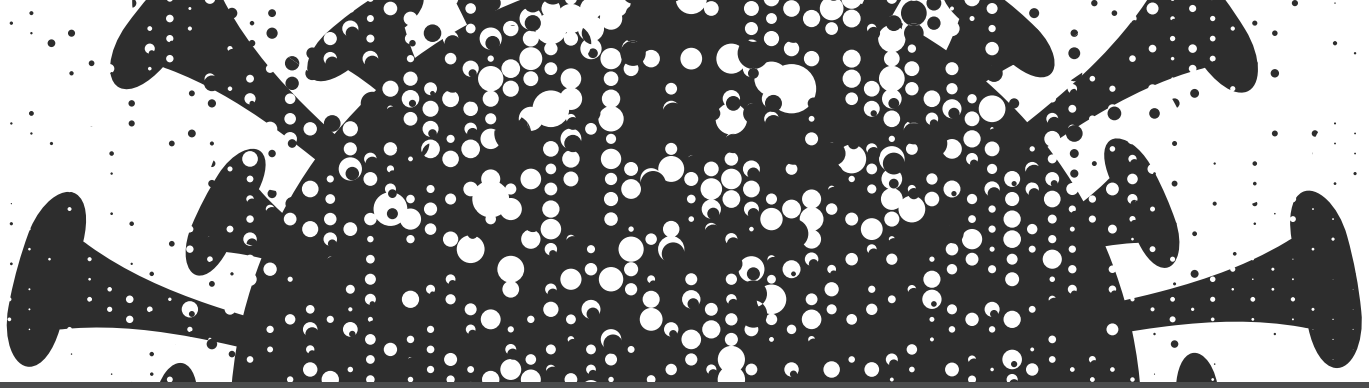


CANINE HERPES VIRUS:

The Now-You-See-It-Now-You-Don't

Killer of Neonatal Puppies

BY **NANCY MELONE, PH.D.**

She sat alone in her van in the dark, empty parking lot of the emergency veterinary clinic. She cried. Two weeks ago, she celebrated the arrival of seven beautiful puppies. In the last hour, she euthanized the last of the seven. Five days without any sleep, futilely nursing sick puppies, she was emotionally spent. The well-meaning young vet did not recognize the symptoms; as a breeder she knew even without previously experiencing it…this was canine herpes virus.

No one wants to consider the prospect of their much-anticipated litter of puppies "fading" painfully, one-by-one, before the end of their second week. Yet studies of litter mortality indicate that between 17%-30% of puppies die before they are 8 weeks old, with three-quarters of those dying before they reach 3 weeks old. As high as this mortality rate seems, even this number does not include fetuses lost in utero through early resorption and late-term abortion.

Oddly, little academic research has been devoted to understanding the reasons for these losses. As such, not much is known about the causes of most neonatal illnesses and deaths. Canine herpes virus type-1 (CHV-1), carrying a near 100% mortality in neonates, is one of two viruses implicated in neonatal deaths.

What Causes Canine Herpes in Dogs?

Canine herpes is caused by the canine herpes virus type-I (CHV-1). (Despite the similarity in name, the virus is not related to the human herpes virus.) The virus was first identified in 1965 by each of three independent research groups who simultaneously investigated the infectious deaths of newborn puppies. Herpes viruses belong to one of three groups: alpha, beta or gamma. CHV-1 is a member of the alpha-herpesvirus group, as are several other herpes viruses of interest to large- and small-animal veterinarians. These alpha-herpesviruses are mucosal pathogens; once they infect an animal, if the animal survives, they establish life-long latent infection residing within the neurological ganglia. At times, the virus becomes active only to return later to dormancy.

Adult dogs often show no symptoms of the virus when infected. In contrast to the benign symptoms in adults, the outcome for infected fetuses is usually resorption or abortion, and for neonates under 3 weeks old it is most often an agonizing death. If a puppy happens to survive systemic infection, it is likely to be seriously compromised.

Where is CHV-1 Most Prevalent?

CHV-1 is found worldwide. Species-specific, the virus infects only domestic and wild canids. Any dog participating in dog shows, performance events, training classes, doggie daycare, dog parks or who is

CHV-1 is a common canine infection among adult dogs spread primarily by direct contact with oral and nasal secretions of a dog that is shedding virus.

in contact with other dogs, has likely been exposed to CHV-1. Ironically, veterinarians whose practices do not specialize in canine reproduction may not recognize CHV-1 even though many of their non-reproducing clients are likely to have been infected with the virus. Infection in adult dogs causes either no symptoms or transient mild respiratory infection, which is easily misdiagnosed as something else (e.g. kennel cough). Moreover, infected dogs can move back and forth between dormancy and contagion, making a precise description of its prevalence even more difficult.

