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Tick-borne Relapsing Fever in the Pacific Northwest: An Underdiagnosed Illness?

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Some 30 cases of tick-borne relapsing fever due to Borrelia *are known to have occurred between 1965 and 1978 in the Pacific Northwest. This disease was found more frequently in young men with a history of wilderness exposure during the summer months. Recurrent fever was the most common symptom with temperatures reaching higher than 39.5°C (103.1°F) in all cases, and many patients had three or more febrile episodes. Splenomegaly was the second most common finding reported. Diagnosis of relapsing fever was made in 20 cases by identifying spirochetes on peripheral blood smears. In ten remaining cases the diagnosis was made on clinical and epidemiologic grounds.*

Information regarding therapy was available in 21 cases. Ten patients received a tetracycline drug and all had a prompt response without relapse. Two of the patients died, a 68-year-old woman with possible myocardial involvement and a newborn infant with infection acquired in utero and meningeal involvement.

The diagnosis was often delayed in spite of outpatient evaluation and admittance to hospital, probably because borreliosis was not considered in the differential diagnosis. Because tick-borne relapsing fever is eventually a self-limited disease in most patients, it is probably not recognized often enough. Awareness of this disease and examination of the peripheral blood smear for spirochetes will lead to earlier diagnosis. Prompt initiation of tetracycline therapy should reduce morbidity associated with borreliosis.

RELAPSING FEVER due to *Borrelia* is one of several acute febrile illnesses commonly included in textbook differential diagnoses, but rarely considered in clinical situations. For this reason, many cases are probably missed each year, particularly in the western United States.

Investigation of a recent case of this disease led to the detection of several more related cases. Further research uncovered 26 unpublished cases plus three previously described cases, supporting the authors' suspicion that relapsing fever is not recognized with sufficient frequency.[1,2]

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This paper presents an index case, a report of an additional case and features of another 28 cases, as well as a review of the literature. Because the diagnosis of relapsing fever can be made by simple examination of the peripheral blood smear, greater familiarity with its characteristics and an appropriate index of suspicion of its presence should result in earlier and more frequent diagnosis.

Patients and Methods

This report is based on data obtained from the Public Health Departments in Oregon and Washington and a hospital located in the area where the index patient became infected. Clinical data available in health department records were meager in several cases. Therefore, no quantitative estimate of the frequencies of signs and symptoms could be made.

Cases described in this report are classified as definite, if spirochetes were found on smears of peripheral blood (20 of 30 cases); or probable, if patients had an unexplained recurrent febrile illness that coincided in time and place with a case of relapsing fever confirmed by findings on blood smears (10 of 30 cases). These cases were seen from 1965 to 1978 and do not include an outbreak of 11 cases in eastern Washington reported recently.[3] Included in this series, however, are three previously published cases of patients: a newborn infant with in utero acquisition of meningeal infection, the infant's mother[1] and a 25-year-old college student.[2]

Analysis of 30 Cases

Epidemiology

The disease typically occurred in patients younger than 40 years old (83 percent), with a mean age of 24.6 years. Of the patients, 63 percent were male. All cases occurred in persons who had been in wooded, high, arid regions of Oregon, Washington or Idaho; two thirds occurred in Deschutes County which lies on the eastern face of the Cascade Mountains in Oregon. Most cases of the disease developed during the months of May to September (Figure 1) and 60 percent occurred between 1976 and 1978.

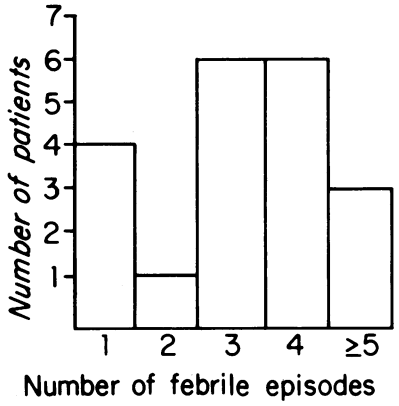

Figure 2.—Number of febrile episodes experienced per patient.

