



CAT SCRATCH FEVER?

By Claudia S. Copeland, PhD

REALLY?

**CATS, FLEAS, AND THE MANY
FACES OF BARTONELLOSIS**

The girl was 15, and for six days had been losing vision in her right eye when she was referred to Drs. Farhan Irshad and Robert Gordon at Tulane's Pediatric Ophthalmology clinic. A former chronic myelogenous leukemia patient, she had been in remission for the past 8 years, on the anti-cancer prophylactic imatinib. Although she had recently had a fever, she had suffered no weight loss, and intermittent headaches and mild eye pain were her only other symptoms. The doctors biopsied her enlarged submandibular lymph node for malignancy, but the tests came back negative. Also, while her lymphadenitis indicated infection, the biopsy was culture negative. Blood cultures and serologic testing for syphilis, Lyme disease, toxoplasmosis, cytomegalovirus, tuberculosis, bartonellosis, and Epstein-Barr virus were all negative. The doctors discontinued the imatinib, which she had been taking without incident, but which has known ocular side effects. But still, the culprit behind the mysterious loss of vision remained at large.



A WEEK LATER, a decisive clue appeared—a characteristic “macular star” pattern on retinal examination. This prompted a repeat screening for IgG against the bacterium *Bartonella henselae*, and whereas the titers had been equivocal the first time around, they had now risen to the level of a clear positive diagnosis. The neuroretinitis causing this teenager’s loss of vision was one of the many and varied manifestations of bartonellosis, a.k.a. Cat Scratch Disease.



Cat Scratch Disease (CSD) is no simple fever, nor is it transmitted only by cats. (In fact the above-described retinitis patient had had no history of contact with cats.) More properly called bartonellosis, according to veterinarian and *Bartonella* expert Dr. Edward Breitschwerdt, the true vector of *B. henselae* infection is not cats, but fleas. Cats, who are generally asymptomatic carriers, are infected by the fleas, and act as reservoirs of the disease.

While infected cats don’t generally show any disease symptoms, bartonellosis can

be a big problem for humans. In immunocompromised individuals, it can be deadly. Even in immunocompetent people who fight off the infecting organism without any need for medical intervention, CSD can be a nasty sickness. In the acute phase, the characteristic swollen lymph nodes and papule at the inoculation site are accompanied by fever, malaise, headache, and/or extreme fatigue, rather like a bad case of the flu plus the headache phase of a migraine, sometimes accompanied by abdominal pain and vomiting. The initial sickness is often followed by

a pronounced fatigue for up to two weeks. Other symptoms are sometimes present as well, including anorexia, splenomegaly, sore throat, parotid swelling, rash, and/or conjunctivitis.

In “classical” CSD, cats transmit *Bartonella* through a scratch or bite, and this injection of bacteria from the infected cat leads to the acute febrile illness commonly called “Cat Scratch Fever.” However, the “classical” triad of a cat scratch/bite, swollen lymph node, and self-resolving fever + headache is far from the only presentation of infection with *Bartonella*. While most CSD is self-limiting, some bartonellosis patients develop an incredibly varied range of unique symptoms, including ophthalmological, neurological, cardiac, and many other manifestations. Moreover, there are plenty of other ways to contract *Bartonella*. Children are especially prone to inoculating themselves by getting

1957



Shot in the Dark Would be weight losers receive injections of human chorionic gonadotropin derived from the urine of pregnant women, rabbits or mares.

1960



Zen The first appearance of the macrobiotic diet in the western world goes heavy on the grains.



1961



Calories-Don't-Count Oh if only this were true! In 1961, Brooklyn doctor Herman Taller invents the CDC diet after losing 65 pounds in eight months. He avoids carbs and sugar but packs in the meat three times a day. The FDA eventually rules this practice as unsafe.



infected flea dirt on their hands, and then rubbing their eyes or an open scratch. Also, in addition to relatively rare cases of bartonellosis transmitted by needle stick or wild animal bite, it is thought that Bartonella can be inoculated into a human directly by flea bites and also by a number of other arthropod vectors: ticks, lice, sandflies, and probably biting flies all harbor Bartonella.