Because latently infected animals may go back and forth from inactive dormancy to active shedding, studies designed to measure the extent of CHV-1 in the population are likely to understate the true extent of exposure and infection. Indeed, depending on the region in which the study is done, these estimates range from 20% to 98%. In breeding kennels and rescue shelters seropositive rates of 100% are not uncommon. If you are a breeder who shows dogs, it is reasonable to assume that your dogs are seropositive for CHV-1, although they may convert from time to time to seronegative (dormant) status, making it difficult for you to determine if it is because she has never been exposed to CHV-1 or if it is because her disease is currently dormant.

Factors that Influence the Spread of CHV-1

Fortunately, CHV-1 does not survive well outside the canine cell or body. Exposure is primarily through dog-to-dog contact rather than from contaminated surfaces or clothing (i.e. fomite transfer). Moreover, the virus is easily killed by common disinfectants and temperatures above 104 degrees Fahrenheit. The half-life of the virus (i.e. the point at which half of the virus is destroyed) at 98.6 degrees Fahrenheit is less than five hours.

CHV-1 persists in the natural world by residing in the dog's ganglionic and lymphoid tissues of the oronasal and genital mucosae. Intermittent shedding of virus through an infected dog's secretions guarantees survival of CHV-1 in the dog population and breeding kennels. Like other herpes viruses, once a dog is exposed to CHV-1 (and survives), the result is life-long latent infection. When the latent (dormant) virus reactivates in a dog, it replicates in the cooler temperatures of mucous membranes (e.g. tonsils, nasal turbinates) and virus shedding takes place. The virus replicates best at a temperature range between 93.2 and 95 degrees Fahrenheit. This is the period when unexposed dogs can become infected. Dogs are particularly prone to shedding virus when they are stressed. Such stress can occur when dogs are traveling, pregnant, taking immunosuppressive drugs, in environments where there are many dogs (e.g., dog shows, performance trials, dog events, boarding kennels) or when new dogs have been introduced to a dog family.

CHV-1 is mostly spread through direct contact with the oral, nasal or (more rarely) genital secretions of dogs that are currently shedding virus. There is typically a high level of viral shedding in dogs with initial systemic infection. Subsequent shedding from latently infected dogs is less and of shorter duration.

Venereal transmission from infected males to previously unexposed females is not believed to be a significant mode of transmission. In contrast, genital localization of the virus in females is an important mode of virus transmission to neonatal puppies during birth.

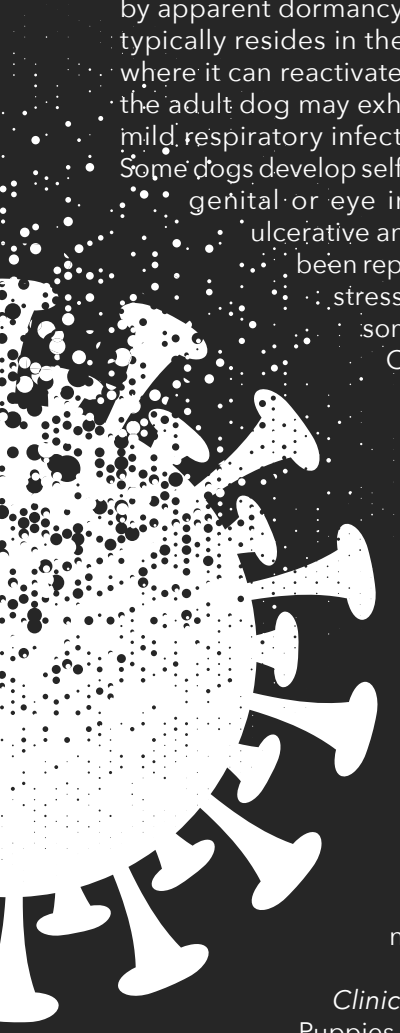
Despite the high rates of exposure, one may not see any symptoms of the disease in infected adult dogs or older puppies. Likewise, neonatal puppies exposed at birth may exhibit no clinical signs of exposure until there is generalized infection and it is too late to save the puppy.

