CLINICAL MICROBIOLOGY REVIEWS, July 1993, p. 193–198
0893-8512/93/030193-06$02.00/0

Vol. 6, No. 3

Q Fever

LARRY G. REIMER

Department of Pathology, University of Utah and Veterans Affairs Medical Center, Salt Lake City, Utah 84148

INTRODUCTION AND HISTORICAL BACKGROUND

In 1935, a number of employees of a meat-packing plant in Brisbane, Queensland, Australia, developed an acute febrile illness but had negative blood and serologic tests for pathogens known to exist at that time (22). John Derrick, the investigator of the outbreak, described a consistent pattern of illness and suggested that this pattern indicated a single entity, which he named "Q" fever. The "virus" of Q fever was transmissible from human blood and urine samples to guinea pigs but could not be cultivated on the usual laboratory media. Even though the etiologic agent was called a virus, rickettsia-like bodies were identified in the spleens of infected laboratory animals. The illness most closely resembled psittacosis or typhus, with acute onset of high fever, headache, and slow pulse, but it did not have an associated rash.

Burnet, using material provided by Derrick, decided that the etiologic organism was a rickettsia (16), leading to its first name, *Rickettsia burneti*. Subsequent work on what eventually proved to be the same organism by Davis and Cox at Nine Mile Creek, Montana (21), was also important in the early understanding of Q fever.

MICROBIOLOGY

Since the first description, the etiologic agent of Q fever has been renamed *Coxiella burnetii*, and it is now identified as a member of the family *Rickettsiaceae*. Assignation to a new genus occurred because of a variety of differences between the Q fever agent and members of the genus *Rickettsia*.

C. burnetii has a guanine-plus-cytosine ratio of 42% compared with 29 to 33% for other rickettsiae (7). This organism is transmitted to humans by inhalation from inanimate as well as animal vector sources rather than by the cutaneous inoculation that is the case for other members of this family. *C. burnetii* grows primarily in cytoplasmic vacuoles (17). It is also more resistant to high temperature, low pH, and environmental drying (7).

Phase variation of the surface lipopolysaccharide of *C. burnetii* is dependent on environmental conditions. Phase I, the virulent phase, is that seen in animal and human hosts with established infection. Phase II occurs after serial passage in the laboratory. Phase I and II organisms differ in amino acid and neutral sugar content, immunogenic surface proteins, surface charge, cell density, and resistance to phagocytosis by macrophages and lymphocytes (3). Further, there appear to be subtypes of lipopolysaccharide with phase I organisms. These subtypes can be demonstrated by immunoblots of lipopolysaccharide fractions, which show that only organisms antigenically in one subgroup are associated with endocarditis (30).

C. burnetii has been shown recently to contain plasmids (65). All isolates studied, whether they are in phase I or phase II, contain plasmids or plasmid sequences incorporated into the genome. Plasmid types appear to differ among isolates associated with different clinical syndromes (66).

C. burnetii cannot be grown by the usual bacteriologic laboratory methods, but it can be cultivated by inoculation into embryonated hen eggs. It can also be grown in cell culture with chicken embryo, mouse embryo fibroblast, green monkey kidney, tick tissue, and J774 and P388D1 macrophage-like tumor cell lines (7).

EPIDEMIOLOGY

Cattle, sheep, and goats are the primary reservoirs for Q fever (6). Infection in humans most often occurs after inhalation of aerosolized organisms or with ingestion of raw milk or fresh goat cheese (11, 13, 24, 46). In the late 1940s, the highest risk of acquisition was recognized as being related to exposure to parturient sheep (78). Latent infection in ewes is activated late in pregnancy. *C. burnetii* appears in the blood and is excreted in urine and feces, and amniotic fluid becomes heavily contaminated, with the placenta containing huge numbers of organisms (up to 10^{12} organisms per g) (72). Air-sampling studies have detected the organism at considerable distances from parturient ewes (34, 72). Because of the association with parturient animals, many cases of infection in humans occur during the birthing season.

