third trimester, it was 16% (6 of 38); in gestational Lyme borreliosis with trimester unspecified, it was 22% (18 of 83); the overall risk in all trimesters was 25% (66 of 263).

Effect of Gestational Antibiotic Therapy

Gestational antibiotic therapy had a protective effect against adverse fetal or neonatal outcome, and the overall adverse outcome risk after treatment in all trimesters was 15% (23 of 157); after no treatment in all trimesters, it was 67% (20 of 30). This protective effect was apparent in all trimesters: 18 compared with 73% in the first trimester, 16 compared with 67% in the second trimester, and 9 compared with 50% in the third trimester.

Rate of Miscarriage and Stillbirth

The overall risk of miscarriage for any trimester of infection was 7.6% (20 of 263 patients). Antibiotic therapy showed a protective effect, with a rate of 2.5% (4 of 157) fetal loss after treated gestational Lyme borreliosis, compared with 30% (9 of 30) without antibiotic therapy.

Rate of Neonatal Death

The overall risk of neonatal death for any trimester of infection was 2% (6 of 263 patients); the rate was less than 1% (1 of 157) with antibiotic therapy, and 7% (2 of 30) without antibiotic therapy, for gestational Lyme borreliosis.

Rate of Neonatal Illness

The risk of nonfatal neonatal illness for any trimester of infection was 15% (40 of 263 patients); the risk was 11% (18 of 157) with antibiotic therapy compared with 30% (9 of 30) without antibiotic therapy for the gestational Lyme borreliosis episode.

Description of Congenital Lyme Borreliosis

Table 11–15 lists the incidence, time of presentation, and clinical manifestations of the various adverse outcomes associated with gestational Lyme borreliosis, including miscarriage, early severe congenital Lyme borreliosis, early mild congenital Lyme borreliosis, and late chronic congenital Lyme borreliosis.

Clinical case reports of mother-infant pairs who illustrate these various manifestations of congenital Lyme borreliosis are presented in the following sections.

ASYMPTOMATIC INFANT WITH GESTATIONAL LYME BORRELIOSIS EXPOSURE

CLINICAL CASE

Mother. A 26-year-old woman developed acute onset of hypertension of 160/140 and severe left facial pain, paresthesia, and paralysis in the thirty-eighth week of her third pregnancy in mid-March of 1991; because of the hypertension, she had a cesarean section for delivery of the infant 2 days later. A diagnosis of idiopathic Bell's palsy was made, and she was treated with prednisone, 40 to 60 mg daily, for less than 1 week, had partial return of motor function after 6 months, but still had residual discomfort, paresthesias, and mild to moderate left facial motor deficits 2 years later.

In 1992, during her next pregnancy, she was treated with oral cephalexin for a first-trimester urinary tract infection and gave birth at term to a second infant in October 1992.

In April 1993, during routine questioning about maternal gestational history because of hospitalization of her then 2-year-old child for gastroenteritis, she reported that ever since the Bell's palsy, she had persistent severe daily headaches; neck aches; intermittent left conjunctivitis; migratory polyarthralgias of the wrists, elbows, knees, and hips; infrequent 10- to 20-cm-diameter round erythematous rashes on her legs that spontaneously resolved; fatigue; and short-term memory deficits. She was an avid hiker and had an over-10-year history of multiple tick bites to her scalp, ears, and neck; she reported that many of these ticks had become fully engorged before removal. In April 1993, she was found to have specific *B. burgdorferi* antibody by polyvalent EIA and IgM Western blot assays.

Initially, she was treated with oral cefuroxime axetil (because of a history of penicillin allergy) for 6 weeks, had a mild Jarisch-Herxheimer reaction on the second day, and had resolution of fatigue and headache and improvement in the residual Bell's palsy symptoms by the end of therapy. She experienced relapse within 1 week of completion of the oral cefuroxime, with fatigue, headache, left eye conjunctivitis, and left facial weakness (the residual Bell's palsy of this patient at the time of this relapse is shown in Figure 11–8). She had a lumbar puncture (spinal fluid *B. burgdorferi* antibody negative, and spinal fluid normal); was treated over 3.5 weeks with intravenous ceftriaxone; had resolution of fatigue, headache, and conjunctivitis and marked improvement of the left facial weakness by the end of therapy; and remained well at 6-month follow-up.

Placenta. No pathologic testing was performed on either placenta.

Infant 1. The baby, who was delivered by cesarean section 2 days after onset of the maternal Bell's palsy, at 38 weeks of gestation, was considered normal at birth. However, he was hospitalized at 5.5 months of age for fever, irritability, lethargy, full fontanelle, and the possibility of culture-negative (bacterial and viral) sepsis or meningitis (normal spinal fluid); responded clinically to intravenous cefotaxime over 3 days; and developed a maculopapular rash on the second day of the cefotaxime treatment that resolved despite continuation of the cefotaxime. He was treated by his pediatrician with oral amoxicillin several times during his first 2 years of life for upper respiratory infections. When the mother's Lyme borreliosis was diagnosed 2 years after the birth of this infant, he was tested and found to have no antibodies to *B. burgdorferi*; he has remained normal at 2.8-year follow-up.

Infant 2. A second baby born to this mother in

October 1992 after a term pregnancy was also normal at birth. At 7.5 months of age, this infant was treated by his pediatrician with oral amoxicillin–clavulanic acid for an upper respiratory infection and developed an erythematous maculopapular rash on the fourth day, which resolved despite continuation of the antibiotic. When the mother's Lyme borreliosis was diagnosed, he was tested and found to be seronegative for *B. burgdorferi* antibodies; he has remained normal at 1.3-year follow-up.

Comments. This mother gave birth to two infants before the diagnosis of Lyme borreliosis (during gestation for the first infant) was made retrospectively 2 years later; this followed routine questioning to obtain a gestational history because of hospitalization of one of the infants for an unrelated illness (bacterial gastroenteritis). Her *B. burgdorferi* seropositivity, Jarisch-Herxheimer reaction (refer to discussion of Jarisch-Herxheimer reaction in section Therapy) after initiation of antibiotic therapy, and impressive clinical response to antibiotic therapy all support the diagnosis of chronic Lyme borreliosis in this patient, although it was made retrospectively.