A neonate's inability to thermo-regulate body temperature and its immature immune system put it at particular risk of the usually fatal generalized infection.

What are the Symptoms of CHV-1?

Symptoms and outcomes vary widely depending on the dog's age and gender. By far the most devastating clinical signs of CHV-1 are seen in pregnant bitches and puppies, particularly those under three weeks.

Clinical Signs in Non-Pregnant Adults
Infection in adults is often asymptomatic, followed by apparent dormancy. In its dormant state, the virus typically resides in the dog's neurologic tissue from where it can reactivate to be shed later. Occasionally, the adult dog may exhibit symptoms associated with mild respiratory infection (e.g., coughing, sneezing). Some dogs develop self-limiting genital lesions. Chronic genital or eye infections (e.g., conjunctivitis, ulcerative and non-ulcerative keratitis) have been reported. These are made worse by stress. There is some speculation that some cataracts may be the result of CHV-1 exposure. Viral shedding in reactivation of previously exposed adults usually lasts one week.



Clinical Signs in Pregnant Bitches
The most common clinical signs of CHV-1 in previously unexposed pregnant bitches are linked to various reproductive failures. These include early fetal loss (resorption), late-term abortion, premature delivery, stillbirth, infertility and the birth of virally compromised neonates.

Clinical Signs in Neonates
Puppies can be exposed to CHV-1 before, during or after birth. Depending on the circumstances, not all puppies may be infected. After infection, replication of the virus occurs within 24 hours. The virus enters the bloodstream and spreads to the neonate's body within three to four days. Neonatal pups under 3 weeks old who acquire CHV-1 but lack immunity from their dam usually die shortly after the onset of symptoms (24-48 hours). Pups 4 to 8 weeks old are normally clinically asymptomatic after infection if body temperatures are not artificially lowered. Clinically affected puppies, if they survive, shed the virus for two to three weeks after recovery.

The most apparent symptoms in infected neonates include yellow-green stool (caused by a compromised liver), loss of suckle reflex, loss of appetite, weakness, lethargy, persistent crying ("mewing"), hemorrhages (nosebleed, small bruises), respiratory difficulty and nasal discharge. Younger puppies usually die before neurologic symptoms develop, but in older puppies, there may be central nervous system abnormalities such as seizures, deafness and blindness.

Temperature regulation in newborns does not develop until two to three weeks. Rectal neonate body temperature is usually 2-3 degrees Fahrenheit lower than in adults. Despite persistent crying they are unable to produce a fever to elevate body temperature. Neonatal immune systems are immature and suppressed at lower temperatures. As such neonates are not only susceptible to CHV-1 but also several other typically fatal infections (e.g., distemper, adenovirus).

Acquired immunity from the dam appears to improve survival of infected puppies. Puppies who nursed from seronegative mothers develop fatal illness when infected with CHV-1, whereas puppies nursing from seropositive bitches became infected but remained asymptomatic. Maternal antibodies or immune memory cells acquired through the milk may explain why naturally infected bitches who give birth to sick puppies, with rare exception, go on to deliver subsequent healthy litters.

How is CHV-1 Diagnosed in Bitches and Neonates?

Definitive diagnosis in both bitches and neonates is typically done using some combination of clinical examination, serologic testing and viral isolation. Hemagglutination, ELISA and immunofluorescence antibody tests are commonly used in diagnosis. Polymerase chain reaction (PCR) is considered the gold standard (more on this test below).

Diagnosis in the Bitch
Serologic testing is the traditional test veterinarians use

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The gold standard for detecting the CHV-1 is polymerase chain reaction (PCR). Unfortunately, this test is not routinely available outside of commercial laboratories.

to diagnose CHV-1. Unfortunately, the viral infection does not prompt a strong immune response. Any test that measures antibodies against CHV-1 may not accurately indicate exposure to the virus. Titers may rise and fall rapidly (i.e., 4 to 8 weeks). Research is inconsistent regarding how long CHV-1 titers last.

In some cases, antibody titers do not last longer than 60 days. In other cases, they have been reported to last up to two years. In general, CHV-1 antibody titers are low. Results range from 1:2 to 1:32. From a practical perspective, this means if antibody titers are high, a breeder can be fairly confident that the bitch was exposed to CHV- 1 but may or may not be shedding. A titer greater than 1:2 with clinical signs suggestive of CHV-1 (e.g., unexplained fetal loss or late-term abortion) is considered diagnostic. A single positive antibody test indicates exposure only, but not necessarily active infection unless there are accompanying clinical signs.