C. burnetii withstands drying and can remain viable in contaminated soil for several years (72). The aerosolized organisms can also travel long distances, as evidenced by the

remote locations of individuals infected in laboratory outbreaks of disease (20, 34).

In recent years, several outbreaks of infection in medical research facilities working with pregnant ewes have been described (20, 34, 50, 69). Large numbers of individuals have developed either clinical illness or positive serologic results in such settings, often with minimal exposure to the sheep and usually without being directly involved in the research effort that utilizes the animals. The typical medical school allows research animals to be held in open areas, and no attempt to isolate them from uninvolved personnel and students is made. Secretaries, janitors, hospital patients, and medical, medical technology, and nursing students have all become infected. Individual exposures resulting in disease included riding in an elevator used previously to transport sheep, being in an office adjacent to a stairwell that opens into the animal quarters on another floor, and petting a sheep one time in a medical center corridor. The potential danger of having sheep in a medical center environment was described as early as 1971, when Schachter et al. identified a 16% seroprevalence rate for Q fever among established investigators versus 0% among new employees (68). More important, whereas many of the primary investigators and their work assistants were seropositive, most of the infections described in these outbreaks occurred in innocent bystanders. Because of these experiences, greater efforts to isolate research animals, especially sheep, are being made (12).

Other modes of transmission that have been described recently include exposure to parturient cats (42, 48, 57) and wild rabbits (49), urban exposure to manure brought from farms as fertilizer (64), and residence along the route of a sheep drive (18).

Occurrence of the disease in the United States is unusual, although public health reporting is required in only 24 states (67). Most reported cases are linked directly to an outbreak of some kind, although sporadic illness almost certainly occurs (9).

PATHOGENESIS

Little is known about the pathologic process associated with infection, since most patients recover, and few autopsy studies have been published. In lung infections, the gross findings resemble those of other bacterial pneumonias except that alveolar cells are mostly histiocytes rather than polymorphonuclear leukocytes. Hemorrhage and extensive areas of necrosis, suggesting vascular injury, are also present (75).

Liver biopsy samples from patients with hepatitis and bone biopsy samples in patients with osteomyelitis show primarily granuloma formation in the majority of patients. The granuloma may be nonspecific or may have a more distinctive doughnut appearance, with a central clear space surrounded by inflammatory cells and fibrin (54, 60, 71). Bone marrow necrosis, again suggesting a vascular lesion, has also been described (15).

The mechanism of involvement with cardiac valves in Q fever endocarditis is poorly understood; only a few cases have been described. Most cases involve the aortic or mitral valve in patients with preexisting valvular disease or prosthetic valves (27, 31, 39, 73, 74, 79), but occasionally cases involve previously normal valves (26). Infection is a very indolent process, since many of the cases described have occurred many years after apparent exposure to *C. burnetii*. Lesions on native valves have been described as including small perforations of the valve, multiple small, pale yellow to brown vegetations, small calcific nodular scleroses (31), and an aneurism at the base of the aorta accompanied by lesions of the aortic valve (31, 79). Major emboli in other organs have been described by some authors, suggesting the presence of significant vegetation formation at the site of infection (26, 73, 74, 77). Prosthetic valves have shown little or no evidence of infection in the valve ring. Instead, vegetation formation and a mild to moderate inflammatory response in infected bioprosthetic valve material or on the surfaces of mechanical valves have been found (27, 31).

C. burnetii enters cells passively, multiplies within cytoplasmic vacuoles (thus expanding the size of the cell), and ultimately destroys the cell. Some of the necrotic changes associated with infection by this organism may be caused by lysosomal enzymes released from the vacuole in addition to or in place of damage caused by the organism directly (7).

CLINICAL MANIFESTATIONS

When many individuals were exposed to *C. burnetii* and serological tests were performed, about 50% of the individuals did not develop overt clinical disease (50). Illness that does occur can be separated into acute and chronic stages (22, 67). These patterns of disease were initially described by Derrick in the original publications concerning Q fever (22) and have changed little since then.

