throughout the tropics and subtropics, where it is highly prevalent though often unrecognized. The incidence peaks from April through June in southern Texas and during the warm months of summer and early fall in other geographic locations. Patients seldom recall exposure to fleas, although exposure to animals such as cats, opossums, and rats is reported in nearly 40% of cases.

Clinical Manifestations The incubation period of experimental murine typhus averages 11 days (range, 8–16 days). Headache, myalgia, arthralgia, nausea, and malaise develop 1–3 days before onset of chills and fever. Nearly all patients experience nausea and vomiting early in the illness.

The duration of untreated illness averages 12 days (range, 9–18 days). Rash is present in only 13% of patients at presentation for medical care (usually ~4 days after onset of fever), appearing an average of 2 days later in half of the remaining patients and never appearing in the others. The initial macular rash is often detected by careful inspection of the axilla or the inner surface of the arm. Subsequently, the rash becomes maculopapular, involving the trunk more often than the extremities; it is seldom petechial and rarely involves the face, palms, or soles. A rash is detected in only 20% of patients with darkly pigmented skin.

Pulmonary involvement is frequently prominent; 35% of patients have a hacking, nonproductive cough, and 23% of patients who undergo chest radiography have pulmonary densities due to interstitial pneumonia, pulmonary edema, and pleural effusions. Bibasilar rales are the most common pulmonary sign. Less common clinical manifestations include abdominal pain, confusion, stupor, seizures, ataxia, coma, and jaundice. Clinical laboratory studies frequently reveal anemia and leukopenia early in the course, leukocytosis late in the course, thrombocytopenia, hyponatremia, hypoalbuminemia, mildly increased serum hepatic aminotransferases, and prerenal azotemia. Complications can include respiratory failure, hematemesis, cerebral hemorrhage, and hemolysis. Severe illness necessitates the admission of 10% of hospitalized patients to an intensive care unit. Greater severity is generally associated with old age, underlying disease, and treatment with a sulfonamide; the case-fatality rate is 1%. In a study of children with murine typhus, 50% suffered only nocturnal fevers, feeling well enough for active daytime play.

Diagnosis and Treatment Serologic studies of acute- and convalescent-phase sera can provide a diagnosis, and an immunohistochemical method for identification of typhus group-specific antigens in biopsy samples has been developed. Cultivation and PCR are used only infrequently and are not widely available. Nevertheless, most patients are treated empirically with doxycycline (100 mg bid orally for 7–15 days) on the basis of clinical suspicion. Ciprofloxacin provides an alternative if doxycycline is contraindicated.

SCRUB TYPHUS

Epidemiology *O. tsutsugamushi* differs substantially from *Rickettsia* species both genetically and in cell wall composition (i.e., it lacks lipopolysaccharide). *O. tsutsugamushi* is maintained by transovarial transmission in trombiculid mites. After hatching, infected larval mites (chiggers, the only stage that feeds on a host) inoculate organisms into the skin. Infected chiggers are particularly likely to be found in areas of heavy scrub vegetation during the wet season, when mites lay eggs.

Scrub typhus is endemic and reemerging in eastern and southern Asia, northern Australia, and islands of the western Pacific and Indian Oceans. Infections are prevalent in these regions; in some areas, >3% of the population is infected or reinfected each month. Immunity wanes over 1–3 years, and the organism exhibits remarkable antigenic diversity.

Clinical Manifestations Illness varies from mild and self-limiting to fatal. After an incubation period of 6–21 days, onset is characterized by fever, headache, myalgia, cough, and gastrointestinal symptoms. Some patients recover spontaneously after a few days. The classic case description includes an eschar where the chigger has fed, regional lymphadenopathy, and a maculopapular rash—signs that are seldom seen in indigenous patients. Fewer than 50% of Westerners develop an eschar, and fewer than 40% develop a rash (on day 4–6 of illness). Severe cases typically manifest with encephalitis and interstitial pneumonia due to vascular injury. The case-fatality rate for untreated classic cases is 7% but would probably be lower if all mild cases were diagnosed.