This puts the breeder at some disadvantage in knowing the bitch's status. A way to get a better handle on the extent of active infection status is to do a second antibody test 10-14 days after the first antibody test. There will be a four-fold increase in antibody levels if there is an active infection.

In contrast, if antibody titers are low, a breeder cannot be certain whether the bitch has never been exposed to the virus or if she has been exposed to CHV-1 but failed to mount a strong immune response. One caution is that serologic tests have not been standardized, so there may be variations in level and prevalence of positive results across different laboratories. If doing the two-test method, use the same laboratory for both tests.

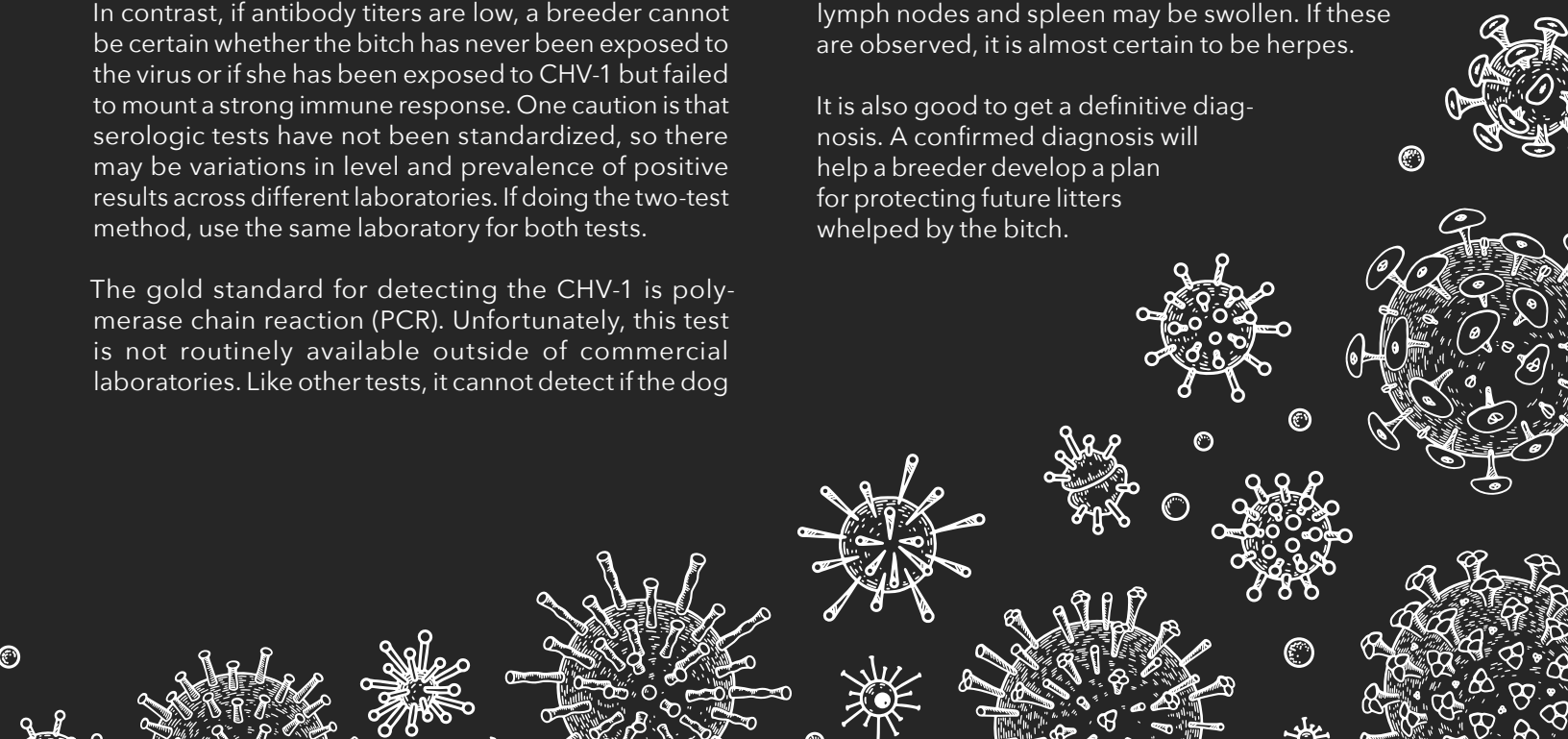
The gold standard for detecting the CHV-1 is polymerase chain reaction (PCR). Unfortunately, this test is not routinely available outside of commercial laboratories. Like other tests, it cannot detect if the dog is shedding and contagious. PCR works by identifying fragments of CHV-1 virus in the animal's bloodstream or on mucosal surfaces. When using fresh tissue and fluid samples, PCR has the advantage of being both highly sensitive (i.e., identifies all dogs with CHV- 1 but also includes some dogs who don't have it) and specific (i.e., misses some dogs who have CHV-1, but if a dog is positive for CHV- 1, the dog most surely has CHV-1). Given its relative accuracy, PCR is likely to advance diagnosis of pregnancy loss in the future.