Acute Infection

After an incubation period of 2 to 6 weeks, typical patients have acute onset of high fever, chills with rigors, severe headache and/or retroorbital pain, general malaise, and myalgia. Additional symptoms may include chest pain, cough, nausea, vomiting, and diarrhea. Symptomatology can vary from one individual to another, but fever, usually higher than 38.5°C, is invariably present. Physical signs of infection often include hepatomegaly and splenomegaly. In contrast to physical signs of other rickettsial diseases, rash is distinctly unusual (7, 19, 22, 24, 34, 58, 67, 70).

Q fever is usually described as an atypical pneumonia, although the actual incidence of respiratory illness with infection ranges widely, from few affected patients to >90% (67). Pneumonia occurs less frequently with disease acquired from research facilities than with disease acquired from other sporadic exposures (50). Chest X rays are not always performed, but when they are, infiltrates involving the lower lobes are found in 4 to 75% of patients (8, 19, 47, 58, 70). Similarly, in various reports, Q fever is described as a rare or frequent cause of community-acquired pneumonias in general. These variations may be related to types of exposures that occur in different geographic areas and to strain variations of the organism.

Chest X-ray patterns are usually similar to those seen with pneumonia caused by mycoplasmas, chlamydiae, and viruses. An unusual characteristic that has been described in some studies is the presence of round, segmental opacities throughout the lung fields (51).

Acute Q fever may also present as hepatitis with features suggestive of viral hepatitis (2). More common are simple elevations in liver function test results and jaundice. Hepatomegaly, hepatic tenderness, and jaundice are seen in as few as 10% of cases in some series and in as many as 65% in others (19, 59). Isolated elevation of liver function tests has been seen in 65 to 85% of cases (59, 70).

Most cases of Q fever are self-limited, with symptoms

resolving in 1 to 2 weeks. Rare complications that can occur as part of the initial illness include encephalitis, pericarditis, myocarditis, and hemolytic anemia. Q fever also has rarely been reported in the presence of other serious underlying diseases including Crohn's disease, Kawasaki syndrome, solid cancers, lymphomas, and leukemias (33, 61). Although the total number of such seriously infected patients is small, the outcome may be worse for them than for normal hosts. In one series, four of five such patients developed chronic infection with endocarditis and one died (61).

Chronic Infection

A small number of patients, probably fewer than 1% of those infected with *C. burnetii*, do not clear the organism and develop disease long after the initial illness or exposure. Most consider chronic disease to imply the presence of endocarditis, but in one series of 16 patients, 7 had endocarditis, 2 had possible other intravascular graft infections, and 7 had chronic febrile illnesses with high serologic titers for Q fever but no specific organ involvement (26). Documentation to prove that Q fever was the cause of illness in the latter cases was not definitive.

The best-described chronic entity with *C. burnetii* is endocarditis (26, 27, 31, 39, 73, 74, 79). Symptoms begin gradually as long as 1 to 20 years after initial infection. Endocarditis tends to occur in older patients (average age of 50), with the majority being males. Symptoms are present for several months before medical care is sought, by which time patients have typical manifestations of endocarditis: fever, hepatomegaly, spenomegaly, elevated liver function test results, microscopic hematuria, hypergammaglobulinemia, thrombocytopenia, petechiae, splinter hemorrhages, clubbing, and occasional evidence of emboli (67). About 90% of the time, patients with endocarditis have either a history of or current findings suggesting valvular heart disease. Almost half of all cases involve the aortic valve, 30% involve the mitral valve, 10% involve both valves, and the rest have not been specified (67). Unlike other causes of endocarditis and characteristic of this infection, routine blood cultures are negative. In any patient population with potential animal exposure, Q fever should always be considered a possible cause of culture-negative endocarditis, and appropriate serologic tests should be obtained.

Additional types of chronic infection are also described occasionally. Other sites of involvement include the liver, bone, aortic grafts, and uterus (26).

