

Review

Aspects of canine distemper virus and measles virus encephalomyelitis

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Canine distemper (CD) is a frequently fatal, systemic morbillivirus infection in the dog and other carnivores: encephalomyelitis is the common cause of death. Susceptibility to canine distemper virus (CDV) is now recognized in a wide range of non-domestic animals, most recently in captive lions, tigers and leopards. Furthermore, closely related viruses have produced CD-like diseases in marine mammals. CDV induces an inclusion-body encephalomyelitis in the dog and demyelination is often a conspicuous feature. Myelin injury is associated with the

presence of virus but the mechanism of demyelination remains incompletely understood. Oligodendrocyte infection may be defective, as has been shown *in vitro*. CDV and measles virus (MV) produce similar systemic disorders in their respective hosts but differ markedly in the frequency of central nervous system (CNS) involvement, and in the pathogenesis of the more common neurological sequelae. Both CDV and MV have been considered as multiple sclerosis agents, and the association of CDV with other human disease has been suggested.

Keywords: canine distemper virus, measles virus, morbillivirus, encephalomyelitis, demyelination, old dog encephalitis, subacute sclerosing panencephalitis, multiple sclerosis

Canine distemper virus: host range

A surprisingly diverse range of domestic and free-living animals are naturally exposed to canine distemper virus (CDV) and develop clinical disease with encephalomyelitis. Historically, CD has been recognized as a disorder of the domestic dog, resulting in the loss of normal good temper (hence 'distemper'). In 1905, the French scientist Carré demonstrated that the infection could be transmitted with a filterable agent [16]. Inactivated CDV vaccines were produced earlier this century and had limited success but the development of efficacious modified-live virus vaccines by the 1960s had a dramatic impact on

the incidence of CDV infection in domestic canine populations. Until this period, cases of CD were routinely seen by veterinarians in small animal practice — weekly if not daily. An effective vaccine was a welcome development, for there is no effective specific therapy for the established disease. We continue to see sporadic cases of CD and it remains a significant pathogen in unvaccinated canine populations. CDV is spread by aerosol and the initial signs of infection in the dog are pyrexia and mucopurulent conjunctivitis, rhinitis and pneumonia. Some dogs have gastrointestinal disturbance. The agent is highly immunosuppressive and secondary bacterial infections of the respiratory tract are the norm. Classically, neurological signs develop a few days to weeks after the respiratory tract infection but often CNS disorders are the only presenting signs.

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NATURAL INFECTION		
<i>Canidae</i>		
Coyote		<i>Procyonidae</i>
Dingo		Bassariscus
Dog		Coati
Fox		Kinkajou
Jackal		Lesser panda
Raccoon dog		Raccoon
Wolf		
<i>Mustelidae</i>		
Badger	Polecat	
Ferret	Skunk	
Marten	Stoat	
Mink	Weasel	
Otter		
<i>Miscellaneous</i>		
		Javelina
		Man?
		Non-human primate
<i>Viverridae</i>		
		Binturong
		Masked palm civet
<i>Felidae</i>		
		Leopard
		Lion
		Tiger
<i>CDV-like virus</i>		
		Dolphin
		Porpoise
		Seal
EXPERIMENTAL INFECTION		
<i>Muridae</i>	<i>Cricetidae</i>	
Mouse	Hamster	

Table 1. Animals known to be susceptible to natural or experimental infection with canine distemper virus

Over the years, disease investigations by zoological and wildlife veterinarians, virologists and pathologists have established that all members of the *Canidae* are susceptible to CDV infection; such include the fox, wolf, dingo, coyote and jackal. As for the domestic dog, the agent persists within these populations, transmitted to the offspring of non-immune dams or to adult canids which have lost their active immunity. A carrier state is not recognized in CD and so infection must be spread from actively diseased animals. The extent of CDV transmission between families of susceptible animals is not known but it probably contributes to some disease outbreaks. The dog and its relatives are only one of several groups of animals known to be at risk for CDV. Eight of the 11 families of carnivores have been reported to be susceptible to CDV [39] and many are listed in Table 1. The range of animals is surprisingly diverse and is not typical of most animal viral diseases. With the exception of rabies virus, which infects all mammalian species, most animal viruses (adenovirus, herpesvirus, coronavirus, parvovirus, etc.) have a limited host range, with related but distinct agents occurring in different species.