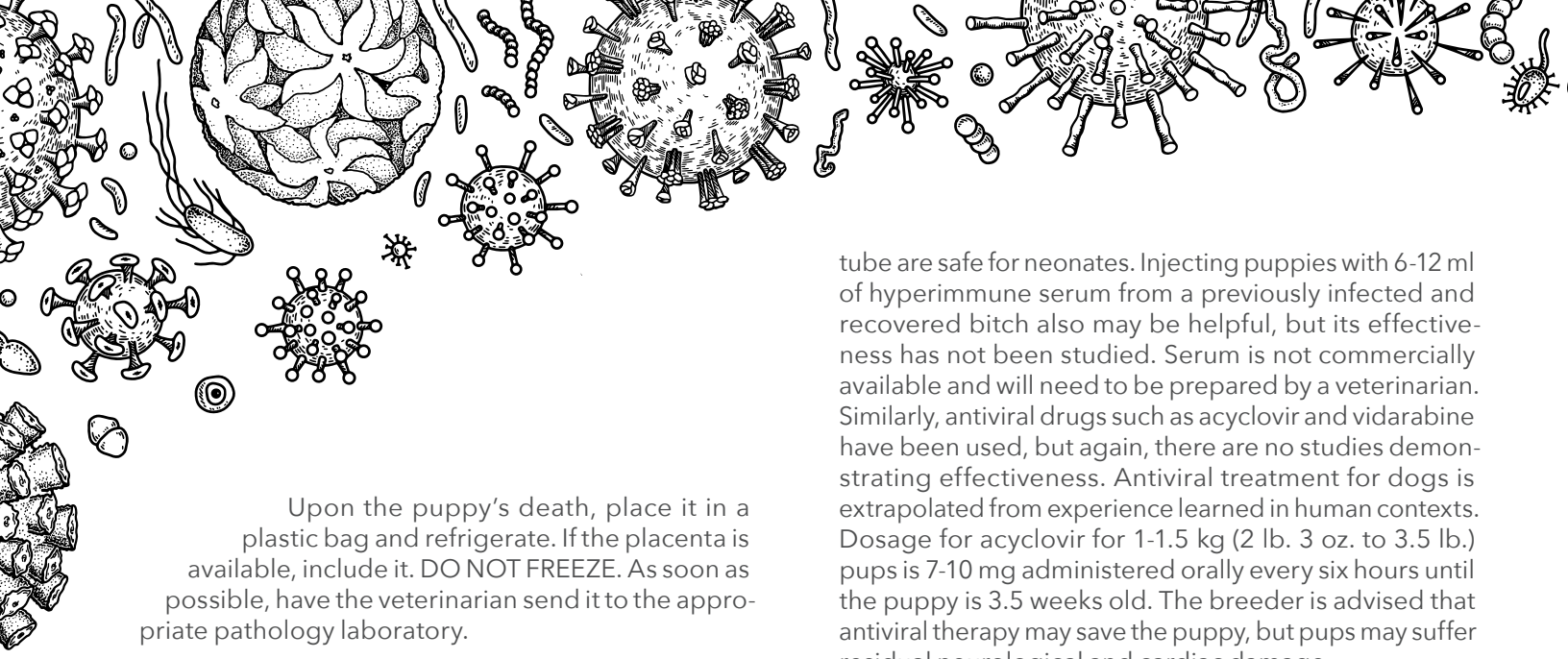
Expedited and Definitive Diagnosis in the Puppy

Confirming a CHV-1 diagnosis in a puppy is much easier than in an adult and is usually done postmortem. When done at a university or laboratory it involves standard necropsy and virus isolation from fresh lung, liver, kidney and spleen. The turnaround time for a definitive diagnosis is four to seven days.