IMMUNITY

Humoral and cellular immunities both appear to play a role in the human response to infection with *C. burnetii*. After initial infection, antibodies are usually detected, and cell-mediated response as measured by skin test and lymphoproliferative response also occur (1, 23, 25, 35, 37, 80). While antibody response may be closely associated with the characteristics of acute disease, cell-mediated immunity is most important in the ultimate eradication of the organism and prevention of chronic manifestations of infection (35). Antibody formation to phase II antigens begins soon after infection, with immunoglobulin M (IgM) responses occurring within a few days and IgA and IgG responses occurring soon thereafter (25, 80). IgM responses to phase I antigen begin during convalescence and may persist at low levels for up to 2 years after acute infection. Patients with chronic manifestations of active Q fever do not have detectable IgM responses but have very high IgG and IgA responses to phase I antigen (25, 80).

Antibodies to *C. burnetii* appear to be important in promoting the uptake of the organism by macrophages and polymorphonuclear leukocytes (7). This uptake can have either positive or negative effects, since both killing and proliferation of *C. burnetii* require an intracellular location of the organism. The presence of antibody may also prevent infection, since in early experimental animal studies inoculation of antibody along with the organism prevented infection (1).

Both uptake and killing of the organism in experimental infection vary with the phase type at the time of inoculation. Phase I organisms are ingested and killed less effectively than phase II organisms (37). Phagocytosis is enhanced more by addition of phase I antibody than by addition of phase II antibody. On the other hand, both phase types can actually multiply within macrophages, phase I organisms more actively than phase II organisms (23).

The cell-mediated response to *C. burnetii* appears important in the inhibition of growth of intracellular organisms. One can enhance killing of *C. burnetii* in guinea pigs by instillation of immune but not nonimmune macrophages (38). Failures of specific cell-mediated responses to *C. burnetii* have been associated with development of chronic infection. In one study of four patients with endocarditis, profound lymphocyte unresponsiveness to *C. burnetii* antigens was found in all four patients; these results contrast with those for a group of patients with acute Q fever who all had active responses to the same antigens (40).

DIAGNOSIS

C. burnetii has been transmitted with minimal exposures in laboratory settings; hence, routine cultivation by clinical laboratories for diagnostic purposes is not recommended. In geographic locations where exposure is known to occur and patterns of illness are typical, specific laboratory diagnosis may not always be necessary. In sporadic cases, however, the illness can be severe enough and have such nonspecific characteristics that laboratory evaluation is required.

The approach to diagnosis is serologic. Antibodies to both phase I and phase II antibodies can be detected by a variety of methods. The method most widely used over the past two decades has been complement fixation (CF). More recently, indirect fluorescent-antibody (IFA) tests and enzyme-linked immunosorbent assays (ELISA) have been introduced. Of these methods, the IFA test is the most subjective, CF is the most tedious to perform, and ELISA is the most convenient to use on a large scale. IFA tests and ELISAs can be used to detect individual antibody subtypes, while CF detects predominantly IgG in all samples tested.

Multiple comparisons of different test methods have been performed. Dupuis et al. compared the IFA test with CF and found IFA tests to be more sensitive, although the authors stated that the general antibody profiles of both tests were similar (25). A more recent evaluation by the same group of investigators showed overall sensitivities of 94, 91, and 78% for ELISA, the IFA test, and CF, respectively, in 213 patients with previous disease (56). Detection of unrecognized disease in blood donors was also highest for ELISA. Specificities of positive tests appear to be similar for all three methods (56).

The pattern of positivity is also important in determining the stage of illness. The ratio of phase II to phase I antibodies is >1 in acute disease, ≥ 1 in subacute disease

(usually hepatitis), and <1 in chronic disease (53). Phase I antibody titers above 200 by CF and very high titers by ELISA and the IFA test appear diagnostic of chronic active infection (endocarditis) (55). The values that should be used to establish a diagnosis of endocarditis are not clearly defined.

