

Rat Bite Fever and *Streptobacillus moniliformis*

Sean P. Elliott*

Department of Pediatrics and Steele Children's Research Center, University of Arizona Health Sciences Center, Tucson, Arizona

INTRODUCTION	13
HISTORICAL ASPECTS	13
BIOLOGY	14
Morphology	14
Growth Characteristics	14
Pathogenesis	14
EPIDEMIOLOGY	14
Geographic Distribution	14
Animal Infectivity	15
Rats	15
Mice	16
Other animals	16
Human Infectivity	16
CLINICAL FEATURES	16
Initial Symptoms	16
Disease Progression	16
Outcome	17
Review of English Literature	18
Epidemiology	18
Clinical findings	19
Complications	19
Differential Diagnoses	19
Diseases	19
Sodoku	19
Haverhill Fever	19
U.S. experience	19
United Kingdom experience	20
DIAGNOSIS	20
Culture	20
Fatty Acid Profiles	20
Other Methods	20
TREATMENT	20
CONCLUSIONS	21
REFERENCES	21

INTRODUCTION

Disease following the bite of a rat has been known in India for over 2,300 years, but it has been described worldwide much more recently as rat bite fever. This term describes two similar yet distinct disease syndromes caused by *Streptobacillus moniliformis* or *Spirillum minus*. Rat bite fever caused by *S. moniliformis* is more common in North America, while *S. minus* infection, also known as sodoku, is more common in Asia. Streptobacillary rat bite fever, the subject of this review, is a systemic illness classically characterized by relapsing fever, rash, migratory polyarthralgias, and a mortality rate of 13% when untreated. Often associated with the bite of a wild or laboratory rat, rat bite fever historically has affected laboratory technicians and the poor. As rats have become popular as pets,

this has changed such that children now account for over 50% of the cases in the United States, followed by laboratory personnel and pet shop employees. Over 200 cases of rat bite fever have been documented in the United States, but this is likely a significant under-representation because rat bite fever is not a reportable disease. Further, rat bite fever has a nonspecific presentation with a broad differential diagnosis, and isolation and identification of its causative organism, *S. moniliformis*, is not straightforward. Thus, the challenges of diagnosis and broadened demographic exposure demand close attention to this disease and its causative organism by clinicians.

HISTORICAL ASPECTS

Rat bite fever was first reported in the United States in 1839 (89). An association with a specific pathogen was not reported until 1914, when Schottmüller described *Streptothrix muris ratti*, isolated from a rat-bitten man (71). This association was confirmed in the United States in 1916 (9). In 1925, the organism

* Corresponding author. Mailing address: Department of Pediatrics, University of Arizona Health Sciences Center, 1501 N. Campbell Ave., Tucson, AZ 85724-5073. Phone: (520) 626-6507. Fax: (520) 626-5652. E-mail: selliot@peds.arizona.edu.

was renamed *Streptobacillus moniliformis* (48), a name that has remained in general use since, although some reports refer to *Actinomyces* or *Actinobacillus muris* (41, 87). A milk-associated outbreak of disease occurred in Haverhill, MA, in 1926 and was described by Place and Sutton (60). The organism found at this time was named *Haverhillia multiformis* by Parker and Hudson (55), although this most likely represents *S. moniliformis* disease. Any review of the literature regarding rat bite fever is complicated by the near-simultaneous description of *Spirillum minus*, the primary cause of rat bite fever in Asia, which is known by many as sodoku. Unfortunately, some reports discuss both organisms simultaneously, blurring the distinction between the two diseases and epidemiologic distributions that are, in fact, distinct.

BIOLOGY

Morphology

Streptobacillus moniliformis is a highly pleomorphic, filamentous, gram-negative, nonmotile, and non-acid-fast rod. It usually appears straight but may be fusiform and may develop characteristic lateral bulbar swellings. The organism is typically arranged in chains and loosely tangled clumps (Fig. 1). It varies in its dimensions, from 0.1 to 0.5 μm by 2.0 to 5.0 μm , up to 10 to 15 μm , with long, curved segments up to 100 to 150 μm (65). *S. moniliformis* exists in two variant types, the normally occurring bacillary form and the inducible or spontaneously occurring, cell wall-deficient L form, growing with a "fried-egg" colony morphology. The L form is considered nonpathogenic (28); spontaneous conversion between the two forms in vitro has been reported and is felt by some to be responsible for clinical relapses and resistance to therapy (72).

Spirillum minus, the other etiologic agent of rat bite fever, was discovered during the 19th century and initially named *Spirocheta morsus muris* or *Sporozoa muris*. It was renamed *Spirillum minus* in 1924. The organism is a short, thick, gram-negative, tightly coiled spiral rod which measures 0.2 to 0.5 μm and has two to six helical turns. Because *Spirillum minus* cannot be cultured on synthetic media, initial diagnosis relies on direct visualization of characteristic spirochetes with Giemsa stain, Wright stain, or dark-field microscopy (86).

Growth Characteristics

S. moniliformis is an extremely fastidious organism that needs microaerophilic conditions to grow, making microbiological diagnosis difficult. Optimal growth requires Trypticase soy agar or broth enriched with 20% blood, serum, or ascitic fluid. The bacteria grow slowly (2 to 3 days) and may take as long as 7 days. Typical colonies have a "cotton ball" appearance on media, while colonies on agar appear circular, convex, grayish, smooth, and glistening (69). After 5 days of growth, some colonies may demonstrate the "fried-egg" appearance seen with the L form. Importantly, the 0.05% sodium polyanethol sulfonate ("Liquoid") that is added to most commercial aerobic blood culture bottles as an anticoagulant inhibits the growth of *S. moniliformis* at a concentration as low as 0.0125% (74). However, Trypticase soy agar or broth, resin bead culture systems, and anaerobic culture bottles may dem-

onstrate growth because sodium polyanethol sulfonate typically is not added (46, 68, 75). Once the organism has grown, confirmation of its identity occurs by conventional biochemical and carbohydrate fermentation analysis (Table 1). Serologic testing and gas-liquid chromatographic analysis of the fatty acid profile have also been used and are discussed below.