Fortunately, both infants were normal at birth and remained so. However, both had erythematous maculopapular rashes, possibly reminiscent of Jarisch-Herxheimer reactions, between 5.5 and 7.5 months of age within the first few days of either intravenous third-generation cephalosporin or oral amoxicillin therapy, which was given in one case for an episode of "rule out sepsis and meningitis" with negative viral and bacterial cultures, and in the other case for an upper respiratory infection. It is not known whether either of these infants ever acquired the spirochete gestationally, as both infants were *B. burgdorferi*–seronegative, but they were not tested by the in vitro lymphocyte proliferative assay, which may be more sensitive in detection of congenital Lyme borreliosis.

This mother-infant group illustrates the possibility that infants born after untreated gestational Lyme borreliosis may be normal. A possible explanation for this could be that transplacental spread of the spirochete is variable; that spirochetemia may not yet have occurred at the time the first infant was delivered, which was within 2 days of onset of the Bell's palsy; that the oral cephalosporin therapy during the first trimester of gestation of the second infant may have partially treated the Lyme borreliosis, sufficiently to prevent transplacental spread to the fetus; or that if transplacental spread of infection occurred in either of these two infants, the courses of antibiotic therapy given by the pediatrician for other illnesses during the first year of life may have been beneficial in prevention of symptomatic congenital Lyme borreliosis. ■

MILD EARLY CONGENITAL LYME BORRELIOSIS

CLINICAL CASE (patient 23 in Table 11–8)

Mother. A 38-year-old woman visited a lake for 4 days in mid-April 1987, and the day after returning home, found and removed an engorged tick attached to her groin. A 1-cm indurated erythematous patch had developed at the bite site and resolved a few days after she applied topical Neosporin ointment. She conceived in mid-May 1987, developed a mild flulike illness 1 week later at 3 weeks of gestational age, developed an asymptomatic rash on her trunk at 4 weeks, and presented at 4.5 weeks with low-grade fever, a dense erythematous maculopapular rash of her trunk and proximal extremities (see Fig. 11–7*A*), and two larger (1- to 2-cm) erythematous patches with central clearing (see Fig. 11–7*B*).

She was referred for infectious disease evaluation for suspected rubella, but because of the appearance of the rash and the history of the tick bite, the diagnosis of Lyme borreliosis was considered; she was treated immediately at 4.5 weeks' gestation with intravenous ceftriaxone 2 g daily and showed improvement in the rash after 2 days; however, she developed severe watery diarrhea, which necessitated a change to penicillin 500 mg four times daily for the remainder of the 2-week course. The rash resolved completely after 8 days, and she remained well throughout the rest of the pregnancy, except for mild toxemia in the last trimester; she delivered a term infant by cesarean section because of nonprogression of labor. Maternal polyvalent ELISA serum antibody to *B. burgdorferi* was initially negative at presentation at 4.5 weeks' gestation, became positive at 5.5 weeks, remained positive through 12 weeks, and was negative at delivery. In vitro lymphocyte proliferative assay for *B. burgdorferi* was positive at 16 weeks' gestation, at delivery, and at 1 month post partum, but the level decreased with time. She has remained well after 6.5 years, as assessed by verbal follow-up.

Placenta. Focal chorioamnionitis and subchorionic nodules were found (refer to discussion of placental pathology in section Pathology and Pathogenesis).

Infant. The infant was normal at birth except for a sacral dimple and 0.5-cm bilateral inguinal adenopathy of initially unclear significance (patient 23 in Table 11–8). The child weighed 3461 g and had a normal pediatric ophthalmology examination, normal brain-stem auditory evoked response evaluation, normal head ultrasound, normal electrocardiogram, normal chest and long bone x-rays, and normal complete blood count. Spinal fluid included three mononuclear cells, protein 53 mg/dl, glucose 37 mg/dl; both blood and spinal fluid were negative for polyvalent EIA *B. burgdorferi* antibody. In vitro lymphocyte proliferative assay for *B. burgdorferi* was positive on both cord blood and infant blood at 1 month of age but was lower at 1 month.

After the result of the proliferative assay was obtained, the infant was treated with intravenous ceftriaxone 100 mg/kg daily for 2 weeks and developed an intensely erythematous generalized maculopapular rash on the sixth day of treatment, which resolved despite continuation of the antibiotic. The inguinal adenopathy resolved by the end of the antibiotic therapy; the infant remained clinically well at 15 months, and by verbal report continued to be well at almost 6 years of age. ■

CLINICAL CASE (case 26 in Table 11–8)

Mother. In early April 1989, a 29-year-old woman in the seventeenth week of pregnancy camped in a wooded area frequented by deer and had several small tick bites, including one that was deeply embedded in her scalp. At 18 weeks' gestation, she developed on her thigh at one of the tick bite sites a 10 × 5-cm-diameter erythematous oval "bull's-eye" rash that lasted 3 weeks and then spontaneously resolved. Between 20 and 28 weeks' gestation, she experienced low-grade fever, myalgias, fatigue, stiff neck, dizziness, photophobia, and migratory polyarthralgias, especially of the knees, and between 23 and 26 weeks, she had recurrence of the rash.

At 28 weeks, she took oral erythromycin 250 mg four times daily for 10 days, and her symptoms resolved. She then heard about Lyme disease, obtained and began oral cefuroxime axetil 1 g twice daily from 33 weeks to the time of delivery, and remained well except for mild knee arthralgias. She reported that her urine had been positive for Lyme antigen at a commercial laboratory at 32 weeks.

At delivery, maternal blood was negative for polyvalent EIA *B. burgdorferi* antibody, but blood obtained 1 day post partum was positive by the *B. burgdorferi* in vitro lymphocyte proliferative assay (LPA). After delivery, because of recurrence of headache, photophobia, flulike symptoms, and knee arthralgias, she was treated with oral doxycycline 100 mg twice daily for 1 month, improved within 24 hours, and recovered by the end of therapy. Long-term follow-up information is unavailable.

Infant. The infant was normal at birth except for diffuse small retinal hemorrhages with white centers; weighed 3461 g; and had a normal brain-stem auditory evoked response evaluation, normal electrocardiogram and two-dimensional echocardiogram, and normal complete blood count and liver enzyme panel. Cord blood and infant's blood on the first day, at 2.5 weeks, and at 7 weeks were all seronegative for polyvalent EIA *B. burgdorferi* antibody, but blood from the first day was positive by the in vitro LPA for *B. burgdorferi*.

