelde et al., 1982a, b; Cerruti-Sola et al., 1983; Appel et al., 1982).

Both humoral and cell-mediated immune responses appear to have a decisive role in the outcome of a CDV infection (Krakowka et al., 1975, 1978; Appel et al., 1982). The time of onset of a virus-specific cytotoxic T cell (Tc) response may be critical for clearance of virus from the CNS. The temporal onset as well as the magnitude of this response appears to be determined at the level of both the host and the virus. The degree of immunosuppression, the ability to mount a virus-specific immune response, and subsequently to surmount viral invasion and prevent establishment of persistent CNS infection may in part be determined by the susceptibility of lymphocyte subpopulations to CDV infection (Casali et al., 1984; Appel et al., 1982; Cerruti-Sola et al., 1983). It appears that some CDV strains induce a delayed and low Tc response and that these same strains cause persistent CDV infection with development of non-inflammatory demyelinating encephalitis (Appel et al., 1982). Furthermore, the degree of immunosuppression may determine the type of demyelination, i.e. without or with an inflammatory component (Appel et al., 1982; Summers et al., 1979, 1984; Cerruti-Sola et al., 1983; Krakowka et al., 1978). These findings and the indications that autoimmune reactions that occur during the inflammatory stage of demyelination may be epiphenomena (Cerruti-Sola et al., 1983) should make CDV infections in dogs an extremely useful model for studying virus–cell and virus–host interactions in subacute and chronic demyelinating diseases, including the unresolved problems surrounding ‘bystander’ and virus-induced autoimmune demyelination (Lampert & Rodriguez, 1984; ter Meulen & Carter, 1982; Waksman, 1984). Furthermore, this model may be useful for determining how and why an infection becomes rekindled with the development of progressive disease during adolescence (e.g. ODE and SSPE). With the application of monoclonal antibody and molecular virology techniques it should now be possible to characterize viral epitopes that elicit specific immune reactions (Buchmeier et al., 1984; Rammohan et al., 1981; Krakowka et al., 1978) and determine virulence and persistence of the morbilliviruses (Seif et al., 1985; Rozenblatt et al., 1985).

Virus-related immunosuppression and increased susceptibility to secondary microbial infections

A prominent feature of many virus infections is the virus-related immunosuppression of the host. It is under this heading that the following naturally occurring virus diseases in ‘non-conventional’ laboratory animals will be described: feline and bovine leukaemia, swine influenza, rinderpest, canine parvovirus disease, feline panleukopenia and infectious bovine rhinotracheitis. Immunosuppression may also be seen in some virus infections mentioned above in other contexts (e.g. Marek’s disease, canine distemper, pestivirus infections) and will not be further commented on here. Independent of the mechanism(s) involved in the virus-induced immunosuppression, the most significant common feature of these diseases is the increased susceptibility to secondary (bacterial, parasitic, viral) infections. The clinical symptoms and lesions caused by the primary viral infection may be rather innocent, with virus clearance and complete resolution of lesions within a short period of time, if secondary infection does not occur. A secondary bacterial infection, however, will severely aggravate the condition; thus, it is
notable that in some diseases, e.g. canine distemper and the 'bovine respiratory disease complex', many of the so-called cardinal clinical signs are attributable to the secondary bacterial infections (McCullough et al., 1974; Yates, 1982).

Cats infected with feline leukaemia virus (FeLV) appear to be immunosuppressed as early as the preneoplastic stage of leukaemogenesis as revealed by increased susceptibility to FIP virus, haemobartonella and various bacterial infections, by a prominent leukopenia, as well as reduction in various lymphocyte functions in vitro (Olsen et al., 1981). The mechanism(s) whereby FeLV induces suppression in the preneoplastic stage is not completely elucidated, but seems to be independent of FeLV-induced T cell transformation (for review, see Olsen et al., 1981; also Wainberg et al., 1983; Orosz et al., 1985). Rather, the suppression may be an effect of FeLV products or structural components causing metabolic, rather than sensu stricto immunological defects (Olsen et al., 1976; Mathes et al., 1979; Orosz et al., 1985). One component specifically, a 15000 mol. wt. protein, has strong immunosuppressive effects both in vitro and in vivo (Mathes et al., 1979). This protein inhibits lymphocyte surface receptor mobility, probably by inducing microtubule polymerization (Nichols et al., 1979), and may also cause decreased interleukin-2 production (Wainberg et al., 1983), suppressed responsiveness to lymphokines (Orosz et al., 1985) and suppression of interferon-gamma production (Lin et al., 1984; Engelman et al., 1985). This may evidently interfere with cell-antigen and cell-cell interactions, thereby preventing a normal immune response (Orosz et al., 1985). Whether the virus (components) also interferes with the non-specific defence mechanisms, such as neutrophil and MΦ functions or induction/production of interferon-alpha and -beta which are of importance early in an infection, remains to be investigated.

