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# WILL THE REAL AGENT OF CAT-SCRATCH DISEASE PLEASE STAND UP?[1]

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ABSTRACT

Cat-scratch disease has been recognized since 1889 in association with the oculoglandular syndrome of Parinaud. The epidemiologic association with cats was first made in 1931 and further substantiated throughout the years, refining the interaction predominantly to kittens. Putative infectious agents have included numerous species of bacteria, chlamydiae, and viruses. The cultivation of *Afipia* spp. in the late 1980s appeared to answer the mystery of the identity of the agent. However, even more recent analysis, which has combined traditional microbiology, molecular methods, and additional epidemiology, has demonstrated that *Bartonella* (*Rochalimaea*) *henselae* is the definitive agent of cat-scratch disease. Our understanding of the pathogenesis of cat-scratch disease and other diseases caused by *Bartonella* species is incomplete and the spectrum of diseases continues to emerge. We review historic and modern efforts to understand the etiology of cat-scratch disease and related syndromes.

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## HISTORICAL PERSPECTIVE

Detailed presentation of the many meaningful contributions made by primary researchers, microbiologists, and primary care and specialized clinicians towards an understanding of cat-scratch disease is beyond the scope of this review. The following discussion briefly highlights some of the key events in the history of cat-scratch disease. For additional review, Warwick (87) provides an excellent summary of the early literature with over 560 cited references. In general, even though the identity of the organism responsible for causing cat-scratch disease remained an open question for many years, much of the clinical and epidemiologic findings has remained consistent and relevant to our current understanding of cat-scratch disease.

Parinaud described what is believed to be the first reports of cat-scratch disease in 1889 (63). He associated conjunctivitis and enlargement of regional lymph nodes with contact with animals (Parinaud's oculoglandular syndrome). In 1913, Verhoeff carefully examined specially stained histologic sections from patients with Parinaud's syndrome and demonstrated "irregular masses" of a "filamentous organism." He labeled the syndrome as a "mycotic disease" (85). His detailed descriptions portray an organism bearing more resemblance to bacteria than fungi and could be the first observations of the true etiologic agent in tissue.

The association between cats and the disease was first made by Debré et al in Paris in 1931 (25). Debré examined a 10-year-old boy who had played and slept with cats and then presented suppurative epitrochlear nodes. Debré initially diagnosed the adenitis as tuberculous but noted the disease healed spontaneously. Other patients followed with similar exposure to cats and regional adenitis that resolved uneventfully, and Debré published his findings in 1950.

As noted in a review by Moriarity (59), Foshay noted a similar syndrome in the United States also in the 1930s. Foshay made an antigen preparation from

pus aspirated from the lymph nodes of cat-scratch disease patients. When injected into subjects with history of the disease, the antigen preparation elicited a positive intradermal reaction. In 1946, Rose performed a skin test on a fellow physician, Hanger, with material from Hanger's enlarged epitrochlear node. Hanger's Siamese cat had putatively inflicted a wound on the hand distal to this enlarged node (59). The antigen elicited an intense tuberculin-like response. It is from these studies that the skin test came to be called the Hanger-Rose skin test. Likewise, during the late 1940s, Debré used antigenic preparations supplied by Foshay to demonstrate positive skin tests in his patients (24).

The initial published case report in the United States is credited to Greer & Keefer in 1951 (36) and was later followed by a series of articles by Daniels & MacMurray (21–23). These reports laid the foundation for our current understanding of the clinical course of the disease as well as its key epidemiologic factors. Diagnostic criteria for the disease were established and included the following: 1. lymphadenitis, 2. a positive skin test, 3. the presence of an identifiable inoculation site, 4. the history of cat contact, and 5. the absence of other diseases.