By 2.5 weeks, the infant had become somewhat listless and slept more than expected; spinal fluid showed a slight lymphocytic pleocytosis, slightly elevated protein, and normal glucose. MRI scan of the brain was normal, complete blood count was normal, liver enzymes were normal, and there was slight hyperbilirubinemia, but the retinal lesions had spontaneously resolved. The infant was treated with intravenous ceftriaxone 75 mg/kg daily for 4 weeks, developed a "pale spell" on the second day of therapy, became more active and alert after 3 days of therapy, and was completely well by completion of antibiotic therapy. A repeat lumbar puncture was performed at the end of the antibiotic therapy but was traumatic; long-term follow-up is unavailable.

Comments. The preceding two mothers both had gestational erythema migrans with systemic symptoms, both were treated with antibiotic therapy during pregnancy, and both delivered infants who were clinically normal at birth except for minor manifestations of early congenital Lyme borreliosis. The infant born to the mother with gestational Lyme borreliosis treated within 2 weeks of onset had only inguinal adenopathy, rash, and a sacral dimple (dimple is of unclear significance); the one born to the mother with symptoms of gestational Lyme borreliosis persisting for 10 weeks before antibiotic therapy had evidence of mild neurologic symptoms, transient retinal lesions, mild lymphocytic meningitis, and mild hyperbilirubinemia. Both infants had episodes resembling Jarisch-Herxheimer reactions shortly after initiation of ceftriaxone therapy at 2 weeks of age; both had resolution of their manifestations of early congenital Lyme borreliosis by the end of antibiotic therapy. Both infants and mothers were seronegative for polyvalent EIA *B. burgdorferi* antibody at delivery and positive by the *B. burgdorferi*–specific in vitro LPA.

These mother-infant groups illustrate the observation that infants with congenital Lyme borreliosis and mothers who have been treated with antibiotics for gestational Lyme borreliosis may be seronegative by antibody assays at delivery or in the peripartum period, and they may be positive by the *B. burgdorferi*–specific LPA.

These cases illustrate the importance of prompt and aggressive antibiotic therapy for gestational Lyme borreliosis. In one of these cases, the intravenous ceftriaxone had to be discontinued because of severe diarrhea and therapy was completed with high-dose penicillin; in the other case, the mother was treated with prolonged oral cefuroxime axetil through the time of delivery. Longer courses of intravenous antibiotic therapy have been more effective in the treatment of other manifestations of Lyme borreliosis. Recommendations for optimal antibiotic therapy of gestational Lyme borreliosis, for mild symptoms of congenital Lyme borreliosis such as inguinal adenopathy and mild lethargy as well as for the more obvious symptoms of severe congenital Lyme borreliosis are discussed in the section on gestationally exposed newborn infants; also, recommendations are made to begin antibiotic therapy promptly after birth to prevent later clinical sequelae. ■

SEVERE EARLY CONGENITAL LYME BORRELIOSIS

CLINICAL CASE (patient 24 in Table 11–8)

Mother. A 34-year-old woman had a tick bite between mid-April and late May 1987 at 6.5 to 12.5 weeks' gestation; she was treated with oral amoxicillin 250 mg three times daily for 10 to 14 days for sinusitis and flulike symptoms at 5 to 7 weeks', and at 20 to 22 weeks' gestation. A routine fetal sonogram performed at 17 weeks was normal, but another done at 24 weeks because of decreased amniotic fluid showed marked intrauterine growth retardation. Fetal blood sampling at 24.5 weeks showed normal chromosomes and no evidence of intrauterine viral infection; the infant was

delivered by cesarean section at 34 weeks' gestation. The mother remained clinically well following delivery and was seronegative for polyvalent EIA *B. burgdorferi* antibody at 1 week, 9 months, and 10 months after delivery; she was also negative by the *B. burgdorferi* LPA at 9 and 10 months.

Placenta. Pathologic evaluation showed chronic fibrosing villitis, which is described in the section on the placenta in Pathology and Pathogenesis.

Infant. The infant was small for gestational age (1050 g, 34 weeks) and had a low Apgar score; a "blueberry muffin" rash and profound thrombocytopenia that required platelet transfusions; hepatomegaly and hyperbilirubinemia; meconium ileus that required enemas; severe dilated cardiomyopathy with biventricular dysfunction and low voltage on electrocardiogram that required intensive cardiopulmonary support with intubation, mechanical ventilation, and pressors; and a transient patent ductus arteriosus. Several additional abnormalities were noted, including a pilonidal dimple, flexion contractures of the large joints (hips, knees, and elbows), longitudinal striations and dense sclerotic transverse metaphyseal bands of the long bones, a large forehead and split sutures, a full fontanelle, and bilateral inguinal adenopathy. Head ultrasound showed diffuse punctate increased parenchymal echogenicity, skull x-rays showed no calcifications, liver enzymes were normal, brain-stem auditory evoked response evaluation was normal, and ophthalmologic examination was normal. Figure 11–9 shows the meconium ileus, cardiomegaly, and sclerotic metaphyseal bands of this patient.

This infant was initially considered to have culture-negative bacterial sepsis and was treated with intravenous ampicillin and gentamicin for 6 days, but failed to improve and continued to require platelet transfusions and intensive cardiovascular support. Because of the maternal gestational history of tick bite, the possibility of congenital Lyme borreliosis was raised, and intravenous ceftriaxone (100 mg/kg per day) was added on the seventh day and continued for 1 week; within 24 hours, the platelet count stabilized, the pressors were able to be discontinued, and the infant began to recover. Spinal fluid on the sixth day showed an elevated protein but no pleocytosis. The dense sclerotic transverse metaphyseal bands present in all of the long bones during the first week gradually resolved during ceftriaxone therapy. Extensive evaluation for bacterial and viral causes of this fulminant sepsis was unrevealing; neither did the infant have detectable polyvalent EIA *B. burgdorferi* antibody. The infant was eventually discharged from the hospital at 2 months of age in good condition.

By 9 months, she demonstrated growth retardation, mild developmental delay, mild lower extremity spasticity, and persistently small head circumference; the possibility of congenital Lyme borreliosis was reconsidered. At 9 but not at 10 months, she was found to have polyvalent EIA *B. burgdorferi* antibody; at 9 and 10 months, she had a positive *B. burgdorferi* in vitro LPA; and between 9 and 10 months, further evaluation included a normal spinal fluid with no detectable *B. burgdorferi* antibody, a normal electrocardiogram, normal complete blood count, slightly elevated liver enzymes, and MRI scan of the brain that showed left parietal parenchymal lesions of increased T_2 signal. She was treated with intravenous ceftriaxone (75 mg/kg daily) for 3 weeks for neuroborreliosis. She subsequently improved and exhibited normal growth and development at follow-up at 2.5 years of age.