Much less is known about the effect of bovine leukaemia virus (BoLV) on the immunological responsiveness and antimicrobial defence mechanisms of cattle. However, BoLV is known to suppress the humoral response to administered antigens, especially the IgM response (Trainin et al., 1973, 1976). The blastogenic response to phytohaemagglutinin and concanavalin A is also decreased in cattle with persistent lymphocytosis (the preneoplastic stage) whereas the pokeweed mitogen response is increased (Muscoplat et al., 1974a). This may be due, at least in part, to the greatly increased proportion of B lymphocytes in the peripheral blood of cattle with persistent lymphocytosis and lymphosarcoma (Muscoplat et al., 1974b; Kenyon & Piper, 1977a), especially BoLV-specific B cells (Kenyon & Piper, 1977b; Thorn et al., 1981). This subpopulation is separable from the BoLV-containing B cells (Kenyon & Piper, 1977b) and may be BoLV-specific memory cells (Thorn et al., 1981). Interestingly, the actual and relative size of this latter subpopulation decreases drastically at the time of development of clinical lymphosarcoma (Kenyon & Piper, 1977b), thus indicating that a memory lymphocyte population may have a role in the control of virus infection (Thorn et al., 1981). BoLV appears to be an exogenous type C retrovirus which in most infected cattle persists without inducing persistent lymphocytosis or lymphosarcoma (Ferrer et al., 1974, 1980). Thus, in view of recent developments within the area of human viral carcinogenesis, bovine leukaemia could certainly be explored as a model for studying the mechanisms controlling cell transformation, and benign and malignant proliferation (Ferrer et al., 1980), as well as the direct and indirect effects of the virus infection on the susceptibility of the host to pathogenic and opportunistic microbial infections. In these contexts it is also interesting to note that susceptibility to BoLV infection shows a strong familial association which is perhaps best explained in terms of inherited variations in immune responsiveness (Blood et al., 1979; Ferrer, 1980). Finally, BoLV appears to be antigenically related to the AIDS-associated retroviruses (Thiry et al., 1985).

Rinderpest is an acute, highly contagious disease of ruminants and swine caused by a virus of the genus Morbillivirus within the family Paramyxoviridae (Kingsbury et al., 1978). The disease is characterized by high fever and focal, erosive lesions confined largely to the mucosa of the alimentary tract (Blood et al., 1979). Rinderpest virus (RPV) has, like two other morbilliviruses CDV and measles virus, a marked affinity for lymphoid cells, which are lytically infected (Yamanouchi, 1980). A marked leukopenia subsequently develops, even in an otherwise clinically mild infection, and also following vaccination (Blood et al., 1979). Immunosuppression is therefore to be expected, but most probably only of a transient nature, as a strong
immunity develops conferring resistance to subsequent infections (Kahrs, 1981). RPV is not known to cause persistent infection (ter Meulen & Carter, 1982; Kahrs, 1981), but this aspect has perhaps not been sufficiently studied (Kahrs, 1981). Susceptibility to RPV is strongly dependent on the genetic make-up of the host (Blood et al., 1979; Scott, 1985). For this reason as well as for the apparent lack of ability or tendency of RPV to establish persistent infections, in contrast to measles virus and CDV, it might be rewarding to study the immunology of RPV infection in more detail. It may thus be asked whether the mechanism(s) behind the immunosuppression caused by CDV and RPV, respectively, differ and whether this explains why CDV-associated immune dysfunction persists (Krakowka et al., 1980) whereas apparently RPV-associated suppression is overcome (Yamanouchi, 1980). Much could be learned about virus-host interactions from this comparative model.

The classical picture of canine parvovirus (CPV)-induced disease is that of an acute, severe gastroenteritis. However, as with many other viral diseases, the clinical picture is changing, either due to increased population immunity or to changes in virus virulence or both. Thus, subacute disease and subclinical infections are now becoming prevalent. Perhaps somewhat out of context, but not to be forgotten, is also the myocarditis caused by CPV and which in itself presents a model system for viral pathology. However, despite the lack of clinical CPV disease, the dog may become immunosuppressed, as revealed by decreased responsiveness of peripheral blood lymphocytes and Peyer’s patch lymphocytes to mitogens, and an increased susceptibility to other canine pathogens (Olsen & Krakowka, 1984; Olsen et al., 1984). The mechanism whereby CPV suppresses lymphocyte reactivity remains to be elucidated. Nevertheless, one can anticipate the serious consequences a suppression of the common mucosal immune system (McDermott & Bienenstock, 1979; Silverman et al., 1983) may have on resistance to infections in general. In this context it might also be rewarding to look at the effect of other enteric viruses (Babiuk, 1984; Tyrrell & Kapikian, 1982) on the general immunological responsiveness of the host, in order to understand better the mechanisms of pathogenesis of dual infections, so as to be able to control them.