## HISTORICAL EPIDEMIOLOGY

Daniels & MacMurray (23) and Carithers (12) presented data from over 1350 cases of cat- scratch disease and were among the first investigators to contribute to a more detailed epidemiology of cat-scratch disease. Although cases were documented throughout the year, cat-scratch disease was found to be seasonal in the fall and winter months. Clusters of the disease were noted in Nova Scotia; Worms, Germany; and Minneapolis and St. Paul (87). Children were recognized to be affected more frequently than adults. Of Carithers' patients, 87% were less than 18 years of age (12), whereas 30% of patients described by Daniel & MacMurray were less than 10 years and two thirds less than 30 years of age (23). Cat contact was shown to be a consistent factor in analysis of the disease. However, from a precise epidemiologic point of view, one must be cautious when interpreting cat contact as an unbiased risk factor for acquisition of cat-scratch disease if cat contact was used in any way as an element for reaching a provisional diagnosis (as would be expected and quite appropriate in a normal clinical setting). Warwick details cat contact in 90.3% of cases involving 916 patients from 6 studies (87). Daniel & MacMurray (23) noted contact with cats in 148 of 160 cases (92.5%) and report significant traumatic involvement (bite, scratch, and/or an abrasion while cleaning a cat cage) in 110 of 148 cases (76.3%). Carithers reported that 89% of 200 patients had involvement with cats less than 1 year old (12).

Anecdotal reports of unusual exposures to other mammals were documented. Margileth reported an example of an animal handler who contracted cat-scratch disease after having been bitten by a monkey (53), and Daniel & MacMurray recorded a case apparently associated with handling a wild rabbit (23). Dogs were associated with about 4% of cases in at least one patient series (55). In addition, a number of inanimate objects, including fish hooks, pins, splinters of wood, and porcupine quills, have been implicated in possible inoculation and transmission of the disease (12).



## CLINICAL PERSPECTIVES AND PATHOLOGY

As previously noted, many reports have served as the foundation for our current understanding of the clinical perspective of cat-scratch disease.

Carithers (13) details that within a week of exposure (3–30 days) a papule typically appears on the skin at the site of inoculation. Thorough examination of patients is essential in order to locate a primary inoculation site, which can often help differentiate cat-scratch disease from other clinical entities. The initial lesion is generally erythematous and nonpruritic and resolves within several days to weeks [upper range, five months (54)] without scarring. The lesion may go through a cycle similar to chicken-pox lesions (from a macule to a papule to a vesicle to encrustation). Within 3 weeks after inoculation [range 5–50 days (54)], regional lymphadenopathy occurs at a site proximal to the inoculation. Carithers' (12) study of 1200 patients (with 1302 involved nodes) noted lymphadenopathy most commonly in the following nodes: axillary (45%), cervical (14.7%), submandibular (11.4%), inguinal (10.9%), preauricular (6.7%), femoral (6.5%), clavicular (2.4%), epitrochlear (1.8%), chest (4 cases), and postauricular (2 cases). Of these patients, 85% had single node involvement, whereas the remaining had multiple nodes affected. Bilateral, noncontiguous lymphadenopathy was noted in 1.9% of patients in which either multiple distinct sites of inoculation were detected or the original inoculation was at a central site that allowed drainage to regional lymph nodes on each side (12).

Nodes were noted to become enlarged and tender. The larger the node, the more likely suppuration will occur. Debré & Job (24) reported suppuration in 50% of 77 patients in their review. Others (13, 23, 32, 56, 76) have noted suppuration ranging from 8.5–40% of cases.

Constitutional symptoms included fever in 30–50% of cases (in spite of the disease's early designation as cat-scratch "fever"), malaise (30–45% of cases), anorexia\emesis\weight loss (10–15% of cases), splenomegaly (12% of cases), pharyngitis (9%), parotid swelling (2%), and pulmonary symptoms (0.2%) (12, 13, 59). Dermatologic manifestations were noted in 5% of cases

and may consist of a macular rash, erythema nodosum, a papulovesicular rash, petechiae, urticaria, or erythema annulare (54).

Atypical manifestations of the disease have been noted in 5–20% of patients. Most commonly described were Parinaud's oculoglandular syndrome, central nervous system involvement (including encephalopathy, encephalitis, radiculitis, myelitis, polyneuritis or neuroretinitis), osteolytic lesions, thrombocytopenic purpura, and granulomatous hepatitis (13, 23, 74). These atypical manifestations raised questions as to whether this was a single disease entity or multiple disease entities (38, 87).

Margileth notes that the lymphadenopathy generally resolves spontaneously in two to four months but occasionally persists for longer than a year (54). Reinfection is extremely rare. In a preliminary review of 2900 patients, Margileth reported three cases of suspect cat-scratch disease in women over 30, of which two women had apparently distinct disease episodes 18 months apart, and the third woman appeared to acquire the disease three times (55).