Comments. This mother-infant pair illustrates the presentation of severe early congenital Lyme borreliosis as fulminant neonatal sepsis; the need to consider Lyme borreliosis in the differential diagnosis of culture-negative sepsis; and the need to include optimal intravenous antibiotic therapy for Lyme borreliosis, such as third-generation cephalosporins, if Lyme disease is considered. This case also indicates the failure of short oral courses of antibiotic therapy in the prevention of severe congenital Lyme borreliosis and the need for more aggressive antibiotic therapy of gestational Lyme disease.

The unusual finding of sclerotic transverse metaphyseal bands in the long bones, which faded during the ceftriaxone therapy in this infant and in one other infant (case 25 in Table 11–8) with congenital Lyme borreliosis, may eventually prove to be a useful diagnostic finding in severe congenital Lyme borreliosis.

The initial clinical presentation of this infant resembles the description by Lampert[31] of the infant with infantile multisystem inflammatory syndrome who was later found to have chronic Lyme borreliosis, as well as the description of some reported infants who had fulminant early congenital Lyme sepsis,[26, 32, 33, 36, 39] although this infant did not have the severe cardiac malformations found in some of these patients. ■

LATE CONGENITAL LYME BORRELIOSIS

CLINICAL CASE (patient 25 in Table 11–8)

Mother. A 35-year-old mother of five children visited a tick-infested farm with her entire family for 2 weeks every summer from 1988 through 1990, and she and several family members had occasional tick bites during this time. During the first 6 weeks of her next pregnancy, between mid-March and late April 1990, she developed a flulike illness that progressed to pneumonia and was associated with unusually large nonpruritic, nontender, vesiculobullous, and even purulent round or oval skin lesions on her legs. She was treated with almost continuous antibiotic therapy for the first 10 weeks of gestation, initially oral erythromycin (333 mg three times daily) for 7 weeks; followed by cefaclor (250 mg three times daily) for 3 days, intravenous cefuroxime (750 mg three times daily) for 4 days, and oral cephalexin (500 mg four times daily) for 2 weeks; and then oral cefixime (100 mg daily) for 10 days at 12 to 13 weeks. The large erythematous skin lesions intermittently reappeared during the second and third trimesters, and she

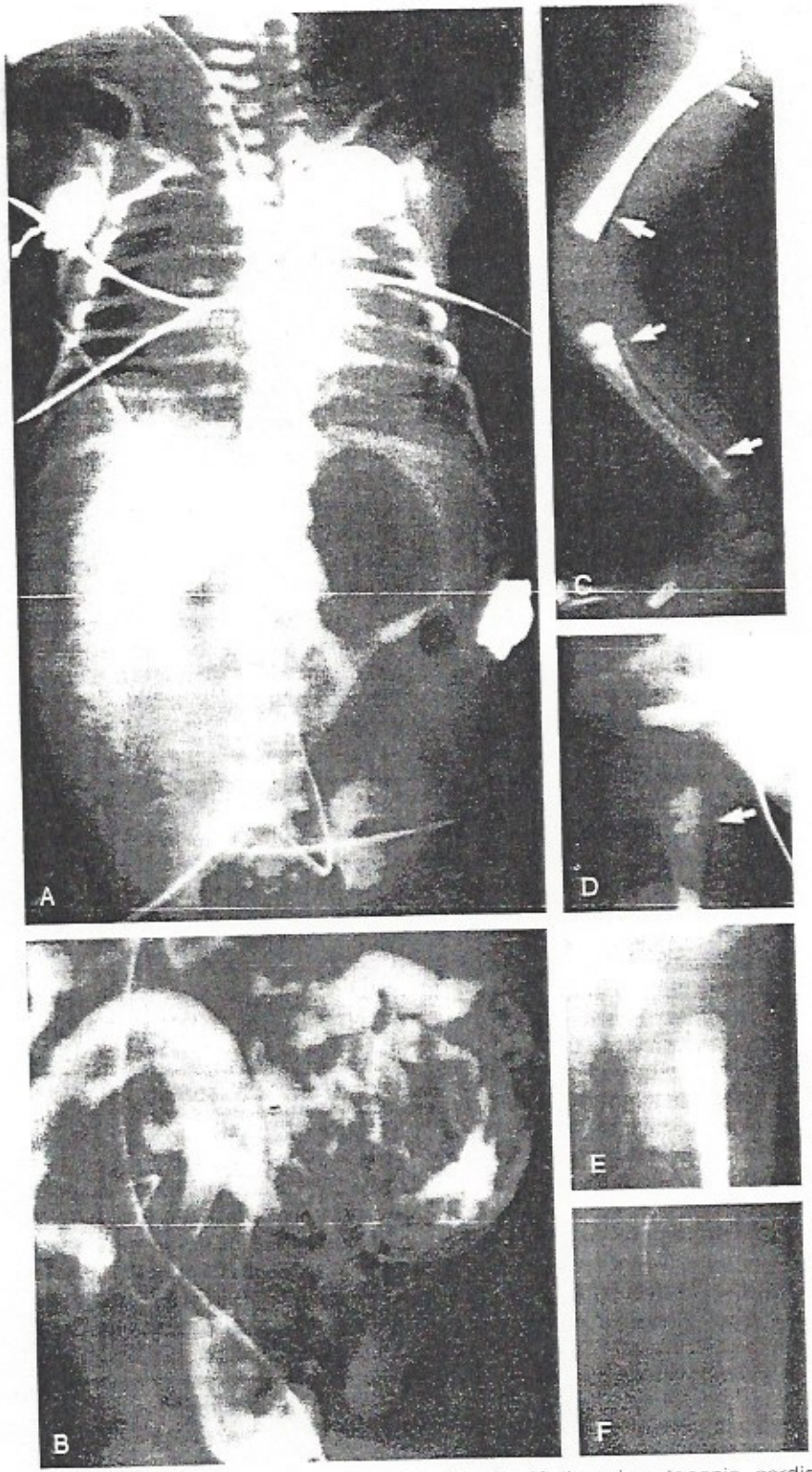

FIGURE 11–9 Congenital Lyme disease. An infant presented at birth with thrombocytopenia, cardiomyopathy, meconium ileus equivalent, and intrauterine growth retardation. *A*, Chest and abdominal radiograph at 1 day of age show cardiomegaly and mottled increased density in the right lower quadrant from inspissated meconium. *B*, Lower GI study at 1 day of age demonstrates impacted meconium in the distal ileum. Bone radiographs show *(C)* sclerotic transverse metaphyseal bands at birth (arrows), *(D)* fading metaphyseal bands after antibiotic therapy for 5 days (arrow), *(E)* further fading of the metaphyseal bands after antibiotic therapy for 16 days, and *(F)* resolution of the metaphyseal bands by 7 months (patient 24 in Table 11–8)

developed progressive arthralgias and arthritis of her hips, knees, and lower back; by the time of delivery, in December 1990, she was unable to walk without stooping over. The skin lesions, polyarthralgias, and polyarthritis recurred after delivery and continued intermittently for 4 months post partum; she also noted headaches, fatigue, and short-term memory lapses.