Attempts to protect susceptible zoo and wildlife animal species against CD have sometimes had regrettable consequences. Modified-live CDV vaccines, intended for use in the domestic dog, may themselves be fully lethal to some animals, for example black-footed ferrets and lesser Pandas [14, 15]. The black-footed ferret was almost rendered extinct because of CDV vaccine-induced

encephalomyelitis. Another colony was found but almost lost to natural CDV infection; fortunately a small group of these animals survived and has formed the nucleus of a breeding colony in attempts to re-establish this animal [62]. Given this danger to non-domestic animals which are susceptible to CDV, our laboratory has provided killed vaccine (which is not commercially available in the United States) to zoos and wildlife parks for years.

Sporadically, we encounter episodes of CDV inclusion body encephalomyelitis in the dog induced by live vaccine [28]. Such may involve single or (less often) multiple animals. The reason for this occurrence is unclear, given that millions of vaccine doses are administered to dogs yearly without untoward sequelae. One episode was associated with a particular batch of vaccine [20] and perhaps this syndrome results from inadequate attenuation. In the future, subunit vaccines [55], which should be safer, may replace the current whole virus products.

We are continually surprised by the appearance of CD in animals not thought to be at risk for this disease. From 1987, epidemics of a previously unrecognized viral infection killed large populations of seals, porpoises and dolphins in the North Sea, Baikal Lake and the Mediterranean. Mortalities were in the thousands. At first thought to be classical CDV, nucleotide sequencing and monoclonal antibody studies now suggest that these CD-like diseases were caused by closely related but distinct morbilliviruses which have been designated phocid (seal), porpoise and dolphin distemper [10, 22]. Mortalities in fresh water seals in the Baikal Lake,