Clinical Presentation

Although the clinical data available for each patient varied considerably, a composite of recorded symptoms accurately reflects a characteristic clinical presentation. Recurrent fever, the most common symptom, occurred in all but four patients in whom a diagnosis was made and treatment begun during the first fever cycle (Figure 2). The temperature was higher than 39.5°C (103.1°F) in all cases. The onset of fever was acute and dramatic as was its resolution. Of the 20 patients in whom descriptions of fever patterns

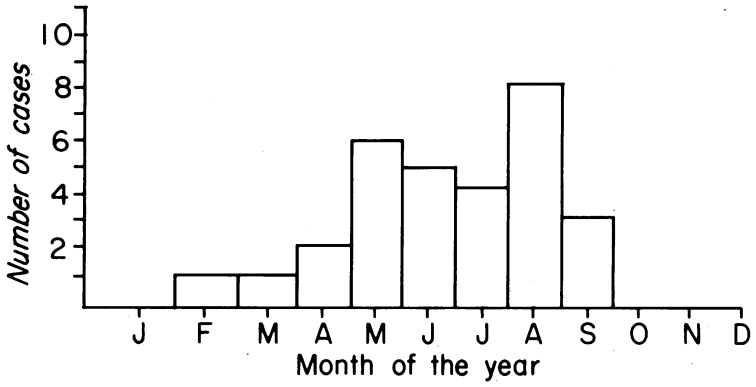

Figure 1.—Occurrence of 30 cases of relapsing fever by month of the year.

were available, 15 had three or more febrile episodes. The four persons whose conditions were diagnosed and treated during the first episode of fever included the index patient described below, an infant born to an infected mother, a 25-year-old man admitted to Duke University Medical Center whose peripheral blood smear was being evaluated for malarial parasites when spirochetes were noted, and a 27-year-old man from Deschutes County whose blood showed the heaviest spirochetemia seen in that region (one or more spirochetes per oil-immersion field). At least three patients with fever were admitted to hospitals and discharged without a diagnosis before borreliosis was recognized during a subsequent febrile period. Many had seen physicians as outpatients one or more times before a correct diagnosis was made. Ten cases were diagnosed retrospectively on clinical and epidemiologic grounds.

Other symptoms mentioned frequently were chills, sweating, malaise, anorexia, myalgia, cough and headache. After fever, splenomegaly was the most commonly recorded physical sign.

Diagnosis

The diagnosis was confirmed by detection of spirochetes in peripheral blood smears in 20 cases (Figure 2). Nine cases (30 percent) of relapsing fever showed no connection with any associated cases. However, it was shown that 7 definite cases were directly associated with 14 coincident cases. The 14 cases had been recognized because of their connections with the 7 "primary" cases, and at least 7 of these 14 patients had already consulted a physician before the correct diagnosis was made.

Response to Therapy

Information regarding therapy was available in 21 cases. Ten patients treated with tetracycline or a tetracycline derivative had prompt response to therapy. Five patients were given penicillin. One of the latter patients had a relapse, but subsequently responded to tetracycline. Both of the patients who died had been treated with penicillin and a second drug—the 68-year-old woman (case 2) had been given penicillin and kanamycin and a newborn infant had received penicillin and chloramphenicol. Four patients had Jarisch-Herxheimer reactions. At least seven patients received no therapy but had a gradual resolution of symptoms.

Reports of Cases

CASE 1. A 30-year-old man employed by the US Forest Service came to the University of Washington Hospital emergency department following two days of spiking temperatures to 40°C (104.0°F), shaking chills and progressive weakness, malaise and myalgias. He had been staying in a cabin in Bull Prairie, Oregon, where another person (a patient included in this report)had become ill three weeks earlier. The other patient had been admitted to hospital in a nearby town. We called the hospital and were told that the patient in question had been diagnosed as having relapsing fever. Our patient was unaware of any recent tick bites.

On physical examination, the patient's temperature was 39.6°C (103.3°F) and an erythematous, papular rash and several ecchymoses were noted. Bruising was easily induced and a Rumpel-Leede test was positive. The neck was supple. An examination of the heart and lungs showed no abnormalities. The abdomen was obese with hypoactive bowel tones and a hepatic span of 10 cm. Results of a neurological examination were within normal limits.

Analysis of urine showed proteinuria (2+) and two to eight erythrocytes per high-powered field; otherwise, findings were normal. The hematocrit, leukocyte count and differential were within normal limits. Platelet count was 98,000 per cu mm. The total bilirubin was 3.2 mg per dl, alkaline phosphatase 65 units per liter (normal 20 to 105 units per liter) and serum aspartate aminotransferase transaminase (formerly serum glutamic oxaloacetic transaminase, SGOT) 144 units per liter (normal <25 units per liter). A Wright-stained smear of peripheral blood was positive for spirochetes (Figure 3).