It is important to recognize that individuals with previous infection remain seropositive for prolonged periods after their illnesses have resolved. Except for the high titers to phase I antigen seen in endocarditis, single positive titers cannot be used to establish a diagnosis in patients with known animal exposures.

TREATMENT

A number of antimicrobial agents have been used to treat infections caused by *C. burnetii*, and results have been variable. It has been difficult to evaluate the utility of each of these agents, since most patients improve with or without treatment, only a small number of patients go on to chronic or life-threatening infection, and the outcome for the small number of patients with chronic infection has not been radically altered by the choice of antimicrobial agent. Since which patients will eventually develop chronic, severe disease cannot always be predicted, it seems appropriate to attempt to treat most patients identified with active infection.

Since the organism does not grow on the usual laboratory media, in vitro studies of antimicrobial agents have been difficult. Methods used include cell culture assays, usually with L-929 mouse fibroblast cell lines, and inoculation of chicken embryos. By these methods, the most active agents include rifampin, sulfamethoxazole-trimethoprim, tetracycline and its analogs, and quinolones; somewhat active agents include chloramphenicol and erythromycin; and inactive agents include amoxicillin and amikacin (62, 82). Tests with other penicillins, aminoglycosides, and cephalosporins have not been reported recently. In susceptibility test studies, apparent susceptibility patterns have differed. Explanations for in vitro variations include differences among isolates and in the ages of the cell cultures used for inoculation of the organism-antimicrobial agent combination (81). The different degrees of resistance seen among different strains are most likely explained by variable permeability of the cell walls of these strains rather than by mutational alterations (81).

The choice of antimicrobial agent for treating disease in human cases is based more on tradition than on scientific study, since controlled clinical trials of different agents have not been performed. In acute infection, tetracycline shortens the duration of fever by about 50% when the drug is administered within the first 3 days of illness (67), and it remains the drug usually recommended in this setting (4). Cases of endocarditis have been treated with tetracyclines (26, 79) or tetracyclines combined with sulfamethoxazole-trimethoprim (27, 31, 76). A more recent paper described treatment with doxycycline alone and doxycycline combined with rifampin, a quinolone, or sulfamethoxazole-trimethoprim. There were too few patients to allow an adequate comparison of regimens, but those patients who received doxycycline with a quinolone tended to do better (43). It is apparent that antimicrobial agents administered to patients with endocarditis are not bactericidal. Prolonged therapy lasting up to 3 years or until antibody titers fall below an arbitrary value is recommended. Valve replacement has frequently been required (31, 39, 73).

PREVENTION

Attempts to prevent transmission of infection to humans have involved several strategies. Attempts to eradicate infection from animal herds have been either unsuccessful or too costly, although there is some evidence that herds with lower rates of positivity have a smaller risk of transmission than herds with larger rates (63). Vaccination programs for dairy cattle have decreased the number of organisms shed by parturient animals but have not eliminated *C. burnetii* completely (14, 28). Since most animals are asymptomatic and some may shed the organism despite being seronegative (32), it is difficult to screen for or eradicate infection in all of them (63). Attempts at identifying disease-free herds for use in research facilities have therefore been unsuccessful.

Isolation precautions in research facilities have been introduced recently to limit exposure of researchers and also of innocent bystanders in research and medical facilities (12, 29).

Researchers and others at high occupational risk are often vaccinated (10, 36, 52, 67, 80). Vaccines made up of variable combinations of phase I or phase II antigens to various strains of *C. burnetii* have been in existence since 1938. Vaccines to phase I antigen appear much more potent. A majority of individuals receiving vaccine develop antibodies, and results of some studies have suggested that vaccine provides protection against disease, most recently in abattoir workers in Australia (45). The appropriate marker for determining an adequate protective response to vaccination, however, has not been established. Skin test reactions to intradermal administration of vaccine may work best, but severe local skin reactions to vaccine are a persistent problem, primarily in individuals who have preexisting antibody from natural exposure (41, 44). Such reactions have been dramatic enough to require surgical drainage of subcutaneous abscesses in some instances. A recent phase I vaccine developed by the U.S. Army appears promising for use in high-risk individuals (5).

