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NEWSLETTER

Healthy Cats and *Bartonella*:
Bartonella are More Important than FeLV and FIV

Evelyn E. Zuckerman, Editor **Winter 2007** **Vol. 6, Number 1**

In This Issue:

In the winter 2007 issue of the NVL Newsletter we will cover the importance of determining if healthy cats are infected with *Bartonella*. Healthy infected cats are prone to develop any of the *Bartonella* inflammatory diseases and can transmit the bacteria to people. There has been a long standing controversy as to whether or not *Bartonella* cause any disease in cats, even though there are ample publications that show *Bartonella* are disease-inducing bacteria.[1, 2]

We strongly recommend that all healthy cats be tested for *Bartonella* as a part of their normal health exams which include FeLV and FIV tests, examination of the stool for intestinal parasites, and routine vaccinations.

Healthy Versus Disease:

Stedman's Medical Dictionary, 25th Edition defines:

Healthy: "Well; in a state of normal functioning; free from disease."

Morbus or Morbid: "Disease and diseased or pathologic."

Disease: "1. Morbus; illness; sickness; an interruption, cessation, or disorder of body functions, systems, or organs. 2. A morbid entity characterized usually by at least two of these criteria: recognized etiologic agent(s), identifiable group of signs and symptoms, or consistent anatomical alterations."

Syndrome: "The aggregate of signs and symptoms associated with any morbid process, and constituting together the picture of the disease."

Pathogenic and Non-Pathogenic Microorganism:

All micoorganisms must infect susceptible healthy hosts in order to propagate. They can be classified into 3 general groups: 1) Non-pathogenic microorganisms: these are non-disease-inducing and live commensally with their hosts, many of which are actually beneficial. 2) Chronic pathogenic microorganisms: these are minimally non-pathogenic for a time and live harmlessly for long periods within their host (chronic persistent infection) and induce disease after a long "latent period" or induce disease when the host is under stress (*Herpes viruses*) or is immunosuppressed (*Mycobacterium avium*).[2] *Bartonella*, FeLV and FIV are examples of this type of microorganism. 3) Acute pathogenic microorganisms: these infect their hosts and quickly induce disease, some resulting in chronic non-life threatening diseases and others inducing death rapidly in their infected hosts (Plague, *Parvovirus*, Ebola virus).

Healthy Animals:

A healthy animal, by definition, is one that does not exhibit any signs of a recognizable disease syndrome, even though they may be infected with a known pathogenic microorganism. For example, cats can be healthy carriers of FeLV, FIV, FIPV, *Toxoplasma* or *Bartonella*. Cats are known to mask clinical signs of disease far more effectively than dogs or humans. During our FeLV clinical studies we often examined cats with large lymphosarcoma mediastinal masses or severe anemias where the owner had not noticed any signs of illness, such as increased respiration, until the day before coming to the clinic.

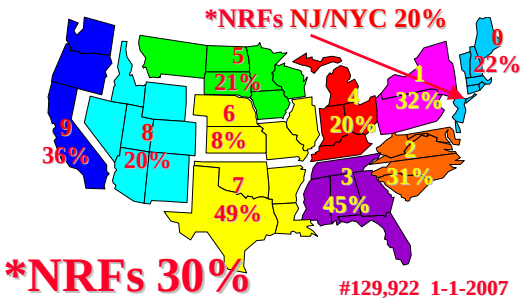
Many practitioners consider cats to be healthy even though they have gingivitis, skin papules or mild conjunctivitis. However, these may be signs of acute or chronic disease processes and may lead to more severe general pathology. A 3 month-old kitten with gingivitis most likely has an infectious cause for the gingivitis since it has not lived long enough to develop significant tartar to cause the gingivitis. Even though the gingivitis many be the only clinical abnormality noted, the practitioner should not discount this early sign of a systemic disease. The cause may be FIV, FeLV or *Bartonella* or a combination of these microorganisms.

Bartonella-Infected Healthy Cats:

The major risk factor for *Bartonella* infection of cats is not their contact with other infected cats, but rather, factors that increase the exposure to arthropod flea and tick vectors which are responsible for almost all of the transmission of *Bartonella* between cats. These risk factors are: stray or shelter origin, outdoor cat, living in multi cat households, a history of fleas or present flea infestation. In our initial study of healthy cats with no reported risk factors, performed in the metropolitan New York/New Jersey area from the Oradell Animal Hospital, the prevalence was 20%.[3] This is the baseline or denominator for all of our studies of the prevalence in other areas of the United States and for cats with *Bartonella* inflammatory diseases.

As of January 1, 2007, after testing 129,922 cats, we have derived a *Bartonella* prevalence map based on the climate of the United States as differentiated by the first number of the postal zip codes. Nationwide, the prevalence in healthy cats with no reported risk factors is 30%.

***Bartonella* Prevalence in Healthy Cats Based on the First Number of Zip Code**



***NRFs= No reported risk factors**

The prevalence increases in hot and humid climates as shown in the map above and is highest in the southern states of Florida, Texas, Louisiana, the Gulf states, and the Pacific coast states and is lowest in the northern states. The high prevalence parallels the year-round flea and tick incidence in the warmer more humid climates and people living in these areas are at increased risk of zoonotic infection. As of January 1, 2007 we have found that 11,973 of 31,924 (37%) healthy cats (with known or no reported risk factors), were infected with *Bartonella* (See Table below).

Bartonella Prevalence in Cats:

Status	Number Tested	Number Positive	% Positive
Healthy	31,924	11,973	37%
1) No RFs*	6,912	2,054	30%
2) With RFs	25,012	9,919	40%
Diseased Cats	94,911	43,367	46%
Not Specified**	3,087	1,384	45%
Totals	129,922	56,724	44%

*** RF= risk factors ** Diagnosis not given**

Thus, veterinarians should realize that 1 of every 3 healthy cats that they examine are carrying *Bartonella* which are capable of infecting them, their hospital personnel, and the cat owner's family members. Practitioners should re-examine their policy regarding *Bartonella* testing.