Pathogenesis

Because of the relatively low incidence and low mortality rate of rat bite fever when recognized and treated, little information describing the pathogenesis of *S. moniliformis* exists. However, the organism appears to be capable of producing morphological findings not customarily associated with bacterial infections. Autopsy of rat bite fever victims demonstrates pronounced erythrophagocytosis, hepatosplenomegaly, interstitial pneumonia, and lymph node sinus hyperplasia (72). Endocarditis and myocarditis have also been demonstrated, along with degenerative changes in the kidneys and liver (1). Radiological data suggest that rat bite fever may be considered a cause of damage to physes and acrophyses, mimicking frostbite damage (53), and clinical data suggest that *S. moniliformis* may have a predilection for synovial and serosal surfaces (67). Biopsy of skin lesions seen in rat bite fever has demonstrated leukocytoclastic vasculitis (90). Experimental infection in mice (70) results in a progressive polyarthritis, beginning with fibrinopurulent exudate within the joint space and adjacent periosteum in the first 24 h of infection. This changes to a predominantly macrophage presence on day 4, followed by periarticular abscess and necrosis on day 7. Periostitis develops by 2 weeks and is followed by fibrous connective tissue proliferation after 3 weeks. The degree of polyarthritis depends on the size of the inoculum. It is of concern that persistence of organisms within joint spaces at 3 months of infection may occur despite the clearance of organisms from blood, liver, and spleen (70).

EPIDEMIOLOGY

More than 2 million animal bites occur each year in the United States, and rats are responsible for approximately 1% of these (30). Historically, the typical victim of rat bite fever was a child under 5 years old living in poverty, and over 50% of reported cases in the United States were children (37, 65). Now that rats have become popular pets and study animals, the demographics of potential victims have broadened to include children, pet store workers, and laboratory technicians. Over 200 cases of rat bite fever have been documented in this country, but this represents a significant underestimate because neither the disease nor its causative organism is reportable to health departments. The youngest reported case of rat bite fever was in a 2-month-old infant (72), and the oldest reported case occurred in an 87-year-old man (82). The risk of infection after a rat bite appears to be 10% (23, 35), and the mortality rate of untreated rat bite fever is approximately 13% (65, 91).

Geographic Distribution

Most reports of *S. moniliformis* originate from the United States, although other Western Hemisphere reports have come from Brazil, Canada, Mexico, and Paraguay. Most European

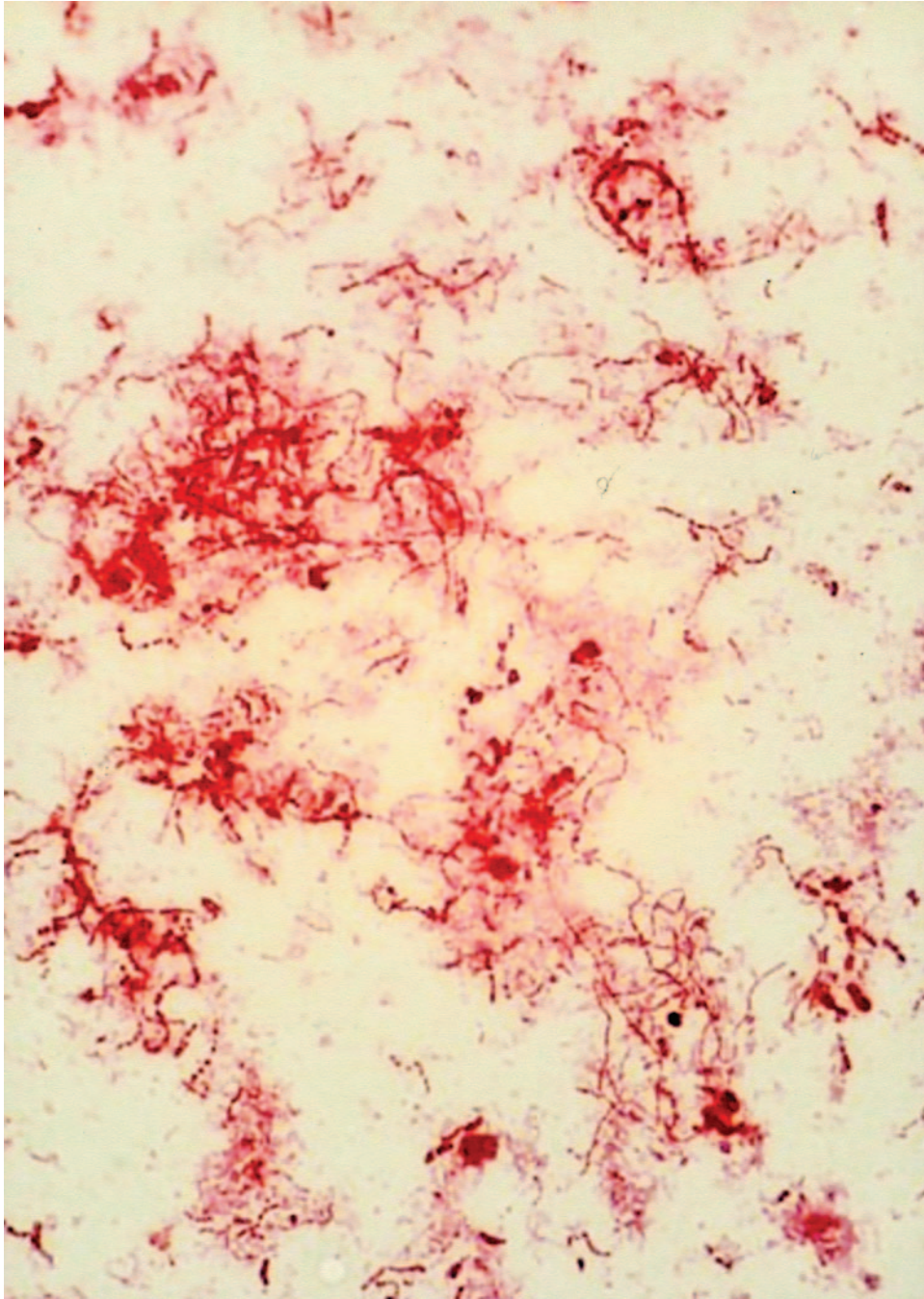


FIG. 1. Gram-stained smear of *S. moniliformis* on blood agar medium, demonstrating pleomorphic gram-negative bacilli in chains and clumps with irregular, lateral bulbar swellings (photo courtesy of L. Wilcox, Hamilton Regional Laboratory Medicine Program, and D. Yamamura, Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada).

reports come from the United Kingdom and France, but sporadic reports from Norway, Finland, Germany, Spain, Italy, Greece, Poland, Denmark, and The Netherlands also exist. Australia has also demonstrated some cases. Few reports from Africa exist, other than one report of sodoku from Kenya (8) and two episodes of squirrel bite-associated disease in Nigeria (33), probably underestimating the presence of *S. moniliformis*. Most reports from Asia document cases of sodoku, caused by *Spirillum minus* and not discussed here (91). Within the United

States, most early reports originate from the eastern half of the country. However, *S. moniliformis* now appears to have migrated to the West Coast (13, 32), and cases are documented nationwide (34).