CONCLUSIONS

Since the original description of Q fever by Derrick (22), much work has been accomplished. Beginning with the identification of the etiologic agent as a member of the rickettsial group, we have come to understand a great deal about the complex nature of *C. burnetii*, particularly its complex surface structure resulting in phase variation. Much of the recent effort to understand *C. burnetii* has arisen from the large number of biomedical scientists who have been infected with this agent within their own research institutions. Outbreaks of Q fever in medical facilities continue to occur where research on sheep is undertaken without adequate isolation precautions. The human response to the infection is complex; both humoral and cellular immunities are important in controlling infection, which results in self-limited disease in most individuals. The occasional patient who does not control the organism may have a prolonged, difficult illness that can tax our diagnostic and therapeutic acumen.

Continued efforts to understand the nature of the disease process in such individuals and to develop more effective preventive measures for individuals and populations at high risk of acquiring infection with *C. burnetii* are needed.

REFERENCES

1. **Abinanti, F. R., and B. P. Marmion.** 1975. Protective or neutralizing antibody in Q fever. Am. J. Hyg. **66**:173–195.

2. **Alkan, W. J., Z. Evenchik, and J. Eshchar.** 1965. Q fever and infectious hepatitis. Am. J. Med. **38:**54–61.
3. **Amano, K.-I., and J. C. Williams.** 1984. Chemical and immunological characterization of lipopolysaccharides from phase I and phase II *Coxiella burnetii*. J. Bacteriol. **160:**994–1002.
4. **Anonymous.** 1992. The choice of antibacterial drugs. Med. Lett. **34:**49–56.
5. **Ascher, M. S., M. A. Berman, and R. Ruppanner.** 1983. Initial clinical and immunologic evaluation of a new phase I Q fever vaccine and skin test in humans. J. Infect. Dis. **148:**214–222.
6. **Babudieri, B.** 1959. Q fever: a zoonosis. Adv. Vet. Sci. **5:**81–154.
7. **Baca, O. G., and D. Paretsky.** 1983. Q fever and *Coxiella burnetii*: a model for host-parasite interactions. Microbiol. Rev. **47:**127–149.
8. **Baranda, M. M., J. C. Carranceja, and C. A. Errasti.** 1985. Q fever in the Basque country: 1981–1984. Rev. Infect. Dis. **7:**700–701.
9. **Bell, J. A., M. D. Beck, and R. J. Huebner.** 1950. Epidemiologic studies of Q fever in southern California. JAMA **142:**868–872.
10. **Bell, J. F., L. Luoto, M. Casey, and D. B. Lackman.** 1964. Serologic and skin-test response after Q fever vaccination by the intracutaneous route. J. Immunol. **93:**403–408.
11. **Benson, W. W., D. W. Brock, and J. Mather.** 1963. Serologic analysis of a penitentiary group using raw milk from a Q fever infected herd. Public Health Rep. **78:**707–710.
12. **Bernard, K. W., G. L. Parham, W. G. Winkler, and C. G. Helmick.** 1982. Q fever control measures: recommendations for research facilities using sheep. Infect. Control **3:**461–465.
13. **Biberstein, E. L., D. E. Behymer, R. Bushnell, G. Crenshaw, H. P. Ripmann, and C. E. Franti.** 1974. A survey of Q fever (*Coxiella burnetii*) in California dairy cows. Am. J. Vet. Res. **35:**1577–1582.