Diagnosis and Treatment Serologic assays (indirect fluorescent antibody, indirect immunoperoxidase, and enzyme immunoassays) are the mainstays of laboratory diagnosis. PCR amplification of *Orientia* genes from eschars and blood also is effective. Patients are treated with doxycycline (100 mg bid orally for 7–15 days), azithromycin (500 mg orally for 3 days), or chloramphenicol (500 mg qid orally for 7–15 days). Some cases of scrub typhus in Thailand are caused by strains that have high doxycycline or chloramphenicol minimal inhibitory concentrations (MICs) but that are susceptible to azithromycin and rifampin.

EHRLICHIOSES AND ANAPLASMOSIS

Ehrlichioses are acute febrile infections caused by members of the family Anaplasmataceae, which is made up of obligately intracellular organisms of five genera: *Ehrlichia*, *Anaplasma*, *Wolbachia*, *Candidatus* Neoehrlichia, and *Neorickettsia*. The bacteria reside in vertebrate reservoirs and target vacuoles of hematopoietic cells (Fig. 211-4). Three *Ehrlichia* species and one *Anaplasma* species are transmitted by ticks to humans and cause infection that can be severe and prevalent. *E. chaffeensis*, the agent of HME, and an *E. muris*–like agent (EMLA) infect predominantly mononuclear phagocytes; *E. ewingii* and *A. phagocytophilum* infect neutrophils. Infection with *Candidatus* Neoehrlichia mikurensis is less well characterized, but the agent has been identified in human blood neutrophils.

Ehrlichia, *Candidatus* Neoehrlichia, and *Anaplasma* are maintained by horizontal tick-mammal-tick transmission, and humans are only inadvertently infected. Wolbachiae are associated with human filariasis, since they are important for filarial viability and pathogenicity; antibiotic treatment targeting wolbachiae is a strategy for filariasis control. Neorickettsiae parasitize flukes (trematodes) that in turn parasitize aquatic snails, fish, and insects. Only a single human neorickettsiosis has been described: sennetsu fever, an infectious mononucleosis–like illness that was first identified in 1953 and is associated with the ingestion of raw fish containing *N. sennetsu*–infected flukes.

HUMAN MONOCYTOTROPIC EHRLICHIOSIS

Epidemiology More than 8404 cases of *E. chaffeensis* infection had been reported to the Centers for Disease Control and Prevention (CDC) as of April 2013. However, active prospective surveillance has documented an incidence as high as 414 cases per 100,000 population

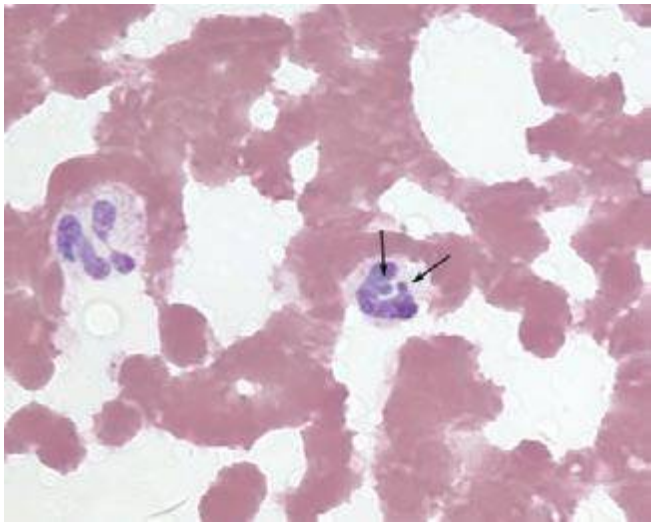

FIGURE 211-4 Peripheral-blood smear from a patient with human granulocytotropic anaplasmosis. A neutrophil contains two morulae (vacuoles filled with *A. phagocytophilum*). *(Photo courtesy of Dr. J. Stephen Dumler.)*