

(1). Spotted fever is caused by a variant member of *R. conorii*, which is transmitted by the dog tick *Rhipicephalus sanguineus* (2,3). The disease has a broad spectrum of clinical signs, from asymptomatic to fatal (4,5). Symptoms and signs include fever, headache, vomiting, myalgia, conjunctivitis, and a typical maculopapular or purpuric rash. The tache noir at the site of the tick bite, which is found in patients in Europe, is seldom, if ever, seen in Israel.

The first patient, a 6-year-old boy, was taken to the pediatric emergency room with high fever and a diffuse rash, approximately 1 week after visiting a cousin who had similar complaints. Physical examination showed temperature of 40°C, chills, diffuse maculopapular rash all over the body, including the hands and feet, hepatosplenomegaly, and lymphadenopathy. Blood tests showed neutropenia, thrombocytopenia, and hyponatremia. Because *Rickettsia* was included in the differential diagnosis, immunofluorescent assay (IFA) for *Rickettsia* was performed and intravenous doxycycline (2 mg/kg/day) was initiated. One week later, the boy's 8-month-old sister was brought to the emergency room with similar complaints, and 2 days afterwards his 2-year-old sister began to have the same symptoms. A detailed history revealed that all children had played on a lawn frequented by dogs.

All three siblings had fever, chills, and diffuse maculopapular rash all over the body, including the hands and feet. An IgM IFA test for *R. conorii* from the first child was negative on the day of admission and became positive 8 days later. On the day of the boy's hospital discharge, his 8-month-old sister was taken to the emergency room. Her serology test was negative on admission but became positive 7 days later. The third (2-year-old) sibling's first blood test was negative, and the family did not agree to a second blood test. All three children responded well to doxycycline (2 mg/kg/day, with a double dose the first day) for 5 to 7 days. Most symptoms subsided within 48 hours.

Spotted fever is usually a sporadic illness and is not spread from person to person. Clusters of cases have been reported. Yagupsky reported spotted fever in Israel in a few children living near each other in an agricultural settlement (6). A report from the Delaware Division of Public Health described a group of children who had been camping together where contact with ticks

was likely (7). This case illustrates that spotted fever may be acquired even without direct contact with animals, through exposure to ticks in places frequented by infected animals. Our report suggests that Rickettsial illness should be considered in the differential diagnosis of fever with rash in disease-endemic areas, even if the timing of similar complaints in several family members suggests a contagious viral illness.

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### Iron and the Role of *Chlamydia pneumoniae* in Heart Disease

**To the Editor:** Chronic infection of the coronary arteries by *Chlamydia pneumoniae* has been proposed as a heart disease risk factor (1). One reason for this proposal is the organism's association with one or more other risk factors for heart disease (2). However, an independent pathogenic role for *C. pneumoniae* in heart disease is unlikely if its presence is only a marker for another risk factor. In the Helsinki Heart Study (3), markers of chronic *C. pneumoniae* infection were a significant risk factor for a cardiac event, independent of most traditional

risk factors; however, some association with known risk factors was seen, including a positive association with smoking and an unexpected negative association with spare-time physical activity.

We postulate a key role for iron, a proposed risk factor for heart disease (4-6), in promoting the growth of *C. pneumoniae* in coronary arteries. Iron is an essential growth factor for nearly all pathogenic microorganisms (7). In particular, the growth of *C. pneumoniae* in a human lung cell line and in Hep-2 cells is strongly inhibited by iron restriction or by use of the iron chelator deferoxamine (8, P. Saikku, pers. comm.). Excess iron is present in atherosclerotic lesions. Seven times more iron is present in atherosclerotic than in healthy arteries (9).

Among proposed risk factors for heart disease, iron provides the most conceptually straightforward explanation for the presence of *C. pneumoniae* in coronary vessels. We propose that chronic infection of coronary arteries by *C. pneumoniae* occurs only if excess iron is present in vivo. Excess iron is defined as stored iron or iron in excess of the amount needed to maximize hematocrit. This implies that *C. pneumoniae* can establish infection in the coronary arteries only if a threshold level of available iron is present. Confirmation of the hypothesis could explain an association of *C. pneumoniae* with coronary atherosclerosis and, more generally, with ischemic heart disease and would be consistent with the greater susceptibility of men than women to *C. pneumoniae* infection (2) and myocardial infarction. Moreover, confirmation of the hypothesis would leave open the question of whether *C. pneumoniae* is directly atherogenic or merely finds fertile ground for growth in arteries because of the presence of iron above some threshold level.

Until age 20, men and women show few differences in prevalence of antibody titers against *C. pneumoniae*. After age 20, the prevalence of markers diverges sharply, with men showing a much steeper rise than women. This is similar to the patterns observed for both stored iron levels and rate of myocardial infarction in men and women, especially between the ages of 20 and 50 years (4,5). In later years, prevalence rates for *C. pneumoniae*

markers do not rise as steeply for women as the curves for stored iron level or myocardial infarction rates (2). These patterns are compatible with associations between stored iron, myocardial infarction rate, and markers for infection with *C. pneumoniae*. Another relevant observation is the negative association of markers with spare-time physical activity (2). Such activity is associated with lower stored iron levels (10), which may decrease vulnerability to *C. pneumoniae*.