14. **Biberstein, E. L., H. P. Riemann, C. E. Franti, D. E. Behymer, R. Ruppanner, R. Bushnell, and G. Crenshaw.** 1977. Vaccination of dairy cattle against Q fever (*Coxiella burnetii*): results of field trials. Am. J. Vet. Res. **38:**189–193.
15. **Brada, M., and A. J. Bellingham.** 1980. Bone-marrow necrosis and Q fever. Br. Med. J. **281:**1108–1109.
16. **Burnet, F. M., and M. Freeman.** 1937. Experimental studies on virus of "Q" fever. Med. J. Aust. **2:**299–305.
17. **Burton, P. R., J. Stueckemann, R. M. Welsh, and D. Paretsky.** 1978. Some ultrastructural effects of persistent infections by the rickettsia *Coxiella burnetii* in mouse L cells and green monkey kidney (vero) cells. Infect. Immun. **21:**556–566.
18. **Centers for Diseases Control.** 1984. Q fever outbreak—Switzerland. Morbid. Mortal. Weekly Rep. **33:**355–356, 361.
19. **Clark, W. H., E. H. Lennette, O. C. Railsback, and M. S. Romer.** 1951. Q fever in California. VII. Clinical features in one hundred eighty cases. Arch. Intern. Med. **88:**155–167.
20. **Commission on Acute Respiratory Diseases.** 1946. A laboratory outbreak of Q fever caused by the Balkan grippe strain of *Rickettsia burnetii*. Am. J. Hyg. **44:**123–167.
21. **Davis, G., and H. R. Cox.** 1938. A filter-passing infectious agent isolated from ticks: isolation from *Dermacentor andersoni*, reactions in animals, and filtration experiments. Public Health Rep. **5:**2259–2267.
22. **Derrick, E. H.** 1937. "Q" fever, a new fever entity: clinical features, diagnosis, and laboratory investigation. Med. J. Aust. **2:**281–299.
23. **Downs, C. M.** 1968. Phagocytosis of *Coxiella burnetii*, phase I and phase II by peritoneal monocytes from normal and immune guinea pigs and mice. Zentralbl. Bakteriol. Parasitenkd. Infektionskr. **206:**329–343.
24. **Dupont, H. T., D. Raoult, P. Brouqui, F. Janbon, D. Peyramond, P.-J. Weiller, C. Chicheportiche, M. Nezri, and R. Poirier.** 1992. Epidemiologic features and clinical presentation of acute Q fever in hospitalized patients: 323 French cases. Am. J. Med. **93:**427–434.
25. **Dupuis, G., O. Peter, M. Peacock, W. Burgdorfer, and E. Haller.** 1985. Immunoglobulin responses to acute Q fever. J. Clin. Microbiol. **22:**484–487.
26. **Ellis, M. E., C. C. Smith, and M. A. J. Moffat.** 1983. Chronic or fatal Q-fever infection: a review of 16 patients seen in north east Scotland (1967–1980). Q. J. Med. **52:**54–66.
27. **Fernandez-Guerrero, M. L., J. M. Muelas, J. M. Aguado, G. Renedo, J. Fraile, F. Soriano, and E. Villalobos.** 1988. Q fever endocarditis on porcine bioprosthetic valves. Ann. Intern. Med. **108:**209–213.
28. **Geddes, A. M.** 1983. Q fever. Br. Med. J. **287:**927–928.
29. **Grant, C. G., M. S. Ascher, K. W. Bernard, R. Ruppanner, and H. Vellend.** 1985. Q fever and experimental sheep. Infect. Control **6:**122–123.
30. **Hackstadt, T.** 1986. Antigenic variation in the phase I lipopolysaccharide of *Coxiella burnetii* isolates. Infect. Immunol. **52:**337–340.
31. **Haldane, E. V., T. J. Marrie, R. S. Faulkner, S. H. S. Lee, J. H. Cooper, D. D. MacPherson, and T. J. Montague.** 1983. Endocarditis due to Q fever in Nova Scotia: experience with five patients in 1981–1982. J. Infect. Dis. **148:**978–985.
32. **Hall, C. J., S. J. Richmond, and E. O. Caul.** 1982. Laboratory outbreak of Q fever acquired from sheep. Lancet **i:**1004–1006.
