Reference Point

A review of canine parainfluenza virus infection in dogs

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Canine parainfluenza virus has been recognized as an infectious cofactor in the canine respiratory disease complex or CITB (commonly known as kennel cough) for almost 50 years. It was shown to be a prevalent and highly communicable agent that was commonly implicated in outbreaks of CITB whenever thorough etiologic investigations were undertaken. Soon after its discovery, it was included in vaccines for dogs. Although poorly documented, there is undoubtedly less CPIV-associated disease in vaccinated populations, and as for many pathogens, especially in small animal medicine where there are usually no economic incentives to do so, definitive etiologic diagnoses of CPIV are rarely obtained or even attempted. Arguably, it has become a forgotten virus.

**Historical Perspective**

Simian virus 5, or parainfluenza virus 5, canine parainfluenza 2, or simply canine parainfluenza, has an interesting, if somewhat confusing, history as the multiple monikers imply. The confusion over its name and host range began when the virus was first isolated. From a clinical perspective, although this virus has come to be primarily associated with respiratory disease in dogs, it was actually first found in monkey cells, not in dogs, hence the original simian designation. Simian virus 5 was one of several agents that hemagglutinated RBCs, a feature of the then newly described paramyoviruses, and that were found in cultures of rhesus and cynomolgous monkey kidney cells in 1956. It was unceremoniously named simply on the basis of the chronology of isolation, with SV-5 being the fifth virus identified. On the basis of this discovery, it was then thought that monkeys were the natural host of SV-5, but epidemiological studies conducted in the 1960s revealed that monkeys in the wild did not have antibodies to SV-5. Instead, evidence indicated that they seroconvert in captivity, and it was proposed that infection of monkeys occurs only after contact with humans. This led to the still unresolved controversy concerning the infectivity and pathogenicity of SV-5 in humans and other species from which it has been isolated.

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Shortly after the discovery of CPIV, experimental infections conducted in the 1960s and 1970s with the virus alone demonstrated that uncomplicated CPIV infection resulted in mild to moderate upper respiratory disease or no discernable clinical disease at all in dogs. On the basis of results of the original epidemiological studies and the likely benefits that would derive from prophylaxis, parenteral vaccines for CPIV were developed in the mid 1970s followed by intranasal vaccines in the 1980s, both of which are currently formulated as combination vaccines. Trace through the multitude of mergers and acquisitions that have occurred in the veterinary biologics industry, many of the original vaccines or vaccine viruses are still in use today but under different names. In the 1980s, studies in dogs provided additional insights into the pathophysiology of CPIV infection and human respiratory and, to a lesser extent, neurologic disease. In addition, in vitro studies of SV-5 as a prototype parainfluenza virus conducted from the 1980s to the present with target cells from several species have provided insights into the pathogenesis of parainfluenza virus infection in dogs. Nevertheless, aside from a few epidemiological studies conducted outside of North America, there has been relatively little primary research done on CPIV in dogs for more than 20 years.

**Characteristics of CPIV**

Canine parainfluenza virus is in the genus *Rubulavirus* of the subfamily Paramyxovirinae, order Mononegavirales, of the family Paramyxoviridae. In addition to CPIV, the *Rubulavirus* genus includes the distantly genetically and antigenically related HPIV types 2 and 4 and mumps virus. As with other PIVs in the *Rubulavirus* and *Respiravirus* genera, CPIV is a spherical to pleomorphic, 150- to 200-nm virion consisting of a nucleocapsid surrounded by a lipid envelope that is obtained as the nucleocapsid buds from the plasma membrane of an infected cell. All PIVs, including CPIV, have a single-stranded, nonsegmented, negative-sense RNA genome of approximately 15,000 nucleotides (or 15,246 in the case of CPIV) that comprise 6 genes arranged in invariant order: N-P-M-F-HN-L. A unique differentiating feature of CPIV, compared with other mammalian PIVs, is the presence of a seventh gene, the SH gene, that is located between the fusion (F) and hemagglutinin-neuraminidase (HN) genes on the gene map. These 7 genes encode for 8 proteins. The nucleocapsid or ribonucleoprotein core of the virus is formed by an association of the nucleoprotein (N) and the phosphoprotein (P) and large (L) proteins, together with the genome. The viral RNA-dependent RNA polymerase that is essential for the transcription of viral mRNA and replication of genomic RNA is formed by a complex of the P and L proteins. The nonglycosolated matrix (M) protein is the most abundant viral protein in an infected cell and is located on the inner face of the envelope. It is an essential organizational protein of the virus that affects assembly, budding, and release of progeny virions. The homotetrameric HN and homotrimeric F glycoproteins are found on spikes in the envelope and mediate attachment to and penetration of the host cell, respectively. The extracellular domains of these transmembrane proteins are the most likely to induce protective antibody responses. In addition to these 2 structural envelope proteins found in all PIVs, CPIV codes for another transmembrane structural protein, the SH protein. This protein modulates apoptosis in infected cells. Another differentiating feature among genera and species of PIV is the presence of a variable number of accessory proteins that result from RNA editing or insertion of G nucleotide residues, that are not templated by the virion RNA, into the P gene, probably by the viral polymerase. This editing that results in alternative reading frames is characteristic of the subfamily Paramyxovirinae and allows the P gene to encode multiple proteins. For CPIV, the 1 accessory V protein is translated from an unedited mRNA, whereas the P protein is translated from an edited mRNA that has 2 G residues that are not templated by the virion mRNA. The V protein has a high degree of sequence conservation among the PIVs, whereas the P protein is more variable. In CPIV, V is a multifunctional structural protein that binds to a soluble but not polymeric N protein and affects IFN biology, the cell cycle, and apoptosis.