While a definitive diagnosis may be preferred, time may be of the essence to save other puppies. Although most general practice veterinarians may not be experienced at diagnosing herpes in puppies, they can do it with an informal necropsy. Typically, the puppy's organs will present with necrotic lesions. The general practice veterinarian looks for pinhead-sized red spots on the kidneys, liver, adrenal glands and lungs. In addition, lymph nodes and spleen may be swollen. If these are observed, it is almost certain to be herpes.

It is also good to get a definitive diagnosis. A confirmed diagnosis will help a breeder develop a plan for protecting future litters whelped by the bitch.





Upon the puppy's death, place it in a plastic bag and refrigerate. If the placenta is available, include it. DO NOT FREEZE. As soon as possible, have the veterinarian send it to the appropriate pathology laboratory.

Is There a Treatment for Infected Neonates?

Overwhelmingly, the literature characterizes treatment of systemically affected puppies as "unrewarding." In addition, experts caution that the prognosis for puppies that do survive is guarded or poor because of the likelihood of irreparable damage to the central nervous system, lymphoid organs, kidneys and liver.

A breeder who elects to save puppies (i.e., go beyond palliative care) must confront the likelihood of this negative outcome in survivors. These are always very personal and agonizing decisions. If attempts are made to save puppies, action must be taken before the onset of any symptoms, acknowledging that sometimes symptoms do not appear before death.

In cases in which overt efforts are made to save the litter, breeders are advised to place puppies in an incubator set at 95 degrees Fahrenheit at 50% humidity since the virus cannot replicate at higher temperatures and puppies are unable to regulate body temperature on their own yet. *Once symptoms are present, elevating environmental temperature will not eliminate infection.*

The general recommendation is to provide supportive care (warmth, nutrition, rest and hydration) and prevent secondary infections by administering broad-spectrum antimicrobials. Amoxicillin, amoxicillin with clavalonic acid, and cephalexin administered orally or with a feeding tube are safe for neonates. Injecting puppies with 6-12 ml of hyperimmune serum from a previously infected and recovered bitch also may be helpful, but its effectiveness has not been studied. Serum is not commercially available and will need to be prepared by a veterinarian. Similarly, antiviral drugs such as acyclovir and vidarabine have been used, but again, there are no studies demonstrating effectiveness. Antiviral treatment for dogs is extrapolated from experience learned in human contexts. Dosage for acyclovir for 1-1.5 kg (2 lb. 3 oz. to 3.5 lb.) pups is 7-10 mg administered orally every six hours until the puppy is 3.5 weeks old. The breeder is advised that antiviral therapy may save the puppy, but pups may suffer residual neurological and cardiac damage.

How Do I Reduce the Risk to My Pregnant Bitches and Puppies?

Practically speaking, eliminating CHV from a breeding kennel is impossible and screening for infected dogs is not practical. While CHV-1 is a devastating virus in unexposed pregnant bitches and neonates, subsequent litters from an affected bitch have very low risk of developing clinical disease.

Breeders should be advised that some veterinarians and pathologists may tell them not to breed the bitch again, but that is a risk-averse recommendation motivated by theoretical possibilities of recurrence. In contrast, most theriogenologists and reproduction veterinarians, based on empirical observation, are of the opinion that bitches with litters suffering previously from CHV-1 fetal loss or neonatal deaths will likely go on to produce unaffected litters in the future.

Dogs at highest risk are bitches that have not been exposed to CHV-1 and neonates, under 3 weeks, whose thermoregulation and immunity are not well developed. It is the bitch who is young, highly confined or lives an isolated life who is at highest risk of not having developed immunity and becoming infected with CHV-1 when pregnant or nursing neonates. Many co-owned breeding bitches living as single pets in families would fit that description.

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While not uniformly recommended, the cautious breeder may wish to run titers on both the bitch and the stud dog prior to breeding.

There is currently no vaccine to prevent the virus in adult dogs. There is a vaccine administered to pregnant bitches to minimize risk in fetal and neonatal puppies. Merial produces a vaccine – Eurican® Herpes 205 – that is available in Europe. If given to bitches at the time of breeding and again in 6-7 weeks, it has been scientifically demonstrated to offer protection to fetuses and neonates. The vaccination must be given again with each pregnancy. Bitches with latent infection may also be given the vaccination. Unfortunately, the vaccine is not available in the U.S., and according to several authors and veterinarians I have spoken with, it is not likely to become available in the future.