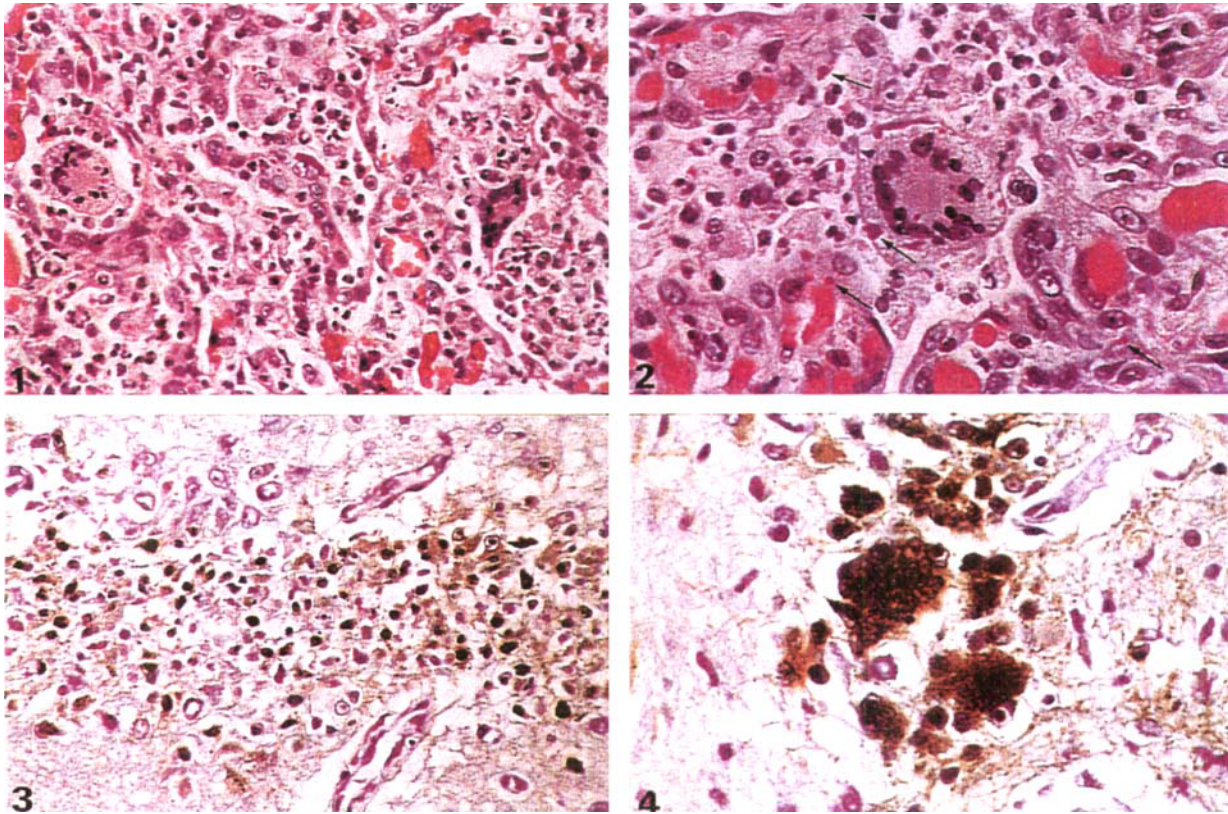


Figure 1. Canine distemper virus (CDV) infection in a tiger. Giant cell pneumonia. H & E. $\times 230$.

Figure 2. Enlargement of an alveolar giant cell. Note the eosinophilic viral inclusions (arrows). H & E. $\times 370$.

Figure 3. CDV encephalitis in a leopard. Infection of granule cells in the hippocampus. Immunocytochemical preparation employing a monoclonal antibody to the viral nucleocapsid. $\times 230$.

Figure 4. CDV encephalitis in a leopard. A group of antigen-positive syncytial astrocytes in the hippocampus. Immunocytochemical preparation employing a monoclonal antibody to the viral nucleocapsid. $\times 370$.

however, appeared to result from infection with conventional CDV [61].

In 1991, we reported [6] the occurrence of CDV infection in javelinas (collared peccaries), a small pig-like feral animal which lives in the south-western states of the USA, Central and South America. Over the last 12 months, we have investigated three separate episodes of CDV infection in lions, tigers and leopards in the USA [7]. Seventeen animals died in the largest focus in California: CDV-infected raccoons are thought to be the source of this outbreak. Most affected cats were initially lethargic and anorexic with gastrointestinal and/or respiratory signs, but subsequently developed seizures and succumbed (Figures 1–4). Before these episodes we would not have considered these large cats to be susceptible to CDV. Experimental infection of domestic cats with CDV in the 1970s showed virus replication and seroconver-

sion but no evidence of disease [3]. What precipitated these episodes of CD in zoo cats is not known; concurrent infection with immunosuppressive feline lentivirus or oncovirus are possible factors. Serum samples made available to us from separate populations of circus lions and tigers have shown that many animals were seropositive and so have been exposed to CDV. In contrast, most exotic felids kept isolated in zoos were seronegative.

There is a single report of natural CDV encephalitis in a monkey (*Macaca fuscata*) [63] and at times the issue of human infection has been raised. Most relevant to this discussion was the intriguing proposal that CDV may be the aetiological agent of multiple sclerosis (MS). Measles virus (MV) has been a prime MS candidate for a number of years and CDV is a closely related paramyxovirus which can produce demyelination of the CNS in the dog. The CDV–MS association was raised because of an

apparent connection between prolonged pet animal contact and some cases of MS [18]. Thus MS would be a zoonosis, an animal infection transmissible to man; in subsequent reports, dogs and CDV specifically became the focus of attention. A flurry of epidemiological and serological studies followed which largely failed to support a dog-MS association [4, 59]. MS has continued to be seen in some countries in which dog numbers were diminished (such as Iceland) and more widely in the western world despite the dramatically reduced incidence of CDV infection in dogs following the introduction of effective vaccines three decades ago. If MS represents the delayed expression of a childhood infection with CDV, the children of small animal veterinarians and perhaps dog breeders would be at increased risk for exposure to canine agents such as CDV and should (as adults) develop MS in above-average numbers. Particularly this would have been so before effective CD vaccines became available.

As well as MS, ownership of a family dog has been implicated in other diseases of man such as lupus erythematosus and Paget's disease of bone [32, 41, 46]. CDV has not been associated with human lupus but has been incriminated in Paget's disease. Recent *in situ* hybridization studies have suggested that in some cases of Paget's disease, the well-recognized inclusions in osteoclasts are CDV [25] although MV, respiratory syncytial virus and parainfluenza type 3 were among earlier proposals.