The early studies of CPIV conducted in the 1960s demonstrated that CPIV can grow in cells from a variety of species in vitro, including canine, feline, mink, bovine, pig, simian, and human cells. Virus or virus-infected cells hemagglutinated or hemadsorbed, respectively, RBCs from many species, including human, chicken, guinea pig, rat, rabbit, dog, cat, and sheep. Characteristically, growth in cultured cells was associated with a cytopathic effect comprising plaque formation, syncytia, and intracytoplasmic inclusion bodies. There were some differences reported in the presence and size of syncytia and inclusion bodies, depending on the target cell of infection. Subsequently, isolate-specific differences in syncytium formation were reported for the 2 neurotropic CPIVs, CPI+ and CPI−, and were presumptively associated with differences in infectivity, tropism, and virulence in vivo. In addition, phenotypic differences in plaque morphology were associated with the tendency of the CPI+ isolate to develop persistent infection in vitro without apparent cell fusion; however, the potential clinical relevance of these observations remains poorly understood.

There is little known about genomic and protein differences that could be related to virulence among CPIVs isolated from dogs, at least in part because of the small number of field isolates that have been examined. In the mid 1980s, differences were reported in restriction fragment polymorphisms between attenuated (vaccine) and virulent isolates of CPIV and also between the low-passage virulent isolate and sequential passages of this isolate. Unfortunately, this potentially informative research was not followed up with sequencing or in vivo studies. There are few CPIV genome sequence data, and much of these data are derived from viruses that have been passaged in vitro. Studies conducted in the early 1990s documented a 99% sequence identity in the conserved P/V gene between the CPI− isolate and the W3 simian isolate and a 1.7% to 2.4% variation in the predicted amino acid sequence of the SH protein among simian (W3), human (LN), and...
and canine (CPI+ and CPI−) isolates. On the basis of a 2004 study on the phylogeny of the potentially variable F gene, it was proposed that the 5 canine isolates that were examined fell into 2 clades: the American neurotropic CPI+ and CPI− isolates (clade 1), 2 Scottish isolates (H221 and 78524), and 1 Japanese isolate (T1; clade 2). However, the level of variation among these viruses was quite small (1%). Potentially more relevant direct sequencing of CPIV isolates from an outbreak of respiratory disease in kenneled dogs revealed 100% sequence identity in PCR products amplified from 2 tracheal samples, which did not differ from the CPIV vaccine isolate, but this involved the use of primers directed toward the N protein gene, which would be expected to be highly conserved among isolates. As previously mentioned, the early use of polyclonal sera in HI tests revealed few antigenic differences in the HN protein among the few SV-3/CPIV isolates that were tested. In most cases, reciprocal or near-reciprocal titers were detected when convalescent sera and different isolates, including those from species other than dogs, were compared in cross-HI tests; however, biological assays such as HI and VN performed with polyclonal antibodies are likely to detect cross-reactive responses. Cross-reactive responses are more likely to occur if an animal has been repeatedly exposed to the same PIV, either through infection or immunization, or a different but related PIV, leading to an immunologic default to the recognition of conserved regions of cognate proteins. Application of a panel of 50 monoclonal antibodies to SV-5 isolates in the 1980s revealed no differences between the 2 canine isolates (M7 and CPI+) that were examined and only minor differences in the HN, F, and P proteins between the SV-5 isolates from dogs, compared with those from other species. A subsequent study with these monoclonal antibodies found that 1 antibody with an epitope common to both P and V proteins could differentiate between CPI+ and CPI− isolates. This difference in reactivity was traced to a single amino acid change (leucine to proline), and it was suggested, but never proven, that this alteration in protein structure and antigenicity could be related to the persistent phenotype of the CPI− isolate.

**Pathogenesis of CPIV Infection**

Similar to other PIVs, the pathogenesis of CPIV infection at the cellular level begins when the HN glycoprotein in the viral envelope binds to N-acetylneuraminic (sialic) acid residues, probably with specific linkages and not indiscriminately, on the glycoproteins and glycolipids of host cells. This binding occurs by virtue of the hemagglutination activity of the HN protein that is favored at extracellular (neutral) pH and halide concentration. The sialic acid receptor is a ubiquitous molecule on cell surfaces, which potentially allows a variety of cells in the respiratory tract to be targets of CPIV infection. Unfortunately, and in contrast to some other PIVs of veterinary interest, notably the Respirovirus BPIV type 3, there have been no classic time course electron micrographic studies of CPIV pathogenesis to specifically identify the range of epithelial cell types that are infected by CPIV in vivo in dogs. There are few data beyond 2 studies demonstrating the CPIV antigen in unidentified bronchial epithelium by IF and immunohistochemical staining that address the specifics of CPIV tropism. Once bound, the HN protein interacts with and probably causes a necessary conformational change in the F protein, resulting in fusion between the viral envelope and the host cell membrane. However, findings from previous studies indicate that minor amino acid differences in the F protein of CPIV can abrogate the need for this HN-F interaction and allow HN-independent fusion. Moreover, it has been suggested that highly fusigenic viruses are actually selected against in vivo. Nevertheless, once fusion between the virus and target cell occurs, there is probably a refolding of the proteins in the cell membrane that allows the viral nucleocapsid to enter the cytoplasm. After uncoating or removal of the M protein from the nucleocapsid by an unknown mechanism, viral replication occurs in the cytoplasm and is associated with the variable presence of intracytoplasmic inclusion bodies. Production of progeny virions first involves viral polymerase-mediated transcription of mRNAs that serve as a template for the translation of viral proteins and then, after viral proteins accumulate, RNA replication through an intermediate or plus-stranded antigenome that is an exact complimentary copy of the genome as well as the transcription of mRNAs that serve as a template for the translation of viral proteins. There are 2 notable posttranslational modifications of viral glycoproteins. The first, which is a prerequisite for viral infectivity, is cleavage of the inactive F protein precursor (F0) into a fusigenic form comprising F1 and F2 subunits that remain linked by disulfide bonds when inserted into plasma membrane. This cleavage is accomplished by endocytic proteases, notably furin, of the exocytic secretory pathway of the Golgi. The second modification, which prevents self-bonding of viral particles and reattachment to infected cells and facilitates budding, is the stripping of sialic acid residues from newly formed viral glycoproteins. This is accomplished by the neuraminidase activity of the HN protein that is favored by the lower pH and halide concentration in intracellular organelles that transport the glycoproteins to the cell surface. The M protein plays multiple roles in the assembly, budding, and release of progeny viruses, including coordinating the assembly and intracellular transport of nucleocapsids to the cell membrane and the transport of F and HN glycoproteins from the endoplasmic reticulum and Golgi to the cell membrane, concentration of viral glycoproteins in the host cell membrane, and bud formation of nascent virions from the host cell plasma membrane. A study conducted with cultured polarized epithelial cells in the 1970s indicated that as with other myxoviruses, budding of CPIV preferentially occurs from the apical (luminal) surface of infected cells; however, this has not been confirmed in vivo in infected dogs. Although, as indicated, much is now known about the molecular mechanisms of virus-host cell interactions involved in infection and replication of PIVs, including CPIV, there is much less known about the specific nature of cell injury in vivo. Whether CPIV-infected cells in vivo die because of necrosis, apoptosis,
or another mechanism has not been formally examined. In contrast to other PIVs, it was recognized in the mid 1960s and confirmed in the 1980s that there is a tendency, at least in cell culture, for CPIV to cause persistent, productive infection (for up to 40 days) that does not kill cells or block cellular RNA or protein synthesis. Subsequently, it was demonstrated with viral mutants that the SH protein blocks programmed cell death, or apoptosis; mutants that lacked SH caused accelerated cytopathic effect and death by apoptosis of infected canine renal epithelial (Madin-Darby canine kidney) cells. In addition, it has been shown that the V protein inhibits apoptosis and slows progression of the cell cycle. Prolongation of the cell cycle may promote the transport of viral glycoproteins to the cell surface, permitting viral assembly and budding to occur. From the perspective of the virus, preventing cell death and affecting the cell cycle would be beneficial in prolonging the duration and efficiency of production of progeny. Whether or not these in vitro phenomena affect the CPIV pathogenesis in vivo in infected dogs is unclear. Although CPIV-mediated modulation of cellular injury could account for a relatively mild clinical course and lesions, as has been described in experimental infections, it has been suggested that persistence of CPIV, at least in the respiratory tract, is unlikely to occur in dogs. This was based on the observation that CPIV had not been isolated in nasal or pulmonary explant cultures obtained 4, 6, or 12 weeks after infection and the finding that susceptible dogs did not become infected when comingle with recovered animals; however, application of more sensitive, currently available virus detection techniques, notably PCR assay, may yield different results and interpretations.