Animal Infectivity

Rats. The rat appears to be the dominant natural reservoir of *S. moniliformis*, which likely is a member of the commensal

TABLE 1. Results of biochemical tests performed on the parent strain and an L-phase variant of *Streptobacillus moniliformis*^a

Test	Result	
	Parent strain	L-phase variant
Oxidase	Negative	Negative
Catalase	Negative	Negative
Indole	Negative	Negative
Nitrate	Negative	Negative
Hydrogen sulfide	Negative	Negative
Arginine hydrolysis	Positive	Positive
Methyl red	Negative	Negative
Phenylalanine deaminase	Negative	Negative
Citrate	Negative	Negative
Urea hydrolysis	Negative	Negative
Esculin hydrolysis	Weak reaction	Weak reaction
Glucose fermentation	Positive	Positive
Galactose fermentation	Weak reaction	Positive
Maltose fermentation	Weak reaction	Positive
Mannose fermentation	Weak reaction	Weak reaction
Other carbohydrates	Negative	Negative
TSI agar with serum (butt/slant)	Acid/acid	Acid/acid

^a Data are from references 17, 72, and 91.

flora of the rat's upper respiratory tract. Healthy rats may demonstrate the organism in cultures of the nasopharynx, larynx, upper trachea, and middle ear (56). Healthy domesticated or laboratory rats demonstrate *S. moniliformis* colonization 10% to 100% of the time, while wild rats appear to be 50% to 100% colonized (16). Most rats are asymptotically colonized but occasionally may demonstrate signs and symptoms of disease.

Mice. Because mice are a preferred animal model for research, a significant amount of effort has been expended to identify their risk of colonization and disease from *S. moniliformis*, as summarized by Wullenweber (91). It is well documented that laboratory mice may show symptoms of infection with *S. moniliformis*, ranging from septic lymphadenitis to polyarthritis and multiorgan microabscesses leading to septicemia, cachexia, and death (30, 91). However, it appears that not all strains of mice are equally susceptible to streptobacillosis and, in fact, many inbred strains demonstrate mild to no disease whatsoever. This is important from a laboratory personnel health risk perspective, as some animals may be asymptomatic carriers with the potential to transmit disease via exposure to saliva, as are rats. The persistence of *S. moniliformis* in mice is debated in the literature and ranges from none (91) to 6 months (70). Overall, there appears to be a low risk of rat bite fever from the bite of a healthy, inbred laboratory mouse. However, this may be different if the bite is by an outbred strain or wild mouse.

Other animals. There are reports of infection or colonization in such potential pets as guinea pigs (44), gerbils (90), ferrets (31), cats (82, 91), and dogs (16, 57, 82). However, no confirmatory evidence exists to prove the risk of transmission from either cats or dogs. More likely, the latter two animals are colonized only transiently after attacking or eating a rodent colonized with *S. moniliformis* (57). Rat bite fever in nonhuman primates (rhesus macaque and titi monkey) has been reported, and streptobacillary disease in turkeys and koalas has been demonstrated (83).

Human Infectivity

The reported incidence of rat bite fever caused by *S. moniliformis* from laboratory rat bites is low. Of 65 cases of documented rat bite fever since 1938 that were reviewed for this article, only 8 (12%) were attributed to a laboratory rat exposure. This likely does not represent the true incidence of disease in humans because of low clinical suspicion by clinicians and the organism's strict growth requirements. Similarly, the incidence of wild-rat-associated disease is seriously underestimated, as not all cases of rat bite fever are associated with an actual bite. *S. moniliformis* may also be acquired by handling of the animal or by exposure to its excreta or saliva. Nineteen of the 65 reviewed cases (29%) documented no bite or known exposure, consistent with literature reports that 30% of patients report no known bite (15, 32). However, as stated above, 10% to 100% of domestic rats and 50% to 100% of wild rats carry *S. moniliformis*, and a known bite causes infection approximately 10% of the time. Thus, rat bite fever and rat colonization with *S. moniliformis* represent a significant public health threat that remains unrecognized.

CLINICAL FEATURES

Rat bite fever is associated with three clinical syndromes in the literature. Rat bite fever caused by *S. moniliformis* infection is the predominant form seen in the United States. Disease caused by *Spirillum minus* is known as sodoku and occurs primarily in Asia. Ingestion of *S. moniliformis* via contaminated food causes Haverhill fever, so named for the first description of an outbreak in Haverhill, MA.

Initial Symptoms

S. moniliformis-associated rat bite fever is a systemic illness classically characterized by fever, rigors, and migratory polyarthralgias. After exposure, the incubation period ranges from 3 days to over 3 weeks but typically is less than 7 days. Many patients report symptoms suggestive of an upper respiratory tract infection during this time. If a bite has occurred, it typically heals quickly, with minimal residual inflammation and no significant regional lymphadenopathy. Persistence of significant induration at the bite site should suggest an alternate diagnosis, including sodoku.

At disease onset, fevers begin abruptly and may range from 38.0°C to 41°C. Rigors associated with fevers are prominent. Fever may resolve in 3 to 5 days but can relapse. Other frequently reported symptoms in the initial phase of illness include headache, nausea, vomiting, sore throat, and severe myalgias.

Disease Progression

As rat bite fever progresses, over 50% of patients develop migratory polyarthralgias. The severity of pain and the presence of swelling and erythema indicate arthritis (38, 67, 80). Reports also document the presence of synovitis and nonsuppurative arthritis suggestive of rheumatoid arthritis (40, 47, 67). The joints involved include both large and small joints of the extremities. Many patients experience arthritis of at least the knee and ankle during their illness. Migratory polyarthral-



FIG. 2. Petechial and purpuric lesions on the foot of a rat bite fever patient.

gia is the most persistent finding of rat bite fever, lasting several years in some patients.

Nearly 75% of patients develop a rash that may appear maculopapular, petechial, or purpuric (20) (Fig. 2). Hemorrhagic vesicles may also develop on the peripheral extremities, especially the hands and feet, and are very tender to palpation (Fig. 3). Appearance of this rash, especially the hemorrhagic vesicles, in the setting of an otherwise nonspecific set of disease signs and symptoms should strongly suggest the diagnosis of rat

bite fever. The rash may persist beyond the other, more acute, symptoms. Approximately 20% of rashes desquamate, especially those with hemorrhagic vesicles (20).

