REVIEW

COMPARATIVE ASPECTS OF PATHOGENICITY OF MEASLES, CANINE DISTEMPER, AND RINDERPEST VIRUSES

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(Received, January 21, 1980. Accepted, March 28, 1980)

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Morbillivirus subgroup of family Paramyxoviridae consists of measles virus (MV), canine distemper virus (CDV), and rinderpest virus (RV). Similarities in their biological and virological properties as well as their serological correlation have been well established (Imagawa, 1968; Waterson et al., 1963; Yamanouchi et al., 1970a; Orvell and Norrby, 1974). Moreover, similarities in pathogenicity are also noticed in their respective natural hosts, i.e., measles in humans, distemper in dogs, and rinderpest in cattle.

Recently, increasing attention has been paid on pathogenicity of MV since MV causes not only acute measles but also slow virus infection, i.e. subacute
sclerosing panencephalitis (SSPE). In addition, MV is suspected of causing some chronic central nervous diseases such as multiple sclerosis (Adams and Imagawa, 1962), and autoimmune diseases such as systemic lupus erythematosus (SLE) (Zhdanov and Parfanovich, 1974). Accordingly, interactions between MV and the host's immune system have become the subjects for intensive study to understand in vivo pathogenicity of MV and to clarify the potential of MV as an etiological agent of such chronic diseases.

MV infection in macaque monkeys has been used as a sole animal model which closely resembles MV infection in humans (Sergiev et al., 1960; Nii et al., 1964; Yamanouchi et al., 1970, 1973). However, experimental MV infection in these animals is of mild nature and can be roughly compared to the cases of vaccination with live measles vaccine in humans. In addition, difficulty in procurement of measles-susceptible monkeys as well as worldwide shortage of monkeys for biomedical research limit the efficient use of this animal model.

Because of close relationship among MV, CDV and RV, one may speculate similar aspects in their pathogenesis. In this sense, experimental infection of laboratory animals with CDV or RV seems to provide a useful approach to study pathogenesis of MV infection from the standpoint of comparative virology.

This review briefly summarizes the findings on pathogenesis of MV, CDV, and RV in laboratory animals with a hope to give some clue to understand the pathogenesis of acute measles and other related chronic diseases.

1. Pathogenesis

1.1. Pathogenesis of MV infection

*Humans.* General clinical course of measles was described in detail by Kempe and Fulginiti (1965), and can be summarized as shown in Fig. 1 by adding some virological and immunological information.

The virus invades the host through the respiratory tract and infection initiates at the regional lymph nodes in the respiratory system. By the primary viremia in a form of virus-infected leukocytes, virus infects various lymphoid tissues including the spleen and lymph nodes leading to the secondary viremia. Virus growth in the lymphoid tissues results in the production of the Warthin-Finkeldey-type giant cells characteristic to MV infection and may induce marked destruction of lymphocytes, which is presumed to be the cause of decrease of peripheral blood lymphocytes including both T and B cells (Wesley, Coovadia and Henderson, 1978). Such virus-induced damage on lymphocytes may be the cause of the immunosuppression, which usually occurs 2–5 weeks after MV infection as discussed in the section 3.1. of this review.

Histological changes in the lymphoid tissues of humans in normal course of measles have not been well investigated. Limited data on autopsy cases of fatal measles indicate degenerative and/or necrotic changes mostly in the thymus and less frequently in the peripheral lymphoid organs such as the spleen, lymph nodes, Peyer's patches, and tonsils (White and Boyd, 1973; Chino et al., 1979), in addition
to the giant-cell formations.

The secondary viremia spreads the virus infection to the epithelial tissues. Although growth of measles virus at the sites of the skin rashes is still controversy (Kimura, Tosaka and Nakao, 1975), the demonstration of virus antigen in the biopsied skin (Suringa, Bank and Ackerman, 1970; Olding-Stenkvist and Bjorvatn, 1976) is compatible with the hypothesis of Burnet (1968) that enanthema, usually called Koplik's spot, and exanthema are produced as a result of T cell-mediated delayed-type hypersensitivity to virus antigen in the mucous membrane and epidermal cells, respectively.

During MV infection, strong immune response develops; anti-viral antibodies such as virus-neutralizing, hemagglutination-inhibition, and complement-fixing antibodies are produced around 14 days after infection. Development of cell-mediated immunity is also suggested by the detection of cytotoxic T cells (Kreth, ter Muelen and Eckert, 1979), positive macrophage-migration inhibition (Utermohlen and Zabriskie, 1973) and virus-specific lymphocyte blastogenesis (Ruckdeschel, Graziano and Mardiney, 1975; Kreeftenberg and Loggen, 1977).

The virus grown in the epithelial cells of the lung is excreted by coughing and transmit the infection to other susceptible persons. In rare cases, giant-cell pneumonia develops, and invasion of the virus into the central nervous system
(CNS) leads to measles encephalitis in rare cases.

In vitro studies indicate that MV can grow in lymphoblastoid cell lines of both T and B cell types (Joseph, Lampert and Oldstone, 1975; Sullivan et al., 1975; Barry et al., 1976; Minagawa et al., 1976; Minagawa and Sakuma, 1977). In small lymphocytes, MV is thought to exist in a silent state that can be activated to produce mature virus in lymphoblastoid cells (Osunkoya et al., 1974a,b; Lucas et al., 1978). Virus-infected small lymphocytes may carry the virus to various parts of the body particularly to the epithelial tissues and the brain.

Monkeys. Pathogenesis of MV infection has been studied in macaque monkey such as rhesus and cynomolgus monkeys by several groups (Sergiev et al., 1960; Nii et al., 1964; Yamanouchi et al., 1970, 1973; Tajima and Kudo, 1976). We compared histopathological changes and virus growth patterns in the lymphoid tissues of cynomolgus monkeys with various types of MV including live attenuated vaccine strains, laboratory strains, and wild virus in throat washings of measles patients or of the homogenate of the lymphoid tissues of the monkeys inoculated with the throat washings of measles patients. No clinical sign of the disease was noticed in the monkeys regardless of the virus strains. Only wild MV produced typical Warthin-Finkeldey-type giant cells in various lymphoid tissues. MV antigens were demonstrated in these giant cells suggesting formation of giant cells as a result of virus growth in situ (Yamanouchi et al., 1970, 1973).