In human medicine, an area of investigation in the pathogenesis of pediatric PIV infections has been the potential role of these viruses as a risk factor for the development of airway hyperreactivity and chronic airway obstruction later in life. A considerable part of this research has actually been done with CPIV infection in dogs and has fortuitously provided greater insights into CPIV-associated pathophysiological changes in dogs. Experimentally, infection of 2- to 3-month-old laboratory Beagles with CPIV consistently resulted in transient airway hyperresponsiveness to aerosolized histamine. Hyperresponsiveness paralleled the course of clinical signs of upper respiratory disease, peaking 6 days after inoculation and resolving by 12 to 14 days. Infected dogs still had reduced pulmonary function (lower functional residual capacities and lower specific lung conductance), compared with controls, 2 weeks after infection when they no longer had clinical signs. These responses were more pronounced in the case of dual or sequential infection with CPIV and canine adenovirus type 2 or Bordetella bronchiseptica. Chronic inflammation of airways, including bronchiolitis obliteratorum, could persist for more than 6 months after infection. Dual infection with CPIV and B bronchiseptica, compared with infection with CPIV or B bronchiseptica alone, also resulted in increased concentrations of the inflammatory mediator and bronchoconstrictor thromboxane A as well as neutrophilia in bronchoalveolar lavage fluid. Together, these studies indicate that infection with CPIV, especially in puppies and when combined with other common respiratory pathogens, can have pulmonary physiologic and chronic inflammatory effects beyond those normally attributed to acute viral infection.

As originally observed in early studies of CITB outbreaks and later confirmed prospectively, CPIV infection results in more severe respiratory disease when complicated by coinfection with other viruses and bacteria. This pathological synergism in CITB is similar to PIV infections in other species, notably BPIV type 3 infection and shipping fever in cattle. Certainly, loss of cilia and death of ciliated epithelium due to CPIV infection and resultant disruption of the normal mucociliary function of the mucociliary escalator could predispose to secondary infection. Conversely, there is some evidence that subclinical infection with B bronchiseptica can predispose dogs to CPIV infection and result in more severe clinical disease than infection with either pathogen alone. This phenomenon may also result from an effect on cilia or, in this case, the ciliosstatic effect of colonization by B bronchiseptica. It has been documented, at least in vitro, that the V proteins of PIVs mediate virus-specific suppressive effects on innate immunity mediated by type 1 (α and β) IFNs as well as INF-γ, which could further predispose to coinfection after infection with CPIV. It is thought that CPIV counteracts IFN responses in 2 ways: by blocking the activation of the IFN-β promoter and by disrupting IFN signaling pathways by targeting the essential signaling protein, signal transducer, and activator of transcription-1 for degradation in proteosomes. In addition, at least some isolates of CPIV, including CPI-, are poor inducers of the inflammatory cytokines (chemokines) IL-8 and macrophage chemotactic protein-1 in human lung epithelial cells, which in vivo could affect the recruitment of blood leukocytes into the infected lung and development of adaptive immune responses. Another mechanism by which some PIVs, notably BPIV type 3, enhance the potential for coinfection is by infection of pulmonary alveolar macrophages and suppression of their various immune functions. It has been categorically stated in at least 2 textbooks that CPIV does not infect macrophages. However, there are neither published longitudinal electron micrographic studies, as there is for BPIV, nor in vitro infectivity studies that would more definitively address the possibility of infection of pulmonary alveolar macrophages by CPIV, as has been recently published on influenza virus.