Outcome

Untreated, rat bite fever has a mortality rate of approximately 10%, ranging from 7% to 13% (15, 54, 65, 80, 91). Reported causes of death include endocarditis, refractory peri-



FIG. 3. Hemorrhagic vesicles on the first and third toes of a patient with advanced rat bite fever.

cardial effusion, bronchopneumonia, pneumonitis, periarteritis nodosa, volvulus, and overwhelming septicemia, with organisms found in both the adrenal glands and bone marrow at autopsy (14, 15, 62, 65, 72, 76). Although some patients appear to show spontaneous recovery from serologically confirmed disease (5, 13), a lack of effective antibiotic treatment is highly associated with death. Initiation of an appropriate antibiotic regimen usually precipitates rapid resolution of acute symptoms. However, some patients experience prolonged migratory polyarthralgias, fatigue, and slowly resolving rash.

Review of English Literature

Epidemiology. A review of the English language literature reveals 65 discrete case reports that provide full descriptions of the clinical presentation (2, 3, 5–7, 13–16, 18, 21, 22, 24–27, 29, 31, 33–36, 38–43, 45–47, 49–52, 54, 58, 61–65, 67–69, 77, 79, 80, 82, 84, 87, 90). Many additional cases are described within case series in which signs and symptoms specific to each case are not detailed (3, 54, 65, 69, 88). The 65 detailed cases were reported from 1938 to 2005 and primarily come from the United States,

although the United Kingdom, Europe, Canada, Australia, and Nigeria are also represented. The patient ages range from 2 months to 87 years. Fifty (77%) of the rat bite patients described were male. Twenty-six (40%) of the exposures occurred from a wild rat, 8 (12%) were from a laboratory rat, and 3 (5%) were from a pet shop rat. Twenty-two (34%) of the patients described a nonbite or nonrat exposure. The remaining cases occurred in association with bites from a ferret (one), mouse (one), squirrel (two), gerbil (one), and dog (one).

Clinical findings. Symptoms described include fever (92%), rash (61%), polyarthralgias (66%), myalgias (29%), nausea and vomiting (40%), headache (34%), and sore throat (17%). The mean temperature achieved during the cases was 39.4°C. Patients' laboratory values reveal an average white blood cell count of 12,200 per cubic millimeter, with a polymorphonuclear cell and band form predominance. Only five patients demonstrated white blood cell counts higher than 15,000 per cubic millimeter. More significantly, the average erythrocyte sedimentation rate was 69 mm per hour. Only four patients had erythrocyte sedimentation rates below 15 mm per hour; these patients all had laboratory values obtained either very late in their clinical course or after recovery. Seven (10.8%) of the patients died, consistent with the published average mortality rate of 10%.

Complications

Published complications of rat bite fever include endocarditis, myocarditis, pericarditis, systemic vasculitis, polyarteritis nodosa, meningitis, hepatitis, nephritis, amnionitis, pneumonia, and focal abscesses (14, 24, 35, 54, 62, 78, 79, 83). Of these, endocarditis is the best described and carries the highest mortality rate (64). Seventeen patients with endocarditis associated with *S. moniliformis* infection have been described (14, 50, 58, 64, 68). A 1992 review of 16 of these patients (68) revealed that 8 of them had valvular disease prior to the onset of endocarditis, most commonly rheumatic heart disease. Most cases were defined by multiple positive blood cultures and had typical symptoms of rat bite fever accompanied by murmur (100%), petechiae (13%), Osler's nodes (13%), hepatosplenomegaly (33%), anemia (33%), and cardiac dysrhythmia (13%). Echocardiography was performed for four patients and demonstrated valvular vegetations in only two patients. The reported mortality rate associated with *S. moniliformis* endocarditis is 53% (68), and death may occur from 2 weeks to 3 years after symptom onset (58). However, a majority of these deaths occurred in the absence of effective antimicrobial therapy (14).

Differential Diagnoses

Diseases. The differential diagnosis of symptoms typical of rat bite fever (fever, rash, polyarthralgias) is extensive (27, 54, 63, 78). Possible bacterial causes include sepsis from such bacteria as *Streptococcus pyogenes* and *Staphylococcus aureus*, disseminated gonorrhea, meningococcemia, *Streptococcus pyogenes*-associated diseases (scarlet fever, rheumatic fever, post-streptococcal reactive arthritis), Lyme disease, ehrlichiosis, and brucellosis. Rickettsial infections, especially Rocky Mountain spotted fever, must be considered in areas where such infections are endemic. Such spirochetal infections as leptospi-

rosis and secondary syphilis are also possible. It is of note that up to 50% of rat bite fever patients have a falsely positive Venereal Disease Research Laboratory (VDRL) test; however, a negative treponemal test can be used to rule out syphilis. Many potential viral causes exist, although Epstein-Barr virus, parvovirus B19, and coxsackieviruses are especially prominent. Relapsing fevers may suggest *Borrelia recurrentis*, malaria, and typhoid fever. Noninfectious causes include collagen vascular diseases and drug reactions.

Sodoku. Infection caused by rat bites in Asia is likely to be caused by *Spirillum minus* and is designated sodoku (*so*, rat; *doku*, poison). This entity differs from rat bite fever not only in geographic distribution but also clinically. After an incubation period of approximately 14 to 18 days, the bite site becomes indurated and may ulcerate, with associated regional lymphadenopathy. Fevers have regular relapses separated by afebrile periods lasting 3 to 7 days. Approximately 50% of patients develop a violaceous red-brown macular rash which occasionally has plaques or urticarial lesions. Joint manifestations are rare (1, 27).

Haverhill Fever

Haverhill fever refers to an outbreak of epidemic disease resulting from *S. moniliformis*-contaminated milk. The first reports were from a 1926 outbreak in Haverhill, MA, and described an illness termed erythema arthriticum epidemicum caused by an organism named *Haverhillia multiformis* (55, 60). This organism was later shown to be identical to *S. moniliformis* (10). Patients with Haverhill fever develop signs and symptoms identical to those of rat bite fever. However, the absence of rat exposure and the presence of a large number of patients with common temporal and geographic exposure should suggest Haverhill fever.