Time course of wild MV growth and histological changes are of transient nature as illustrated in Fig. 2. The other strains of MV including unattenuated laboratory strains passed only for one or two generations in cell cultures failed to produce histological changes except a few strains which sometimes produced giant cells in the localized areas of the spleen.

Thus, the wild virus which was not adapted to grow in cell cultures in vitro is considered to maintain virulence at some degree in monkeys. Yet, general clinical patterns are much milder than those in measles in humans. Enhancement of clinical signs or of histological changes by the immunosuppressive treatments of monkeys with anti-thymocyte serum (ATS) or cyclophosphamide was not effective (Yamanouchi et al., unpublished).

Spontaneous MV infection mostly without marked clinical signs occurs very frequently in macaque monkeys after they are brought into human society (Yamanouchi, Shishido and Honjo, 1973). However, severe epizootics of MV infections rarely occur (Potkay et al., 1966; Hall et al., 1971). In these cases, typical clinical signs of skin rashes and fever as well as marked histological lesions are observed. Giant cells are abundant in the lymphoid tissues and lung. Factors determining such severe clinical course in contrast to subclinical infections in most of the monkeys are unknown.

There are evidences indicating that marmosets have higher sensitivity to MV infection than macaque monkeys. In a marmoset colony, spontaneous MV infection resulted in deaths of 326 animals with giant-cell pneumonia (Levy and Mirkovic, 1971). Experimental infection was also reported to cause fatal disease in which marked necrotic lesions of the lymphoid tissues were characteristics
Fig. 2. Virus growth and histological changes in lymphoid tissues of MV-infected monkeys.

(Klutch, Lorenz and Albrecht, 1979). It is interesting that giant-cell formations are rarely observed in the lymphoid tissues of these animals in contrary to the findings in humans and macaque monkeys. Since marmosets are considered to be partially defective in T-cell responsiveness (Niblack and Gengozian, 1976), this defective immune status might cause abnormal response to MV infection.

By detailed histopathological and immunofluorescent examinations on experimental MV infection in cynomolgus monkeys, we found that most of the giant cells consisted of reticulum cells involving lymphocytes less frequently. In the spleen, both the giant cells and virus antigens were most frequently found in the light zone but not in the dark zone of the germinal center, the former consisting mainly of reticulum cells and the latter of stem cells and lymphoblasts. The mantle zone of the lymph nodes in which small lymphocytes are the major population also lacked the giant cells or virus antigens. Accordingly, reticulum cells are suggested to serve as the major site of virus growth (Yamanouchi et al., 1973; Chino and Yamanouchi, 1974).

Significance of efficient virus growth in reticulum cells in the germinal centers remains to be clarified. These dendritic reticulum cells are generally thought to play such important immunological roles as antigen trapping and presentation (Hanna and Hunter, 1971). Therefore, virus growth in these cells might provide an effective antigenic stimulus to produce strong antibody response. It may cause
also the persistence of immunological memory by producing a large number of memory cells since the germinal center is considered to be the central site for the production of immunological memory (Nossal et al., 1968).

1.2. Pathogenesis of CDV infection

General course of natural distemper was described in detail by Appel and Gillespie (1972). Infection is initiated through the respiratory tract, which is considered to be the natural route of transmission. Clinical course varies among dogs, even among puppies of the same litter, some of which develop inapparent infection and others fatal infection. The most characteristic clinical sign is fever with a bimodal pattern; the first occurs 3–6 days pi and the second several days after the first. Respiratory signs including cough and coryza and such gastrointestinal signs as diarrhea and vomiting are also manifested. As skin lesions, rashes and pustules of the abdomen are sometimes observed; the latter is considered to be caused by bacterial complication.

Virological studies on CDV pathogenesis were conducted by Appel (1969) in experimental infection of SPF dogs by aerosol exposure to virulent CDV. In 2 days, viral antigen is found in mononuclear cells, which are probably macrophages, in the bronchial lymph nodes and tonsils. During the first week pi, leukocyte-associated viremia follows and viruses spread rapidly to the spleen, thymus, bone marrow, various lymph nodes, lamina propria of the intestines, and Kupffer cells in the liver.

Neutralizing antibody is detected 8–9 days pi. Most dogs show rapid antibody rise and virus antigen is eliminated within 2–3 weeks in these dogs, whereas in the other animals that fail to produce protective antibody level, viral antigen tends to persist in the epithelium of the alimentary and urogenital tracts, and exocrine and endocrine glands in addition to the distribution mentioned above. Thus, correlation between virus elimination and antibody response is suggested.

Lymphoid necrosis with reticulum cell hyperplasia is the primary feature of histological lesions. Multinucleated giant cells and inclusion bodies are also demonstrated.

Marked lymphopenia is found in the peripheral blood from 1–7 weeks pi. Depletion of lymphocytes in the lymphoid tissues is also observed. Electronmicroscopically, accumulation of viral nucleocapsids is demonstrated in lymphocytes in the thymus and lymph nodes (McCullough, Krakowka and Koestner, 1974). Therefore, the destruction of lymphocytes is considered to be the result of viral cytopathic effect caused by virus growth in situ. Similar histological and ultrastructural findings were reported for minks infected with mink-passed CDV by Tajima, Itabashi and Motohashi (1971). As one of the mechanisms for lymphopenia in virus infections, effect of corticosteroid secretion, which is triggered by stress from virus infection, has generally been postulated. This possibility was investigated by observing the lymphoid lesions in CDV-infected adrenalectomized dogs (Jacoby and Griesemer, 1970). Although adrenalectomy before CDV inoculation exhibited little influence on the intensity, character, or duration of CDV-
induced leukopenia, the extent of depletion of small lymphocytes in the lymphoid tissues was significantly diminished. Thus, the lymphoid lesions were suggested to be partially mediated by the adrenal glands, most probably through adrenocorticosteroid secretion.

The virulence of CDV correlates well with the capacity to grow in macrophage cultures in vitro (Appel, 1978). Virulent CDV grows well in cultures of dog alveolar macrophages showing cytopathic effect, whereas attenuated CDV does not. Adaptation to in vitro growth in epithelial cells leads to the loss of virulence as well as the loss of capacity to grow in macrophage cultures. Moreover, reversion of virulence was noticed after serial passages of attenuated CDV in dog alveolar macrophage cultures.