The basic pathologic finding in a cat-scratch disease–infected lymph node is formation of stellate necrotizing granulomata. Histologic examination of the lymph node shows consistent stages of change as follows: follicular lymphoid hyperplasia with little distortion of normal architecture, microabscess formation, and rimming of the abscesses by epithelioid histiocytes with occasional giant cells. All changes may be seen simultaneously within the node.

The value of antibiotic therapy for treatment of cat-scratch disease in otherwise healthy persons has remained equivocal. It is reasonably clear from uncontrolled observations of large numbers of treated patients that no one class of antibiotic clearly produces consistent, readily measured, positive, and rapid beneficial effects (55). Antibiotic therapy benefit analysis may have been hampered by a lack of suitable controls and lack of readily measured parameters of efficacy. For example, several of the hallmark signs of cat-scratch disease appear to be themselves spectacular proliferative cellular immunologic responses to antigen of the infecting agent, and it may be unreasonable to expect such signs, such as grossly enlarged lymph nodes, to regress rapidly even under the best scenarios of antimicrobial therapy. In addition, the possibility remains that the disease causing agent may be sequestered and inaccessible to the effects of commonly used antibiotics or, even if antibiotics are effective at halting microbial replication, that antigen may continue to stimulate host immune responsiveness (and hence prolong symptoms) in the absence of viable organisms. It is significant that persons with grossly impaired immune responsiveness (and who may have greatly altered signs of infection) respond well to certain antibiotic therapy (49) (see below).

## SEARCH FOR THE AGENT

Warwick (87) has previously detailed the early history of the search for the infectious agent of cat-scratch disease. Based largely on apparent serological evidence, early prime suspects were organisms of the psittacosis\ornithosis\ lymphogranuloma venereum\trachoma group (collectively designated as the POLT group). Mollaret (58) reported positive POLT complement fixation titers in 46% of his patients with cat-scratch disease. Kalter (44), Gifford (34, 35), and Fowler & Bailey (32) made similar findings; however, Bedson (4) did not. These studies did not include appropriate controls and included only observations for patients diagnosed with cat-scratch disease. Subsequent controlled studies (87) revealed positive POLT titers in only 26–36% of cat-scratch disease patients, whereas 2–3% of non–case controls were positive. These conflicting reports and inconsistent results, coupled with the lack of response of patients to the POLT skin-test antigen, discounted these organisms as possible etiologic agents of cat-scratch disease.

Viruses were entertained as possible causes of cat-scratch disease. As early as 1951, Mollaret (58) presented data suggestive of a viral infection. Dodd and coworkers (27) demonstrated a hemagglutinin in pus from ten cases of cat-scratch disease. The hemagglutination was inhibited by specific serum. Turner and colleagues (84) also reported a hemagglutinating virus antigenically related to herpes simplex. The presumptive virus hemagglutinated rabbit and rat cells but lacked characteristic virulence and cytopathic properties of the herpes virus. Kalter and colleagues (42, 43) also described herpes-like virus particles associated with cat-scratch disease. Based on the inability to cultivate the organism on routine bacteriologic media, it was commonly held that viruses were the cause of disease, and Blank (7), in a 25-year perspective on viral diseases of the skin, mentioned that viruses were being pursued as the cat-scratch disease agent. Similarly, Emmons (30), writing on the search for the etiology of cat-scratch disease in 1974, commented that future research should emphasize new viral isolation methods in order to discover the elusive agent. The questionable efficacy of various antibiotic treatments for relieving the signs of cat-scratch disease infection almost certainly contributed to the concept that the hypothetical infectious agent was unlikely to be of bacterial origin, thereby making the possibility of a viral agent more plausible. However, the lack of consistency in viral isolation or demonstration of viral inclusions in tissue did not support a role for these agents.

Boyd & Craig (8) raised the possibility that an acid-fast bacteria might be responsible for cat-scratch disease. A photochromogenic acid-fast organism was cultivated from eight patients diagnosed with cat-scratch disease. Five of the eight gave minimal positive reactions to Hanger-Rose skin tests, while six

of the eight reacted positively to a skin-test antigen for nontuberculous acid-fast organisms. This report raised a number of interesting concerns, including the possibility of confusing mycobacterial disease and cat-scratch disease when relying on nonstandardized skin-test reagent. In retrospect, it appears likely that these patients had atypical mycobacterial infection of the lymph nodes rather than cat-scratch disease (87).