**Clinical Signs and Lesions Associated With CPIV Infections in Dogs**

In the first studies of outbreaks of CPIV-associated respiratory disease, a variety of clinical signs of differing severity were reported, including the dry, harsh, hacking cough for 2 to 6 days that is typical of CITB as well as several days of pyrexia, mucous nasal discharge, pharyngitis, and tonsillitis; however, the common involvement of multiple pathogens in CITB makes it difficult to ascribe signs attributable to CPIV alone. Similarly, given the frequent involvement of coinfecting agents in CITB, it is difficult to assign CPIV specificity to lesions found in cases of naturally acquired respira-
tory disease in dogs. Additionally, because most dogs with CITB recover, the availability of material found at postmortem examination is limited. Nevertheless, the histopathologic lesions associated with tracheobronchitis reported in a natural outbreak of CPIV-associated disease in dogs are similar to lesions for PIV infections in other species.\textsuperscript{17} Vacuolation and death of tracheal and bronchiolar epithelial cells lead to disorganization and sometimes hyperplasia of the luminal epithelial lining.\textsuperscript{1,3,8} This is accompanied by variable infiltration of the epithelium and lamina propria with a mixed population of inflammatory cells as well as exudate in the lumens that is sometimes grossly visible.\textsuperscript{10,38} Local inflammation and congestion in the olfactory mucosa may also be responsible for dysfunction of sense of smell that has been associated with acute CPIV infection.\textsuperscript{64}

There have been numerous attempts to reproduce respiratory disease in dogs with CPIV alone to study viral pathogenesis and test vaccine efficacy by use of parenteral, intranasal, intratracheal, or aerosol delivery, singly or in combination.\textsuperscript{7,8,12,16,18,26,49–53,65} In most cases, clinical signs of respiratory disease were absent or very mild, beginning 7 to 9 days after virus exposure and lasting for 3 to 5 days. There was sometimes serous nasal discharge and mild pharyngitis and tonsillitis. Pyrexia was absent or mild (1°C to 2°C, 2°C to 4°C above normal) for several days. Tracheal palpation was often required to elicit minimal coughing, and weight loss or leucopenia was not generally observed. Gross lesions were usually absent following experimental CPIV infection; however, multifocal pulmonary petechiation was also reported,\textsuperscript{8,65} apparently similar to that reported in infection; however, multifocal pulmonary petechiation was not generally observed. Gross lesions were usually absent following experimental CPIV infection; however, multifocal pulmonary petechiation has been reported,\textsuperscript{8,65} apparently similar to that reported in a field outbreak of CITB in which CPIV was isolated in 2 patients with intra-alveolar hemorrhage.\textsuperscript{10} The role of CPIV in the pathogenesis of this lesion is unclear. In 1 study,\textsuperscript{18} gross consolidation of lungs was reported, but the involvement of other pathogens was not ruled out. Histologic lesions reported in experimental CPIV infections include catarrhal rhinitis with mixed inflammatory cell infiltration in the mucosa and submucosa as well as tracheobronchitis and bronchiolitis with loss of ciliated cells, epithelial hyperplasia, and prominence of goblet cells.\textsuperscript{18} There was often a variable mixed inflammatory cell infiltrate in the mucosa, submucosa, and submucosal glands and inconsistent exudation in lumens. Changes detected on histologic examination were most severe approximately day 2 to 10 after infection.\textsuperscript{1,12,38,66}

A potentially major limitation in available studies of respiratory disease induced by experimental CPIV infection in dogs is that all studies have used CPIV isolates that had been passaged in vitro, sometimes extensively, or in noncanine cells. Passage in vitro can lead to attenuation, possibly from de facto selection of variants in a virus population that do not grow well in vivo. Indeed, passage in vitro, often in xenogeneic cells or in cell types that a virus does not target in vivo, is a commonly used method to obtain modified-live vaccine viruses (including CPIV) that are apathogenic in vivo.\textsuperscript{19,48} Inocula of other paramyxoviruses produced by passage in vivo in neonates have been used to reproduce respiratory disease more similar to that observed in naturally acquired infections\textsuperscript{56,57} with those viruses. Similar methodology may be relevant to the further study of CPIV.

Although natural infection of dogs with CPIV are generally self-limiting and restricted to the respiratory tract (primarily the upper respiratory tract), there have been several reports documenting isolation of the virus from outside that body system. In the first study\textsuperscript{3} on CPIV infection and a subsequent study\textsuperscript{60} on dogs with mixed viral infections, CPIV was isolated from the spleen, liver, and kidney, but not associated with disease or lesions in those organs. In the late 1970s, CPIV was isolated from the CSF of a dog with posterior paresis that later recovered.\textsuperscript{68} Subsequently, intracerebral inoculation of this isolate (CIP+) into young gnotobiotic puppies produced acute encephalitis characterized by seizures, myoclonus, and progressive neurologic signs within a few days after inoculation. An antigenically and phenotypically slightly different isolate (CIP–) was reisolated from these cases.\textsuperscript{7,30} In the 1980s, a CPIV-like virus was isolated from the intestinal contents of a 6-week-old puppy with fatal acute hemorrhagic enteritis, but was not definitively implicated in a causal role.\textsuperscript{69} A CPIV was also repeatedly isolated from the prostatic fluid of a dog without clinical signs.\textsuperscript{70} Currently, it is not known how often the neurologic, gastrointestinal, or other nonrespiratory forms of CPIV infection develop under natural conditions, but this is suggested to be uncommon. It is also not known what restricts CPIV to the respiratory tract in most infected animals. Although the phenotype of CPIV budding has only been studied in vitro, where only apical budding was documented,\textsuperscript{63} it is likely based on the finding that with other PIVs, at least some isolates of CPIV can bud from the basolateral surfaces of infected cells, which would allow systemic dissemination of the virus.\textsuperscript{17} Moreover, beyond the respiratory tract, there is ubiquity of sialic acid–containing receptor molecules and cytosolic enzymes that could cleave the F protein precursor (F0), which would produce systemic infection.\textsuperscript{17} This is evinced by the ability of CPIV to infect and replicate in a variety of cell types from dogs and other species,\textsuperscript{1,70} although there are likely as yet largely unrecognized differences among isolates in these properties. On the basis of what has been previously reported for other PIV infections, it is likely that the immune response to CPIV restricts infection and disease to the respiratory system in most infected individuals.\textsuperscript{17}