Comparison of the Prevalence of FeLV, FIV and *Bartonella* in Healthy Cats

Most practitioners include FeLV and FIV testing as part of their routine health examination of new cats but few include *Bartonella* testing. The prevalence of FeLV and FIV infection in healthy cats is quite low, whereas the *Bartonella* prevalence is 20 times higher. We have tested 4,360 healthy cats for FeLV, FIV and *Bartonella* and the data are given in the Table below. FeLV and FIV are not known to be transmissible to humans, whereas *Bartonella* are transmissible and can even cause death under rare conditions. Thus, *Bartonella* is more important for the health of cats and their owners than FeLV and FIV.

Prevalence of FeLV, FIV and *Bartonella* in Healthy Cats

Test*	Number Tested	Number Positive	% Positive
FeLV	4,360	60	1.4%
FIV	4,360	75	1.7%
Bartonella	4,360	1,530	35%

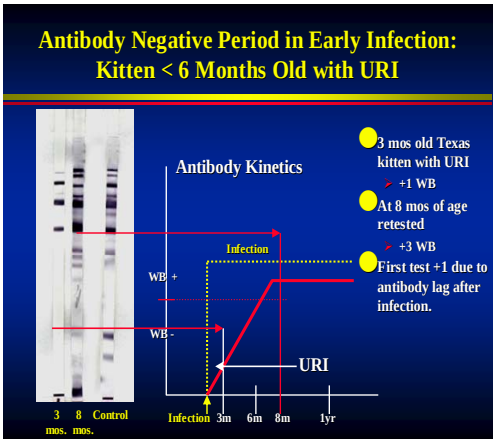
*** 5 cats (0.1%) were infected with all 3 organisms.**

Healthy Cats, Especially Kittens, Transmit *Bartonella* to People:

Bartonella are found in the blood plasma, inside erythrocytes and endothelial cells and in tissues of infected cats. In order to be transmitted to people, the organism must be present on the claws (scratch), in the mouth (bites) or on the fur (contact- no abrasion) of infected cats. Infected kittens are rapidly growing and have changing dentition leading to the probability that *Bartonella* can leak into the oral cavity. The loss of kitten teeth or oral trauma due to rough play, chewing and playful fighting, can lead to *Bartonella* in the mouth. Cats groom themselves frequently thereby depositing *Bartonella* organisms from the oral cavity onto their fur or claws. The fact that kittens and children are playful toward each other presents the conditions needed for the zoonotic transmission from kittens to children. Boys tend to play more roughly with kittens than do girls, which is reflected in the higher incidence of cat scratch disease in boys.

***Bartonella* testing of healthy cats should be part of the routine feline health protocol, especially before their first birthday.**

Bartonella antibody negative kittens, 6 months or younger, present a problem for the practitioner. Kittens under 6 months of age with *Bartonella*-like inflammatory diseases (gingivitis, URI, conjunctivitis, rhinitis, uveitis, gastroenteritis, etc.) may be infected but have not yet had enough time to develop antibody. *Bartonella* appear to be able to infect young kittens and induce an inflammatory disease before the development of detectable antibody. Thus, test negative kittens with inflammatory diseases should be retested 8 weeks after the first test to see if they were "incubating the infection." An example of one such Texas kitten's tests is presented below.



Although we make this recommendation, only 270 (4%) of the 6,534 Fe*Bart*® Test negative kittens, with an inflammatory disease, were retested 8 weeks later. 45 of the 270 retested kittens (17%) were found to be infected. Thus, many practitioners allow these kitten's infections to go undetected and the kittens are prone to develop *Bartonella* inflammatory diseases. These kittens can transmit the bacteria to a person in the household. In this regard, we have observed *Bartonella* transmission to a person from an initially test-negative kitten with an inflammatory disease who was not retested as recommended. Not adhering to our recommendation may make the practitioner legally responsible for the zoonotic consequences, should they occur.

Transmission of *Bartonella* from Healthy Cats to People:

We presented our human *Bartonella* disease findings at The 5th International Conference on *Bartonella* as Emerging Pathogens, in conjunction with the 20th Meeting of the American Society for Rickettsiology, at the Asilomar Conference Grounds, Pacific Grove, California, September 2-7 2006.[4] We investigated 84 human patients with serologically or biopsy confirmed *Bartonella* diseases and identified 70 cats that transmitted the bacteria. 40 of the 70 cats (57%) were healthy while 30 had *Bartonella* induced inflammatory diseases. 29 of the 70 (41%) cats were kittens under 1 year of age. Thus, more than half of cats that transmit *Bartonella* are healthy and almost half are kittens less than 1 year of age.

We recommend that all healthy cats, especially kittens younger than 1 year of age, be tested for *Bartonella* as a part of their normal health examinations.

Treatment of *Bartonella* Infection:

As has been reviewed in previous Newsletters, therapy of *Bartonella* infected cats is effective.[5] It is very important to stress rigorous flea and tick prevention for *Bartonella* test-negative cats and infected cats that have been treated. **AFTER TREATMENT WE ARE UNABLE TO RETEST PREVIOUSLY POSITIVE CATS TO DETERMINE *BARTONELLA* RE-INFECTION.** However, we can retest *Bartonella* test negative cats should they subsequently be infested with fleas or ticks.

Risk Factors for *Bartonella* Infection in Healthy Cats (Fleas & Ticks)

Risk Factor*	Number Tested	% Infected
None Reported	840	20%
Stray origin	8,380	40%
Shelter cat	5,124	32%
Multi cat household	14,121	41%
Exposed to Infected cat	3,646	53%
History of fleas	4,709	47%
Present flea infestation	1,307	42%
Lives in CSD household	628	58%
Totals:	37,915	42%

1/1/07 *Many cats had multiple risk factors.