As previously noted, Verhoeff (85) described a filamentous, pleomorphic organism in histological sections from patients with Parinaud's syndrome. Verhoeff's organism was classified as "leptothrix" (often used interchangeably with the genus *Leptotrichia* by many investigators at that time). Henry (38) likewise described her isolates from conjunctival biopsies as leptothrix. She further made note of similar organisms in smears from the mouths of cats and questioned whether cat-scratch disease and Parinaud's disease may be caused by the same organism. Subsequently, Cassidy & Culbertson (14) disputed the notion that leptothrix was involved in the disease process and instead established that the organism was a saprophyte. No further investigations attempting to link leptothrix with cat-scratch disease have appeared in the literature.

Other bacteria have likewise been proposed to be the agent of cat-scratch disease. Gerber and colleagues (33) detailed growth of a pleomorphic gram-positive organism recovered from a lymph node of a patient with the syndrome. Using the Warthin-Starry stain, the organism was found to be morphologically similar to those observed by Verhoeff in 1913. Electron microscopy of broth cultures detailed the morphology to be consistent with gram- positive organisms. Biochemical and physiological analysis placed the organism most closely to the *Rothia* genus. No other reports describing *Rothia* sp.-like organisms have appeared in the cat-scratch disease literature.

In 1981, Wear and colleagues (88) at the Armed Forces Institute of Pathology (AFIP) assisted in the histopathologic evaluation of a lymph node from an 11-year-old child with laboratory findings consistent with cat-scratch disease. By using the Warthin-Starry silver impregnation technique, many small bacteria were visualized in the tissue section and proved to be gram-negative with the modified Brown-Hopp's tissue Gram stain. Over the following two years, histopathologic examination of lymph nodes from 37 patients, provisionally diagnosed with cat-scratch disease, revealed pleomorphic gram-negative organisms in 34 of 39 nodes (88). Of these patients, 11 had been exposed or scratched by cats; 28 had no apparent cat exposure.

In tissue sections stained by the Warthin-Starry method, bacilli were visualized in skin at the primary inoculation site (57) within the walls of capillaries, within macrophages lining the sinuses, in thrombosed vessels, and in clusters and as single organisms in areas of necrosis. These organisms stained positively by immunologic methods with sera from patients with cat-scratch disease (88)

but not with antisera to *Legionella pnemophila*, *Rickettsia rickettsii*, *Rickettsia conorii*, or *Rickettsia tsutsugamushi*.

The Warthin-Starry stain has been used to demonstrate the presence of bacilli in as many as 85% (88) of cat-scratch disease cases; however, other competent laboratories have not found the Warthin-Starry stain as reliable for diagnostic purposes (26), and the test is often regarded as somewhat capricious to implement and interpret. Organisms show focal distribution, with numerous organisms in one area and virtually none in other locations. The earlier that lymph nodes are examined in the course of the disease, the more abundant are the organisms. Typical bacilli may be difficult to detect by the time the lymph node suppurates.

Efforts to grow organisms from cat-scratch disease patient tissues continued at the AFIP and climaxed in the isolation of a putative causative organism by English in 1988 (31). A gram-negative bacterium or its cell-wall defective form were isolated from the lymph nodes of ten patients with cat-scratch disease. Over the ensuing four years, one isolate in particular was especially well characterized (10, 31, 62). The name *Afipia felis* was designated for this organism in honor of the institution (AFIP) where the isolation had been achieved. However, this much-heralded announcement regarding the identity of the etiologic agent of cat-scratch disease was soon to be challenged. Confirmatory immunologic evidence for *A. felis* cat-scratch disease infections was not forthcoming; likewise, direct microbiologic evidence linking *A. felis* and cat-scratch disease (e.g. isolation) was not reported by other laboratories.