In March 1991, the history of this maternal gestational illness and tick exposure was discovered on routine questioning during hospitalization of the then 3-month-old infant for severe failure to thrive. As part of the evaluation of the infant for possible congenital infection, maternal blood was sent and found to be seropositive for polyvalent EIA *B. burgdorferi* antibody. Figure 11–5*D* shows one of the mother's recurrent skin lesions, and a skin biopsy of this lesion showed the superficial and deep dermal perivascular lymphocytic inflammatory infiltrates commonly seen in erythema migrans lesions, but no spirochetes were seen.

She was treated with oral doxycycline 100 mg twice daily and showed initial improvement of the lesions, was changed to intravenous ceftriaxone 1 week later because of subsequent intensification of the skin lesions and recurrence of fever and arthralgias, and was changed back to oral doxycycline after 3 days of ceftriaxone because of development of a generalized erythematous nonpruritic maculopapular rash that was considered by her physicians to be an allergic reaction. The headache, memory loss, fatigue, and skin lesions resolved after 6 weeks of doxycycline, but the right hip arthritis and polyarthralgias persisted, and 1.5 years later, she developed chronic palpebral conjunctivitis and distal paresthesias of her hands and was treated with several weeks of intravenous ceftriaxone with good clinical improvement.

Placenta. No placental pathologic examination was performed.

Infant. The infant was born after 37 weeks' gestation, had birth weight of 3490 g, and was considered normal at birth, but developed neonatal hyperbilirubinemia and nursed poorly. He was treated with intravenous ampicillin and a third-generation cephalosporin for suspected sepsis and urinary tract infection at 1 week of age, and developed a generalized erythematous maculopapular rash thought to be an allergic reaction. Bilateral inguinal hernias were repaired at 1 month of age, and he received a short course of oral cefaclor for otitis media at 2 months of age.

His very experienced mother noted that he became increasingly limp and listless, held his head and neck to the right, slept almost all day, and fed poorly. He presented at 2.5 months of age for infectious disease evaluation to look for possible congenital infection because of severe failure to thrive, developmental delay, growth retardation, and gastroesophageal reflux with recurrent vomiting and recurrent aspiration pneumonias; he was found to have hepatomegaly, erythematous abdominal and distal extremity rough maculopapular rash, lethargy, marked proximal hypotonia, distal hyperreflexia and hypertonia, jitteriness, alternating exotropia, and some dysmorphic features consisting of cupped ears, upturned nose, small chin, a unilateral simian crease, and pectus excavatum. The collecting system was slightly dilated and the kidneys slightly small; there were dense transverse metaphyseal bands in the long bones, an MRI scan of the brain was normal, brain-stem auditory evoked response evaluation was normal, spinal fluid was unremarkable, and chromosome analysis was normal. He underwent fundoplication and feeding gastrotomy because of inability to swallow without aspiration, and the exotropia was surgically corrected.

Evaluation for possible congenital infection was initially unrevealing, and the spinal fluid and serum were both negative for polyvalent EIA antibody to *B. burgdorferi*. However, because of the presence of metaphyseal bands (which were reminiscent of those in an earlier infant with congenital Lyme borreliosis), the maternal gestational history, and the maternal Lyme seropositivity, the diagnosis of late congenital Lyme borreliosis was still considered, and both the infant and mother were found to have positive responses in the *B. burgdorferi* in vitro LPA.

The child received a total of 7 weeks of intravenous ceftriaxone (100 mg/kg daily) between 2.5 and 7 months and showed dramatic improvement in neurologic function. When initial attempts were made to use a less aggressive and shorter course of intravenous ceftriaxone, he experienced relapse with evidence of loss of developmental milestones; finally, after a total of 7 weeks of intravenous ceftriaxone followed by a 1-year course of oral amoxicillin (40 mg/kg daily) from 7 months to 19 months of age, he remained clinically well and continued to progress to essentially normal neurologic status by 3 years of age. He had gradual resolution of the scaly erythematous maculopapular abdominal and distal extremity rash by the completion of the ceftriaxone therapy. He gradually improved neurologically, regained lost developmental milestones, and resolved the majority of his focal neurologic findings, including the subtle right hemiparesis, mild proximal hypotonia, and distal hyperreflexia, by 2 years of age. At follow-up at 3 years of age, he remained well, was at an appropriate developmental level, and was slowly learning to take food by mouth. At 8 years of age, he had reached an almost age-appropriate developmental and intellectual level, but developed regression of reading, spelling, and vocabulary skills, a seizure disorder, and episodic unilateral knee and ankle arthritis, with no additional *B. burgdorferi* exposure; the arthritis and deterioration of language skills responded to intravenous ceftriaxone therapy. At 9 years of age, he has regained almost all of the lost language skills, but exhibits delayed dentition and structural dental anomalies.

Figure 11–10*A* to *J* shows the gastroesophageal reflux, aspiration, strabismus, facial dysmorphia, severe hypotonia, rash, and metaphyseal bands in the first few months of life; Figure 11–10*K* shows the patient at 2 years of age.