Natural distemper sometimes leads to distemper encephalitis and hyperkeratosis, so-called hard pad disease. Although most dogs quickly recover from CDV infection, virus spreads to the epithelial tissues infecting such cells as epidermal cells and neurons in dogs which fail to mount enough antibody response, and tends to persist in these cells. Such virus persistence in the epidermal cells of the footpads and in the brain is considered to result in hard pad disease and distemper encephalitis, respectively.

1.3. Pathogenesis of RV infection

**Cattle.** Clinical course of natural rinderpest in cattle was described by Plowright (1968) and can be briefly summarized as follows. Infection is considered to occur through the respiratory tract. The clinical course is divided into prodromal, mucosal and convalescent phases. After an incubation of 2–9 days, the disease is initiated by the prodromal phase, which is recognized by a sudden onset of fever. At this phase, high titers of virus are demonstrated in various lymphoid tissues and mucous membranes of the intestines. Virus growth occurs also in the nasal mucosa and lungs.

The mucosal phase is characterized by the appearance of oral lesions consisting of necrotic foci, superficial erosion and capillary hemorrhages in the mucosa of the oral cavity. Skin lesions considered to be analogous to the exanthema of measles developed. Unlike measles, the skin lesions are not produced consistently, and tend to appear more frequently with a virus strain of low virulence. Diarrhea appears 4–7 days after the pyrexia and 1–2 days after the mucous and skin lesions.

Since rinderpest is a highly dangerous infectious disease of cattle causing severe economical damages, handling of virulent RV is strongly prohibited. Therefore, virological studies on RV infection in cattle is very limited.

**Rabbits.** Fukusho and Nakamura (1940) developed live attenuated RV vaccine by passages of virulent RV more than 1,000 times in rabbits. This lapinized RV (L strain) does not show any virulence in cattle but is highly virulent in rabbits. We examined extensively experimental infection with this RV in rabbits (Yamanouchi et al., 1974a, b; Chino and Yamanouchi, 1974). Intravenous (iv) inoculation of rabbits with RV L strain in a homogenate of the virus-infected lymphoid tissues of rabbits results in the development of fever higher than 40°C and severe
diarrhea 2–4 days pi. Skin lesions are not produced. These clinical signs disappear rapidly and rabbits become apparently normal within 7–10 days.

Histologically, formation of giant cells and necrotic changes are characteristic lesions in the lymphoid tissues. Virus antigens are demonstrated by the immunofluorescent technique corresponding to the development of these histological lesions.

Time sequential changes in the degree of histological lesions and the amount of virus antigen are schematically illustrated in Fig. 3. Although all the lymphoid tissues are affected by the virus, the mesenteric lymph nodes and the gut-associated lymphoid tissues such as Peyer's patches, cecal tonsils and sacculus rotundus appear to be attacked by virus most severely as primary target tissues. The most marked necrosis of lymphoid cells is observed in these organs, but giant cells are only transiently demonstrated. These necrotic lesions in the intestinal lymphoid tissues may probably be involved in the manifestation of diarrhea. In contrast, the superficial lymph nodes, thymus, and spleen show more marked formation of giant cells at higher degrees and lymphoid necrosis at relatively a lower degree than the
other lymphoid tissues. No significant histological changes nor virus antigens are detected in the bone marrow. These lymphoid lesions are rapidly repaired and virus antigens are similarly eliminated within 10 days in spite of their severe nature. After 10 days, virus antigens tend to persist for additional several days in the mucosal tissues of the intestines.

These general patterns of histological changes and virus growth indicate that RV affects primarily the lymphoid tissues as the major target and subsequently the epithelial tissues.

2. IMMUNE MECHANISMS IN RECOVERY FROM PRIMARY INFECTION

2.1. Recovery from MV infection

Immune mechanisms are considered to play essential roles in recovery from primary virus infections. Currently the following two approaches are generally employed to study this problem. The first, observations of the clinical course of virus infections in patients with various types of immunodeficiency provide an indirect proof for relative importance of humoral and cell-mediated immunities as the recovery mechanism (Allison, 1974). The second, immunosuppressive treatments of laboratory animals provide an experimental situation similar to those in the immunodeficient patients that is so-called “experiment of nature” (Good and Zak, 1956).

The first approach has been employed for studying the recovery mechanism from MV infection in humans. Fatal measles pneumonia is known to occur frequently in children whose cell-mediated immune functions are impaired but with normal levels of immunoglobulin (Nahmias et al., 1967), whereas MV infection in children with X-linked agammaglobulinemia, who lack the antibody production but retain the cell-mediated immune functions at normal level, takes the normal course indistinguishable from that in children with normal immune capacities (Good and Zak, 1956). Thus, cell-mediated immunity is considered to be of special importance in recovery from measles (Burnet, 1968).

In contrast to these findings in immunodeficient patients, Chino et al. (1979) found neither hypoplastic nor aplastic thymuses in 14 fatal cases of measles pneumonia and encephalitis, suggesting fatal course of MV infection in the presence of intact thymus functions. This finding indicates that immune functions other than cell-mediated immunity may also be involved in the recovery mechanism.

MV infection in children with malnutrition frequently shows aggravated course (Dossetor, Whittle and Greenwood, 1977; Axton, 1979). Although malnutrition seems to cause some impairment of immune functions, details are unknown.

Motility of neutrophils is reported to decrease significantly at the acute stage of measles and recover quickly 11 days after rash (Anderson et al., 1976). As to the mechanism for such neutrophil dysfunction, the following three possibilities are suggested; (1) direct virus infection of neutrophils, (2) overconsumption of energy source due to the ingestion of a large amount of antigen-antibody complex, and (3)
an increased corticosteroid level due to the stress by virus infection. Since fatal measles pneumonia is usually complicated with secondary bacterial infection, possibility of the fatal outcome caused by severely impaired neutrophil function may have to be considered.

The second approach in laboratory animals is difficult because of lack of a suitable animal model. We failed to aggravate the clinical course or increase the intensity of the histological lesion by treatment of cynomolgus monkeys with ATS or cyclophosphamide at the time of inoculation with wild MV (Yamanouchi et al., unpublished), although the treatment with the same lot of ATS caused a marked depletion of T-dependent areas in the lymphoid tissues in control monkeys and increased mortalities in monkeys inoculated with other viruses such as vaccinia or varicella viruses (Chino et al., unpublished).