Although the association with cat-scratch disease may not have been immediately apparent, the search for the causative agent took an interesting, important twist in 1983 when Stoler and coworkers (77) noted an atypical subcutaneous infection in an HIV positive individual. The lesions were characterized by neovascularization with presence of Warthin-Starry–staining rod-shaped organisms, and the pathologic description "bacillary angiomatosis" was applied. The once descriptive pathologic term bacillary angiomatosis is now commonly used to refer to the syndrome. Additional reports followed, detailing infections predominantly in HIV positive patients, and the clinical spectrum of bacillary angiomatosis grew to include lesions in lymph nodes, brain, bone, liver (peliosis hepatis), and spleen (18, 45, 49, 65, 82). The presence of Warthin-Starry–staining bacilli in these lesions led several authors to speculate as to the possible role of the cat-scratch disease bacillus in disseminated disease recognized as bacillary angiomatosis (6, 45, 47, 51). Furthermore, several reports of bacillary angiomatosis cases noted a history of patients having cat contact prior to disease onset (45, 80, 82).

The discovery of another important piece of the cat-scratch disease puzzle began to fall into place with the advent of novel approaches to the study of

uncultured organisms (71, 92). Polymerase chain reaction (PCR) and consensus oligonucleotide primers were used to amplify eubacterial 16S rRNA gene sequences from wide varieties of bacteria. Subsequent nucleotide sequence analysis of the amplified products and comparison of these sequences with 16S rRNA genes of previously studied organisms provided a method for reasonably sophisticated genotypic identification of organisms without the necessity of isolating the organisms in pure culture. Armed with powerful new molecular techniques, Relman et al (71) identified bacilli present in biopsied bacillary angiomatosis lesions as being closely related to *Rochalimaea quintana* (even though an isolate was not obtained). *R. quintana* had been previously regarded primarily as the historically significant agent of trench fever, best remembered as a louse-borne disease very prevalent among troops fighting in Europe during World War I (78).

Independently, researchers in Oklahoma (73) and Houston, Texas, and the Centers for Disease Control and Prevention (CDC) (66) succeeded in isolating *Rochalimaea*-like bacteria from febrile, bacteremic, predominantly immunocompromised (but non-bacillary angiomatosis) patients. By applying genotypic analysis, together with traditional methods, these blood isolates were well-characterized (66, 90) and named *Rochalimaea henselae* in honor of Diane Hensel, who is credited with having made several of the early isolations (66, 73). 16S rRNA analysis (similar in concept to that used by Relman et al) was used to help identify the Houston isolate as a novel species and immediately demonstrated that the *R. henselae* 16S rRNA gene sequence was identical to sequences that had been described previously in bacillary angiomatosis lesions (66). The apparently diverse syndromes described among immunocompromised patients had been linked to a common agent.

Initial successful efforts to cultivate *R. henselae* showed that the organism was relatively fastidious (it required an enriched blood agar substrate), relatively slow growing (some primary isolates required a month to produce colonies), and required $CO_2$ (66, 90, 91).

Meanwhile, Tappero and colleagues were studying the epidemiology of bacillary angiomatosis and bacillary peliosis to determine environmental risk factors associated with disease (82). Patients diagnosed with bacillary angiomatosis ($N = 48$, confirmed by histology with a subset of 22 confirmed by PCR for detection of *Rochalimaea* sp.) and control patients ($N = 94$) were selected from hospitals and clinics in the San Francisco area. Among the variety of environmental factors studied, the most significant finding in unmatched analysis was that case patients ($N = 32$) were more likely than control patients ($N = 37$) to report a recent cat scratch or cat bite. Although history of traumatic cat contact was statistically associated with bacillary angiomatosis, one third of

the case patients in this study had no known exposure to cats. By 1993, Koehler and coworkers had isolated not only *R. henselae* but also, rather surprisingly, *R. quintana* organisms directly from cutaneous lesions in patients with bacillary angiomatosis on solid phase media (48). Various reports suggested that appropriate antibiotic therapy (e.g. tetracycline and erythromycin) of such immunocompromised patients dramatically relieved signs of infection; however, prolonged courses of antibiotics were necessary to prevent recrudescence or reinfection (45, 47, 49, 65– 67).

Using the Houston isolate of *R. henselae*, researchers at the CDC in Atlanta developed an indirect fluorescent antibody (IFA) assay to assist in the epidemiologic characterization of *Rochalimaea* sp.-associated disease among immunocompromised patients. The assay proved reliable in a preliminary blinded study and detected high titers of *Rochalimaea* sp.-specific antibodies in patients with bacillary angiomatosis (80, 83). No antibodies were noted in non–bacillary angiomatosis patients, with the exception of one patient diagnosed with cat-scratch disease (80).