Reasons to Screen Healthy Cats for *Bartonella* Infection:

1. To reduce the number of infected cats, the bacteria's natural reservoir host, in order to reduce the number of *Bartonella* infected flea and tick vectors.
2. To prevent infected healthy cats from developing any of the many chronic debilitating inflammatory diseases caused by *Bartonella*.
3. To prevent zoonotic transmission from healthy kittens and adult cats to children, adults, and especially to immunosuppressed people.
4. To reduce the incidence of feline *Bartonella*-induced diseases of humans and keep the family of your clients safe.

It is more cost effective to prevent *Bartonella* diseases than to diagnose and treat them once they occur. *Bartonella* testing of healthy cats should be part of your routine feline health protocol.

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NEWSLETTER

5th International Conference on *Bartonella* as Emerging Pathogens

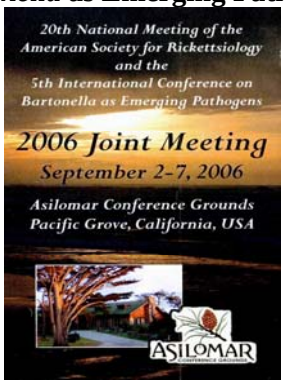
Evelyn E. Zuckerman, Editor **Spring 2007** **Vol. 6, Number 2**

In This Issue:

In the Spring 2007 issue of the NVL Newsletter we will discuss the scientific presentations at the 5th International Conference on *Bartonella* as Emerging Pathogens held in conjunction with the 20th Meeting of The American Society for Rickettsiology, September 2-7, 2006 at the Asilomar Conference Grounds, Pacific Grove, California.

Abstracts

5th International Conference on *Bartonella* as Emerging Pathogens:



The combined meeting had participants from around the world including Australia, Asia, Europe, Russia, China, and North and South America. There were 199 abstracts at the meeting. The majority presented data on Rickettsia, whereas 42 abstracts were *Bartonella* topics. Twelve *Bartonella* abstracts were concerned with human topics, 5 were canine, 5 were small mammal, (rodent), 4 were cat, and 1 was *Bartonella* in cattle. Eight abstracts presented molecular aspects, 3 presented methods of detection (PCR and culture), and 2 each covered vectors and other topics.

Whale watching off of Asilomar

Cat *Bartonella* Abstracts

Cytokine Production Profiles in Experimentally *Bartonella* henselae Infected Cats. H. Kabeya and S. Maruyama, Nihon University, Japan.

This study described the changes in several cytokines as a result of experimental infection with *Bartonella henselae* in 6 SPF cats. All 6 cats developed specific IgG antibody to *Bartonella* proteins indicating infection. Interestingly, *Bartonella* was not always recovered in culture during the bacteremic phase. Some cats were culture positive then culture negative to be followed by culture positive again. The expression of mRNA levels of IFN-γ, IL-4, TNF-α, IL-12p40, IL-10 and TGF-β dramatically increased during bacteremia. The authors concluded that the cell-mediated immune response may play a significant role in the control or elimination of *Bartonella* in cats.

Editor's Note: The *Bartonella* culture isolation variability in known infected SPF cats shows that culture is not an accurate method for diagnosing *Bartonella* infections. In contrast, all 6 infected cats produced antibody against *Bartonella*. In addition, since the elimination of *Bartonella* infection in untreated cats is slow, or non-existent in many cats, the cell-medicated immune response and cytokines may play pivotal roles in the inflammatory process that induces diseases seen in *Bartonella* infected pet cats.

Antibiotic Susceptibility of *Bartonella henselae* Isolated from Domestic Cats in Japan. H. Tsuneoka, M. Tomita and M. Tsukahara. Yamaguchi University School of Medicine, Japan.

These authors isolated *Bartonella* from pet cats in Japan and tested the isolates for susceptibility to various antibiotics. As has been shown by previous workers, *Bartonella* are susceptible to many antibiotics and azithromycin and minocycline were most effective.[1,2] Other antibiotics that were effective include: erythromycin, clarithromyscin, ciprofloxacin, gentamicin, ceftriaxone, and amoxicillin.

Genomic Diversity in Feline and Clinical *Bartonella henselae* Isolates. H. Lindroos, *et al*. Uppsala University, Sweden.

This group studied the genomic diversity of 37 isolates of *Bartonella henselae* isolated from cats and humans from 4 continents. The variation in gene content was low and did not relate to geographic origin or animal host (cat versus human). However, there were frequent gene rearrangements which may facilitate persistent infection by generating antigenic diversity leading to immune escape and persistence.

Epidemiology of *Bartonella* Infection in Domestic Animals and Wildlife: An Update. B. Chomel, R. W. Kasten, and J. Henn. University of California, Davis, CA.

This review described the detection of various *Bartonella* species in a diverse group of domestic and wild animals. Canids, particularly dogs, have been found to be infected with 6 species of *Bartonella*, some of which have been shown to infect people.[3] Dogs are much less likely to transmit their *Bartonella* to people than are cats. *Bartonella* have been found in coyotes, gray foxes and raccoons.[3] In addition to pet cats, pumas, bobcats, lions and cheetahs have also been found to be infected.[4,5] Small woodland rodents, voles, mice, rats, and chipmunks have also been shown to carry *Bartonella*.[6] Deer, cattle, sheep, and horses have also been found to be infected. Finally, *Bartonella* has been found in a marine mammal, the dolphin, and in bat ticks and bats.[7,8,9,10]

Animals Recently Found to be Infected with *Bartonella*

Puma

Dolphin

Raccoon

Bat

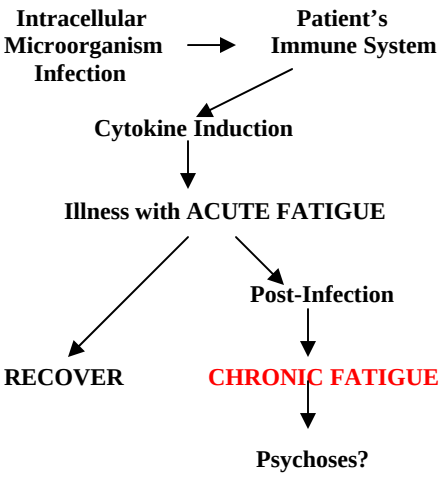
Human *Bartonella* Abstracts

Although there were 12 human *Bartonella* abstracts, we will only discuss 3 in this issue. In addition, we will summarize an important abstract concerning chronic illnesses associated with Rickettsiae, including chronic fatigue. These 3 abstracts bring together observations concerning the chronic illnesses of humans associated with *Bartonella* infections from cats.