The failure in aggravation of MV infection in such partially immunosuppressed monkeys may have been due to the essentially mild nature of MV infection in monkeys.

2.2. Recovery from CDV infection

Correlation between rapid antibody response and virus elimination from the target organs was pointed out in experimental CDV infection in SPF dogs (Appel, 1969) as mentioned in the Section 1.2. In animals, which showed delayed rise of neutralizing antibody or failed to produce protective antibody level, fatal encephalitis developed, whereas those with rapid antibody response recovered. From this finding, relative importance of antibody in recovery from CDV infection is suggested.

Thus far, effect of immunosuppression on the course of CDV infection has not been reported.

2.3. Recovery from RV infection

Experimental approach by the immunosuppression has been attempted by us to analyze the recovery mechanism from RV infection in rabbits (Kobune et al., 1976). Treatment of rabbits with ATS or combined treatment with adult thymectomy and ATS, both of which were confirmed to suppress significantly cell-mediated immunity in rabbits, failed to alter the recovery process, in terms of clinical signs, of virus clearance from the blood and lymphoid tissues, and of repair of the lymphoid lesions.

On the other hand, whole body irradiation with 800 R of r-ray aggravated the clinical course of RV infection, resulting in an increased fatality rate (Kobune, Chino and Yamanouchi, to be published). Histological examinations revealed marked necrosis and hemorrhages in the lymphoid tissues, hemorrhages and ulcers in the gastrointestinal tract, and decrease of hematopoietic cells and hemorrhages in the bone marrow. In contrast, rabbits whose femur was shielded with a thick lead plate during r-ray irradiation recovered from RV infection. Histological changes in these irradiated animals under shielding were also similar to those in untreated rabbits except for slight atrophy of the thymus in the
formers. These results suggest an important role of the radiosensitive bone marrow cells in recovery from RV infection. Accordingly, the relative role of neutrophils and macrophages as bone marrow cells was investigated in selective suppression experiments. Selective suppression of neutrophils was attempted by the iv administration of nitrogen mustard but failed to modify the clinical course of RV infection. In contrast, suppression of macrophages by the iv administration of carageenan or silica resulted in fatal RV infection with histological lesions essentially similar to those observed in the r-ray experiment. Delayed treatment with carageenan later than 4 days pi, however, was ineffective in aggravation of the clinical course and all animals survived. These results indicate the essential role of macrophages probably as an early defense mechanism.

3. IMMUNOSUPPRESSION DURING INFECTION

3.1. Immunosuppression in MV infection

In 1908, von Pirquet noticed unresponsiveness of measles patients to the tuberculin skin test, so-called tuberculin anergy. Such depression of delayed type hypersensitivity is not restricted to tuberculin, but to many other skin test antigens such as candida, diphtheria toxoid and vaccinia virus. Contact sensitivity to poisonous ivy and 2,4-dinitrochlorobenzene is also suppressed. Live measles vaccine is also shown to cause such immunosuppression but at a milder degree than natural measles (Brondy, Overfield and Hammes, 1964; Fireman et al., 1969). Thus, MV infection is proved to induce overall suppression of cell-mediated immunity.

Marked lymphopenia involving both T and B cells occurs during natural measles. The decrease of T cells seems to be related to the general suppression of cell-mediated immunity. Although the serum Ig level remains almost normal during measles, the decrease of B cells may indicate the possibility of suppression of antibody production to antigenic stimulus as well (Wesley, Coovadia and Henderson, 1978).

The MV-induced immunosuppression usually occurs at the acute stage and persists for 4–6 weeks, and even for a year in some cases. This means that the recovery in immunological function delays for at least 2–3 weeks or longer than the recovery in clinical signs (Wesley, Coovadia and Henderson, 1978).

The mechanism of MV-induced immunosuppression is unknown. Burnet (1968) speculated that recruitment of a large number of T cells to the site of MV growth may cause transient reduction in the number of T cells which can react to other antigens. Finkel and Dent (1973) noticed impaired in vitro proliferative response of the peripheral blood lymphocytes to phytohemagglutinin (PHA) during acute measles, but only at a suboptimal dose of PHA. Since T-cell response to the suboptimal dose of PHA is more dependent on macrophages than to the optimal dose, they suggested that the major effect of MV may be on macrophages rather than on lymphocytes.

Several reports confirmed the finding that MV can infect both T and B lymphocytes in vitro as described in the Section 1.1. MV infection in vitro was also
shown to induce suppression of lymphocyte response to PHA and purified protein derivatives (PPD) or Old Tuberculin (Zweiman, 1971). However, it is premature to elucidate the in vivo immunosuppression mechanism from these in vitro studies since so many variable factors in culture condition are involved in vitro lymphocyte response and moreover these studies employ lymphocytes collected from measles-immune donors.

Experimental approach to the mechanism of MV-induced immunosuppression was attempted by McFarland (1974) using the mouse system of cell co-operation for production of an anti-hapten response. In the mice infected with a hamster brain-adapted HNT strain, suppression of antibody production to hapten, 2,4-dinitrophenyl, was demonstrated. By the passive transfer of spleen cells of the virus-infected mice to irradiated uninoculated mice, the spleen cells from carrier-primed mice showed decreased helper function but the spleen cells from hapten-primed mice showed normal antibody response. This result indicates that MV suppresses helper T-cell activity.

Very recently, we examined the effect of MV infection in guinea pigs on delayed-type hypersensitivity (Yamanouchi et al., to be published). MV infection in tuberculin-sensitized guinea pigs caused transient suppression of skin reaction to PPD. In spite of the suppressed state in skin reaction, spleen cells responded normally to PPD in vitro. On the other hand, these animals showed suppressed skin reaction to a skin-reacting factor (SRF), i.e., supernatant obtained from the tuberculin-sensitized spleen cells cultured in vitro with PPD. Since SRF is considered to be lymphokine mediating skin reaction, these results may indicate that MV infection affects the stage of cellular infiltration at the skin reaction site but not the stage of lymphokine production by T cells.