In urban Louisiana, though, it is safe to say that bartonellosis risk is all about fleas. Fleas carry the bacteria, and Louisiana, as most pet owners can testify, is a haven for fleas. Since we don't have the kind of winter freezes that kill off flea populations in colder climates, we are faced with bigger flea-related problems. According to the CDC, about 40% of cats are thought to be Bartonella carriers at some point in their lives. In Louisiana, though, with our flea-favoring climate, the percentage appears to be quite a bit higher. An informal study by Jefferson Animal Hospital in Baton Rouge found that over 55% of their healthy pet cats were positive for *B. henselae*. It stands to reason that the prevalence is probably even higher in feral cats as they do not receive flea treatment. Cats contract Bartonella not only through flea bites but also flea dirt (flea feces), which contacts wounds made when the cats scratch themselves. Humans can also contract CSD through flea dirt, so washing hands after petting cats is recommended, as is refraining from touching open-skin lesions or mucous membranes after petting cats. Of course, cats should not be allowed to lick any open wounds.

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Beyond Cat Scratch Fever—diverse manifestations of Bartonellosis

While Dr. Breitschwerdt acknowledges that in normal healthy people, CSD symptoms usually resolve without treatment, a growing body of evidence is indicating that Bartonella is not as benign as traditionally thought. Ophthalmological symptoms, for one, are quite common. In addition to neuroretinitis, experienced by up to 2% of CSD patients, other ocular manifestations include optic neuritis, anterior and posterior uveitis, Parinaud's oculoglandular syndrome, and even macular holes.

Bartonellosis can also become a severe cardiac disease. Recent reports from countries as disparate as Brazil, Japan, Laos,

Egypt, and France have described cases of endocarditis that are culture-negative, but seropositive and/or positive by PCR, for Bartonella. One report estimated that 2% of endocarditis cases are due to Bartonella infections. These studies emphasize the importance of molecular testing for Bartonella in endocarditis cases, as treatment for Bartonella-based endocarditis is relatively simple and inexpensive compared with treatment for endocarditis with other etiology. Bartonella can also infect the liver, kidney, lungs, spleen, bone, and muscle tissue.

Neurological ramifications extend beyond the eyes, as well; patients have suffered from severe symptoms like encephalitis, as well as extended CSD sequelae such as headaches



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Clinical presentations are remarkably diverse, making diagnosis difficult. Bartonellosis patients have presented with encephalitis, meningitis, convulsions, loss of consciousness, muscle weakness, inability to walk, myalgia, numbness, urinary retention, lethargy, sleep disturbances, psychological illness such as hallucinations and depression, and expressive aphasia (inability to talk), as well as combinations of these.

and fatigue that continue for months, and peripheral symptoms like paresthesias. Clinical presentations are remarkably diverse, making diagnosis difficult. Bartonellosis patients have presented with encephalitis, meningitis, convulsions, loss of consciousness, muscle weakness, inability to walk, myalgia, numbness, urinary retention, lethargy, sleep disturbances, psychological illness such as hallucinations and depression, and expressive aphasia (inability to talk), as well as combinations of these.

With more sensitive detection methods, bartonellosis is being implicated in more and more unexplained cases of strange neurological syndromes. In one striking case, a family of a mother, father, and two boys had experienced an infestation of woodlouse hunter spiders. The boys were both clearly bitten by the spiders. Soon after the extermination of the infestation, the previously healthy mother and both sons developed recurrent rash-like skin lesions, disruptive sleep patterns and the boys developed anxiety accompanied by episodes of inconsolable crying, panic attacks, and neuromuscular symptoms. (The father did not develop any symptoms.) A year later,

the oldest son was seen for enlarged lymph nodes in the neck, and the mother had developed a host of neurological symptoms including fatigue, headaches, joint pain, eye pain, insomnia, memory loss, disorientation, irritability, weakness in the upper extremities and loss of sensation to both legs. Then, the youngest son was diagnosed with Guillain-Barré syndrome, and subsequently with chronic inflammatory demyelinating polyneuropathy. By this point, he was unable to even climb stairs.

The mother contacted Dr. Breitschwerdt, and a team of researchers, Mascarelli et al., set out to investigate the family. All three patients, the mother and the two children, tested positive for *B. henselae*. Upon antibiotic therapy, their symptoms receded, with the exception of minor residual symptoms such as joint stiffness and dizziness. In addition, the researchers collected woodlice (land-dwelling crustaceans) and woodlice hunter spiders (predators of woodlice) from the area around the initial infestation. Enhanced PCR confirmed by sequencing revealed *B. henselae* in both the woodlice and the woodlice hunter spiders. This was the

first documentation of *Bartonella* in woodlice or spiders.