Rickettsiae and Chronic Illness, Including Fatigue. S. Graves, N. Unsworth, and J. Stenos, Australian Rickettsial Reference Laboratory, Australia.

The authors describe a chronic fatigue syndrome in 2 patients associated with previous clinical syndromes caused by *Rickettsia honie*. Acute fatigue, along with headache, fever, myalgia, arthralgia and cerebral dysfunction, are caused by many infectious agents and are probably mediated by cytokines. In some patients, chronic fatigue is observed as a post-infectious sequelae in infections caused by intracellular microorganisms such as viruses (EBV), *Rickettsiae*, and *Bartonella* (Editor's addition). The symptoms are similar to, but less severe than, those of acute infections and suggest dysregulated cytokines as a possible cause.

Genesis of Post-Infection Chronic Fatigue



Musculoskeletal Manifestations of Cat-Scratch Disease. E. Maman, *et al*. Tel-Aviv Sourasky Medical Center, Tel Aviv University, Tel-Aviv, Israel.

This was a large 11 author multi-center study of 913 cases of cat scratch disease (CSD) over an eleven year period. The authors note that, before their study, CSD was a common cause of regional lymphadenopathy, affecting mainly children and adolescents. (Editor's note- recent studies and our abstract that follows show that 50% of CSD cases occur in people older than 21 years of age). Musculoskeletal manifestations (MMs) were considered rare and it was the aim of this study to determine how often MMs (myalgia, arthritis, arthralgia, tendonitis, osteomyelitis, and neuralgia) occur in patients with CSD.[11,12,13,14,15]

Surprisingly 96 of the 913 (10.5%) CSD patients developed MMs. Myalgia occurred in 53 patients and was often severe, lasting an average of 4 weeks (1 to 26 weeks). Arthropathy (arthritis/ arthralgia) occurred in 50 (5.8%) patients lasting an average of 5.5 weeks (1-240 weeks). In 7 patients the arthropathy lasted more than 1 year and 5 patients developed chronic disease. Tendonitis (mainly of the Achilles tendon), neuralgia, and osteomyelitis occurred less frequently. Patients with MMs were significantly older than those that did not develop MMs. Patients who developed MMs had an average age of 31.5 years compared to an average age of 15 years for the controls. Arthropathy was associated with female gender and with erythema nodosum. The authors described several cases of extreme, long lasting, chronic fatigue syndrome in world class athletes who were "unable to pull themselves out of bed or the chair."

This study found that musculoskeletal sequelae occur in 10% of CSD patients. Osteomyelitis, the most well known MM of CSD, was the rarest in this study.[15] Therapy with azithromycin or rifampin was not effective in alleviating the chronic musculoskeletal symptoms.

Our meeting abstract is reproduced below. With the assistance of many of you, we interviewed several hundred cat owners who were diagnosed with, or were thought to have, a *Bartonella* disease derived from their association with a cat that we tested for *Bartonella*. Our aim was to determine the signs of their illnesses, whether their veterinarian had discussed the zoonotic dangers of feline *Bartonella* with them BEFORE they became ill, and to determine their physician's knowledge of *Bartonella* diseases derived from cats. As you will see, we found that both veterinarians and physicians need to become more aware of the dangers of feline derived *Bartonella* infection in people. We are most thankful to those of you who asked your clients to call us so that we could administer our *Bartonella* disease questionnaire.

Human Bartonellosis: Diseases Caused by Feline *Bartonella*- 84 Cases. W. D. Hardy, Jr., & E. E. Zuckerman, National Veterinary Laboratory, Franklin Lakes, NJ.

The CDC does not require reporting of human *Bartonella* infections or diseases. In addition, the American Association of Feline Practitioners does not recommend *Bartonella* tests for healthy cats. We investigated 84 human patients with serologically or biopsy confirmed *Bartonella* diseases, associated with cats, to assess if physicians are aware of the varied clinical signs of bartonellosis and if the CDC and AAFP recommendations regarding testing of healthy cats are appropriate. 68 (81%) patients had classical cat scratch disease (CSD) with the regional lymphadenopathy prodrome and 14 (17%) had a papule at the scratch or bite site. 46 of the 68 CSD patients had no sequelae after the prodome, whereas 22 patients had 13 various sequelae such as chorioretinitis, mononucleosis syndrome, vegetative valvulitis, or meningoencephalitis. 16 patients had no prodrome of classical CSD and had: chorioretinitis (3), arthritis (2), neurological disease (2), myositis (2), and various other conditions (7). There were 8 veterinarians and 7 veterinary technicians who were infected via occupational exposure. The routes of infection were: 38 unknown, 37 scratches, 3 bites, 3 by giving oral medication to their *Bartonella* infected cats, 1 via excessive licking of a child, and 1 each via flea and tick bites. 17 patients were examined by 3 or more physicians (maximum 10) before a diagnosis of CSD or Bartonellosis was made. 67 of 70 (96%) offending cats were serologically positive for *Bartonella*. 40 cats (57%) were healthy whereas 30 had *Bartonella* induced inflammatory diseases. 29 of the 70 (41%) cats were kittens under 1 year of age. Offending cats were identified and most treated however, 4 patients were told by their physicians to remove their cats. Our findings suggest the recommendations regarding the testing and treatment of healthy cats, especially kittens, be reconsidered and that physicians should become more aware of the varied clinical manifestations of bartonellosis.