### 3.2. Immunosuppression in CDV infection

CDV-induced immunosuppression has exclusively been studied in its natural host, dogs. Suppression of cell-mediated immunity during wild CDV infection was reported in the dogs inoculated with R252 strain of CDV, a field isolate with high neurovirulence (Krakowka, Cockerell and Koestner, 1975; Mangi et al., 1976). In the experiments by Mangi et al., CDV infection in susceptible dogs induced profound and prolonged suppression of delayed-type skin reaction to keyhole limpet hemocyanin (KLH) persisting for more than 7 weeks. Since severe lymphopenia occurred together with the immunosuppression in CDV-susceptible dogs, destruction of T cells by CDV infection was speculated as a possible mechanism of immunosuppression. On the other hand, transient suppression of cell-mediated immunity was induced by CDV infection in the dogs previously immunized with CDV vaccine; suppression of the skin reaction to KLH, picryl guinea-pig albumin and PPD was observed 3–21 days pi, and in vitro response of lymphocytes to an antigen such as PPD and KLH as well as to a mitogen such as PHA and Pokewood mitogen (PWM) was also suppressed 3–14 days pi and 3–7 days pi, respectively. No significant alteration in the total count of circulating leukocytes was observed except for a transient increase in circulating T cells.
Therefore, virus-induced destruction of lymphocytes as suggested in CDV-susceptible dogs may not be involved in the mechanism of immunosuppression, and instead antigen competition is postulated.

Krakowka, Cockerell and Koestner (1975) obtained essentially similar results; they noticed decreased in vitro response of lymphocytes to PHA as well as decreased peripheral leukocyte counts in dogs infected with CDV. However, no significant retention of skin allografts over control dogs was observed in CDV-infected dogs despite the depressed lymphocyte activity.

Attenuated CDV fails to suppress response of lymphocytes to PHA, thus the capacity of this immunosuppression was used as one of the criteria for virus virulence (Appel, 1978).

### 3.3. Immunosuppression in RV infection

The immune function of cattle in natural infection with wild RV is not documented.

Immunosuppressive effect of lapinized RV L strain was studied by two groups (Penhale and Pow, 1970; Yamanouchi et al., 1974b). Penhale and Pow demonstrated that RV suppresses antibody production to chicken red blood cells (RBC) in rabbits.

We showed that RV suppresses both humoral and cell-mediated immunities in rabbits (Yamanouchi et al., 1974b). The capacity of rabbits to produce IgM antibody-forming cells to SRBC in the spleen was significantly suppressed for 14 days or longer after virus infection. Both IgM and IgG antibodies in the serum were similarly suppressed. In contrast, production of memory cells was not impaired. Delayed-type hypersensitivity to tuberculin was suppressed at both expression and induction phases; delayed-type skin reactions to PPD in tuberculin-sensitized rabbits was completely suppressed for 3–14 days pi or longer after RV infection, and sensitization to tuberculin was inhibited or delayed by RV infection at the time of immunization with Freund’s complete adjuvant. In vitro response of peripheral blood lymphocytes to PHA was also suppressed for 3–28 days pi. Although the effect of virus on lymphocyte subpopulation was not investigated in this study, suppression of antibody production to SRBC may be understood as a suppressive effect on helper T cells. Lack of suppression of memory-cell production, which is relatively independent to T cell-helper function, is compatible with this explanation. In this sense, suppression of both antibody production and delayed-type hypersensitivity may be considered to reflect suppressed cell-mediated immunity.

The time course of immunosuppression closely correlates with that of severe lymphopenia. Marked destruction of the lymphoid tissues involving both thymus-dependent and thymus-independent areas is induced from 3 days pi in association with the immunosuppression, and then these lesions are rapidly repaired. Therefore, the destruction of lymphocytes by RV appears to be primarily responsible for the immunosuppression.

Recently LA strain of RV, that had been further attenuated through passages
in chicken embryos (Nakamura and Miyamoto, 1953) and induced only subclinical infection in rabbits, was shown to induce transient suppression of in vitro response of lymphocytes to PHA and Concanavalin A 3–7 days pi (Fukuda and Yamanouchi, to be published). Although LA strain produces histological lesions of giant cells in the lymphoid tissues indicative of virus growth in situ, necrotic lesions are not detected. This finding also supports the hypothesis of the immunosuppression mechanism primarily due to the destruction of lymphocytes.

4. Autoimmunity

4.1. MV and autoimmunity

The concept that virus may act as a trigger for development of autoimmunity has been proposed by the demonstration of various types of autoantibodies after virus infection as well as by the demonstration of virus-like structures in the tissues of patients with autoimmune diseases (Asherson, 1968; Kawano, Millar and Kimmelstiel, 1969; Haas and Yunis, 1970; Laitinen, Vesikari and Vaheri, 1972; Phillips and Christian, 1973; Alekberova et al., 1975; Shirodaria et al., 1979). Among several candidate viruses as triggers for autoimmunity, MV has been paid special attention.

The lymphocytotoxic antibody, which reacts with both the autologous and allogeneic lymphocytes at low temperatures, was detected at a high frequency in the sera of measles patients (Mottironi and Terasaki, 1970). The presence of demyelinating antibody, which destroys the myelin sheath in vitro, was also demonstrated in the sera obtained at the acute phase of measles (Yonezawa, 1971). The presence of DNA with base sequences complementary to RNA of MV was disclosed in the tissues of patients with SLE (Zhdanov and Parfanovich, 1974). Although this finding could not be confirmed in other laboratories, it proposed a unique hypothesis of the integration of conventional non-oncogenic virus as a mechanism of virus persistence which leads to the development of autoimmune diseases (Zhdanov, 1975).

In spite of these findings on clinical materials, no experiment in an animal model of autoimmunity related to MV infection has been reported. We conducted a preliminary study on the monkeys inoculated with MV but failed to detect autoantibodies. Since measles in monkeys is of mild infection as discussed previously in the Section 1.1, development of an animal model with severer clinical course is required for this purpose.

4.2. CDV and autoimmunity

No attempt to detect autoantibodies in natural infection of CDV in dogs has been reported.

Krakowka et al. (1973) demonstrated such anti-myelin antibodies that react to the isolated myelin antigen in the complement fixation test or the immunofluorescent technique in most of the dog sera obtained at various phases of spontaneous demyelinating encephalitis. Demyelinating antibody similar to that detected in
measles patients was also found in the sera of these dogs (Koestner et al., 1974). These anti-myelin responses are considered to be caused by the alteration of the membranes of glial cells by the persistence of CDV in the brain and may be involved in the mechanisms of demyelination.