The Immune Response to CPIV Infection in Dogs

As mentioned, CPIV has evolved specific mechanisms to suppress the innate immune response, thereby promoting its survival in the intracellular microenvironment. Prior to its isolation, the first evidence for the existence of CPIV in dogs was actually the detection of antibodies to related PIV, including a CPIV-like virus (DA) from human blood during a search for potential reservoirs of human PIV infections.\textsuperscript{2} Similarly, during the course of the first isolations of CPIVs from naturally infected dogs, HI and VN antibodies against various CPIV isolates were demonstrated.\textsuperscript{10} Shortly thereafter, there was a limited examination of the kinetics of systemic antibody responses in CPIV-seronegative dogs.
that were intranasally inoculated with 1 of 3 isolates of the virus.17,38 Both HI and VN antibodies were detectable as early as 7 days after infection, usually peaked in titer by day 21, and persisted at that level until at least day 42.6 It has been stated that the canine immune response to CPIV is slow,38 and there are some reported differences in the rapidity of the serum antibody responses,6,12,18,38 but these could be because of differences in the dose or infectivity of laboratory-propagated isolates that were used in experimental infections. Aside from some data reporting that VN titers declined to undetectable concentrations by 3 to 4 months after experimental infection,4 little is known about the duration of CPIV-specific serum antibody responses. Although it has long been stated in textbooks15,21 and generally assumed that local specific (antibody) immunity is important in CPIV infections, there is no published characterization of mucosal immune responses in naturally or experimentally infected dogs. There are also no published data concerning passive immunity in bitches or puppies.

There are neither published studies involving a formal examination of the isotypes of systemic or local canine antibody responses to CPIV nor studies regarding the examination of the antigen specificity of antibody responses in dogs. By definition, HI antibody tests measure the response to HI protein, and it is likely that VN responses are targeted primarily to the F protein.17,72 It has been revealed in hamsters, which have restricted infection with CPIV-like agents, that monospecific antisera against both major envelope glycoproteins, HN and F, have VN capacity in vitro and in vivo that may occur by blocking virus entry into cells, limiting the spread of virus from cell to cell as a consequence of fusion, or both in the case of anti–F protein responses.72

There are no published data concerning the cell-mediated immune response to CPIV in dogs. Nevertheless, extrapolating from what is known about PIV-specific immune responses in their respective natural hosts, it is likely that cytotoxic (CD8+) lymphocytes together with secretory antibodies probably confer short-lived, incomplete protection against reinfection, whereas VN antibodies in the serum provide long-term disease-sparing effects in the lower respiratory tract.17

**Diagnostic Approaches to CPIV Infection in Dogs**

As is the case for other respiratory pathogens, the most definitive antemortem diagnostic approach to active CPIV infection is detection of the agent in nasal secretions.17,38 Although it has not been formally examined with CPIV, experience with other paramyxoviruses suggests that the use of polyester-tipped swabs may yield optimal results when attempting isolation.87 As previously mentioned, CPIV grows readily in epithelial and mesenchymal cells from a variety of species, although the use of primary canine cells, as used in early studies,5 may improve the sensitivity of detection of field isolates. Confirmation of CPIV isolation in cell culture is a 2-step process involving assessment of cytopathic effects, including intracytoplasmic inclusion bodies and syncytium formation, which varies among isolates, and hemadsorption with guinea pig erythrocytes17,38 or definitive staining with IF38 or immunohistochemical techniques.39 As with other paramyxoviruses such as canine distemper virus and in contrast to canine herpesvirus, CPIV is relatively labile in storage and transport. Failure to recognize this can result in false-negative isolation results. Rapid diagnosis of CPIV can also be attempted by IF staining of cells made from smears of nasal swabs.17,38 Polymerase chain reaction tests have been developed and applied in the field for potentially more sensitive and rapid diagnosis of CPIV infection.36 Such tests are available from commercial diagnostic laboratories in North America. Although not formally examined, we suggest that dogs that received intranasal and, perhaps parenteral, CPIV vaccines may have false-positive PCR results for an indeterminate period after vaccine administration, obviously making this a diagnostic consideration.

Serologic testing by use of acute and convalescent samples optimally collected 10 to 14 days apart can be used as an adjunct to antemortem diagnosis of CPIV infection. Traditionally, this has been accomplished with HI or VN tests, but ELISA is a more rapid, if less used, alternative.26 Several factors complicate the use of serologic testing in the diagnosis of CPIV. The overall endemcity of infection, persistence of maternal antibodies, and routine vaccination mean that many dogs, especially puppies, may have antibodies to CPIV in the absence of recent exposure. Furthermore, reports from early studies5,73 documented that some animals with antibody titers may not have a serologic response following infection. The timing of sampling relative to infection and onset of disease can also be an issue.73 Some of these problems could be addressed by use of an IgM-specific ELISA to differentiate recent versus previous exposure to the virus, as has been used with canine distemper virus.38 Notwithstanding the limitations of serologic evaluation, stored paired serum samples may be the only way to document the involvement of CPIV in outbreak situations when virus detection attempts are not undertaken or fail to yield positive results.73

In dogs that die of respiratory disease, the presence of tracheobronchitis or bronchiolitis lesions is suggestive of CPIV infection, which can be most efficiently and consistently definitively diagnosed with immunohistochemical staining.39