A study of coagulation times gave these results: the prothrombin time was 15 seconds with a control of 12.5 seconds and 54 percent activity. Partial thromboplastin time was 57 seconds with a control of 39 seconds; a 1:1 mix with normal serum corrected the patient's time to 45 seconds. Thrombin time was 27 seconds with a control of 19. Fibrinogen was 326 mg per dl and fibrin degradation products were more than 10 but less than 40 μg per ml.

The patient was treated with 500 mg of tetracycline given orally every six hours. Defervescence occurred within 24 hours with rapid resolution of the other symptoms. Serial measurements of co-

agulation times showed progressive improvement and values obtained 36 hours after admission had returned to normal. Thrombocytopenia persisted, however, and the platelet count at the time of discharge on the third hospital day was 78,000 per cu mm.

CASE 2. A 68-year-old woman was admitted to an Oregon community hospital on August 19, 1968, with complaints of fever, chills, shortness of breath and chest pain. Several days earlier the patient had been fishing on a nearby river and claimed to have been "bitten by chiggers." Subsequently, there was an abrupt onset of dyspnea, orthopnea, nonproductive cough and pleuritic chest pain of the left anterior quadrant. She had no known history of any cardiopulmonary disorder. The patient was first seen by a local physician and then admitted to hospital with a preliminary diagnosis of congestive heart failure secondary to acute viral myocarditis.

On initial examination, the temperature was 39.0°C (102.2°F), heart rate 108 beats per minute and blood pressure 94/50 mm of mercury. She appeared acutely ill. No rash was noted. Rales were present posteriorly over the lower third of both lung fields. Findings of cardiac examination appeared to be normal. The liver extended 3 cm below the left costal margin and was tender. Trace pedal edema was present.

The hemoglobin value was 12.3 grams per dl and the leukocyte count was 17,000 per cu mm with 85 percent neutrophils, 8 percent lymphocytes and 7 percent monocytes. The erythrocyte sedimentation rate was 114 mm per hour. Serum lactic dehydrogenase was 420 units per liter (normal <290), creatine phosphokinase 3 units per liter (normal 5 to 100) and SGOT 53 units per liter. An electrocardiogram showed low frontal plane voltage with diffuse ST and T changes, as well as an intraventricular conduction delay consistent with incomplete left bundle branch block.

The patient was placed on a cardiac monitor and a transient supraventricular tachycardia was noted and treated with lidocaine. She received no antibiotics for the first 24 hours and her temperature pursued a hectic pattern with late afternoon elevations on two days reaching 40.5°C (104.9°F). On the second hospital day, therapy with administration of penicillin and kanamycin was begun. Twelve hours later, corticosteroid therapy was started when the patient showed deteriorating mental status and worsening dyspnea. The following evening, the patient's condition was noted to have improved, with a clear sensorium and less shortness of breath. She continued to do well until the fourth hospital day when severe cardiac dysrhythmia occurred, and she died suddenly. The presence of spirochetes in six blood culture samples was later confirmed by the Oregon Public Health Department laboratory.

Discussion

Borreliosis was known as a clinical entity by Hippocrates but it did not receive the name of relapsing fever until 1843. The agent was first discovered by Obermeier in Berlin in 1861, and Motschutkoffsky first fulfilled Koch's postulates in 1876 by injecting subjects (including himself) with serum from an infected patient. Münch first showed that the disease could be transmitted by an arthropod vector, and the tick-borne hypothesis as a major mechanism of disease transmission was advanced by Nicole and Anderson in 1927.[4]

There are two types of relapsing fever, tick-borne (endemic) and louse-borne (epidemic). There have been an estimated 50 million cases worldwide of relapsing fever in the first half of this century, with an average mortality of 10 percent.[4] The vast majority of these cases have been louse-borne and have occurred outside the United States.

The first account of the disease in the United States was reported in Philadelphia in 1844. Relapsing fever in this country is almost exclusively tick-borne; and the earliest outbreaks of relapsing fever, occurring in Philadelphia and New York, are the only known louse-borne cases. The first endemic focus of tick-borne relapsing fever was recognized in Colorado in 1915, and this variety has continued to occur sporadically ever since. Some 322 cases were reported in California between 1921 and 1961. The first case reports from Washington were by Davis in 1932,[5] and Hemingway reported the first case from Oregon in 1940.[6] The latter case occurred in Deschutes County, where two thirds of the patients described in this report became infected. By 1932, borreliosis had been recognized as endemic to 13 far-western states.