Canine distemper: a demyelinating encephalomyelitis

The CNS lesions produced by CDV and their pathogenesis have been under investigation for years, most actively since the 1960s. In part because of the need to maintain or have access to a distemper-free dog colony, few groups have participated in this work. The main investigators have been at Ohio State University, the University of Bern and our group at Cornell. Some investigators in other centres have yielded to the temptation to study CDV encephalitis in smaller and more convenient laboratory animals such as mice and hamsters [11, 21]. Although these studies have yielded interesting data, we remain concerned about the conclusions drawn when a (canine) virus is transmitted to an unnatural host by intracerebral inoculation. For example, a mouse model has been employed 'to investigate the basis of CDV

neurotropism' [11]. In an elegant demonstration of viral proteins and mRNA in this mouse model, the investigators concluded that cerebellar, ependymal and meningeal infection were lacking, all sites which are consistently positive in the dog. It is our belief that biologically relevant data will most likely be forthcoming from studies of an infectious agent in its natural host, transmitted by the normal route. Thus our studies with CDV *in vivo* have used specific-pathogen-free dogs infected by intranasal inoculation. For human agents, experimentation in the natural host is not possible: then animal models are the only alternative.

Naturally, not all dogs infected with CDV die; this varies with the viral strain under experimental conditions, and may also vary in nature. There is also a great variation in mortality rates among different species. A number of studies have addressed the question of protective immune responses in CD. Prompt humoral and cellular antiviral immune reactions are found in recovering dogs, are delayed in persistently infected dogs and are lacking in animals which die [2, 5, 35]. Viral neutralizing antibodies are directed against the envelope glycoproteins while cytotoxic cellular responses developing 1–2 weeks post-infection are associated with recovery [5, 47]. Based on histopathological and CSF interferon studies of experimental CDE [49, 52, 57], we feel that in a CDV-infected dog, the virus gains access to the CNS in virtually all cases. In some it is successfully cleared and the damage done is minimal. In other dogs, it persists and these animals develop clinical encephalomyelitis which can vary from acute to chronic. Remitting-relapsing disease has been described [30] but is exceptionally rare.

In the course of experimental studies with CDV in the dog, we found that the presence of CNS infection could not always be detected by signs of neurological disorder (myoclonus, ataxia, etc — see [56] for review). Some dogs with canine distemper encephalomyelitis (CDE) have virus-specific antibody in CSF [60] but this is most consistent in chronic infections. However, the presence of viral encephalomyelitis, whether acute or chronic, is faithfully indicated by the presence of interferon in CSF [57]. In contrast to CSF, serum interferon lasts only for about 2 weeks post-infection. If interferon was absent from CSF, post-mortem studies showed that CDV could not be demonstrated in or recovered from the brain and histopathology showed only mild, focal gliosis indicative of a resolving encephalitis. The presence of

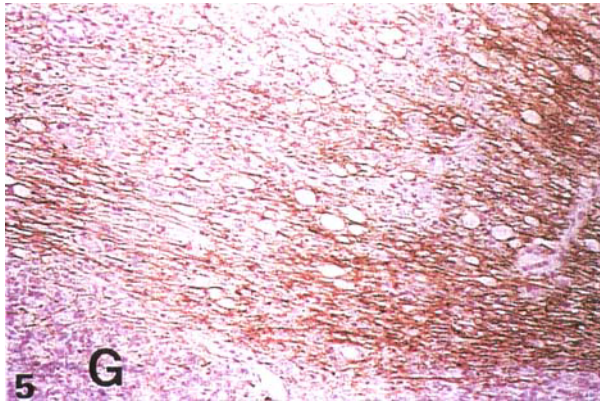


Figure 5. CDV encephalitis in a dog. Large area of myelin loss in the cerebellar white matter (G is granule cell layer). Immunocytochemical preparation employing a polyclonal antibody to myelin basic protein. $\times 95$.