4.3. RV and autoimmunity

Evidence for autoimmunity in natural infection of cattle with RV is not documented.

In the rabbits infected with L strain of RV, we demonstrated development of two types of autoantibodies, antinuclear antibody (ANA) and cold hemagglutinating antibody (HA) (Fukuda and Yamanouchi, 1976). By the indirect immunofluorescent technique using diploid human embryonic lung cells or rabbit kidney cells as targets, ANA of 7S nature which reacts with the nuclei of the cells is demonstrated in all rabbits 2 weeks after the iv inoculation of RV; the maximum titer reaches up to 1280 or higher 3–4 weeks pi. However, this ANA response is transient and disappears in 6–10 weeks pi. Various treatments to suppress or enhance immune functions failed to modify this ANA response, although levamisole tended to enhance and prolong ANA response to some degree (Fukuda and Yamanouchi, unpublished).

Cold HA also developed transiently from 1–6 weeks pi. This antibody is of 19S nature and is able to react with rabbit RBC, both autologous and allogeneic cells, at 4°C without anti-Ig serum, but does not react with RBC at 37°C. Thus it is considered to be the same type of antibody commonly observed in autoimmune hemolytic anemia which occurs frequently following the infection of mycoplasma pneumonia or infectious mononucleosis. However, any clinical sign of hemolytic anemia has not been detected in these rabbits.

The following mechanisms are generally speculated for virus-induced autoimmunity; (1) cross antigenicity between the virus and self antigens, (2) modified self antigens in viral envelopes, and (3) virus-induced disturbance of the immune regulatory system. Development of these two antibodies showed a transient pattern in contrast to the prolonged or probably life-long pattern of virus-neutralizing antibody. Moreover, the formalin-inactivated virus failed to produce the autoantibodies. Thus, virus infection is considered to act as a trigger of autoantibody production, and the cross-antigenicity appears to be unlikely.

Suggestive evidence for the autoimmune mechanism was obtained by the comparison of the pathogenicity of L and LA strains of RV (Fukuda and Yamanouchi, to be published). L strain which is virulent for rabbits produced marked histological lesions in the lymphoid tissues consisting of both giant-cell formation and necrosis, whereas LA strain which is less virulent for rabbits produced only giant-cell formation but not necrotic lesion. Immunosuppression was more profound and prolonged in L-strain infection than in LA-strain infection. Although virus-neutralizing antibody developed to a slightly higher titer in LA-strain infection, autoantibodies were detected only in L-strain infection. These findings may indicate that virus-induced damage of lymphoid cells as demonstrated by the
lymphoid necrosis is related not only to the immunosuppression but also to the development of autoimmunity. Possibly the virus-induced destruction of lymphocytes may provide a strong antigenic stimulus consisting of the cellular components released in a large amount from the damaged lymphocytes on the host whose immune functions are disturbed by virus-induced immunosuppression.

5. Neurovirulence

5.1. Neurovirulence of MV

Measles is sometimes complicated with encephalitis which occurs about one week or sometimes 1–2 months after rash at an approximate frequency of 0.1%. Pathogenesis of this measles encephalitis has not been well investigated. The presence of intranuclear and cytoplasmic inclusion bodies in the autopsied brains of measles encephalitis is considered to indicate the growth of MV in the brain (Adams, Baird and Filloy, 1966). Only one report claims the isolation of MV by co-culture of patient’s brain with Vero cells (ter Meulen et al., 1972). Increased MV-neutralizing antibody in the cerebrospinal fluid (CSF) can also be taken as an indirect proof for the growth of MV within the brain (Skoldenkerg et al., 1976).

The mechanism of invasion of MV into the CNS is unknown. Whether the low frequency of measles encephalitis reflects that of virus invasion into CNS or that of onset of neurological symptoms provided that MV invades at much higher frequency is still controversial. During natural measles and even after measles vaccination, abnormal patterns of electroencephalogram are noted in approximately 50% of patients (Gibbs et al., 1959; Pampiglione, Griffith and Bramwell, 1971). If this indicates direct attack on CNS by virus, the latter possibility seems to be more likely. However, an indirect effect of virus pathogenicity outside CNS remains to be clarified as an alternative possibility as a cause for the abnormal electroencephalogram.

Demonstration of the association of MV with SSPE has stirred much attention on the neurovirulence of MV. Thus, numerous studies have been reported within these 10 years for the neurovirulence of measles and SSPE viruses in laboratory animals including monkeys, mice, hamsters and ferrets. These results are well described in several reviews (ter Meulen, Katz and Muller, 1973; Agnarssdottir, 1977; Morgan and Rapp, 1977; Fraser and Martin, 1978), therefore the present review will deal only with the recent findings obtained in animal models.

In spite of the apparent capacity of MV to produce both acute and slowly progressing encephalitis in humans, production of such CNS diseases in laboratory animals seems very difficult. Thus far, production of acute encephalitis is limited to rodents except for a few reports in monkeys. Moreover, the neurovirulence in humans and laboratory animals appears not to correlate to each other significantly. For instance, some attenuated vaccine strains show higher neurovirulence in newborn mice and hamsters than do wild MV strains (Shishido et al., 1973).

As to the susceptibility of laboratory animals to the CNS infection with MV,
hamsters and ferrets appear to have relatively high susceptibility followed by mice in spite of their relative resistance to systemic infection with MV. It is rather peculiar that neither clinical signs nor histological lesions of CNS was observed in the monkeys intracerebrally inoculated with MV in spite of their high susceptibility to the systemic infection as indicated by the virus growth in the lymphoid tissues. In neurovirulence tests of several strains of attenuated measles vaccines, we have never observed significant histological lesions in CNS of the monkeys intracerebrally inoculated. The wild MV, contained in homogenate of the MV-infected monkey lymphoid tissues, produced typical giant cells in the lymphoid tissues but failed to produce the CNS lesions (Yamanouchi et al., 1976). Thus far, the significant histological lesions in CNS of the monkeys were reported only for the HNT strain which is a hamster-brain adapted virus and apparently retains high neurovirulence in various rodents (Albrecht et al., 1972).

Production of chronic CNS disease by measles or SSPE virus as a model for the study of pathogenesis of SSPE is one of the intensive research subjects in many laboratories. However, only acute encephalitis is produced and models of chronic encephalitis are limited.