Comments. This mother-infant pair illustrates the ability of *B. burgdorferi* to cause severe progressive neurologic deficits consistent with chronic

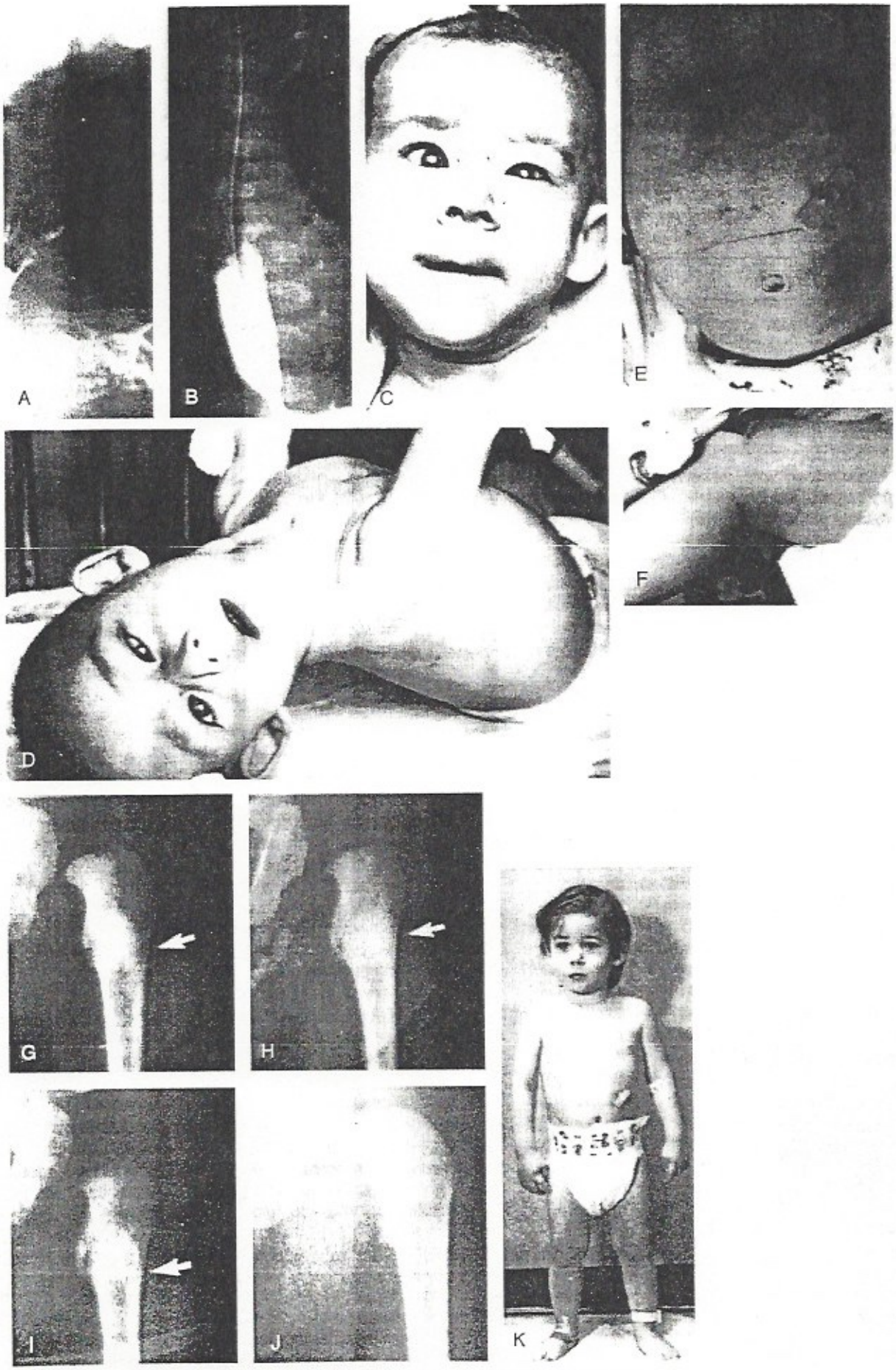

FIGURE 11–10 *See legend on opposite page*

neuroborreliosis, and the failure of oral erythromycin and oral cephalosporins to prevent these complications. However, the prolonged first-trimester courses of oral antibiotics may have sufficiently stabilized the gestational spirochetal infection to allow the pregnancy to be carried almost to term. Although there were several dysmorphic features in this infant, the significance of the cupped ears is unclear, as there were two other siblings with slightly "lop" ears.

The neurologic recovery of this patient during the prolonged course of antibiotic therapy and the near-normalization of his developmental level by 3 years of age lend support for such prolonged therapy until it appears that maximum recovery of neurologic function has occurred. The later development of arthritis, seizure disorder, and deterioration of language skills with no additional *B. burgdorferi* exposure, and improvement after antibiotic therapy are suggestive of a relapse of Lyme disease, and provide support for the use of additional antibiotic therapy for such relapses. The infant reported by Markowitz and colleagues who was normal at birth and later developed cortical blindness may represent this type of clinical manifestation of congenital Lyme borreliosis.[36] ■

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The demand for diagnostic testing for Lyme disease is great, particularly in Lyme-hyperendemic areas.[734–737]

False-positive serologic results for Lyme disease may occur because of cross-reactivity with other bacteria, particularly other spirochetes (Table 11–16); because of intra- or interlaboratory variability of assay results[529, 738, 739, 741]; or because of cross-reactivity seen in other diseases, including autoimmune disorders[224, 233, 236, 252, 742, 743] such as systemic lupus erythematosus, rheumatoid arthritis, and Reiter's disease; peridontal disease[245]; viral infections[233, 744–746] such as Epstein-Barr Virus (EBV), varicella-zoster Virus (VZV), and parvovirus B19; and non-Lyme meningoencephalitis or other neurologic diseases.[223, 233] Another problem is that seropositivity in residents of Lyme-endemic areas reflects the frequency of seropositivity of the area and may be unrelated to clinical illness.[254] Because ehrlichiosis and babesiosis occur in the same geographic distribution as Lyme borreliosis, and share many of the same tick vectors, seropositivity for these agents may reflect true exposure rather than cross-reactivity with *B. burgdorferi*[481–484, 486]; however, some cross-reactivity may be due to a heat shock protein of *B. burgdorferi* and the agent of human granulocytic ehrlichiosis (HGE) that shares amino acid sequence homology. Cross-reactivity is greatest, even by Western blot assay, between relapsing fever *Borreliae* and *B. burgdorferi*, which are usually distinguishable clinically, and are vectored by different tick species that do not share the same habitat niches; however, the geographic distribution of the tick vectors may overlap in some areas of the south central and southwestern United States.[477] Recognition that cross-reactivity may produce false-positive *B. burgdorferi* seroprevalence data in non–Lyme-endemic countries without known tick vectors is important.