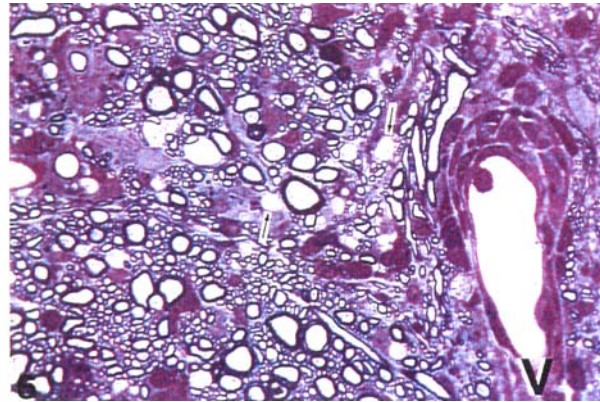


Figure 6. CDV myelitis in a dog. Spinal cord white matter. The blood vessel (V) has a perivascular cuff and a leucocyte is adherent to the endothelium. A few demyelinated axons are evident, some shown by arrows. One micron toluidine blue stained resin section. $\times 370$.

CSF interferon at both the early and later stages of demyelinating encephalitis suggests that its source is from glial cells rather than from lymphocytes.

It is an unexplained curiosity that only some of the morbilliviruses are neuropathogenic. This is a property of CDV, the marine animal distemper viruses and measles but not rinderpest in cattle nor peste des petits ruminants in goats and sheep. CDV induces a panencephalitis in the dog and can be shown to infect virtually all cells in the central nervous system (CNS) both neuroectodermal and mesodermal. There are CDV strain variations however. Some strains (for example Snyder Hill) produce predominantly grey matter disease with little demyelination while others (R252, A75-17) cause white matter disease with demyelination (Figures 5 and 6) [34, 52]. The isolation of the latter two strains was important for allowing experimental study of subacute to chronic demyelinating encephalomyelitis in the dog.

The white matter lesion is a mixture of primary demyelination and some axonal injury, typically with spheroid formation. White matter lesions initially evolve in the absence of haematogenous inflammatory cells (early phase) and viral antigens are most readily demonstrated in early lesions. A lymphoplasmacytic inflammatory component is acquired later and these immunocompetent cells appear to be important for diminished expression of viral proteins [1] and viral clearance [13]. Demyelination occurs in multiple foci wherever the virus has seeded but is consistently to be found in fibre tracts in close proximity to CSF pathways,

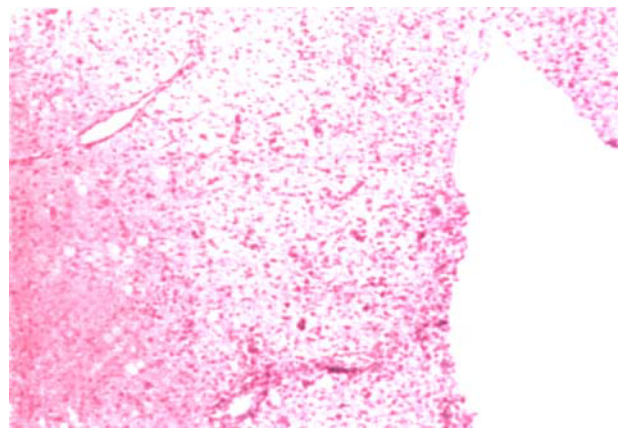


Figure 7. CDV encephalitis in a dog. White matter adjacent to the fourth ventricle to show the periventricular disposition of lesions. H & E. $\times 105$.

such as the rostral medullary velum, cerebellar peduncles and optic tracts. Infection of the choroid plexus epithelium, which occurs early in the course of the disease, results in the shedding of virus into CSF. Furthermore, it appears that the resident macrophages of the surface of the choroid plexus epithelium (Kolmer cells) also become infected, detach into the ventricles and are deposited on the ependymal surfaces. This pathway results in ependymal infection and an ensuing periventricular demyelination (Figure 7) [2, 29, 50]. White matter injury is reflected by elevated levels of myelin basic protein in CSF [54].