As a cell-free SSPE virus, HBS strain obtained by adaptation of SSPE Mantomtooth strain into the hamster brain was shown to produce subacute encephalitis in weanling hamsters, whereas the same virus produced acute encephalitis in newborn hamsters (Johnson and Norrby, 1974). The cell-associated SSPE viruses usually exhibit high neurovirulence not only in newborn animals but also in adult animals (Katow et al., 1973; ter Meulen, Katz and Kackell, 1973). Most of animals succumb to acute encephalitis. However, histological lesions are mainly of neuronal degeneration and cellular infiltration in limited areas of CNS. In animals with immunity to MV at appropriate degrees, chronic encephalitis involving larger areas of CNS can be produced as shown in the hamsters inoculated with the Niigata-1 strain (Katow et al., 1973), ferrets with D. R. strain (Thormar, Arnesen and Mehta, 1977) and rhesus monkeys with IP 3 strain (Albrecht et al., 1977). These results indicate an importance of immune status of the hosts in the course of virus-induced encephalitis.

5.2. Neurovirulence of CDV

In natural distemper in dogs, the CNS disease mostly associated with demyelinating encephalomyelitis occurs frequently several weeks or months after the first sign of the disease; the frequency of distemper encephalitis is 10–30%, which is much higher than that of measles encephalitis in humans. Postvaccinal inclusion-body encephalitis following the administration of live CDV vaccine was also reported (Hartley, 1974). In rare cases, old dog encephalitis (ODE), which is considered to be an analog of SSPE in humans, is also induced by the persistence of CDV in the CNS. ODE was first known as disseminated encephalomyelitis of mature dogs. Virological examinations revealed the similarity between ODE and SSPE (Lincoln et al., 1971, 1973); CDV antigens are demonstrated in the gray matter of CNS by the immunofluorescent technique, intranuclear inclusion bodies
are present in neuron and glial cells in which viral nucleocapsids are detected by electron microscopy, and extremely high virus-neutralizing antibody to CDV is demonstrated in the serum. Recently, infectious virus was isolated from eight cases of ODE; all the isolates were cell-free virus in contrast to the cell-associated nature of SSPE isolates (Imagawa et al., 1979).

In contrast to the failure in producing experimental CNS disease in primates with MV similar to natural measles as mentioned in the previous Section 5.1, several strains of CDV were shown to produce demyelinating encephalomyelitis in dogs indistinguishable from natural distemper. Thus, CDV infection in dogs provides a useful model to study the pathogenesis of virus-induced demyelinating encephalitis (Wisniewski, Raine and Kay, 1974; McCullough, Krakowka and Koestner, 1974).

Pathogenesis of distemper encephalitis was studied in experimental infection in SPF dogs by two groups (Appel, 1969; Koestner et al., 1974). Appel pointed the importance of early antibody formation in the defense mechanism; dogs which failed to produce antibody or showed delayed development of antibody developed fatal distemper encephalitis as well as of acute systemic distemper. It is presumed that invasion of CDV into CNS occurs with virus-infected lymphocytes as carrier. Such infection of CNS with CDV seems to be a regular and non-specific event of systemic dissemination of the virus (Summers, Greisen and Appel, 1978). Immunofluorescent examinations revealed CDV antigen in ependymal and meningeal mononuclear cells but not in the blood vessels (Vandevelde and Kirstensen, 1977; Summers, Greisen and Appel, 1978). This finding indicates that virus infection of CNS begins in meningeal macrophages, spreads to mononuclear cells and cerebrospinal fluid (CSF) cells, then to ependymal and glial cells, and finally to neurons. Since the virus antigen was also demonstrated in the neuronal process, involvement of cell-to-cell spread of virus without cytopathic effect seems to be possible as well (Vandevelde and Kirstensen, 1977).

In natural CDV encephalitis, CDV antigen was demonstrated in the gray matter of the brain, especially in necrotizing lesions in a large amount, indicating the direct cytopathic effect in situ. A small amount of virus antigen was found in demyelinating lesions, mainly in the cytoplasmic and nuclear inclusion bodies in astrocytes. Therefore, demyelination is presumed to be mediated by virus-induced damage of astrocyte functions (Vandevelde and Kirstensen, 1977). Similarly, CDV-induced demyelination was demonstrated to be more closely related to virus growth in glial cells than in neurons (Raine, 1976).

Involvement of immune mechanisms in CDV-induced CNS disease has been indicated. Age at the time of CDV exposure seems to be important in determining the CNS lesions as well as the outcome of the disease; infection of R252 strain of CDV into puppies at 6 to 10-day old resulted in 90% fatality without marked CNS lesions, whereas the same virus induced persistent CNS infection with the lesions of demyelinating encephalomyelitis in about one-half of weanling dogs (Krakowka and Koestner, 1976). Moreover, passive administration of anti-CDV antibody to puppies at the time of CDV exposure induced more extensive
CNS lesions especially in the gray matter than puppies treated with normal serum. Autoimmune process is also proposed as a mechanism of CDV-induced demyelination by Krakowka et al. (1973) who demonstrated anti-myelin antibody in the sera of dogs with spontaneous demyelinating encephalomyelitis as described in the Section 4.2.

CDV exhibits neurovirulence in various laboratory animals including mice (Adams and Imagawa, 1957) and hamsters (Motohashi, Kishi and Nakamura, 1964). Recently we demonstrated that a certain laboratory strain of CDV originated from the Onderstepoort strain is highly virulent in cynomolgus monkeys as well as in adult mice and hamsters (Yamanouchi et al., 1977). Intracerebral inoculation induced histological lesions of encephalomyelitis in monkeys, i.e., neuronal damages associated with inflammatory changes such as perivascular cuffings and glial proliferation. About half of the monkeys survived sometimes showing mild neurological signs. Neutralizing antibody to high titers was demonstrated in CSF as well as in the serum. At autopsy, histological lesions of subacute encephalitis with sclerosing lesions were demonstrated. Immunosuppression with cyclophosphamide or ATS resulted in fatal clinical course in all monkeys. Histologically, the CNS lesions consisting primarily of degenerative and inflammatory changes tended to be suppressed. These results suggest involvement of immune mechanisms in the genesis of this encephalomyelitis.

5.3. Neurovirulence of RV

Little information is available for the neurovirulence of RV in cattle, the natural host. Non-purulent encephalitis occurs rarely in cattle, however virological examination has not been conducted.