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For more *Bartonella* references:
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NEWSLETTER

Dogs and *Bartonella*

Summer 2007

Evelyn E. Zuckerman, Editor **Vol. 6, Number 3**

In This Issue:

The Summer 2007 issue of the NVL Newsletter is the first of several Newsletters that will give an overview of *Bartonella* infection in healthy and sick dogs. This is especially relevant as summer is the height of the tick and flea season in many parts of the country. Subsequent Newsletters will cover canine *Bartonella* testing and diseases in more detail.

Dogs

Background:

Dogs cannot relax when it comes to *Bartonella*.

Yes dogs, like cats, are susceptible to infection with *Bartonella* but they are less likely to transmit the bacteria to humans than are cats. However, dogs appear to be exposed less or are less susceptible to infection by *Bartonella*. Dogs are infected much less often (~4 times less) than cats living in the same geographical areas.

Bartonella Species Found in Dogs:

Early studies found that dogs were mainly infected with *Bartonella vinsonii* whereas cats were mainly infected with *Bartonella henselae*.[1-2] Subsequent studies have found that dogs are infected with 6 *Bartonella species* (*B. henselae, vinsonii*, *clarridgeiae*, *elizabethae*, *woshoensis*, and *quintana*) and like cats, they are more often infected with *Bartonella henselae*.[2-16]

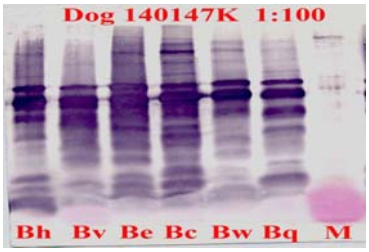
Both cat and dog fleas carry and transmit *Bartonella*, but ticks appear to transmit *Bartonella* among dogs more often than do fleas.[14]

Like cats, dogs have the same risk factors for *Bartonella* infection: flea or tick infestation or a history of infestation, stray or shelter origin, living in multi dog or cat households, living with a *Bartonella*-infected cat or dog, and living in hot and humid climates. In this regard, field dogs or dogs kept outdoors are more likely to be exposed to ticks than dogs kept indoors most of the time.

Western Blot *Bartonella* Test:

As with cats, we utilize the WB technique for serologic testing of dogs for *Bartonella* infection (Figure 1). The WB technique is more specific and more sensitive than IFA or ELISA tests and is used as the confirmatory serological method for many pathogen serologic assays.

Figure 1



Western Immunoblot of a seropositive dog showing cross-reactivity to 6 *Bartonella* species: *B. henselae*, B. *vinsonii*, *B. elizabethae*, *B. clarridgeiae*, *B. weissi (bovis)*, and *B. quintana* (M= molecular weight markers).

Similar to cats, *Bartonella* infection in dogs is also correlated with hot and humid climates (Table 1) and we have mapped the prevalence of infected healthy dogs by the first number of their zip codes (Figure 2). The overall infection in healthy dogs, with no reported risk factors, is only 5% compared to 20% in cats with no reported risk factors (Table 2). Healthy dogs who have risk factors for exposure to fleas and ticks compared to dogs with no reported risk factors are 3 times (17% versus 5%) more likely to be infected.

Figure 2

NVL Geographic Prevalence* of *Bartonella* Infection in Healthy Dogs Based on First Number of Zip Code

Healthy dogs infected in: Zip 0: 6/63= 10%; Zip 1: 32/616= 5%; Zip 2: 2/9= 22%; Zip 3: 2/8= 25%; Zip 4: 0/27= 0%; Zip 5: 2/7= 29%; Zip 6: 0/2= 0%; Zip7: 7/22= 32%; Zip 8: 0/1= 0%; Zip 9: 7/42= 17%

***Based on *Bartonella* western blot antibody test.**

Table 1
Geographic Occurrence of *Bartonella* in Dogs

Geographic Area	Percent Infected
New Jersey- NVL	4%
North Carolina/Virginia	3.6%
Southeast- US Healthy	10%
Sick	27%
Southwest- US Army Dogs	9%
California	3%
Israel	10%

We have tested 3,665 dogs for *Bartonella* infection by western immunoblot (WB) (Figures 1 & 2, Tables 2 & 3).

Table 2
NVL Occurrence of *Bartonella* in Dogs

Status	Number Tested	Number Positive	% Positive
Healthy	802	58	7%
1) No RFs**	641	31	5%
2) With RFs*	161	27	17%
Diseased Dogs	2,730	404	15%
Not Specified***	133	25	19%
Totals	3,665	487	13%

* RFs= risk factors for *Bartonella* infection- flea & tick exposure.
** No risk factors reported by veterinarian.
*** No diagnosis given.

Dog *Bartonella* Diseases:

There have been numerous publications documenting the diseases caused by *Bartonella* in dogs.[1-16] The *Bartonella* inflammatory-granulomatous disease spectrum in dogs is quite different from those of cats. Canine *Bartonella* diseases include: heart disease- endocarditis, myocarditis, vegetative valvulitis, and arrhythmias, liver disease- peliosis hepatis, and granulomatous hepatitis, ocular disease- uveitis and chorioretinitis, lymphadenopathy (itis), granulomatous rhinitis, thrombocytopenia and anemia.[1-16]

In addition to the published canine *Bartonella* diseases, we have found *Bartonella spp.* associated with myositis, arthritis, polyarthritis (arthropathy), neurological disease and fever (Table 3). In collaboration with Dr. Charla Jones, Board Certified Veterinary Cardiologist at Veterinary Cardiology & Medicine Service, Austin, Texas, we have found *Bartonella* associated with heart diseases in both cats and dogs. Texas is a high *Bartonella* incidence state.