U.S. experience. Although Haverhill fever is named for the site of the first published description of epidemic *S. moniliformis*-associated disease, an earlier outbreak likely occurred in 1925 in Chester, PA (60). In this episode, approximately 400 cases occurred with striking similarity of onset, symptoms, course, and epidemiologic relation to a milk supply. The following year, 86 cases developed over a 4-week period in Haverhill, a small manufacturing city. These cases were investigated by Place and Sutton (60), and the organism responsible was described by Parker and Hudson (55). The ages of the patients ranged from 8 months to 54 years, and 41% were male. The patients came from 39 families, representing 231 people and an attack rate of 36%. The milk supply in every case came from one dairy, either directly or through four stores selling the dairy's milk products. The milk from the dairy was not pasteurized. Although no cultures from the milk demonstrated *S. moniliformis*, pasteurization of the milk products was associated with the end of the outbreak.

The onset of symptoms in the 1926 outbreak was acute and associated with sudden development of rigors, emesis, or severe headache. Initial symptoms resolved after 3 to 4 days and included fever (97%), vomiting (62%), headache (56%), chills (55%), dizziness (16%), and irritability (8%). However, fever recurred 2 to 3 days later and was associated with the onset of polyarthralgias and polyarthritis. Rash appeared from the first to the fifth day of disease, was most marked at the distal

extremities, and was mostly "rubelliform" in nature. The rash progressed over 3 days to include hemorrhagic lesions and lasted an average of 6 days. Polyarthritides was the most persistent symptom, lasting from 1 week to several months and severely limiting activity and weight bearing. Wrists and elbows were most frequently involved, followed, in order, by knees, shoulders, fingers, and ankles. Associated laboratory findings demonstrated an average white blood cell count of 11,500 per cubic millimeter, with 70% polymorphonuclear cells. Blood cultures in 11 of 17 cases and joint fluid aspirate cultures in 2 of 2 cases demonstrated an organism subsequently named *Haverhillia multiformis*, with characteristics identical to *S. moniliformis*. Outcomes were uniformly excellent, with no deaths and few permanent sequelae. Several patients, however, experienced chronic, recurring arthralgias.

United Kingdom experience. A second reported outbreak of Haverhill fever occurred in 1983 in 208 children at a boarding school in Chelmsford, Essex, United Kingdom (59). In a description of four cases from this outbreak (74), the clinical features were described as abrupt onset of fever with headache, peripheral erythematous rash, polyarthralgias, and subsequent sore throat. Initial diagnoses included viral illness (especially coxsackievirus), meningococcal septicemia, and erythema multiforme. The point source of the outbreak appeared to be raw milk, ingested by many students at the school. Students developed symptoms at school and were sent home to recover from an apparent viral epidemic, thus explaining the subsequent appearance of cases in London, Leeds, and Nottingham. Blood cultures from the four described patients demonstrated *S. moniliformis*, and the information was provided to health care workers caring for other students to assist with diagnosis and management.

DIAGNOSIS

Culture

Growth characteristics are discussed separately (see "Biology," above).

Fatty Acid Profiles

Fatty acid profiles obtained by gas-liquid chromatography, together with characteristic growth, can be used for rapid identification of *S. moniliformis*. The major cellular fatty acid peaks are tetradecanoic acid (14:0), palmitic acid (16:0), octadecanoic acid with linoleic acid (18:2) and oleic acid (18:1), and stearic acid (18:0) (66, 69). High-resolution polyacrylamide gel electrophoresis in conjunction with computer analysis has also been used to distinguish and confirm strains of *S. moniliformis* (19).

Other Methods

Serologic assays and slide hemagglutination tests, although used historically (12, 55, 70) and in some animal research (10, 91), are currently not available for use with humans. Although these assays are sufficiently sensitive, the increasing demand for rapid, more-sensitive tests likely has detracted from their utility. Molecular methods such as PCR show promise and have been used successfully with humans and laboratory ani-

mals (4, 7, 11, 43, 85). A PCR assay specific for *S. moniliformis* has been described by Boot et al. (11); it uses primers designed on the basis of 16S rRNA gene base sequence data of human and rodent strains of *S. moniliformis* (forward primer, 5' GCT TAA CAC ATG CAA ATC TAT 3'; reverse primer, 5' AGT AAG GGC CGT ATC TCA 3'). These primers showed 100% complementarity to *S. moniliformis* ATCC 14674^T and *S. moniliformis* ANL 370-1. The PCR assay generated a 296-bp product which, when discriminated by BfaI restriction enzyme treatment, generated three fragments (128, 92, and 76 bp) specific to *S. moniliformis*. This assay has been used by others to examine both human- and animal-derived specimens and has been found to distinguish *S. moniliformis* from other organisms with great accuracy (4, 11, 85). However, until such an assay becomes more readily available, a diagnosis of *S. moniliformis*-associated rat bite fever requires a high clinical index of suspicion coupled with the appropriate use of culture and attention to ruling out alternate diagnoses.

TREATMENT

Penicillin is the treatment of choice for proven or highly suspected cases of rat bite fever. Tests of *S. moniliformis* antibiotic susceptibility by the disk diffusion method usually demonstrate sensitivity to penicillins, cephalosporins, carbapenems, aztreonam, clindamycin, erythromycin, nitrofurantoin, bacitracin, tetracycline, teicoplanin, and vancomycin; intermediate susceptibility to aminoglycosides, fluoroquinolones, and chloramphenicol; and resistance to trimethoprim-sulfamethoxazole, polymyxin B, and nalidixic acid (69, 91). Antibiotic susceptibility tests performed by broth microdilution usually demonstrate the following MICs: penicillin, <0.03 µg/ml; cephalothin, <0.03 µg/ml; ceftriaxone, <0.03 µg/ml; vancomycin, 0.5 µg/ml; tetracycline, 0.25 µg/ml; erythromycin, 2 µg/ml; streptomycin, 8 µg/ml; and gentamicin, 1 µg/ml (68). Only one penicillin-resistant *S. moniliformis* strain has been demonstrated (81), and that was over 50 years ago.

Adults with rat bite fever should receive 400,000 to 600,000 IU/day (240 to 360 mg) of intravenous penicillin G for at least 7 days, but this dose should be increased to 1.2 million IU/day (720 mg) if no response is seen within 2 days (65). Children should receive 20,000 to 50,000 IU/kg of body weight/day (12 to 30 mg/kg/day) of intravenous penicillin G for 5 to 7 days, followed by 7 days of oral penicillin V, 25 to 50 mg/kg/day (maximum, 3 g/day) divided four times per day (27, 73). For penicillin-allergic patients, both streptomycin and tetracycline appear to be effective (61, 68), but erythromycin use has been associated with treatment failures (35). Cephalosporins have also been used successfully (16, 20) and may be considered if cross-allergenicity with penicillin is felt to be unlikely. Other antimicrobials may be considered, based on the in vitro susceptibility data presented above, but no published evaluations of their effectiveness exist.