In rabbits, neither L nor LA strain induced any significant lesions or clinical signs of the CNS involvement after intracerebral inoculation. Although the virus recovered from persistently infected cells is generally suspected of high neurovirulence, VRP34 virus obtained from Vero cells persistently infected with LA strain and exhibiting a nature of mutant virus was found to lack neurovirulence in rabbits (Kobune and Yamanouchi, to be published).

As to the neurovirulence in rodents, Imagawa (1965) demonstrated that the intracerebral inoculation of LA strain into day-old CFW mice resulted in neurological signs 14 days pi, and that the latent period was shortened after passages in mice.

**CONCLUSION**

Three morbilliviruses, MV, CDV, and RV, were shown in the present review to express closely resembling pathogenicity in their natural hosts and laboratory animals, in addition to the similarities of their biological and virological characteristics, as summarized in Table I. The major target organ is the lymphoid tissues for all the three viruses both in natural and experimental hosts. Thus, essentially similar histological lesions are produced in the lymphoid tissues i.e.,
TABLE I
Comparison of pathogenicity of three morbilliviruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Natural host</th>
<th>Animal model</th>
<th>Route of infection</th>
<th>Incubation period (days)</th>
<th>Fever</th>
<th>Respiratory signs</th>
<th>Conjunctivitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV</td>
<td>Human</td>
<td>Respiratory tract</td>
<td>SC(1)</td>
<td>10-12</td>
<td>Biphasic</td>
<td>Occasionally</td>
<td>Occasionally</td>
</tr>
<tr>
<td></td>
<td>Monkey</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDV</td>
<td>Dog</td>
<td>Dog</td>
<td>Respiratory tract</td>
<td>IN(2), IP(3)</td>
<td>Biphasic</td>
<td>Occasionally</td>
<td>Occasionally</td>
</tr>
<tr>
<td></td>
<td>Cattle</td>
<td>Rabbit</td>
<td>Respiratory tract</td>
<td>6-9</td>
<td>Monophasic</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IV(4)</td>
<td>2-3</td>
<td>Monophasic</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

1) SC: subcutaneous; 2) IN: intranasal; 3) IP: intraperitoneal; 4) IV: intravenous.

<table>
<thead>
<tr>
<th>MV</th>
<th>Histological lesions in lymphoid tissues</th>
<th>Lymphopenia</th>
<th>Immunosuppression</th>
<th>Autoantibody</th>
<th>Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Giant cell</td>
<td>Inclusion bodies</td>
<td>Lymphoid necrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Lymphocytotoxic antibody anti-myelin antibody</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Life-long</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>Life-long</td>
</tr>
<tr>
<td>CDV</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>anti-myelin antibody</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Life-long</td>
</tr>
<tr>
<td>RV</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ANA Cold HA</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Life-long</td>
</tr>
</tbody>
</table>

Giant cells and inclusion bodies both of which indicate virus growth in situ, and lymphoid necrosis which is suggested to be caused by direct or indirect effect of virus on the lymphoid cells. Lymphopenia and immunosuppression which may cause virus-induced destruction of the lymphoid cells are also produced by all the three viruses. Therefore, one may speculate partially similar types of interactions between the virus and the host immune systems among these viruses, although some differences are noticed in the degree and types of clinical signs. In this respect, comparative studies of these virus infections in each animal model may be useful to analyze various immunological aspects of their pathogenesis.

MV infection in monkeys is subclinical and immunological approach in monkeys is rather difficult compared with that in other laboratory animals. Therefore, the use of this model is very limited. Instead, MV infection in guinea pigs may be expected to provide a useful model for elucidating the mechanism of virus-induced suppression of delayed-type hypersensitivity because of large
accumulation of basic knowledge on delayed type hypersensitivity in guinea pigs.

CDV infection in dogs offers an excellent model for elucidating the mechanism of virus-induced demyelinating encephalomyelitis. It is interesting that localized antibody response within CNS was demonstrated in CDV infection in monkeys, both MV-susceptible and MV-immune ones (Yamanouchi et al., 1979). Because of anatomical similarities in CNS of humans and monkeys, this experimental system may be employed as a unique model for studying the immune response in CNS, which may contribute to immunological analysis of various chronic CNS diseases.

RV infection in rabbits can be used as a model of systemic infection, especially on the aspects of immunosuppression and autoimmunity.

It is worthy to note that all three viruses each requires a fresh isolate or laboratory animal-passed virus to express high virulence in systemic infections in laboratory animals. When virus is adapted to grow in cell cultures in vitro,
it fails to cause virulent infection. This tendency is clearly demonstrated in CDV (Rockborn, 1959; Harrison, Oxer and Smith, 1968), and similar tendencies are also considered for MV (Yamanouchi et al., 1970a) and RV (Yamanouchi et al., 1974b). The use of the infected tissue homogenate as an inoculum, however, hampers virological approach. Yet, virological examinations to find the difference between these virulent viruses and cell culture-adapted viruses will give a clue to understand the nature of virus virulence.

It should be pointed out that CDV retains the highest neurovirulence among the three morbilliviruses inducing encephalomyelitis not only in its natural host but also in non-human primates. Since CDV is ubiquitous in human community, theoretical possibility of zoonosis with CDV must be considered. Recent epidemiological findings (Cook, Dowling and Russell, 1978) indicating possible association of multiple sclerosis and CDV infection brought much attention on the neurovirulence of CDV as one of candidate etiological agents of multiple sclerosis. In this regard, extraordinarily high neurovirulence of CDV in primates as well as in its natural host, may deserve further study on some chronic neurological diseases from a standpoint of zoonosis.

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ABBREVIATIONS

ANA: anti-nuclear antibody; ATS: anti-thymocyte serum; CDV: canine distemper virus; CNS: central nervous system; SCF: cerebrospinal fluid; HA: hemagglutinin; KLH: keyhole limpet hemocyanin; MV: measles virus; ODE: old dog encephalitis; pi: post inoculation; PHA: phytohemagglutinin; PPD: purified protein derivatives; PWM: pokeweed mitogen; RBC: red blood cell; RV: rinderpest virus; SLE: systemic lupus erythematosus; SRBC: sheep red blood cell; SRF: skin reacting factor; SSPE: subacute sclerosing panencephalitis.