Table 3

***Bartonella* Infected Dogs with Inflammatory Diseases- NVL Data**

Disease	# +/ # Tested	% +	X
Healthy- No RFs	31/641	5%	X
Myositis/ Myopathy	29/104	28%	5X
Arthritis/Arthritis	72/297	24%	5X
Heart Disease	34/183	19%	4X
Anemia	19/115	17%	3X
Lymphadenopathy	40/265	16%	3X
Neurological Disease	26/167	16%	3X
Fever	57/374	15%	3X
Ocular Disease	82/606	14%	3X
Liver Disease	23/182	13%	2X
Thrombocytopenia	17/156	11%	2X
Respiratory Disease	21/207	10%	2X
Oral Disease	33/578	6%	X
Totals	417/2,963	14%	3X

Case Reports:

Morales SF, Breitschwerdt EB, Washabau RJ, et al. Detection of *Bartonella henselae* DNA in two dogs with pyogranulomatous lymphadenitis. J Am Vet Med Assoc 230:681-685, 2007.

This publication describes 2 cases of canine pyogranulomatous lymphadenitis seen at the Department of Clinical Sciences, College of Veterinary Medicine, University of Minnesota.

Case 1: A 6 year-old neutered male Golden Retriever from Massachusetts was seen for anorexia and lameness of the left hind leg. Cytology of multiple joint aspirates revealed neutrophilic arthritis consistent with an immune-mediated polyarthropathy. Bacterial cultures of the joint fluid were sterile for bacteria and a tick serology panel was also negative. IFA serology for *Bartonella henselae* and *vinsonii* was also negative at the Vector Borne Disease Diagnostic Laboratory at NC State University. However, quantitative PCR for *Bartonella* spp was positive from a lymph node biopsy. The dog was treated with doxycycline (5mg/kg PO BID for 6 weeks) and made a complete recovery. NVL did not test this dog for *Bartonella* by western blot.

Case 2: 6 year-old neutered male English Springer Spaniel was evaluated for fever (105°F), anorexia, and lymphadenopathy of 2 weeks duration. CBC showed a mild thrombocytopenia and there was pyogranulomatous lymphadenitis on histology of a lymph node excision. Serology was negative for antibodies against *Aspergillus* spp, *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Histoplasma capsulatum*. However, we found the dog +3 (infected) by the WB test for *Bartonella* spp. Because of the WB result the dog was discharged on enrofloxacin 8 mg/kg, PO, q 24 h and carprofen 2 mg/kg, PO, q 12 h for 7 days. Clinical signs resolved within 7 days. However, 4 months later the dog's signs recurred with fever and generalized lymphadenopathy. Tick serology was negative at this time and the dog was now treated specifically for the *Bartonella* infection with doxycycline for 4 weeks duration. An IFA test for *Bartonella henselae* and *vinsonii* antibodies on serum collected on day 130 was negative. However, PCR for *Bartonella henselae* was positive from a lymph node biopsy. IFA serology and PCR were performed at NC State University. Antibiotic therapy did not resolve the clinical signs but the addition of an immunosuppressive dosage of prednisone resolved all signs. The authors concluded that "In dogs with pyogranulomatous lymphadenitis, serologic testing may not detect antibodies against *B henselae*."

Editor's Comment: This conclusion was made despite the fact that the dog in case #2, tested by WB for *Bartonella* antibodies at this lab at the initial presentation, was positive (+3 infected). Our studies show that the IFA test is less sensitive and less specific than the WB test for detection of antibodies against *Bartonella*. We find that WB serologic testing of dogs for *Bartonella* infection is a valid diagnostic procedure.

Conclusion:

Dogs, like cats, are susceptible to *Bartonella* infection and the subsequent development of chronic inflammatory diseases. Although dogs can be infected, they rarely transmit the bacteria to people and thus we do not recommend routine testing of healthy dogs due to the relatively low prevalence of infection.[19-20] However, healthy dogs that are exposed to frequent tick or flea infestations and dogs with chronic illnesses (Table 3) may benefit from *Bartonella* testing.

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More *Bartonella* references can be obtained at:
www.nlm.nih.gov/

Happy 99th Birthday Mrs. Adeline Shipp

Mrs. Shipp celebrates her 99th birthday on June 12, 2007

The staff of NVL celebrated Mrs. Shipp's 99th birthday at her home on June 12, 2007. Mrs. Shipp reported all of NVL's FeLV and FIV test results by telephone for 25 years before the widespread acceptance of the fax machine. Her pleasant nature and personality was a client builder for the laboratory for many years. Some hospitals would call just to chat with Addie even when no test results were pending. We were most fortunate to have had such an intelligent, industrious and pleasant person as a member of our staff for 25 years. Mrs. Shipp retired from NVL in 1998 at the age of 90!

The NVL staff has a combined 205 years of specialty veterinary testing experience (average 29 years per person). From left to right standing Valerie Sellen 33 years, Mari Bertero 22 years, Gloria Longo 22 years, Dr. Hardy 45 years, Gina Guerriero summer student, Evelyn Zuckerman 33 years. Front Row Mrs. Shipp 25 years (retired at 90 years of age) and Susan Hardy 25 years.

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NEWSLETTER

8th Anniversary of the Fe*Bart*® Test

Evelyn E. Zuckerman, Editor **Fall 2007** **Vol. 6, Number 4**

In This Issue:

November 5, 2007 was the 8th anniversary of our *Bartonella* testing service. We have performed 159,196 Fe*Bart*® screening tests and 9,792 therapy titration tests from 3,073 hospitals in the USA, Canada, and the Caribbean since November 5, 1999. **We thank all the veterinarians and veterinary technicians who have helped us gather biological evidence of the importance of *Bartonella* in cats, dogs and people.** In the Fall 2007 Newsletter, Dr. Hardy will reflect on our work with *Bartonella* and relate it to our previous retrovirus research.