Patients with *S. moniliformis* endocarditis require dual therapy with high-dose penicillin G in combination with streptomycin or gentamicin (50). The currently recommended dose for adults is 4.8 million IU/day (4.8 g) of intramuscular procaine penicillin G if the isolate is susceptible to 0.1 µg/ml. If the isolate is more resistant, 20 million IU/day (12 g) of intravenous penicillin G should be used (65, 68) for adults. Children should receive 160,000 to 240,000 IU/kg/day (96 to 144 mg/kg/

day), up to the adult maximum of 20 million IU/day (12 g) (68, 73). Successful treatment of adults with a 4-week regimen has been demonstrated (50). The appropriate treatment length for children is not known, although 6-week regimens generally are considered effective for other causes of bacterial endocarditis. The use of streptomycin appears to enhance activity against the cell wall-deficient L forms of *S. moniliformis* (68); one might anticipate that other aminoglycosides would provide the same benefit.

CONCLUSIONS

Rat bite fever, caused by *S. moniliformis*, is an under-recognized and under-reported disease characterized by abrupt onset of fever, rigors, and migratory polyarthralgias; it carries a mortality rate of approximately 10%. Although *S. moniliformis* is exquisitely susceptible to penicillin, most patients experience treatment delays due to the nonspecific nature of the clinical features, a broad differential diagnosis list, and difficulties in culture diagnosis. However, the changing epidemiology of rodent exposure, together with the risk of severe, invasive disease if left untreated, suggests that rat bite fever and *S. moniliformis* should occupy a more prominent place in our diagnostic thinking.