**Epidemiology of CPIV Infections**

The status of being one of the first, and still prevalent, agents causally associated with the syndrome commonly known as kennel cough alludes to the important epidemiological features of clinical CPIV infections. Infection and disease associated with CPIV have long been recognized to be most prevalent in situations where multiple-source dogs are crowded, enhancing the potential of droplet transmission of the virus.5–11 Under these conditions, CPIV spreads rapidly and a high percentage of dogs become infected in a short time as documented in the seminal work of Binn et al.11,74 and Binn and Lazar75 in the 1960s and 1970s, in the era before vaccination.11,74,75 In laboratory and military dogs, the prevalence of CPIV antibodies increased from 3% at the time of arrival at the kennels to 72% 6 weeks later, and CPIV was isolated from 50%...
(27/54) of dogs that developed respiratory disease. In another previous study, the point prevalence of isolation of CPIV alone or in combination with other agents from samples of the respiratory tract was 37% (10/27). Aside from these observational studies, there are no formal investigations of specific cofactors in transmission, such as the role of fomites and the survival rate of the virus in the environment, as has been examined with human PIV in environments such as hospitals and nurseries. As well, the physiologic sequelae of stress are likely an important cofactor in CPIV infection, but have not been examined. The probable role of climate and seasonal weather variation in transmission and seasonal prevalence of infection, as has been shown with BPIV type 3 in calves, is not known for CPIV in dogs. Although early serologic surveys from many countries on several continents have indicated the widespread prevalence of CPIV, there is still little known about the prevalence of CPIV in household dogs, aside from the likelihood that it is much lower. Two previous studies on small numbers of dogs found an apparent resistance to CPIV infection 3 weeks or 10 weeks after initial experimentally induced CPIV infection that was associated with serum neutralizing antibody in the latter case. Beyond that, virtually nothing is known about the potential for, and (immunologic) constraints on, CPIV reinfection in previously exposed dogs, nor is it clear how CPIV maintains itself in canine populations. Throughout the literature on CPIV, there are statements about the wide host range of CPIV. As perhaps would be expected, and on the basis of published information about interspecific transmission of other PIVs, antibodies to CPIV have been detected in a wide range of wild canid species, although data are limited. Two studies conducted in the 1990s found a similar prevalence of CPIV-reactive antibodies in coyotes, which are probably the canid species most likely to have interactions with domestic dogs in North America. In 1 study, 10 of 17 wild caught coyotes had antibodies that neutralized CPIV, and there were no significant differences in prevalence among ages, sexes, or capture seasons. In another study, 7 of 12 wild caught coyotes that had been commingled for sale and transported to fox chases had antibodies that neutralized CPIV. In comparison, 31 of 42 red and 0 of 17 gray foxes documented a low prevalence of infection and there were no significant differences with domestic dogs in North America. In 1 study, 7 0 of 17 wild caught coyotes had antibodies that neutralized CPIV, and there were no significant differences in prevalence among ages, sexes, or capture seasons. In another study, 7 0 of 17 wild caught coyotes that had been commingled for sale and transported to fox chasing enclosures had antibodies that neutralized CPIV. In comparison, 31 of 42 red and 0 of 17 gray foxes from the same vendor had CPIV-neutralizing antibodies. In a more recent study, 0 of 9 gray wolves from Alberta, Canada, had antibodies to parainfluenza viral antigens. Unfortunately, this study of CPIV-reactive antibodies in other carnivores, including urids, felids, and mustelids, used PIV 3 (HPIV type 3 or BPIV type 3) as the antigen in an ELISA and also found a low prevalence of usually zero; on the basis of the results of a previous study, this may have failed to detect CPIV-reactive antibodies in exposed animals because of the low sequence identity between Rubula and Respira PIVs. Potential variation in CPIV populations among wild canid hosts has not been examined, and there are no published reports of isolates from these animals.

Domestic ferrets can be experimentally infected with canine-derived CPIV isolates, shed virus, and develop mild clinical respiratory disease and lesions similar to those found in dogs. The virus can also cause encephalitis if inoculated intracerebrally, as in dogs. In contrast, the few available serologic studies of wild mustelids documented a low prevalence of infection and exposure. In 1 study, 0 of 26 river otters in New York state had CPIV-neutralizing antibodies. In a survey of 5 species of wild mustelids in France, only 11 of 480 sera reacted to parainfluenza viral antigens. Again, unfortunately, these data were derived via an ELISA in which the specific PIV used as an antigen was not indicated. Nevertheless, this apparent low prevalence of exposure to CPIV in wild mustelids could be a reflection of the relatively solitary lifestyle in which these animals live as adults under natural conditions and not the inability of the virus to replicate in these species. A previous study documented that domestic cats can be infected with CPIV and can shed the virus from the respiratory tract. No clinical disease was reported in CPIV-infected cats. The role of cats as reservoirs for CPIV infection in dogs has not been examined.

The classic study that is consistently referenced as documentation of the ability of CPIV to infect and cause disease in laboratory rodents was performed in the 1960s by 2 virologists at Yale Medical School; however, examination of this study reveals data that are far from convincing. In mice, although the virus was reisolated from the respiratory tract, blood, and, in some cases, other organ systems after intranasal or intraperitoneal inoculation of the human DA isolate, no clinical disease was observed. Perhaps more elucidative was the pathological changes or lack thereof that were documented in intranasally inoculated mice. There was no graphic evidence of the hallmark lesions of CPIV and other PIVs, tracheitis, or bronchiolitis. Results on histologic examination were equivocal peribronchioilar and perivascular edema with some infiltration of mononuclear cells, the latter being consistent with a mild response by bronchus-associated lymphoid tissue that would occur following the presence of any foreign protein (monkey tissue) in the rodent lung. The interstitial infiltration in sections of lung shown was probably atelectasis resulting from a failure to inflate the lungs prior to fixation. These results may, to some extent, be explained by attenuation of the challenge virus that was serially passed in rhesus monkey kidney cells from 190 to 311 times during the course of that study, however, a subsequent study on lower passage viruses has shown that CPIV is nonpathogenic in either clinically normal or severe combined immunodeficient mice. Similarly, although virus could be reisolated from the respiratory tract as well as from other organ systems including blood after intranasal infection of Syrian hamsters by use of the high-passage inoculum used in the initial mouse experiments, no clinical disease or lesions were reported. There has also been no clinical disease or lesions reported in a later study involving hamsters as a model for CPIV infection. In contrast, CPIV can be lethal in signal transducer and activator of transcription-1 knockout mice that are unable to respond to INF.