In CD, myelin injury has a characteristic spongy quality. Ultrastructurally, there is splitting of myelin lamellae with intramyelinic oedema and macrophage stripping of compact myelin sheaths [45, 53]. Myelin is phagocytosed by macrophages in bulk or as small droplets which are taken up by clathrin-coated pits [53]. The biochemical basis for this spongy myelin injury, characteristic of CDV, is unexplained. It is reminiscent of the effects of tumour necrosis factor on myelin [48] and of the changes found in Canavan's disease, now associated with aspartoacylase deficiency [23]. Demyelination is accompanied by prominent astrocyte hypertrophy in the white matter. CDV infection in astrocytes produces intracytoplasmic and intranuclear inclusions and sometimes astrocytic syncytia. The formation of intranuclear inclusion bodies should be viewed as paradoxical for an RNA virus which replicates entirely in the cytoplasm. This incongruity has recently been clarified by Oglesbee [42]. In brief, his studies show that CDV infection induces a cellular heat shock response which transports viral nucleoprotein into the nucleus.

Although myelinolysis occurs where CDV is present — shown by inclusion body formation, electron microscopy, immunofluorescence, immunocytochemistry and most recently by *in situ* hybridization [65] — virus infection of oligodendrocytes in the brain is difficult to demonstrate [12]. Hence the pathogenesis of the demyelinating lesions in CD has remained a puzzle for years: lytic infection of oligodendrocytes could not be substantiated and immune pathways seemed untenable for a highly immunosuppressive virus. There are interesting parallels between the *in vivo* and *in vitro* situations. Studies of CDV-infected dissociated canine brain cells in culture show oligodendrocyte degeneration and loss but CDV infection of oligodendrocytes could not be demonstrated [64]. Recently it has been reported that oligodendrocytes in culture are indeed widely infected, but the infection is defective and rarely results in translation of viral proteins [66]. It remains to be established whether such a restricted infection of oligodendrocytes can account for their degeneration in culture and whether this scenario is operative *in vivo* also. In our cell culture studies, we also noted the absence of infection in mature oligodendrocytes, while astrocytes, macrophages, fibroblasts and neurons were readily permissive. We did find infection in progenitor cells which had begun to show oligodendrocytic differentiation [44]. Perhaps such early committed oligodendroglial cells are susceptible to con-

ventional CDV infection which is rendered defective with differentiation. A further surprise was that in brain cell cultures the wild type virulent virus induced minimal necrosis while a tissue-culture adapted (vaccinal) virus induced cell lysis and plaques [43].

The early period of non-inflammatory demyelination in the brain is fatal in some dogs while others proceed to a progressive inflammatory phase. This cellular inflammatory response seems to be directed towards virus rather than brain autoantigens and a few dogs with this condition may recover. Although it has been proposed that immune mechanisms may be operative in CDV demyelination [34], immune responses to myelin proteins do not parallel the course of white matter damage and the lesions do not recapitulate those of experimental autoimmune encephalomyelitis [17, 51]. It appears that the inflammatory lesions are more necrotizing with greater axonal injury than the earlier phase, and this could be explained by the release of cytokines from the influx of mononuclear cells. During this inflammatory phase, an antibody-dependent macrophage-mediated release of free radicals has been demonstrated; oligodendrocytes, rich in iron, would be particularly susceptible to injury by such factors [26].

Canine distemper and measles encephalomyelitis

Canine distemper virus (CDV) and measles virus (MV) are two of several related morbilliviruses. In 1985, Norrby suggested that the bovine member of the genus (rinderpest virus) may be the archevirus from which CDV, and later MV, evolved [40]; more recent sequence analyses link rinderpest more closely to MV than to CDV. CDV and MV have similar effects upon their hosts: they induce skin and respiratory tract infections in the young, are highly immunosuppressive, and with dramatically varying frequency (very common in the dog but rare in man) have neurological sequelae. For years, veterinarians have taken advantage of the close antigenic relationship between these two viruses to protect very young puppies against CD. If young pups have maternally-derived antibodies to CDV, this will neutralize CDV vaccines but not MV vaccine. Accordingly, many young pups are vaccinated with MV. The immune response to MV actually does not block CDV infection but an anamnestic immune response prevents the development of disease. At times, there have been expressions of concern

Table 2. Patterns of central nervous system injury in fatal canine distemper and measles virus infections

	CDV	Measles
Inclusion body encephalitis Post-infectious, presumed	Norm	Rare
immune-mediated encephalitis	Rare if ever	Most common
Persistent defective infection of the central nervous system	Rare (old dog encephalitis)	Rare (subacute sclerosing panencephalitis)

about the use of a human agent in dogs. Presumably the apprehension relates to the potential evolution (through mutation) of a highly pathogenic strain. However, MV replicates very poorly in the lymphatic tissues of the dog (although it is satisfactorily immunogenic when given in doses that are 10-fold higher than in human vaccines), is not present in body secretions and so cannot be shed.