Transmission of endemic relapsing fever occurs by the bite of an argasid tick which harbors the spirochetes. The tick is always a species of *Ornithodoros: O hermsi* in the western United States and *O turicata* in the southwestern states. Borreliae have been isolated from *O parkeri* in the

western states, but this species has never been documented as a vector for relapsing fever. Ticks of this genus have a nearly painless bite, a short feeding time (1 to 20 minutes) and a tendency to nocturnal feeding.[7(p191)] *O hermsi,* like other species of *Ornithodoros,* are able to survive months or years without food and once infected with borreliae usually remain infective for life.

The disease appears more likely to occur in visitors to tick infested areas. As reflected by the patients in this series, these are generally young men traveling or working in heavily wooded areas during the summer months. This seasonal incidence has been noted previously with 66.4 percent of 253 cases in California occurring during July and August.[8] Lodging in poorly maintained cabins or other shelters in which ticks and their rodent hosts abide is a major factor in the acquisition of the disease. Recent outbreaks have been reported in other western states, including Colorado[9] and Washington.[3] The former involved 62 cases and is the largest known outbreak of tick-borne relapsing fever in the western hemisphere. In addition, the presence of active, endemic foci of relapsing fever in Colorado[10] and California[11] has been reconfirmed.

Excellent and comprehensive reviews on the clinical manifestations of borreliosis are available.[4,12] Several of the more common features, however, deserve reiteration.

Except for the relapsing nature of the disease, the clinical features are compatible with several illnesses that may or may not involve infection. The incubation period is approximately a week, but may be as brief as 72 hours. A history of tick-bite is confirmed in a minority of patients. The onset is characteristically sudden and typical symptoms include fever, rigors, severe headache and profound malaise. The patient may complain of intense myalgias, particularly in the lumbar region. Weakness and arthralgia may be present as well. Abdominal pain in the left and right upper quadrants is another common complaint. This pain may be associated with nausea, vomiting or diarrhea and may be severe. Respiratory symptoms include dyspnea and nonproductive cough.

The physical examination shows variable findings, but generally the temperature is higher than 39.5°C (103.1°F). Many patients have a rash which varies from a nonspecific macular eruption to classic rose spots or frank petechiae. Nuchal rigidity, without other meningeal signs, may be observed. Abdominal tenderness is common, but peritoneal signs are found only rarely. Splenomegaly is found by examination in slightly fewer than half of the cases,[12] and in this series was the most commonly mentioned physical finding after fever. Splenic tenderness may be present in the absence of overt splenic enlargement. Hepatic tenderness is common with or without associated hepatomegaly, which is noted in approximately 20 percent of cases. Tender lymphadenopathy is often dectected. Icterus is seen in about 40 percent of cases. Neurological changes most frequently involve an altered sensorium related to toxemia. Alteration in reflex and motor function may be present but is not common.

While the above description is nonspecific, the relapsing course of the disease should suggest the diagnosis in the absence of knowledge of previous exposure. Three quarters of the patients in this series with ascertained fever patterns had three or more febrile relapses. The pattern of pyrexial episodes, lasting from less than one day to about two weeks, alternating with afebrile asymptomatic periods lasting about a week, is classic for relapsing fever. The average duration of the initial attack is three to four days, and subsequent attacks are often somewhat shorter. Afebrile intervals vary in length between one and 60 days, although most last about a week. The mean number of relapses in a large series of cases was three, but up to 13 have been reported.[12] In the present series up to five relapses were common. Pyrexia terminates in a crisis, which is usually as abrupt as the onset of symptoms.

The relapsing character of the disease has been shown to be related to antigenic phase variation.[13] The *Borrelia* organism possesses the capability to adapt itself repeatedly to host antibodies by altering its antigenic profile. Each such alteration requires the host to mount a new immune response. The number of such adaptations is limited, and therefore the disease is eventually controlled by immune mechanisms.

The diagnosis should be considered in a patient with a history of a recent wilderness exposure, who has had two or three discrete episodes of high fever of abrupt onset and resolution associated with the first bout of fever. In only one of our patients was the peripheral blood smear examined expressly for *Borrelia* during the initial period of fever, and this was done because of historical information linking this patient to another person with known borreliosis.