Canine parainfluenza-like viruses have been repeatedly isolated from various samples including blood, nasal secretions, and bone marrow from simian species and humans, however, it was recognized early on that at least some of these results were artifactual be-
cause of the common contamination of the monkey cell lines used for isolation with CPIV-like viruses.68 Furthermore, cross-reactions that occur between CPIV and known HPIVs, notably type 2, make interpretation of commonly cited early seroepidemiologic studies difficult. Although early studies3,13,14 documented a mean CPIV seroconversion rate of 30% in wild-caught CPIV-seronegative monkeys and baboons 30 to 90 days after arriving in captivity, no clinical disease was reported following this response to exposure. This response was considered CPIV specific since there was no seroconversion to the CPIV-related Rubulavirus HPIV type 2.3 The source of exposure was assumed to be humans, which was supported by the observation that there was also a 30% seroconversion rate to HPIV type 3 in the same monkeys.3 In a prospective study69 of high-passage CPIV, only 3 of 20 seronegative rhesus monkeys had a detectable virus after experimental intranasal infection, and no clinical disease or seroconversion was observed. In contrast, 5 of 6 clinically normal monkeys had CPIV in their trachea or lungs 9 days after being housed adjacent to 2 infected monkeys. Nonetheless, more than 40 years after these initial studies, there is presently no definitive attribution of a causal link between CPIV infection and disease in primates.13,71 Fur- thermore, from a public health perspective relevant to canine-human interactions, there are no data that substantiate transmission of CPIV from dogs to humans. In fact, early circumstantial evidence suggests that it is unlikely that immunocompetent humans develop productive or clinical infections with CPIV, given that there is no evidence of respiratory disease or seroconversion in the high-risk population of dog handlers who worked closely with the dogs that were the subjects of the initial study on epidemic CPIV in 1968.

Therefore, available data suggest that canids are the primary or only target species for clinical CPIV infections. Among other caniforms, clinical disease associated with CPIV infection has been documented only in ferrets, although other species, notably mustelids, may have a similar susceptibility and response to infection. Phylogenetically more disparate feliforms may have only subclinical infections and may serve as reservoirs, although the latter possibility has not been examined. Beyond carnivores, the preponderance of evidence indicates that CPIV infections are restricted or abortive. At least in rodents, this restriction may be largely attributable to the inability of the viral gene products to subvert the innate immune system, thus allowing early clearance of the virus from infected cells in these animals. The restricted nature of CPIV in primates is more complicated and unresolved. Although CPIV is unlikely to be of clinical concern in immunocompetent humans, its zoonotic potential should probably not be discounted in immunosuppressed individuals, an estimated 40% of whom own pets in the United States.69

**Efficacy of CPIV Vaccines**

Development of vaccines for CPIV began in the 1970s, approximately 10 years after its recognition as a pathogen in dogs. The first was a parenteral modified-live vaccine developed with CPIV, which had been attenuated by > 20 passages in cell culture.19 This vaccine at a dose range of 10^1.9 to 10^3.9 TCID<sub>50</sub> stimulated the production of neutralizing antibodies, which were higher in dogs that received the vaccine IM versus SC, but not different among the doses. Twenty vaccinated dogs had no clinical disease after CPIV challenge (Manhattan strain, sixth passage in primary dog kidney cells), compared with mild to moderate disease typical of CITB in 3 of 5 unvaccinated controls. Vaccinated dogs shed less CPIV for less time after challenge and had an anamnestic serum antibody response; however, there was no direct correlation between the amount of serum antibody at the time of challenge and duration of shedding. In the early 1980s, combination intranasal vaccines containing CPIV together with *B bronchiseptica* were developed and tested.30,54 In the first study20 of such experimental vaccines, seronegative 8- to 16-week-old mixed-breed farm dogs were vaccinated once intranasally with 1 of 3 lots of vaccine containing the D008 isolate of CPIV that had been passed 7 times in vitro (twice in Vero [African green monkey kidney] cells). Twenty of 30 vaccinated dogs shed CPIV for a mean of 4.87 days after vaccination. At the time of group aerosol challenge with a fifth passage (in Vero cells) of the D008 CPIV isolate 18 days after vaccination, all vaccinated groups had increased GMTs of CPIV-neutralizing antibody. Dogs were then challenged with *B bronchiseptica* on day 21 after vaccination, and none had clinical signs of CITB or shed CPIV. In contrast, 9 of 10 unvaccinated control dogs had signs of CITB, and all shed CPIV for at least 1 day after challenge. As in the previous study19 of parenteral vaccination, apparent clinical protection from CPIV challenge was not directly associated with the amount of VN antibody in the serum at the time of challenge. Interestingly, and potentially related to the duration of CPIV-specific immune responses, serum VN antibody had decreased from day 21 to 42 after vaccination and subsequent challenge. Whether or not these dogs, given their source, were truly CPIV naive or just seronegative was apparently not investigated nor reported.

In a second study,24 2 doses (0 and 21 days) of an experimental single-component CPIV parenteral (SC or IM) vaccine were compared with 1 dose of the combination CPIV and *B bronchiseptica* intranasal vaccine in mixed-breed dogs that were reportedly seronegative for both agents at the time of vaccination at 4 to 10 weeks of age. Two weeks after the second dose of parenteral vaccine, dogs were challenged by a combination of individual aerosol (2 mL) and intranasal administration (0.5 mL) of a virulent strain of CPIV (10^1.1 TCID<sub>50</sub>/mL). Two weeks after vaccination, dogs that received the intranasal combination vaccine were similarly challenged with CPIV and then immediately group challenged with aerosol exposure to 3 mL (10^7 to 10^9 colony forming units/mL) of the D-2 isolate of *B bronchiseptica* for 20 minutes. Both groups of vaccinated dogs had only mild coughing for approximately 1 day's duration after challenge, whereas unvaccinated control dogs had clinical signs typical of CITB for approximately 18 consecutive days. Unvaccinated control dogs had detectable nasal CPIV for 70% of days scored (10 days for each dog), whereas parenterally vaccinated dogs had CPIV on na-
nal swabs for 50% of days scored and intranasal vaccinated dogs for 1% of days scored. Increases in the GMT of CPIV-neutralizing serum antibodies were found at the time of challenge 2 weeks after parenteral (GMT = 43, after 2 vaccinations) or intranasal (GMT = 34) administration. There were also anamnestic responses on day 10 after challenge in both the parenteral (GMT = 1,034) and intranasal (GMT = 236) groups. Associations between immune responses and clinical outcomes were not reported, nor were statistical analyses.