REFERENCES

- Adams, J. M., and C. M. Carpenter. 1955. Rat-bite fevers. *Pediatr. Clin. N. Am.* **6**:101–108.
- Anderson, D., and T. J. Marrie. 1987. Septic arthritis due to *Streptobacillus moniliformis*. *Arthritis Rheum.* **30**:229–230.
- Anderson, L. C., S. L. Leary, and P. J. Manning. 1983. Rat-bite fever in animal research laboratory personnel. *Lab. Anim. Sci.* **33**:292–294.
- Andre, J.-M., A. M. Freydiere, Y. Benito, A. Rousson, S. Lansiaux, A. Kodjo, C. Mazzocchi, J.-C. Berthier, F. Vandenesch, and D. Floret. 2005. Rat bite fever caused by *Streptobacillus moniliformis* in a child: human infection and rat carriage diagnosed by PCR. *J. Clin. Pathol.* **58**:1215–1216.
- Arkless, H. A. 1970. Rat-bite fever at Albert Einstein Medical Center. *Pa. Med.* **73**:49.
- Azimi, P. 1990. Pets can be dangerous. *Pediatr. Infect. Dis. J.* **9**:670–684.
- Berger, C., M. Altwegg, A. Meyer, and D. Nadal. 2001. Broad range polymerase chain reaction for diagnosis of rat-bite fever caused by *Streptobacillus moniliformis*. *Pediatr. Infect. Dis. J.* **20**:1181–1182.
- Bhatt, K. M., and N. B. Mirza. 1992. Rat bite fever: a case report of a Kenyan. *East Afr. Med. J.* **69**:542–543.
- Blake, F. G. 1916. The etiology of ratbite fever. *J. Exp. Med.* **23**:39–60.
- Boot, R., R. H. Bakker, S. H. Thuis, J. L. Veenema, and H. DeHoog. 1993. An enzyme-linked immunosorbent assay (ELISA) for monitoring rodent colonies for *Streptobacillus moniliformis* antibodies. *Lab. Anim.* **27**:350–357.
- Boot, R., A. Oosterhuis, and S. H. Thuis. 2002. PCR for the detection of *Streptobacillus moniliformis*. *Lab. Anim.* **36**:200–208.
- Brown, T. M., and J. C. Nununemaker. 1942. Rat-bite fever: a review of the American cases with reevaluation of etiology; report of cases. *Bull. Johns Hopkins Hosp.* **70**:201–236.
- Burke, W. A., O. Kwong, and T. Halper. 1959. Ratbite fever due to *Streptobacillus moniliformis*: a report of two cases. *Calif. Med.* **91**:356–358.
- Carbeck, R. B., J. F. Murphy, and E. M. Britt. 1967. Streptobacillary rat-bite fever with massive pericardial effusion. *JAMA* **201**:703–704.
- Centers for Disease Control and Prevention. 2005. Fatal rat-bite fever—Florida and Washington. *Morb. Mortal. Wkly. Rep.* **53**(SS):1198–1202.
- Centers for Disease Control and Prevention. 1998. Rat-bite fever—New Mexico. *Morb. Mortal. Wkly. Rep.* **47**(SS):89–91.
- Cohen, R. L., R. G. Wittler, and J. E. Faber. 1968. Modified biochemical tests for characterization of L-phase variants of bacteria. *Appl. Microbiol.* **16**:1655–1662.
- Cole, J. S., R. W. Stoll, and R. J. Bulger. 1969. Rat-bite fever. Report of three cases. *Ann. Intern. Med.* **71**:979–981.
- Costas, M., and R. J. Owen. 1987. Numerical analysis of electrophoretic protein patterns of *Streptobacillus moniliformis* strains from human, murine, and avian infections. *J. Med. Microbiol.* **23**:303–311.
- Cunningham, B. B., A. S. Paller, and B. Z. Katz. 1998. Rat bite fever in a pet lover. *J. Am. Acad. Dermatol.* **38**:330–332.
- Dijkmans, B. A., R. T. Thomeer, G. J. Vielvoye, A. S. Lampe, and H. Mattie. 1984. Brain abscess due to *Streptobacillus moniliformis* and *Actinobacterium meyerii*. *Infection* **12**:262–264.
- Downing, N. D., G. D. Dewnany, and P. J. Radford. 2001. A rare and serious consequence of a rat bite. *Ann. R. Coll. Surg. Engl.* **83**:279–280.
- Etscorn, F., and D. D. Blodgett. 1987. Rat-bite fever in the animal laboratory: a precautionary note. *Psychobiology* **15**:345–346.
- Faro, S., C. Walker, and R. L. Pierson. 1980. Amnionitis with intact amniotic membranes involving *Streptobacillus moniliformis*. *Obstet. Gynecol.* **55**:9S–11S.
- Fordham, J. N., E. McKay-Ferguson, A. Davies, and T. Blyth. 1992. Rat bite fever without the bite. *Ann. Rheum. Dis.* **51**:411–412.
- Frank, W. P., and A. G. Bower. 1951. Rat bite fever—response to streptomycin therapy. *Calif. Med.* **74**:42.
- Freels, L. K., and S. P. Elliott. 2004. Rat bite fever: three case reports and a literature review. *Clin. Pediatr.* **43**:291–295.
- Freundt, E. A. 1956. Experimental investigations into the pathogenicity of the L-phase variant of *Streptobacillus moniliformis*. *Acta Pathol. Microbiol. Scand.* **38**:246–258.
- Gilbert, G. L., J. F. Cassidy, and N. M. Bennett. 1971. Rat-bite fever. *Med. J. Aust.* **2**:1131–1134.
- Glaser, C., P. Lewis, and S. Wong. 2000. Pet-, animal-, and vector-borne infections. *Pediatr. Rev.* **21**:219–232.
- Gordon, I. J., and E. S. Jones. 1999. I smell a rat. *Hosp. Med.* **60**:682–683.
- Graves, M. H., and M. M. Janda. 2001. Rat-bite fever (*Streptobacillus moniliformis*): a potential emerging disease. *Int. J. Infect. Dis.* **5**:151.
- Gray, H. H. 1967. Squirrel bite fever. *Trans. R. Soc. Trop. Med. Hyg.* **61**:857.
- Griffith, R. L., and D. W. McNaughton. 1953. Report of a case of rat-bite fever due to *S. moniliformis*. *Public Health Rep.* **68**:947–948.
- Hagelskjaer, L., I. Sorensen, and E. Randers. 1998. *Streptobacillus moniliformis* infection: two cases and a literature review. *Scand. J. Infect. Dis.* **30**:309–311.
- Hambridge, S. J., and J. W. Ogle. 2001. Index of suspicion, case 1. Diagnosis: rat-bite fever. *Pediatr. Rev.* **22**:95–103.
- Hirschhorn, R., and R. Hodge. 1999. Identification of risk factors in rat bite incidents involving humans. *Pediatrics* **104**:e35.
- Hockman, D. E., C. D. Pence, R. R. Whittler, and L. E. Smith. 2000. Septic arthritis of the hip secondary to RBF. *Clin. Orthop. Relat. Res.* **380**:173–176.
- Holden, F. A., and J. C. Mackay. 1964. Rat-bite fever—an occupational hazard. *Can. Med. Assoc. J.* **91**:78–81.
- Holroyd, K. J., A. P. Reiner, and J. D. Dick. 1988. *Streptobacillus moniliformis* polyarthritits mimicking rheumatoid arthritis: an urban case of rat bite fever. *Am. J. Med.* **85**:711–714.
- Homagren, E. B., and G. Tunevall. 1970. Rat-bite fever. *Scand. J. Infect. Dis.* **2**:71–74.
- Hudsmith, L., V. Weston, J. Szram, and S. Allison. 2001. Clinical picture, rat bite fever. *Lancet Infect. Dis.* **1**:91.
- Kadan, D., D. Chih, A. Brett, and M. Segasothy. 2002. A case of rat-bite fever. *Intern. Med. J.* **32**:193–194.
- Kirchner, B. K., S. G. Lake, and S. R. Wightman. 1992. Isolation of *Streptobacillus moniliformis* from a guinea pig with granulomatous pneumonia. *Lab. Anim. Sci.* **42**:519–521.
- Konstantopoulos, K., P. Skarpas, F. Hitjazis, D. Georgakopoulos, Y. Matrangas, M. Anderopoulos, and E. Koutras. 1992. Rat bite fever in a Greek child. *Scand. J. Infect. Dis.* **24**:531–533.
- Lambe, D. W., A. M. McPhedran, J. A. Mertz, and P. Stewart. 1973. *Streptobacillus moniliformis* isolated from a case of Haverhill fever: biochemical characterization and inhibitory effect of sodium polyanethol sulfonate. *Am. J. Clin. Pathol.* **60**:854–860.
- Legout, L., E. Senneville, D. Mulleman, E. Solau-Gervais, R. M. Flipo, and Y. Mouton. 2005. Rat bite fever mimicking rheumatoid arthritis. *Scand. J. Infect. Dis.* **37**:532–533.
- Levaditi, C., S. Nicolau, and P. Poincloux. 1925. Sur le role etologique de *Streptobacillus moniliformis* (nov. spec.) dans l'erytheme polymorphe aigu septique. *C. R. Acad. Sci.* **180**:1188.
- Mandel, D. R. 1985. Streptobacillary fever: an unusual cause of infectious arthritis. *Cleveland. Clin. Q.* **52**:203–205.
- McCormack, R. C., D. Kaye, and E. W. Hook. 1967. Endocarditis due to *Streptobacillus moniliformis*. *JAMA* **200**:77–79.
- McGill, R. C., A. M. Martin, and P. N. Edmunds. 1966. Rat-bite fever due to *Streptobacillus moniliformis*. *Br. Med. J.* **54**:97:1213–1214.
- McHugh, T. P., R. L. Bartlett, and J. I. Raymond. 1985. Rat bite fever: report of a fatal case. *Ann. Emerg. Med.* **14**:1116–1118.
- Oestreich, A. E. 2004. The acrophysis: a unifying concept for understanding enchondral bone growth and its disorders. II. Abnormal growth. *Skeletal Radiol.* **33**:119–128.
- Ojukwu, I. C., and C. Christy. 2002. Rat-bite fever in children: case report and review. *Scand. J. Infect. Dis.* **34**:474–477.
- Parker, F., and N. P. Hudson. 1926. The etiology of Haverhill fever (erythema arthriticum epidemicum). *Am. J. Pathol.* **2**:357.
- Peagle, R. D., R. P. Tewari, W. N. Bernhard, and E. Peters. 1976. Microbial flora of the larynx, trachea and large intestine of the rat after long-term inhalation of 100 per cent oxygen. *Anesthesiology* **44**:287–290.