False-negative serologic results may occur either because the sample was obtained early in the course of the Lyme disease before development of detectable *B. burgdorferi* immune responses,[222, 254] because early antibiotic therapy eliminated or blunted the *B. burgdorferi* immune response,[208, 209, 218, 232, 233, 254, 271, 272, 275] because of intra- or interlaboratory variability of assay results,[529, 738, 739, 741] because of regional antigenic strain variability, or because a low-level true-positive result is masked by cross-reacting antibody that necessitates a high "cut-off" for positivity.[739] Some patients reinfected with *B. burgdorferi* may have only an IgG response, and seropositivity may not be detected if only IgM assays are done in early reinfection.[233]

The practical ability to confirm or exclude Lyme disease by diagnostic assays remains a complicated and controversial problem. Continued development and clinical correlation of new diagnostic assays using increasingly sophisticated molecular biologic tools have improved diagnostic sensitivity and specificity, but the diagnosis of Lyme disease cannot be either made or excluded solely on the basis of these assays. Lyme disease must remain a clinical diagnosis, based on clinical and epidemiologic history, physical findings, and laboratory data other than *B. burgdorferi* serologic tests; the serologic test results may be considered either supportive or nonsupportive of the diagnosis, according to accepted guidelines.[238, 254, 478, 633, 748–750]

Diagnostic Tests

Diagnostic tests for Lyme disease are divided into several categories and are listed in Table 11–16. Practical problems with these tests are low sensitivity or low specificity, wide intra- and interlaboratory variability of the most common commercially available antibody de-

FIGURE 11–10 Congenital Lyme disease. An infant presented at 2½ months of age with developmental delay, hypotonia, failure to thrive, and recurrent aspiration pneumonia. *A*, Barium swallow at 2½ months shows aspiration of barium into the trachea. *B*, Esophagram shows reflux of barium from the stomach into the distal esophagus. *C* and *D*, At 5 months, the patient shows strabismus, a foreshortened nasal bridge, cupped ears, a small mouth and chin, and severe hypotonia. *E* and *F*, At 5 months, the patient had a persistent erythematous, maculopapular rash, most prominent on the trunk and proximal extremities, which faded with antibiotic therapy. Bone radiographs show *(G)* sclerotic metaphyseal bands at 2½ months of age (arrow), *(H)* fading metaphyseal bands after antibiotic therapy for 5 days (arrow), *(I)* further fading of the metaphyseal bands after antibiotic therapy for 6 days (arrow), and *(J)* resolution of the metaphyseal bands by 5 months of age. *K*, The patient at 25 months (patient 25 in Table 11–8).

TABLE 11–16
Cross-Reactivity Between *Borrelia burgdorferi* and Other Spirochetes, *Babesia*, and *Ehrlichia*

	% OF PRIMARY DISEASE SERA WITH POSITIVE RESULT BY DIAGNOSTIC TEST									
							Babesiosis[c]		Ehrlichiosis[d]	
DIAGNOSTIC TEST	Lyme	Syphilis	Yaws, Pinta	Borrelial Relapsing Fever[a]	*Borrelia coriaceae*[b]	Leptospirosis	*B.m.*	WA1	HGE	HME
Bb IFA[e]		13–61	28–40	50	63	0–14			36	2
Bb ELISA[f]		20–100	40–43	45–100[g]		0–23	0	0	0–86[h]	0
ELISA-AC		0–4				5				
Bb WB[i]		0–50		64–100[g]		5–17	0	0	23–90[h]	0
WB (stringent)		0–9								
FTA-Abs[j]	6–43									
MHA-TP[k]	0									
RPR[l]	0									
VDRL[m]	0									
TP WB[n]	0–67									
Other borreliae[o], IFA	54–85									
Leptospira MA[p]	0									
B. microti IFA	0	0						0	0	0
B. microti ELISA	0									
B. microti WB	0									<10
WA1	0									0
HGE IFA	0–6	0		0			0	0		0
HGE ELISA	4–26	0		0						0
HGE WB	4–13	0		0						
HME IFA	0	0					0	3	11–56	
HME WB									0	

[a]*B. hermsii* and *B. recurrentis*, as well as many other borreliae, are the major causes of relapsing fever.
[b]*B. coriaceae* is endemic in soft ticks in California but rarely causes human illness.
[c]*B.m.* = *Babesia microti*; WAI = *Babesia* species WA1.
[d]HGE = human granulocytic ehrlichiosis; HME = human monocytic ehrlichiosis.
[e]*Bb* IFA = *B. burgdorferi* immunofluorescence assay.
[f]ELISA = enzyme-linked immunosorbent assay; ELISA-AC = antibody capture ELISA.
[g]This represents only two patients in one group of two.
[h]Some of these results may represent past or current co-infection rather than cross-reactivity.
[i]WB = Western blot, results from all references listed; WB (stringent) = results from references 233–236, using stringent criteria for positivity.
[j]FTA-Abs = fluorescent treponemal antibody absorption test.
[k]MHA-TP = microhemagglutination assay for antibodies to *Treponema pallidum*.
[l]RPR = rapid plasma reagin test.
[m]VDRL = Venereal Disease Research Laboratory test.
[n]TP WB = *Treponema pallidum* WB.
[o]Other borreliae, IFA = immunofluorescence assay for other borreliae, including *B. hermsii*, a major cause of relapsing fever, and *B. coriaceae*.
[p]MA = microhemagglutination assay for antibodies to *Leptospira*.
Data obtained from references 20, 112, 233–236, 245, 401, 485, 487, 488, 498, 621, 746, 747, 757, 758, and 762.

tection tests,[529, 738, 739, 741, 750] and lack of availability of some of the better research laboratory tests.

CULTURE

The organism grows best in liquid Barbour-Stoenner-Kelly medium II (BSK II)[81, 91] at 35° C, usually takes 2 to 6 weeks to grow, is usually detected by dark-field examination of culture medium every 1 to 2 weeks, and is confirmed as *B. burgdorferi* by IFA with *B. burgdorferi*–specific monoclonal or other antibody, or by *B. burgdorferi*–specific PCR.[175] Use of PCR analysis to detect *B. burgdorferi* growth in culture fluids has produced more rapid detection of positive cultures, with detection of 95% of positive cultures 2 weeks after inoculation, compared with 70% by microscopic examination.[175] Culture is the "gold standard" for confirmation of Lyme disease, but disadvantages of culture are that generally it is not available outside of research institutions, it is cumbersome and time-consuming and is often positive only very early in untreated infection, and the overall yield is quite low.