There are 4 published field trials evaluating the effects of CPIV-containing vaccines in the amelioration of naturally acquired CITB. In the first trial90 conducted in the late 1970s, the incidence of coughing in dogs vaccinated at the discretion of owners with an unidentiﬁed parenteral CPIV vaccine at least 2 weeks, but not more than a year, prior to kenneling was compared with coughing in unvaccinated dogs entering the kennel during the same 1-month period. Of 144 unvaccinated dogs, 33 developed coughs; of 52 vaccinated dogs, 2 developed coughs. These results were indicative of a signiﬁcant \( P < 0.001 \) reduction. The other 3 studies evaluated a combination of intranasal vaccines. The ﬁrst study91 enrolled more than 5,300 puppies in a large puppy gathering and dispersion facility (puppy mill) and its client pet stores. Puppies were vaccinated on arrival at the gathering facility, and 95% were shipped to pet stores within 5 days after vaccination. Puppies were observed for a mean of 3 weeks at both the gathering facility and the pet shops to which they were sent. Overall, the incidence of CITB declined from 40% prior the initiation of the intranasal vaccination program to 25%, 13.4%, and 8% after vaccination in 3 replicates of puppies. Unfortunately, as indicated, this study used only historical controls and the etiology of the CITB was not determined. In a separate trial, there was no difference in the incidence of CITB in puppies that were vaccinated (178/929) versus puppies that received placebo (205/944) and were commingled, which may have been the result of shedding of vaccinal agents and cross immunization. The second study92 was conducted in 2 replicates on 3-week-old puppies at a large breeding facility during endemic (summer) and epizootic (winter) periods. Whole litters of puppies were randomized and received a 1-ml intranasal dose of either a single-component modiﬁed-live \( B \) bronchiseptica vaccine; a double-component \( B \) bronchiseptica and CPIV vaccine; a triple-component \( B \) bronchiseptica, CPIV, and canine adenovirus-2 vaccine; placebo in the winter trial; or the double-component, triple-component, or placebo vaccine in the summer trial. During a 9-week observation period after the single vaccination, spontaneous, etiologically undifferentiated coughing was signiﬁcantly reduced by 32.1%, 45.3%, and 71.2%, respectively, compared with controls in the winter trial, and by 72.7% and 81.8%, respectively, compared with controls in the summer trial. A third ﬁeld trial93 of intranasal CPIV vaccines was conducted in the mid 2000s in a humane shelter. On arrival at the shelter, dogs free of respiratory disease were assigned daily on a rotating basis to receive a double-component (\( B \) bronchiseptica and CPIV), triple-component (\( B \) bronchiseptica, CPIV, and canine adenovirus 2), or placebo vaccine. During a 30-day postvaccination observation period, spontaneous coughing was reduced by 20.7% and 24.4%, respectively, compared with the placebo group, although the authors commented that there was no respiratory disease noted in the facility during the study period.

In the mid 2000s, 2 studies addressed the duration of immunity of CPIV-containing vaccines. In 1 laboratory study,94 12 speciﬁc pathogen–free Beagle puppies were vaccinated once intranasally at 3 weeks of age with a double-component (\( B \) bronchiseptica and CPIV) vaccine and 6 were unvaccinated controls. Fifty-six weeks later, these dogs, together with another unvaccinated control group of 10-week-old seronegative specific pathogen–free puppies, were given a combined challenge with \( B \) bronchiseptica and CPIV. The CPIV challenge comprised a combined intranasal, oral, and aerosol exposure to \( > 10^8 \) TCID\(_{50}\) of Vero cell–propagated D008 isolate of the virus. Although signiﬁcant reductions in clinical signs and shedding of CPIV were reported, the design of the experiment (a single replicate of separately housed groups) did not account for housing pen effect. Alluding to a possible pen effect, 7 of the 12 vaccinated dogs had increases in CPIV-reactive antibody concentrations between 30 and 56 weeks after vaccination, and the antibody concentrations in the remaining animals did not change signiﬁcantly, which would be unusual and contrast with early epidemiological ﬁndings, if the only exposure to CPIV was a single vaccination at time zero. A second study95 addressed duration of immunity by measuring antibodies to CPIV in a population of 332 healthy client-owned dogs \( ≥ 2 \) years of age that had been vaccinated 1 to 4 years prior to commencement of the study. Ninety-eight percent of dogs, regardless of the interval since vaccination, had VN titers \( ≥ 1:16 \) or responded anamnestically to revaccination with a \( ≥ 4\)-fold increase in titer. Interestingly, and attesting to the impact of natural exposure on duration of immunity, dogs considered to have a high-risk lifestyle (frequent commingling) maintained higher concentrations of CPIV-neutralizing antibodies than did dogs with a low-risk lifestyle. A limitation of this unique population-based study was the absence of clinical disease or the exclusions of ill animals from the study population, so that no case-control analysis of the putatively protective titers was possible.

A problem in comparatively evaluating laboratory studies on the efficacy of the CPIV component of various vaccines is inconsistency in CPIV challenge models, particularly with regard to reproduction of disease; it has often been negligible or mild. This may be because of the attenuation of challenge viruses, which usually have been passaged many times in vitro or in other instances sometimes as many as or more times than the vaccine virus. Nevertheless, the results of both experimental infections and ﬁeld trials conducted under a variety of conditions indicate that the use of both parenteral and intranasal CPIV-containing vaccines can result in signiﬁcant reductions in upper respiratory disease typical of CITB. Notwithstanding all of these concerns and lack of knowledge, priming mucosally early in puppyhood with intranasal vaccine followed by boosting parenterally when maternal antibodies levels have declined at 2 to 3 months of age may be the practical approach to immunoprophylaxis. As with most veterinary vac-
cines, there is a dearth of information concerning the duration of immunity of CPIV-containing vaccines at the population level. Therefore, the true duration of clinical immunity, defined as the prevention of reinfection and development of clinical disease, is not currently known, but is likely to be considerably < 3 years.\(^\text{17}\) as implied in the most recent guidelines for canine vaccination.\(^\text{20}\)

**Management of CPIV Outbreaks**

Vaccination alone is often inadequate to prevent CPIV-associated disease, especially in high-density populations. As in other multifactorial respiratory disease syndromes, such as shipping fever in cattle, the impact of CPIV-associated CITB can be controlled, to some extent, by attention to environmental cofactors. The impact of CPIV-associated CITB can be controlled, to some extent, by attention to environmental cofactors.

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