Clearly, *Bartonella* infection extends beyond cats, fleas, and acute febrile illness. In addition, clinical presentations vary widely, even within a single family presumably infected together. So, why do these severe syndromes manifest in some patients, when most people just get a simple case of “Cat Scratch Fever” that spontaneously resolves with no further problems? Dr. Breitschwerdt thinks that there is no single, simple answer; that the variation instead likely lies in a combination of genetics of the patient, strain of *Bartonella*, conditions of inoculation, and/or perhaps other factors. Clearly, there’s a lot we don’t know about this mysterious organism and how it interacts with the human body.

Indeed, Dr. Breitschwerdt believes that bartonellosis may in fact represent a highly underdiagnosed epidemic that is responsible for widespread unexplained chronic and often degenerative neurological diseases, from depression to chronic fatigue syndrome to progressive polyarthritis, especially among veterinarians. “If our research is substantiated in the context of causation and not just

1963

Weight Watchers It may be a little unfair to include this diet, which was founded by Jean Nidetch, a self-described “overweight housewife obsessed with cookies” as a fad, as it is still going strong today.

1964

I’ll drink to that Harkening back to William the Conqueror, the Drinking Man’s Diet is more about drinking than diet and is eventually dubbed “unhealthy” by the Harvard School of Public Health.

1970

Sleeping Beauty This dubious diet is actually nothing more than extended unconsciousness aided by sedatives. Elvis is said to have tried this one.





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“...the southern part of the United States, along with Hawaii, has the highest prevalence of CSD caused by *B. henselae* due to the high colonization and bacteremia in the cat population.”

association,” he posits, “bartonellosis may explain a spectrum of animal and human illnesses.” He recommends that anyone who has been in contact with animals and is suffering from unexplained neurological or psychological symptoms get tested for Bartonella. While certain signs can alert physicians (for example, arthritis patients also reporting blurred vision and numbness in extremities are more likely to test positive for *B. henselae*), most cases of neurobartonellosis have unique clinical presentations, so it may not occur to physicians to test for Bartonella.

Even nearly classical cat scratch disease is easy to miss. Ochsner Children’s Health Center physicians Jake Kleinman and Russell Steele detail the case of a 5-year-old girl with leg pain and swelling that had gotten so severe that she could no longer bear weight on her legs when she presented at Ochsner. Accompanying the pain and swelling were fatigue and decreased appetite. Three weeks earlier, she had seen her primary care physician with fever, sore throat, and an enlarged left submandibular lymph node. Despite the fact that the family had adopted a new pet kitten and the girl had allowed the kitten to lick her face and eyes, the PCP did not suspect CSD. Fortunately, Kleinman and Steele did suspect bartonellosis, and successfully treated the girl with antibiotic therapy. The *B. henselae* infection was subsequently

confirmed by serology. They point out that the southern part of the United States, along with Hawaii, has the highest prevalence of CSD caused by *B. henselae* due to the high colonization and bacteremia in the cat population. It is therefore not unlikely that unusual neurological symptoms may be due to infection with Bartonella.

Hypotheses about the mechanisms underlying the diversity of Bartonella-based illness include autoimmune reactions, neurotoxic reactions, and direct neurological damage. In addition, Bartonella has a number of cellular targets besides neurons, including erythrocytes, epithelial cells, microglia, macrophages, and CD34 progenitor cells. Dr. Breitschwerdt favors an inflammation and immune-mediated etiology: “Bartonella infects endothelial cells, pericytes, erythrocytes, and monocytes within the vasculature throughout the body. The bacteria appear to cause microvascular injury (small vessel disease). This becomes a very chronic inflammatory illness, with the development of secondary immune-mediated and autoimmune phenomena.”

Even severe bartonellosis syndromes clear fairly quickly upon treatment with

appropriate antibiotics (such as azithromycin). Diagnosis is key, and the difficulty due to such highly variable clinical presentations is compounded by the high false-negative rate of laboratory assays. Dr. Breitschwerdt and a team of researchers from North Carolina State University College of Veterinary Medicine (NCSU-CVM) have developed a sensitive diagnostic system based on culturing in a novel growth medium (Bartonella/alpha-Proteobacteria growth medium) followed by PCR, with confirmation by sequencing.

This system, called enhanced PCR or ePCR, ramps up the sensitivity of lab-based diagnosis by increasing the bacterial population before PCR, resulting in up to 10X the sensitivity of conventional PCR. Still, Bartonella is elusive in the body, and remains easy to miss, necessitating repeated testing at different timepoints in the case of a negative result. Repeated testing, though, can be far cheaper than years of clinical confusion and ineffective treatment because of baffling symptoms; bartonellosis is quite treatable in immunocompetent patients. Testing using the NCSU-CVM-developed Bartonella ePCR assay is available through Galaxy Diagnostics (<http://www.galaxydx.com/web/>). ■



1975



Cookies Sanford Siegal, a south Florida doctor, creates weight loss cookies from a mixture of amino acids. Patients consume six cookies a day in addition to a 300-calorie dinner. Something tells me it wasn’t the cookies.