Under optimal conditions, isolation rates from biopsies of active untreated EM skin lesions usually range from 28 to 86%[19, 79, 175, 183, 184] ACA lesions from 10 to 26%[19, 20, 436]; rates are much lower from other sites. Isolation rates from antibiotic-treated or partially treated EM lesions are 0 to 8%,[175, 183, 436] from normal-appearing skin after spontaneous resolution of EM lesions 8%,[436] and from partially treated ACA lesions 0%.[436] Berger and associates achieved an isolation rate of 86% by biopsy inside the peripheral border of the lesion,[183] and 57% by biopsy of perilesional skin just outside the peripheral border; the isolation rate was higher in EM from disseminated infection (88%), than from localized infection (71%); it was 100% in untreated disseminated infection.[183]

The rate of isolation of *B. burgdorferi* from blood

cultures has usually been 1 to 6%[80, 591, 751] in Lyme borreliosis even though hematogenous dissemination occurs clinically. In 1998, Wormser and colleagues[591] found that by using 3 ml of serum instead of 3 ml of whole blood, and inoculating samples within 3 hours of collection, positive cultures were detectable in 2.7 rather than 7.7 weeks, and positive cultures could be obtained in 20% of untreated early EM patients with solitary EM, 50% of untreated early multiple EM patients, and 25% overall of untreated early EM patients. Culturing a larger volume of serum by obtaining six simultaneously drawn 3-ml serum samples increased the yield, especially in patients with solitary EM. Patients with multiple EM had more positive blood cultures than those with single EM, indicating a higher level of spirochetemia. Goodman and co-workers[280] found higher rates of both culture and PCR positivity from plasma than from whole blood, and of PCR positivity from plasma than from serum, indicating possible concentration of spirochetes in plasma.

B. burgdorferi has been successfully grown from skin biopsy specimens of EM,[18, 79, 183, 184, 432] BL,[22] cutaneous B cell lymphoma,[647] ACA,[20, 436] and tick bite site skin biopsies,[307, 752] and of blood,[80, 591] CSF,[95] iris,[284] synovium or joint fluid,[200] ligamentous tissue,[304] bone,[699] myocardium,[607] and placental and fetal tissues.[32–35]

SILVER AND IMMUNOFLUORESCENT STAINS

B. burgdorferi spirochetes may be visualized by Dieterle,[16] Warthin-Starry,[33–35, 79] or Bosma-Steiner[94] silver staining, or by *B. burgdorferi*–specific immunohistochemical monoclonal or polyclonal antibody staining of tissue, or immuno-electron microscopy of blood or CSF.[620] The Bosma-Steiner modification of the Warthin-Starry stain has resulted in much improved sensitivity for demonstration of *B. burgdorferi*.[94]

B. burgdorferi has a characteristic morphology by silver staining that is distinct from that of other spirochetes and even other *Borrelia* species; they are sharply demarcated, short or long, coiled, undulating, or elongated straight forms, of equal thickness, with no irregularities or granularity, and they are found sparsely in tissues, in the superficial dermal papillae, often between collagen fibers, or in vessel walls.[597] *B. burgdorferi* spirochetes have also been found in the endomysial space in a myocardial biopsy by silver staining.[308] Its morphologic appearance may vary in different tissues and with the serologic status of the patient.

The specificity of immunohistochemical staining, including immunogold silver staining, is greater than that of silver staining alone. The sensitivity of detection of *B. burgdorferi* by staining ranges from 25 to 100%.

Spirochetes have been demonstrated in multiple tissues.*

DARK-FIELD EXAMINATION

Dark-field microscopy is not a sensitive method for visualization of *B. burgdorferi* because the number of organisms in infected tissues is very small and the yield is essentially zero, with occasional rare exceptions.[18]

POLYMERASE CHAIN REACTION

PCR is generally considered more sensitive than either culture or special stains for detection of *B. burgdorferi* in multiple tissues or body fluids; it is much faster than culture, providing results in a few days rather than the several weeks required for culture detection of *B. burgdorferi*.[185–187, 317] The sensitivity of PCR for detection of *B. burgdorferi* is highest in fresh or fresh-frozen specimens,[187] but PCR, using short DNA segments to detect DNA degraded by fixation, has even detected *B. burgdorferi* DNA extracted from 67% of de-paraffinized formalin-fixed, paraffin-embedded EM skin biopsies.[753]

Different PCR target gene sequences have been used to detect *B. burgdorferi*.[187] Use of sequences for the 41-kd flagellar antigen and 34-kd Osp B in PCR improved the sensitivity of detection of *B. burgdorferi* in CSF to 67% of patients with very early disseminated Lyme disease, even when CSF *B. burgdorferi* antibody was still negative.[282] Use of an Osp A gene sequence and use of a *B. burgdorferi* RNA polymerase gene sequence detected *B. burgdorferi* DNA in serum and plasma, respectively, of early Lyme disease patients, even before seropositivity developed.[280, 281]

In a comparative study that used a sequence from the *B. burgdorferi* RNA polymerase C gene, PCR was more sensitive than culture for detection of spirochetemia.[280] Other studies, however, have achieved higher culture positivity but did not directly compare PCR.[591]

The *B. burgdorferi* PCR is 100% specific if performed in a reliable laboratory without cross-contamination because the DNA target sequences are selected specifically for lack of cross-reactivity with other spirochetes.[143, 185, 753] These sequences are not present in other closely related *Borrelia* species or other spirochetes, and they are highly conserved among *B. burgdorferi* strains. PCR is generally considered to be useful in the detection of small numbers of *B. burgdorferi* in tissue or body fluid samples,[280–282, 591, 755] is particularly useful in the diagnosis of very early Lyme disease before standard serologic assays become positive,[280, 281] and may be more sensitive and less cumbersome than culture, but its use is limited to research facilities. Although reports of *B. burgdorferi* CSF, plasma, synovial fluid, or skin biopsy, or of urine PCR positivity converting to negativity after antibiotic therapy of neuroborreliosis,[287, 309–311] arthritis,[312, 314] EM,[316, 754] ACA,[143, 316] and BL,[754] suggest a correlation of PCR positivity with active infection, the role of PCR in decisions about antibiotic therapy has not been definitively established[186, 187, 324]; a positive *B. burgdorferi* PCR indicates presence of *B. burgdorferi* antigens; this may be due to either past or present *B. burgdorferi* infection, but it provides no information on organism viability or persistence of active infection because it detects even degraded DNA or residual DNA fragments present inside membrane bound blebs[102, 103] produced by *B. burgdorferi*.[186, 187] PCR has often been noted to have increased sensitivity for the detection of *B. burgdorferi* in clinical specimens obtained from patients after a few

*See references 25, 32–35, 38, 41, 43, 82, 267, 596, 597, 605, 607, 617, 618, 620, 623, and 695.