Recommendations for Pregnant or Soon-to-be Bred Bitches and Neonates

Most experts recommend that during the last three weeks of gestation and the first three weeks following birth, the pregnant bitch and neonatal puppies should have no contact with any other dogs.

Transmission of the disease in adults occurs primarily by direct dog-to-dog contact (e.g., nosing, licking, sniffing, drinking from a common water bowl). Transmission to puppies occurs through contact with maternal secretions via the placenta, during delivery, nursing or licking.

Make certain that the environmental temperature for newborn puppies is kept warm with heated whelping boxes, heat lamps or other devices that do not dehydrate the puppies.

Practice good kennel hygiene.

While not uniformly recommended, the cautious breeder may wish to run titers on both the bitch and the stud dog prior to breeding. Recall, titers test only for exposure (i.e., presence of antibodies); the test does not tell you if the dog is currently contagious. To get a handle on contagion, as discussed previously, one would run two tests separated by 10-14 days (same laboratory) on the bitch and on the stud dog to see if there are dramatic increases in the titer values for either dog. Active status is indicated by a four-fold increase in antibodies on the second test.

In the past, reproduction veterinarians recommended exposing your bitch well in advance of breeding to other healthy dogs that are also exposed to other healthy dogs. In that way, exposure to CHV-1 prior to breeding would be more likely, and that exposure would give her time to produce CHV-1 antibodies that she could pass on to her puppies in the colostrum. It is recognized that CHV-1 antibody levels fluctuate considerably, but a population of memory cells theoretically allows the bitch to fight off infection if she is exposed again. Once a memory cell has been exposed to a pathogen like CHV- 1, it reacts much more rapidly if it encounters that pathogen again. This is why it is believed that most bitches lose at most one litter to canine herpes virus.

Some recent research suggests that previously exposed dogs can be re-infected with CHV-1. These researchers advise vaccinating with Eurican® Herpes 205, which is unfortunately not an option for U.S. dog owners. U.S. breeders should follow recommendations for at-risk unexposed bitches and neonates.

Can I Get Herpes from My Dog?

The short answer is no. CHV-1 is species-specific; it infects only wild and domestic dogs. Unless you are a dog, wolf, fox or coyote, you cannot get it from your dog. If you are human and get herpes, you did not get it from your dog.

Summary Points

- CHV-1 is a common canine infection among adult dogs spread primarily by direct contact with oral and nasal secretions of a dog that is shedding virus.
- Adult dogs often show no symptoms. A mother dog with herpes will not usually appear to be sick. In contrast, by the time neonates show symptoms, it is probably too late to save them, and any who survive are likely to be severely compromised.
- Treatment for neonates is generally considered to be unrewarding.
- Bitches who have lost a litter to CHV-1 typically go on to produce unaffected litters in following pregnancies.

Most experts recommend that during the last three weeks of gestation and the first three weeks following birth, the pregnant bitch and neonatal puppies should have no contact with any other dogs.

- Previously exposed bitches exhibiting sufficient antibody titers are protected. Bitches without sufficient antibody levels or unexposed bitches and their neonates are at risk.
- There are no vaccines to prevent the disease in adults. There is a vaccine administered to pregnant bitches that has been shown to be protective for neonates. This vaccine is not available in the U.S. Where the Merial Eurican® 205 vaccine is available, bitches should be vaccinated.
- Bitches should be isolated in the last three weeks of pregnancy and both bitches and neonates should be isolated during the first three weeks following the puppies' birth. Stress levels should be kept low prior to breeding. Breeders should practice good kennel hygiene and maintain an appropriate environmental temperature in their whelping areas.

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About the Author: Nancy P. Melone, Ph.D., is a graduate of the University of Minnesota in Information and Decision Sciences. For her writing and editing, she received several prestigious Dog Writers Association of America Maxwell Medallions, the Morris Animal Foundation Advances in Canine Veterinary Medicine Award, and several AKC Publication Excellence Awards. A breeder of health-tested, champion Bernese Mountain Dogs under the kennel name, ThornCreek Reg'd., Dr. Melone is a former trustee/treasurer of The Berner-Garde Foundation, Inc. and Bernese Auction Rescue Coalition, Inc. and editor emerita of The Alpenhorn. She currently serves on the Board of the Nederlandse Kooikerhondje Club of the USA and chairs their Health and Genetics Committee.

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