1977



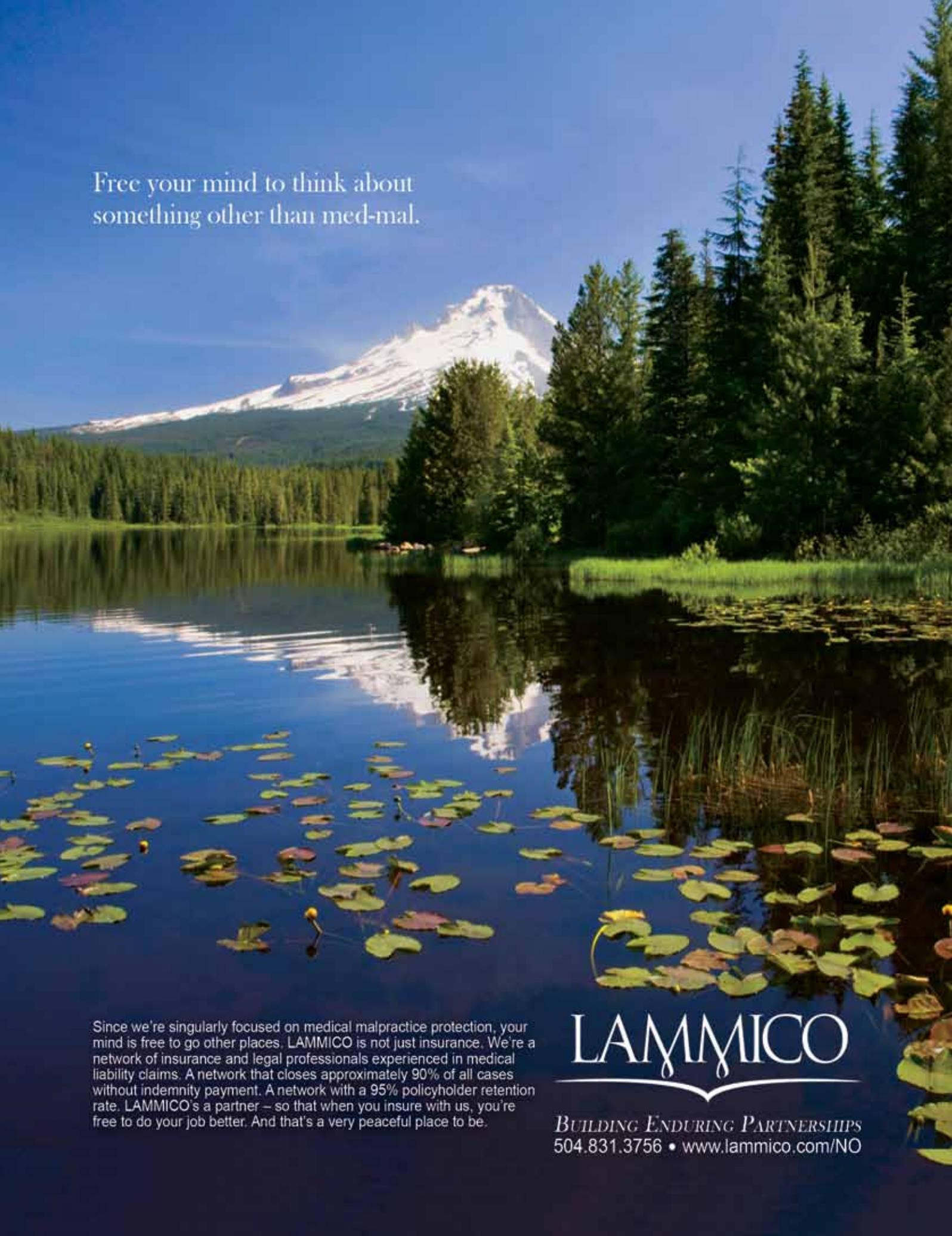
Slim-Fast Another one with some staying power, dieters can still have “a shake for breakfast, a shake for lunch, then a sensible dinner” today.

1978



Scarsdale Perhaps remembered more for the scandal that ensued after Dr. Herman Tarnower was shot by his girlfriend, “The Complete Scarsdale Medical Diet” gained some notoriety.

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