Regnery and colleagues, recalling the previously noted ambivalence regarding the distinctions between some examples of bacillary angiomatosis and cat-scratch disease (6, 45, 47, 51), the absence of cat-scratch disease–associated *A. felis* isolates from more than one research institute, and the absence of convincing serologic evidence linking *A. felis* and cat-scratch disease, applied the new *R. henselae* serologic test to a collection of sera collected from patients with suspect, but unconfirmed, cat-scratch disease (69). Of 41 single serum samples, 36 (88%) demonstrated significant titers to *R. henselae*; high-titered antibodies were not detected when *A. felis* antigen was used with the same sera. Blood donor control sera showed only a low level of reactivity (6%) to the *R. henselae* antigen. This observation provided the first experimental link between *R. henselae* and cat-scratch disease and helped to strengthen the association between cat-scratch disease, bacillary angiomatosis, and related syndromes in immunocompromised patients.

With a new, potentially useful serologic test for confirming a clinical diagnosis of cat-scratch disease, Zangwill and coworkers conducted a systematic evaluation of risk factors for development of cat-scratch disease in Connecticut (93). For the case control study, 56 patients were identified. Matched univariate analysis showed patients were more likely than control group patients to have multiple exposure to cats and kittens in particular. Risk factors included being scratched or bitten by a kitten, being licked on the face by a kitten, sleeping with a kitten, and combing a kitten (93). Bivariate analysis demonstrated a significant association with being scratched or bitten by a cat in a household with kittens (seven times the risk compared to households without kittens). The presence of a cat with fleas in households with kittens was associated with a

sixfold increase in the risk of disease. Of serum samples collected from patients' cats, 39 of 48 (81%) from the noncontrol group and 11 of 29 (38%) from the control group were positive for *R. henselae* antigen. This demonstrated that not only were cats found in households of cat-scratch disease patients likely to have evidence of *Rochalimaea* sp. infections, but also that evidence for feline *Rochalimaea* sp. was relatively common in cats not immediately associated with examples of human disease.

Dalton and colleagues used serologic testing performed at the CDC as an opportunity to evaluate epidemiologic features of 600 suspect cases of cat-scratch disease by applying increasingly strict clinical criteria for diagnosis (19). A large subset of these patients with confirmatory serologic evidence of cat-scratch disease had experienced cat contact (74%); young cats were again commonly implicated. The median age for suspected cat-scratch disease patients submitted for testing was 12 years, with an interquartile range of 7–30 years. Infections were somewhat seasonal, as previously described. Reports were from throughout the United States, although few were submitted or confirmed from the Rocky Mountain states. For patients who met the most strict classical clinical criteria for cat-scratch disease, the serologic test was 95% concordant, prompting Dalton et al to propose that serologic evaluation could be used as a valid criterion for diagnosis.

Similarly, Demers, Bass, and colleagues applied strict criteria for inclusion of patients in their study of cat-scratch disease in Hawaii and demonstrated that, in a blinded test, all of the 38 patients had elevated *R. henselae* antibodies (100% concordance), whereas only 1 of 48 (2%) control group human sera yielded a positive serologic response (26). Recurrent human disease was not noted at least for one year. Of 34 cats identified as probable index cats, 31 were kittens (less than 1 year old), and of these 21 of 29 (72%) were *R. henselae* isolate positive. Adult index cats as well as control group stray cats were largely isolate negative but seropositive, suggesting past infections. Fleas were found on all cats examined. Dogs were not implicated as reservoirs or vectors of cat-scratch disease. No similar convincing evidence was found to suggest that *A. felis* might be an alternate source of cat-scratch disease infection.

*R. henselae* and *A. felis* serologic test results were compared with results from skin-test positive pediatric patients (79). Szelc and researchers demonstrated that positive IFA titers agreed with skin-test postive results in 52 of 56 (93%) cases, while only 1 of 57 (2%) healthy, skin-test negative control patients had positive IFA titers. These data confirmed a correlation between skin-test antigen reactions (using a microbiologically undefined reagent) with the IFA test results (using cultured *R. henselae* as the test antigen). Enzyme-linked immunosorbent assay serologic responses to *A. felis* did not differ between patients and control subjects.

