

Appel M J G. Pathogenesis of canine distemper. *Amer. J. Vet. Res.* 30:1167-82, 1969.
[Veterinary Virus Research Institute, Cornell University, Ithaca, NY]

This paper described the sequential spread of canine distemper virus in the tissues of its natural host, the dog. In addition, the relationship of the immune response to virus spread and disease were reported. [The SCI® indicates that this paper has been cited in over 125 publications.]

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The late Oswald Jones was a Fifth Avenue physician in New York City who made the following observation: a certain percentage of adults who contracted measles developed lung emphysema several weeks or months later. The late James A. Baker was a Rockefeller Fellow who founded the Veterinary Virus Research Institute (now named the James A. Baker Institute) at Cornell University in Ithaca, New York. He was the type of person who talked to his neighbor on an airplane, told him about the importance of studying animal viral diseases, and then got off the plane with a \$50,000 check for research. One day Baker met Jones and they reached an agreement: a study in dogs should be initiated to test the hypothesis that the pathogenesis of emphysema is related to virus infection since distemper in dogs is a disease closely related to measles in man. They needed a graduate student to perform the research and that is how I came to the Baker Institute in Ithaca.

I began to study canine distemper virus (CDV) infection in dogs using histopathology, immunofluorescence, and viral isolation but did not find emphysema in dogs after distemper infection. At about that time, L. Horta-Barbosa from the National Institutes of Health visited our institute and told us about his

successful attempts to isolate measles virus from brains of patients with subclerosing panencephalitis (SSPE), a chronic and fatal disease in children that sometimes follows measles infection. Distemper in dogs causes an encephalitis that is very similar to SSPE. My interest shifted from the lungs to the central nervous system (CNS).

The publication that followed included a detailed description of the spread of CDV in the tissues (particularly in the CNS) of the dog in relation to the immune response. At the time of the study we only looked at antibody responses. Cellular immune responses were virtually unknown at that time and the description of B and T cells was yet to come. The result of our study was fairly clear: in lymphatic tissues there was a race between virus replication and antibody formation. If the latter prevailed before the virus could reach the brain, the CNS did not become infected. If antibody was produced later, the virus could persist in the CNS but was cleared from peripheral tissues. Cellular immune responses were studied later after Bill Shek had developed the technique for distemper. These responses followed a similar pattern.¹

Additional observations stimulated interest: we found that CDV was carried into the CNS by white blood cells acting as a "taxi." We are still convinced today that this is a common route of virus infection of the CNS in general.² At that time I did not know why virus-infected white blood cells would cross the blood/brain barrier. For years afterwards I asked pathologists if there is an immune surveillance in the CNS, but nobody knew. Only this year was my question answered: antigen-stimulated lymphocytes may attach to the endothelium and migrate through the blood/brain barrier.³

There are probably several reasons why this paper was cited. The isolation of a variety of infectious agents from some chronic neurological disorders in the 1950s and 1960s had stimulated great interest in these diseases. Other diseases such as multiple sclerosis (MS) were being researched for a causative agent. The histopathology of CNS tissue in MS and distemper encephalitis are quite similar. In addition, the similarity of histopathological lesion and of the causative viruses of SSPE and canine distemper encephalitis created interest in the study of the pathogenesis of CDV-induced encephalitis in the 1970s and 1980s.⁴ Since my paper contained a detailed description and documentation of CDV in the CNS of dogs, it was cited often in these studies.

1. Appel M J G, Shek W R & Summers B A. Lymphocyte-mediated immune cytotoxicity in dogs infected with virulent canine distemper virus. *Infect. Immunology* 37:592-600, 1982.
2. Summers B A, Greisen H A & Appel M J G. Possible initiation of viral encephalomyelitis in dogs by migrating lymphocytes infected with distemper virus. *Lancet* 2:187-9, 1978. (Cited 25 times.)
3. Wekerle H, Linington C, Lassmann H & Meyermann R. Cellular immune reactivity within the CNS. *Trends Neurosci.* 9:271-7, 1986.
4. Appel M. Canine distemper virus. (Horzinek M, ed.) *Virus diseases of vertebrates*. Amsterdam: Elsevier. (In press.)

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