The diagnosis can be confirmed by careful

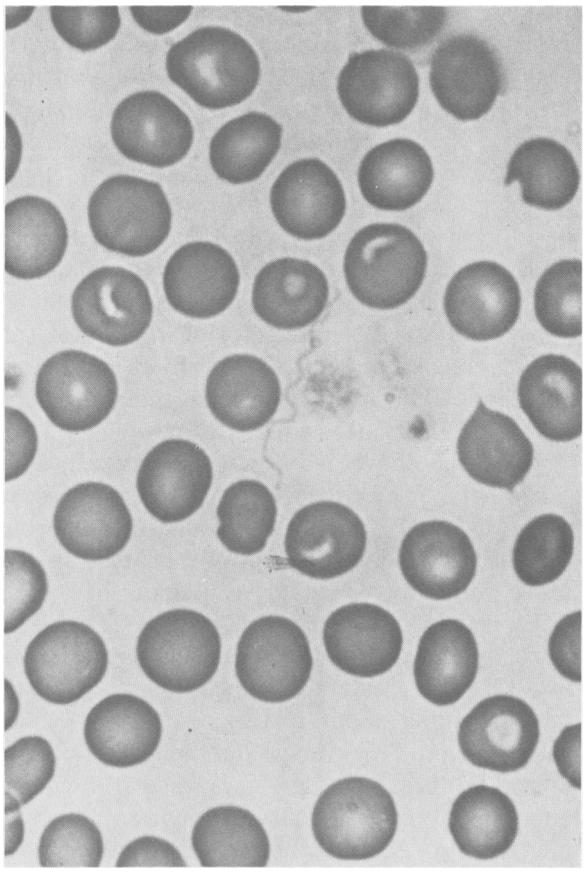

Figure 3.—Spirochetes on peripheral blood smear (Wright stain, reduced from 500× magnification).

examination of a Giemsa- or Wright-stained smear of peripheral blood (Figure 3) in which spirochetes will be found in approximately 70 percent of cases. The yield is increased by examination of serial blood smears, including thick and thin preparations. Evidence suggests that the organisms take refuge in the central nervous system, spleen, liver and bone marrow between attacks. (These organisms are almost never found on blood smears made during afebrile periods.) Dark-field examination of the blood may also be useful as may daily injections of the patient's blood specimens into laboratory mice. The spirochetes may then be seen in blood smears from the animal. Serologic tests are not generally of value in the diagnosis of relapsing fever.[7(p225)]

Other laboratory abnormalities include a mild normocytic-normochromic anemia, elevated levels of hepatocellular enzymes and hyperbilirubinemia. Study of coagulation times will often show multiple abnormalities, even in those patients without clinical evidence of bleeding. In louse-borne relapsing fever, prolongation of the prothrombin time and partial thromboplastin time has been observed, as have circulating fibrin monomers.[14,15] Platelet counts are usually low and range from 30,000 to 250,000 per cu mm in the louse-borne variety. Findings in case 1 show that these changes may also occur with tick-borne relapsing fever and that the abnormalities respond to treatment of the underlying disease.

The pathogenesis of the coagulation abnormalities may be related to a consumptive process initiated by endothelial damage caused by the spirochetes, or to release of factors which activate intravascular coagulation and fibrinolysis or perhaps to a combination of both.

The differential diagnosis depends to a great extent on the geographic locale and the history of activity and travel provided by the patient. Bacterial infections to be excluded include salmonellosis, meningococcemia, brucellosis and plague. Other spirochetal infections, including leptospirosis, and rat-bite fever should be considered along with rickettsial diseases such as typhus, Rocky Mountain spotted fever and Q fever. Viral agents, such as influenza virus and coxsackievirus, as well as members of the arbovirus group (for example, dengue or yellow fever) may cause similar syndromes. Colorado tick fever is also a potential source of confusion. Finally, features of malaria may develop in a very similar fashion. It is of interest that the diagnosis of borreliosis in two cases included in this report was made fortuitously during review of peripheral blood specimens for malarial parasites.

Three key points are important to note in considering a diagnosis of relapsing fever. First, relapsing fever does indeed occur in this country, especially in the western United States. Many of these cases are missed, probably because of the spontaneous recovery of most patients. The difficulty comes in placing this disease in the differential diagnosis of a febrile illness before the classic relapsing pattern of fever is apparent. Second, a bit of epidemiologic investigation can be very rewarding, as was shown in case 1. In this series, fewer than a third of cases were isolated, that is, unrelated to any other reported case. Third, the diagnosis, once thought of, is usually made easily by careful inspection of the peripheral blood smear.