*R. henselae* was isolated from the blood of a cat that was positive for *Rochalimaea*-specific antibody (68). Dolan, Wong, and coworkers (28) successfully made *R. henselae* isolates directly from the nodes of patients with cat-scratch disease, identified the isolates by using simplified genotypic methods, and thus all but completed the cycle of establishing the *R. henselae* etiology of cat-scratch disease.

Koehler and coworkers (46) supplied direct microbiologic evidence for the cat as a reservoir for *R. henselae* in examples of human bacillary angiomatosis. The organism was successfully isolated from seven asymptomatic cats with which four bacillary angiomatosis patients had contact. Furthermore, *R. henselae* was detected by PCR and cultured from cat fleas from an infected cat. Although arthropod vectors have been suggested in the transmission of *Rochalimaea*-associated disease (46, 52, 82), experimental data are currently lacking.

Perkins and colleagues (64) demonstrated *Rochalimaea*- specific nucleic acid sequences in cat-scratch disease skin-test antigen. Anderson and coworkers (2) further demonstrated that DNA sequences present in archival batches of skin-test antigen were specific for *R. henselae* (not *A. felis* or other members of the genus *Rochalimaea*); these skin-test antigens were examples of reagents that had been used for years as diagnostic tests for cat-scratch disease. Anderson and colleagues (3) also detected *R. henselae*-specific but not *A. felis*-specific nucleic acid sequences in 21 of 25 cat-scratch disease lymph nodes from seropositive patients, adding further evidence that *R. henselae* is the agent of cat-scratch disease and confirming the observation that PCR-based assays can be used to identify the species of the infecting agent without requiring isolation.

Recent studies have shown that *R. henselae* infections are a common feature among many cat populations (15–17, 26, 41, 46, 50, 60, 61, 68), that cats typically acquire antibody during the first year of life (15), and that bacteremia in cats can be prolonged and last two or more months (50, 68).

## NOMENCLATURE CHANGE TO *BARTONELLA* FROM *ROCHALIMAEA*

In 1993, after reevaluating the 16S rRNA sequences of *Bartonella bacilliformis*, Brenner, O'Connor, and colleagues proposed a major revision in the classification of the genera *Bartonella* and *Rochalimaea* (11). The results clearly supported combining the two genera within the historically precedent family *Bartonellaceae* (all species retained their species designations, e.g. *R. henselae* simply became *B. henselae*).

The genus *Bartonella* was modified again in 1995 (5) when combined with the genus *Grahamella*. Unification of the genera *Bartonella* and *Rochalimaea*

has resulted in the following species: *B. bacilliformis* (type species and agent of Carrion's disease); *Bartonella vinsonii*, and *B. vinsonii* subsp. *berkoffii* (9); *Bartonella quintana*; *B. henselae*; and *Bartonella elizabethae*. New species from the unification of *Grahamella* and *Bartonella* include the following: *Bartonella talpae*, *Bartonella peromysci*, *Bartonella grahamii*, *Bartonella taylorii*, and *Bartonella doshiae*. These species previously in the *Grahamella* genus and *B. vinsonii* are currently known to exist only within the erythrocytes of nonhuman hosts.



## EXPANDING SPECTRUM OF DISEASE ASSOCIATED WITH *BARTONELLA*

*B. henselae* is now regarded as the primary, and perhaps sole, causative agent of cat-scratch disease. The organism is also a cause of bacillary angiomatosis and bacillary peliosis (48, 81) and has also been associated with endocarditis (37, 39), fever, and bacteremia in adults and children (66, 86, 89, 90).

*B. quintana*, the historical agent of louse-borne trench fever in World War I, is at least one source of bacillary angiomatosis and has been associated with recent examples of endocarditis, fever, and bacteremia in homeless alcoholics in the United States (75) and homeless men in France (29). No association has been made between *B. quintana* and cats; nonhuman alternate vertebrate reservoirs are currently unknown.

*B. elizabethae* was isolated and described from a single patient who was diagnosed with endocarditis and bacteremia (20). No predisposing factors were noted, with the possible exception of lacerations on the patient's fingers from a nonspecified source two weeks before onset of symptoms. Nothing is currently known about the natural history of this organism.