Historically, it was recognized from clinical experience that the neurological expression of CDV infection follows the systemic disease although in many dogs this earlier phase passes unnoticed. Early investigators, who studied natural cases of CDE, found that they could not consistently recover CDV from the brain or transmit the disease to other dogs using CNS as the inoculum. Hence, some felt that this was a post-infectious encephalomyelitis, presumably of allergic type. However, failure to recover the agent can be accounted for by the techniques employed: the practice of grinding the tissue, which exposes it to neutralizing antibody, and the use of non-permissive target cells. Further, virus titres seem to fall in cases in which the CNS infection is protracted and often requires explanting brain tissue to successfully isolate the virus [57]. There is no evidence in ordinary CDE that the virus is defective, in contrast to the defective MV found in human subacute sclerosing panencephalitis (SSPE) (see below).

Experimental investigations showed that CDV spreads to the brain and spinal cord during the early viraemic phase of the infection [2]. The delayed clinical expression of CNS disease, particularly of demyelinating encephalitis, simply reflects the slower pace with which CNS damage evolves. We provided evidence that CDV-infected circulating lymphocytes may inadvertently transport the virus to the CNS (and other organs) [49]. Some of the mononuclear cells that we observed were probably infected monocytes. Entry of infected mononuclear cells into the CNS may reflect upregulation of their surface adhesion ligands [8]. Subsequent studies also demonstrated a role for CDV-infected platelets in disseminating

the virus to the CNS [36]. In marked contrast to measles infection in which encephalomyelitis is rare, approximately 50% of dogs with CDV infection develop clinical encephalomyelitis.

From what we know in the dog, it is natural to wonder whether MV produces an early, subclinical encephalomyelitis. Investigators have pursued this question and have shown EEG abnormalities and CSF pleocytosis in some cases of acute, uncomplicated measles [27]. If there is an early episode of MV invasion, what are the consequences for the patient? The natural history of these two diseases show that the probability of neurological sequelae for the dog with CDV infection, and for man with measles, differ considerably. In a dog with systemic CD, development of clinical encephalomyelitis is common. In contrast, encephalomyelitis complicating measles is fortunately infrequent. Despite the (indirect) evidence of early MV entry into the human CNS, inclusion-body measles encephalitis is rare, often occurring only in the face of devastating immunosuppressive diseases such as leukaemia [33] or, in developing countries, with malnutrition [38]. It is proposed that the more common form of measles-associated encephalitis is an autoimmune disorder and is apparently unrelated to the presence of the MV in the neuraxis [24, 31]. No doubt such cases will now be subject to scrutiny by polymerase chain reaction. In Table 2 we have compared the patterns of CNS injury associated with CDV and MV.

Subacute sclerosing panencephalitis (SSPE) is an exceptionally rare complication of measles with diffuse CNS infection with a defective agent [9, 37]. It is tantalizing that there is a rare form of CDE which is known as 'old dog encephalitis' (ODE) [19]. The clinical manifestations of ODE are of prosencephalic disease with depression and a propulsive gait. At Cornell (a centre for the study of neurological disorders in animals) we have not seen a case of ODE in the last 20 years. However, old dogs are certainly at risk of developing conventional CDE and it is probable that some of the purported cases of ODE

in the literature is simply CDE in old dogs. The pathological findings in ODE are multiple thick, almost pure, lymphocytic cuffs and viral inclusions in neurons and glial cells. Demyelination is not conspicuous. In ODE, the infection may be defective for virus could not be recovered from the brain, in contrast to conventional CDE [58]. Clearly, ODE occurs much too infrequently to be of any practical value for comparative studies. With widespread MV immunization in man, the number of cases of measles has declined, as will cases of SSPE [33]; CDV vaccination may similarly protect against delayed sequelae — ODE — in the dog.

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