The tick-borne disease is generally self-limited and has a mortality of only about 2 percent, mainly in infants and elderly patients. In keeping with the findings of other authors, the only deaths

in this series were those of a newborn infant and a 68-year-old woman. However, the morbidity is significant in terms of prolonged discomfort and disability to patients. It has been shown that an adequate course of antimicrobial therapy is effective both in terminating the current symptoms and in preventing relapses. The recommended therapeutic regimen is 500 mg of tetracycline taken orally four times a day for five to ten days. All patients in this series who were known to be treated with tetracycline responded well without relapse. Chloramphenicol is also effective if tetracycline is contraindicated or unavailable. Of note, however, is the case of the newborn infant who died with meningeal involvement. He was treated with chloramphenicol and penicillin but did not respond.[1]

Following treatment of tick-borne relapsing fever, recovery is typically rapid and complications are infrequent. Complications that have been described include iritis, iridocyclitis and a variety of focal neurological deficits. Pneumonia has been reported, and several patients in our series had a cough. Cardiac involvement has not been described in tick-borne relapsing fever; however, although undocumented, it is suggested by the course of the patient in case 2. Myocarditis has been described in louse-borne relapsing fever.[16] Hemorrhagic occurrences are common in reports of cases in Africa, but are rare in this country, occurring primarily in persons with laboratory evidence of severe coagulopathy. Abortion is frequent in pregnant women with relapsing fever. Intrauterine infection of the fetus is a rare complication which occurred in only one of the cases described in this series.

An additional complication is that of the Jarisch-Herxheimer reaction (JHR) which is characterized by elevation of temperature, aggravation of existing skin lesions and vasoconstriction followed later by hypotension. The JHR has an abrupt onset after initial treatment with antibiotics, and resolves without discontinuation of therapy. Its cause is thought to be related to release of endotoxin by borreliae.[17,18] Four patients in this series had this complication.

REFERENCES

1. Fuchs PC, Oyama AA: Neonatal relapsing fever due to transplacental transmission of *Borrelia*. JAMA 208:690-692, 1969
2. Relapsing fever. Morbidity Mortality Weekly Rep 25:197-198, 1976
3. Thompson RS, Burgdorfer W, Russel R, et al: Outbreak of tick-borne relapsing fever in Spokane County, Washington. JAMA 210:1045-1050, 1969
4. Felsenfeld O: *Borrelia*. St. Louis, Warren H. Green, Inc, 1971
5. Davis GE: *Ornithodoros turicata*, the possible vector of relapsing fever in Southwest Kansas. Pub Health Rep 51, 1936
6. Hemingway MW, Hemingway RW, Arneson EK: Relapsing fever. NW Med 39:362, 1940
7. Burgdorfer W: The epidemiology of the relapsing fevers, *In* Johnson RC (Ed): The Biology of the Parasitic Spirochetes. New York, Academic Press, 1976
8. Wynns HL: The epidemiology of relapsing fever, *In* Moulton FR (Ed): Relapsing Fever in the Americas. Lancaster, Scientific Press, 1942, p 100
9. Relapsing fever. Morbidity Mortality Weekly Rep 22:242 and 256, 1973
10. Edell TA, Emerson JK, Maupin GO, et al: Tick-borne relapsing fever in Colorado. JAMA 241:2279-2282, 1979
11. Malison MD: Relapsing fever. JAMA 241:2819-2820, 1979
12. Southern PM, Sanford JP: Relapsing fever, a clinical and microbiologic review. Medicine (Baltimore) 48:129-149, 1969
13. Coffey EM, Eveland WC: Experimental relapsing fever initiated by *Borrelia hermsi*—II. Sequential appearance of major serotypes in the rat. J Infect Dis 117:29-34, 1967
14. Dennis DT, Awoke S, Doberstyn EB, et al: Bleeding in louse-borne relapsing fever in Ethiopia. E African Med J 53: 220-225, 1976
15. Perine PL, Parry EHO, Vukotick DA, et al: Bleeding in louse-borne relapsing fever—I Clinical studies in 37 patients. Trans Roy Soc Trop Med Hyg 65:776-781, 1971
16. Judge DM, Samuel I, Perine PL, et al: Louse-borne relapsing fever in man. Arch Pathol 95:136-140, 1974
17. Bryeson ADM, Cooper RE, Warrell DA, et al: Studies of the mechanism of the Jarisch-Herxheimer reaction in louse-borne relapsing fever: Evidence for the presence of circulating Borrelia endotoxin. Clin Sci 43:343-354, 1972
18. Galloway RE, Levin J, Butler TE, et al: Activation of protein mediators of inflammation and evidence for endotoxemia in *Borrelia Recurrentis* infection. Am J Med 63.933-938, 1977