Reflections

William D. Hardy, Jr., V.M.D.
Director

In The Beginning:

Cat Scratch Disease (CSD) was first described by Parinaud, a French physician, in 1889.[1] The etiology of CSD remained a mystery for more than a century, until in 1990 Relman and his colleagues, using recombinant DNA technology discovered the bacterial cause from an HIV-infected person.[2] At that time, we were investigating the human retroviruses, HIV-1, HIV-2, HTLV-I and HTLV-II at the Memorial Sloan Kettering Cancer Center.[3] Later, at the Center for Infectious Diseases, Bronx Lebanon Hospital Center, Albert Einstein College of Medicine, Dr. Hardy learned that the clinicians were treating some seriously ill HIV-infected patients who were infected with *Bartonella*.

HIV infected patient with bacillary angiomatosis of the skin caused by *Bartonella henselae* transmitted from his kitten.

Epidemiological studies found that the "cat scratch disease" agent- *Bartonella* was transmitted from cats to people and, as a veterinarian working in a human hospital research setting, it seemed a great opportunity to employ our previous FeLV retrovirus test expertise toward the development of an accurate and practical test for detection of *Bartonella* in cats. We were interested in determining the prevalence of *Bartonella* infection in pet cats and whether or not the bacteria caused diseases in cats similar to those being found in people.

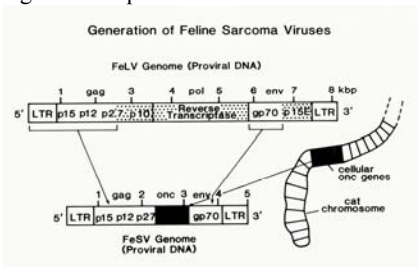
After 5 years of development we found that the most accurate, sensitive and reproducible test for detection of *Bartonella* antibodies was the western immunoblot (WB).[4] The WB has the advantage of detecting the full range of all the antibodies produced against the *Bartonella* proteins by cats. This prevents false positive tests due to cross-reactive antibodies to other microorganisms. Thus, on November 5, 1999 we performed our first *Bartonella* test for the veterinary profession. That first test was submitted from a healthy 4-year-old male DSH by Dr. Jan Rottenberg, Just Cats Veterinary Care, Edison, NJ.

Previous Research Relationship:

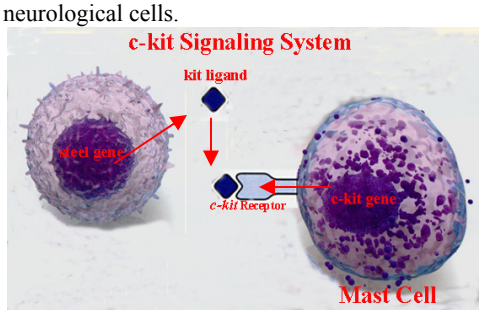
Previous to our interest in *Bartonella,* we spent 24 years in my laboratory, the Laboratory of Veterinary Oncology at Memorial Sloan Kettering Cancer Center, NYC, studying cancer in cats and dogs and retroviruses of cats, humans, mice and cattle. We were the first to show that L-asparaginase was an effective cancer chemotherapeutic agent, that AZT was effective in stopping the replication of a retrovirus- FeLV (later to be the first anti-HIV agent approved) and the first to show that any retrovirus was transmitted contagiously in any animal (FeLV horizontal transmission among cats).[5,6] In 1986 Evelyn Zuckerman, in my laboratory, isolated a feline sarcoma virus (HZ-4 FeSV) from a pet cat which contained a unique viral oncogene.[7]

A young cat with multicentric fibrosarcoma of the hock containing a FeSV with the *v-kit* oncogene.

A viral oncogene is a normal cellular gene that is transduced (taken from) and integrated into the FeLV genome to produce a sarcoma virus.



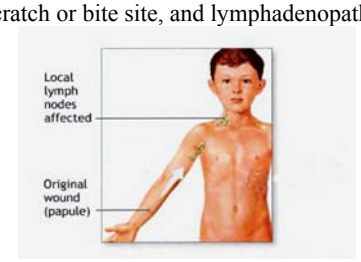
When the newly formed (*de novo*) FeSV infects a susceptible cat cell it can transform it into a cancer cell (sarcoma cell). Our colleague Dr. Peter Besmer in my group, characterized the viral oncogene and named it *v-kit*.[7] The analogous normal cellular gene is called *c-kit* and the gene encodes a cellular receptor called the *c-kit* receptor. The ligand (factor) that reacts with the *c-kit* cell receptor is called the *kit* ligand. *C-kit* is expressed on certain tissues such as gut cells, mast cells, reproductive cells and some neurological cells.



Mutations in the *c-kit* gene have been associated with tumors of the GI tract, testes, mast cell tumors and other tumor types.

Bartonella Immunopathology:

The basic response to *Bartonella* infection in all animals is chronic inflammation characterized by lymphocytic, plasmacytic infiltrates, granuloma formation, and lymphadenopathy. The prodrome (earliest consistent signs) of CSD consists of 1 or all of the following signs: fever, skin papule at the scratch or bite site, and lymphadenopathy.

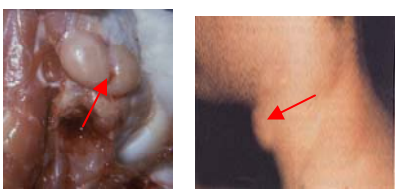


CSD prodrome:
Fever, skin papule and lymphadenopathy

Lymphadenopathy occurred in 71 of the 84 cases of human CSD that we studied.[8] An 8 year summary of our findings of lymphadenopathy in cats and dogs is presented in the Table below.

Lymphadenopathy and *Bartonella*

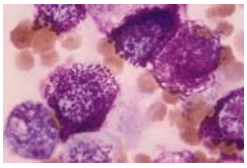
Species:	# *Bartonella* +/ Lymphadenopathy	%
Cat	1,653/3,641	45%
Dog	40/287	14%



Feline and human lymphadenopathy caused by *Bartonella henselae*.