57. **Peel, M. M.** 1993. Dog-associated bacterial infections in humans: isolates submitted to an Australian reference laboratory, 1981–1992. *Pathology* **25**: 379–384.
58. **Petersen, E. S., N. B. McCullough, C. W. Eisele, and J. M. Goldinger.** 1950. Subacute bacterial endocarditis due to *Streptobacillus moniliformis*. *JAMA* **144**:621–622.
59. **Pilsworth, R.** 1983. Haverhill fever. *Lancet* **ii**:336–337.
60. **Place, E. H., and L. E. Sutton.** 1934. Erythema arthriticum epidemicum (Haverhill fever). *Arch. Intern. Med.* **54**:659–684.
61. **Portnoy, B. L., T. K. Satterwhite, and J. D. Dyckman.** 1979. Rat bite fever misdiagnosed as Rocky Mountain spotted fever. *South. Med. J.* **72**:607–609.
62. **Prouty, M., and E. L. Schafer.** 1950. Periarthritis nodosa associated with ratbite fever due to *Streptobacillus moniliformis* (erythema arthriticum epidemicum). *J. Pediatr.* **36**:605–613.
63. **Raffin, B., and M. Freemark.** 1979. Streptobacillary ratbite fever: a pediatric problem. *Pediatrics* **64**:214–217.
64. **Rordorf, T., C. Zuger, R. Zbinden, A. von Graevenitz, and M. Pirovino.** 2000. *Streptobacillus moniliformis* endocarditis in an HIV-positive patient. *Infection* **28**:393–394.
65. **Roughgarden, J. W.** 1965. Antimicrobial therapy of ratbite fever. *Arch. Intern. Med.* **116**:39–53.
66. **Rowbotham, T. J.** 1983. Rapid identification of *Streptobacillus moniliformis*. *Lancet* **ii**:567.
67. **Rumley, R. L., N. A. Patrone, and L. White.** 1987. Rat-bite fever as a cause of septic arthritis: a diagnostic dilemma. *Ann. Rheum. Dis.* **35**:793–795.
68. **Rupp, M. E.** 1992. *Streptobacillus moniliformis* endocarditis: case report and review. *Clin. Infect. Dis.* **14**:769–772.
69. **Rygg, M., and C. F. Bruun.** 1992. Rat bite fever (*Streptobacillus moniliformis*) with septicemia in a child. *Scand. J. Infect. Dis.* **24**:535–540.
70. **Savage, N. L., G. N. Joiner, and D. W. Florey.** 1981. Clinical, microbiological, and histological manifestations of *Streptobacillus moniliformis*-induced arthritis in mice. *Infect. Immun.* **34**:605–609.
71. **Schottmüller, H.** 1914. Zur Ätiologie und Klinik der Bisskrankheit (Ratten-, Katzen-, Eichhornchen-Bisskrankheit). *Dermatol. Wochenschr. Ergänzungsh.* **58**:77.
72. **Sens, M. A., E. W. Brown, L. R. Wilson, and T. P. Crocker.** 1989. Fatal *Streptobacillus moniliformis* infection in a two month old infant. *Am. J. Clin. Pathol.* **91**:612–616.
73. **Shackelford, P.** 1993. Rat-bite fever, p. 235. In S. Kaplan (ed.), *Current therapy in pediatric infectious disease*. Mosby-Year Book, St. Louis, MO.
74. **Shanson, D. C., J. Midgley, B. G. Gazzard, and J. Dixey.** 1983. *Streptobacillus moniliformis* isolated from blood in four cases of Haverhill fever—first outbreak in Britain. *Lancet* **ii**:92–94.
75. **Shanson, D. C., J. Pratt, and P. Greene.** 1985. Comparison of media with and without “panmede” for the isolation of *Streptobacillus moniliformis* from blood cultures and observations of the inhibitory effect of sodium polyanethol sulphonate. *J. Med. Microbiol.* **19**:181–186.
76. **Shvartsblat, S., M. Kochie, P. Harber, and J. Howard.** 2004. Fatal rat bite fever in a pet shop employee. *Am. J. Industr. Med.* **45**:357–360.
77. **Stehle, P., O. Dubuis, A. So, and J. Dudler.** 2003. Rat bite fever without fever. *Ann. Rheum. Dis.* **62**:894–896.
78. **Taber, L. H., and R. D. Feigin.** 1979. Spirochetal infections. *Pediatr. Clin. N. Am.* **26**:377–413.
79. **Tattersall, R. S., and J. T. Bourne.** 2003. Systemic vasculitis following an unreported rat bite. *Ann. Rheum. Dis.* **62**:605–606.
80. **Thong, B. Y., and T. M. Barkham.** 2003. Suppurative polyarthritis following a rat bite. *Ann. Rheum. Dis.* **62**:805–806.
81. **Toren, D. A.** 1953. Mycotic ratbite fever: report of case. *Del. Med. J.* **25**:334.
82. **Torres, L., A. I. Lopez, S. Escobar, C. Marne, M. L. Marco, M. Perez, and J. Verhaegen.** 2003. Bacteremia by *Streptobacillus moniliformis*: first case described in Spain. *Eur. J. Clin. Microbiol. Infect. Dis.* **22**:258–260.
83. **Valverde, C. R., L. J. Lowenstine, C. E. Young, R. P. Tarara, and J. A. Roberts.** 2002. Spontaneous rat bite fever in non-human primates: a review of two cases. *J. Med. Primatol.* **31**:345–349.
84. **Vasseur, E., P. Joly, M. Nouvellon, A. Laplagne, and P. Lauret.** 1993. Cutaneous abscess: a rare complication of *Streptobacillus moniliformis* infection. *Br. J. Dermatol.* **129**:95–96.
85. **Wallet, F., C. Savage, C. Loiez, E. Renaux, P. Pischedda, and R. J. Courcol.** 2003. Molecular diagnosis of arthritis due to *Streptobacillus moniliformis*. *Diagn. Microbiol. Infect. Dis.* **47**:623–624.
86. **Washburn, R. G.** 2005. *Spirillum minus* (rat-bite fever), p. 2810. In G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), *Principles and practice of infectious diseases*, 6th ed. Elsevier Churchill Livingstone, Philadelphia, PA.
87. **Waterson, A. P., and J. Wedgwood.** 1953. Ratbite fever: report of a case due to *Actinomyces muris*. *Lancet* **i**:472–473.
88. **Watkins, C. G.** 1946. Ratbite fever. *J. Pediatr.* **28**:429–448.
89. **Wilcox, W.** 1839. Violent symptoms from bite of rat. *Am. J. Med. Sci.* **26**:245.
90. **Wilkens, E. G. L., J. G. B. Millar, P. M. Cockcroft, and O. A. Okubadejo.** 1988. Rat-bite fever in a gerbil breeder. *J. Infect.* **16**:177–180.
91. **Wullenweber, M.** 1995. *Streptobacillus moniliformis*—a zoonotic pathogen. Taxonomic considerations, host species, diagnosis, therapy, geographical distribution. *Lab. Anim.* **29**:1–15.