Another parvovirus, feline panleukopenia virus (FPLV), also causes enteritis. However, the most remarkable lesions are found in the lymphoid tissues (Gillespie & Scott, 1973), which become severely depleted of lymphocytes and even atrophic. It is therefore not surprising that mortality in the naturally occurring disease has been attributed primarily to secondary bacterial and viral infections (Rohovsky & Griesemer, 1967; Rohovsky & Fowler, 1971), as severe immunological dysfunction would be expected to follow the formation of such lesions. Nevertheless, using various in vivo and in vitro tests to evaluate immune functions in FPLV-infected cats, Schultz et al. (1976) found only minimal effects of FPLV on the cell-mediated immune response (T cell functions) and no effect on the humoral immune response. Increased susceptibility to secondary infections could, however, also be due to inhibition of non-specific defence mechanisms. This has so far not been studied in detail. Despite the lack of detailed knowledge about the mechanisms involved in virus-related immunosuppression it may not be too far-fetched to conclude that even within a particular virus group (e.g. parvovirus, morbillivirus) different viruses may influence the immune system of their respective natural hosts by different mechanisms but with a similar outcome: immunological dysfunction and increased susceptibility to other pathogenic micro-organisms, thus demonstrating the need to choose the appropriate model system for the virus-induced immunosuppression that one is interested in deciphering.

The complexity of virus-induced immunosuppression is well illustrated in bovine herpesvirus type 1 (BHV-1; synonym infectious bovine rhinotracheitis virus) infections of cattle. Again the consequence is increased susceptibility to secondary bacterial infections resulting in severe pneumonia (Yates, 1982). Careful monitoring of various functions has shown that some are increased, others are decreased, whereas others are not affected at all. Thus, migration of PMN, natural cell-mediated cytotoxicity and mitogen responses of peripheral blood lymphocytes are suppressed (Bielefeldt Ohmann & Babiuk, 1985) as are some, but not all functional activities of alveolar macrophages (McGuire & Babiuk, 1984; H. Bielefeldt Ohmann, unpublished data). In contrast, superoxide anion production by PMN is transiently increased and T helper cell
function (interleukin-2 production) only marginally affected. Interferon-induced suppression and suppressor cells can be ruled out as decisive factors in the decreased cell functions. Thus, so far no single factor has been found which can cause the diverse effects on immune responsiveness (Bielefeldt Ohmann & Babiuk, 1985). However, because of the experimental reproducibility of the disease and the many parallels with pneumonia in humans, induced by influenza virus and bacteria (Couch, 1981; Bielefeldt Ohmann & Babiuk, 1985), this naturally occurring disease complex may offer tremendous advantages for both human and veterinary medicine as a model system to study mechanisms of virus-induced dysfunction of host immunological defence mechanisms in respiratory infections.

Despite the early description of severe pneumonia that follows a dual infection by influenza virus and *Haemophilus influenzae* subspecies *suis* in swine (Shope & Francis, 1936), no attempts seem to have been made using this natural model system to elucidate the effects of influenza on host defences. Thus, most studies on the complications similar to those in human influenza have been conducted in mice, ferrets and guinea-pigs to which human (and swine) influenza virus can be adapted, or in natural human cases (for review, see Couch, 1981). Knowledge about the porcine immune system is steadily increasing (Binns, 1982; Pescovitz *et al.*, 1985); miniature pigs are increasingly being used as experimental animals in immunology, transplantation research, etc. Thus, the means are available to study immune functions before, during and after naturally occurring influenza in a homologous virus–host system, and will hopefully facilitate the understanding of the disease in humans (Couch, 1981). Likewise, the swine influenza model could be used for studies of vaccination regimes (Renshaw, 1975), which may be of special value at this time when new approaches in vaccine production via biotechnology are feasible (Chanock & Lerner, 1984).

**CONCLUDING REMARKS**

In this review a number of natural infections in domestic animals have been considered as models for studies of virus–host interactions in acute, chronic and persistent infections. With the growing knowledge of disease mechanisms obtained from small laboratory animals, it has become evident that to understand fully the interplay between virus and host, further studies must integrate immunological, pathological and virological factors. However, such complex systems can, if conducted in a heterologous virus–host system, be difficult to control with respect to experimental artefacts. The obvious alternative is to study natural diseases in easily accessible animal species, with domestic animals lending themselves as obvious tools. Moreover, the new technical tools now available, including monoclonal antibodies, genetic engineering, embryo splitting and embryonic transfer are already available within the veterinary field (Davis *et al.*, 1985; Chanock & Lerner, 1984). Thus, it should now be possible to exploit this field to determine the cellular interactions involved in viral persistence, tolerance, immunosuppression and pathology and eventually to be able to manipulate such interactions for circumvention or alleviation of the disease in the patient, whether human or animal.

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