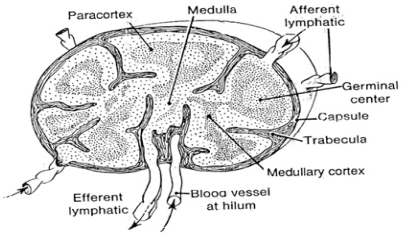
C-kit and *Bartonella*:

Our work with *Bartonella* is related to *c-kit* by the correlation of *c-kit* with mast cells and mast cells to inflammation. Mast cells express *kit* receptors and are very important in both normal and abnormal immune responses such as allergy IBD, and autoimmunity.



Feline mast cells with dark-staining granules containing numerous mediators.

Recent research has elucidated the mechanism that causes lymph nodes to swell or enlarge as a response to infection.[9] The reaction of lymph node swelling is called lymphadenopathy and the process is found to be orchestrated by mast cells. Lymphadenopathy is a common result of *Bartonella* infection in cats, dogs and people. In fact, the most common feature of cat scratch disease is a regional lymphadenopathy of a lymph node or lymph nodes that drain the site of the scratch or bite that transmitted the bacteria.

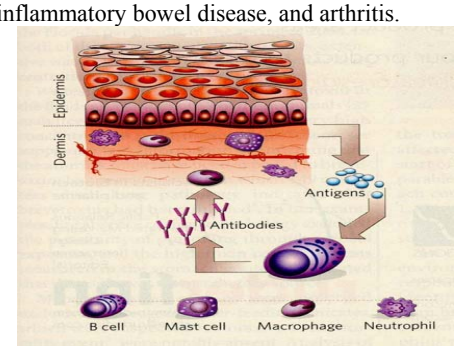


Anatomy of a normal lymph node

Lymph nodes that drain the site of *Bartonella* entry are the center of the adaptive immune response and entrap large numbers of circulating lymphocytes. Here newly recruited naïve T lymphocytes interact with and are sensitized by *Bartonella* antigen loaded antigen presenting cells (dendritic cells from the periphery) and begin the adaptive immune response of reactive T cells and B-cells. Until recently, the signal that causes lymph nodes to begin to react to the distal infection was unknown. That signal has been found to be the release of tumor necrosis factor (TNF) from mast cells positioned as guardians in peripheral tissues, exposed to the external environment, such as the skin, mucous membranes and the GI tract.

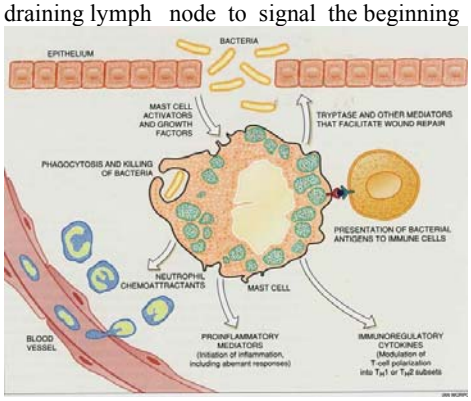
TNF was originally identified in mouse serum after injection with *Mycobacterium bovis* strain bacillus Calmette-Guerin (BCG) and endotoxin. Serum from such animals produced hemorrhagic necrosis, and in some instances, complete regression, of certain transplanted tumors in mice.[10] As the name specifies, TNF causes necrosis in the tumors.

Nearly all cells display receptors for TNF on their surfaces. Their responses to TNF, however, can be very different although TNF signaling is usually used for defense against infection. TNF can direct an infected cell to destroy itself by apoptosis, and the presence of lipopolysaccharide on bacterial surfaces stimulates blood cells to release TNF, which promotes an inflammatory response to fight the infection. Because TNF plays such diverse and often contradictory roles, the body must keep a careful balance to ensure that TNF is applied only when and where it is needed. When this control is lost, it can lead to severe inflammatory illnesses such as septic shock, inflammatory bowel disease, and arthritis.



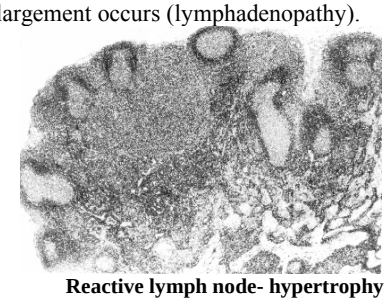
Mast cells and other immune cells poised in the skin and under mucous membranes to sense invasion by microorganisms.

Many cells can produce TNF which is an important mediator for the immune system but only mast cells produce and store TNF. The stored TNF can be released within minutes of mast cells recognizing an invading bacterium such as *Bartonella.* The TNF travels to the draining lymph node to signal the beginning



Mast cells detect *Bartonella* invasions and release their preformed soluble TNF which travels to draining lymph nodes to begin the preparation of an immune defense.

of immune reactivity. Immune activated lymph nodes show a crowding in of lymphocytes from the periphery and loss of their normal architecture (hypertrophy) and enlargement occurs (lymphadenopathy).



Reactive lymph node- hypertrophy

Thus the release of the soluble preformed TNF from mast cells, stationed in the skin, in recognition of *Bartonella,* travels to the draining lymph nodes and is responsible for the lymphadenopathy seen in infected cats and people. Mast cells do not need to migrate to the lymph nodes and exert their effect remotely.

More references are available at:
www.nlm.gov or www.scholar.google.com

These basic immune system observations were made with genetically modified mice using the *c-kit* gene to manipulate mast cell numbers. We are proud that our discovery of *v-kit* from a cat fibrosarcoma enabled the observations of the mechanisms of the immune system to be made.

Postscript:

As luck would have it, in 1975 as a young Post Doctoral Fellow in Dr. Lloyd Old's Laboratory of Tumor Immunology in the Memorial-Sloan Kettering Cancer Center in New York City, I witnessed, and was asked to photograph, the experimental animals in which TNF was discovered.[10]

Discovery of Tumor Necrosis Factor (TNF) in 1975 from a mouse with a necrotic tumor.

At the time of this writing the following number of references on PubMed at the National Library of Medicine:
87,557 TNF, 1,743 FeLV & FeSV, 5,742 c-kit & v-kit, and 2,838 *Bartonella* & Cat Scratch Disease.

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