*B. bacilliformis* infections have long been recognized to occur in mountain valleys of South America. The bacteria are vectored by sand flies and are known to cause widespread and life-threatening disease (1, 72).

## HINDSIGHT OBSERVATIONS

It may seem curious that, over the long course of cat-scratch history, *B. henselae* was not previously isolated and identified. Although the required growth conditions are now recognized to not be particularly exotic, typical hospital microbiology laboratories commonly discard negative cultures much sooner than may be required for *B. henselae* isolation. Bacteremia is rare in otherwise healthy cat-scratch disease (nonimmunocompromised) patients, and cultivation can be thwarted by overgrowth of faster growing contaminants.

Recent advances in genotypic methods for isolate identification certainly played a crucial role in establishing the identity of the isolates from immunocompromised and cat-scratch disease patients; without such methods it is interesting to speculate on whether or not key isolates would have been recognized for what they were. Likewise, it is interesting to speculate how many *Bartonella* species isolates have been made in the past and dismissed as small, weakly staining, gram-negative rods because of a lack of appropriate identification methods.

Historically, much emphasis was put on the presence of Warthin-Starry staining organisms in infected cat-scratch disease tissue; in hindsight it seems worth bearing in mind that the Warthin-Starry test is not a species-specific test but is capable of staining a variety of organisms, including *B. henselae*. All that was previously visualized with Warthin-Starry stain was not necessarily *A. felis*.

A possible role for *A. felis* as a human pathogen remains to be clarified. However, it is clear that current evidence does not support a role for *A. felis* in either currently diagnosed cat-scratch disease or cases of cat-scratch disease previously diagnosed with *B. henselae*–containing skin-test antigen.

## FUTURE DIRECTIONS FOR *BARTONELLA*-ASSOCIATED DISEASE RESEARCH

Many important questions and challenges remain regarding cat-scratch disease and related etiologies. These include careful evaluation of potential *B. henselae* arthropod vectors, determining the plausibility of preventing human disease by preventing feline infections, studying the pathogenesis of human *B. henselae* infections, identifying possible individual virulence factors of organisms, and investigating the natural history of the infection in cats. It is also clear that the distribution, prevalence, and natural histories of other modern-day human pathogenic *Bartonella* species (e.g. *B. quintana*) require further study. Clearly, the extremely serious biphasic disease associated with *B. bacilliformis* deserves renewed attention.

Although it is recognized that *B. henselae* is quite sensitive to a variety of antibiotics in vitro (52), and the symptoms associated with disease in immunocompromised hosts resolve dramatically with antibiotic therapy (49, 67), no consensus exists regarding the efficacy of antibiotic therapy in traditional cat-scratch disease. Carefully designed and executed laboratory and epidemiologic case-control studies are necessary.

It is reasonable to assume that as reliable, validated, safe methods for serologic and nucleic acid-based diagnosis of infection become more widely applied, and methods for isolation and identification of *Bartonella* spp. isolates become

better known, the spectrum (as well as the numbers) of *B. henselae*–associated disease will continue to expand beyond classic cat-scratch disease adenitis. Modern methods for genotypic evaluation, together with enhanced methods for isolation of potential *Bartonella* isolates, should continue to lead to recognition of additional species and perhaps lead to additional *Bartonella* species added to the current list of potential human pathogens.

Estimates of the concordance of the IFA serologic test for confirming cat-scratch disease diagnosis rise to between 95 to 100% when stringent criteria are used for the initial clinical diagnosis. This suggests that not only is the serologic test sensitive, but that when the classical clinical criteria for cat-scratch disease are met, further laboratory testing may not be of significant benefit. The greatest value for validated laboratory testing appears to exist for cases for which all clinical evidence may not be obvious (including disease with serious complications) or when serious alternative diagnosis must be considered (e.g. possible malignancies). Low level serologic prevalence of *Bartonella*-specific antibody among control populations (e.g. 5%) may tentatively be explained by past subclinical infections or perhaps by unspecified serologic cross-reactivity with heterologous antigens. The substantial evidence for high prevalence of *B. henselae* among common house cats suggests that the opportunity for human infections may not be an uncommon event.

It will be interesting to evaluate in hind-sight how accurate are the best present estimates of the prevelance of cat-scratch disease [24,000/year in the United States (40)], and also review what progress has been made towards cat-scratch disease control and prevention.

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