The presence of excess iron in regulating susceptibility to *C. pneumoniae* does not readily explain the geographic gradient in the frequency of antibodies (2). *C. pneumoniae* infection seems to be more prevalent near the equator. In general, acquisition of stored iron is more problematic among impoverished persons, many of whom live near the equator. Parasitic infections that cause chronic iron loss from bleeding in the gut and bladder, along with limited availability of easily absorbed heme iron in meat, tend to minimize iron acquisition in these areas. *C. pneumoniae* may be endemic in populations near the equator, especially among children in tropical urban slums, because of other factors that eliminate any differential effects on the basis of iron levels. In these areas chlamydial antibodies may be a good marker for invasion but not necessarily for disease.

We suggest that, above a modest threshold level of stored iron in vivo, *C. pneumoniae* acquires the ability to colonize coronary arteries. Invasion and colonization by the organism in vivo probably require a concentration of available iron similar to that needed for growth in cell culture. Even in a state of total iron depletion, iron is still present in the body in abundance. However, in iron depletion virtually all iron in the body is functional iron. Functional iron, i.e., iron in hemoglobin, may not be readily accessible to the organism. Our hypothesis implies that stored iron can be mobilized by *C. pneumoniae* for growth. An approach to testing the hypothesis would involve comparing the ability of *C. pneumoniae* to colonize macrophages from stored iron-replete persons with those from persons without stored iron. If the hypothesis is confirmed, maintenance of an iron-depleted state under medical supervision could be recommended as a preventive strategy against recolonization after a course of antibiotic therapy.

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### Filth Flies Are Transport Hosts of *Cryptosporidium parvum*

**To the Editor:** Infection with *Cryptosporidium parvum*, a zoonotic and anthroponotic coccidian parasite (1), may be fatal for persons with impaired immune systems (2), for whom a low number of oocysts can initiate life-threatening diarrhea (1). Insects such as promiscuous-landing synanthropic flies (i.e., coprophilic filth flies) are recognized transport hosts for a variety of parasites (3-5), but not for *C. parvum*. We

assessed the role of synanthropic flies in the mechanical transmission of *C. parvum* oocysts.

Bovine diarrheic feces (20-ml specimens) containing  $2.0 \times 10^5$  oocysts/ml were placed in petri dishes in each of five 4-liter paper cages with approximately 250 pupae of laboratory-reared house flies (*Musca domestica* F58WTZ strain). Three days after the flies emerged, fecal specimens were collected on glass microscope slides placed in each cage. Thirty flies aspirated from each cage on days 3, 5, 7, 9, and 11 after emergence were eluted, and the eluants were processed by the cellulose acetate membrane (CAM)-filter dissolution method (6). Digestive tracts dissected from randomly selected flies and the glass slides with fly excreta were examined by immunofluorescent antibody (IFA) (7), and *C. parvum* oocysts were counted (8). Maggots of *M. domestica* were reared in fly larvae medium (PMI FEEDS, Inc., St. Louis, MO) contaminated with calf diarrheic feces (50 ml) containing  $2.0 \times 10^5$  *C. parvum* oocysts/ml. Resulting pupae were eluted, the eluants were processed by the CAM-filter dissolution method (6), and *C. parvum* oocysts were identified by IFA (7) and counted (8). Diarrheic fecal specimens from a *C. parvum*-uninfected calf were used as negative controls in similar experiments. Randomly selected samples containing fly-derived *C. parvum* oocysts were processed with acid-fast stain (AFS) (8) to check for normal cellular morphologic features.

Ten Victor-type flying-insect traps (Woodstream, Lititz, PA) were baited with rotten fish and placed inside a barn (approximately 880 m<sup>2</sup>) in which a male Holstein calf infected with *C. parvum* (AUCP-1 strain) was housed. The traps were emptied weekly, the flies were counted and identified (5,9), and the inside surfaces of the traps (containing fly excreta), along with the flies, were eluted with 200 ml of eluting fluid (6). The eluting fluid was filtered through a CAM (Millipore, Bedford, MA) (6,8), which was then processed (6), and *C. parvum* oocysts were identified by IFA (7) and counted (8).

The mean number of *C. parvum* oocysts per droplet of *M. domestica* was 4 to 20 (mean  $7.0 \pm 3.2$ ), and the number of droplets increased over time. All flies harbored *C. parvum* oocysts on their external surfaces. On average,  $14.0 \pm 6.8$  fly excreta were counted per 1.0 cm<sup>2</sup> of glass slide. From 1 to 8 *C. parvum* oocysts were