33. **Heard, S. R., C. J. Ronalds, and R. B. Health.** 1985. *Coxiella burnetii* infection in immunocompromised patients. J. Infect. **11:**15–18.
34. **Hornibrook, J. W., and K. R. Nelson.** 1940. An institutional outbreak of pneumonitis. I. Epidemiologic and clinical studies. Public Health Rep. **55:**1936–1954.
35. **Humphries, R. C., and D. J. Hinrichs.** 1981. Role for antibody in *Coxiella burnetii* infection. Infect. Immun. **31:**641–645.
36. **Izzo, A. A., B. P. Marmion, and D. A. Worswick.** 1988. Markers of cell-mediated immunity after vaccination with an inactivated, whole-cell Q fever vaccine. J. Infect. Dis. **157:**781–789.
37. **Kazar, J., E. Skultetyova, and R. Brezina.** 1975. Phagocytosis of *Coxiella burneti* by macrophages. Acta Virol. **19:**426–431.
38. **Kelly, M. T.** 1977. Activation of guinea pig macrophages by Q fever rickettsiae. Cell. Immunol. **28:**198–205.
39. **Kimbrough, R. C., III, R. A. Ormsbee, M. Peacock, W. R. Rogers, R. W. Bennetts, J. Raaf, A. Krause, and C. Gardner.** 1979. Q fever endocarditis in the United States. Ann. Intern. Med. **91:**400–402.
40. **Koster, F. T., J. C. Williams, and J. S. Goodwin.** 1985. Cellular immunity in Q fever: specific lymphocyte unresponsiveness in Q fever endocarditis. J. Infect. Dis. **152:**1283–1289.
41. **Lackman, D. B., E. J. Bell, J. F. Bell, and E. G. Pickens.** 1962. Intradermal sensitivity testing in man with a purified vaccine for Q fever. Am. J. Public Health **52:**87–93.
42. **Langley, J. M., T. J. Marrie, A. Covert, D. M. Waag, and J. C. Williams.** 1988. Poker players' pneumonia. An urban outbreak of Q fever following exposure to a parturient cat. N. Engl. J. Med. **319:**354–356.
43. **Levy, P. Y., M. Drancourt, J. Etienne, J. C. Auvergnat, J. Beytout, J. M. Sainty, F. Goldstein, and D. Raoult.** 1991. Comparison of different antibiotic regimens for therapy of 32 cases of Q fever endocarditis. Antimicrob. Agents Chemother. **35:**533–537.
44. **Luoto, L., J. F. Bell, M. Casey, and D. B. Lackman.** 1963. Q fever vaccination of human volunteers. I. The serologic and skin-test response following subcutaneous injections. Am. J. Hyg. **78:**1–15.
45. **Marmion, B. P., R. A. Ormsbee, M. Kyrkou, J. Wright, D. Worswick, S. Cameron, A. Esterman, B. Feery, and W. Collins.** 1984. Vaccine prophylaxis of abattoir-associated Q fever. Lancet **ii:**1411–1414.
46. **Marmion, R. A., and M. G. P. Stoker.** 1950. Q fever in Britain. Epidemiology of an outbreak. Lancet **ii:**611–616.
47. **Marrie, T. J., E. V. Haldane, R. S. Faulkner, C. Kwan, B. Grant, and F. Cook.** 1985. The importance of *Coxiella burnetii* as a cause of pneumonia in Nova Scotia. Can. J. Public Health **76:**233–236.
48. **Marrie, T. J., A. MacDonald, H. Durant, L. Yates, and L. McCormick.** 1988. An outbreak of Q fever probably due to contact with a parturient cat. Chest **93:**98–103.
49. **Marrie, T. J., W. F. Schlech III, J. C. Williams, and L. Yates.** 1986. Q fever pneumonia associated with exposure to wild rabbits. Lancet **i:**427–429.

50. **Meiklejohn, G., L. G. Reimer, P. S. Graves, and C. Helmick.** 1981. Cryptic epidemic of Q fever in a medical school. J. Infect. Dis. **144:**107–113.
51. **Millar, J. K.** 1978. The chest film findings in 'Q' fever—a series of 35 cases. Clin. Radiol. **29:**371–375.
52. **Peacock, M. G., P. Fiset, R. A. Ormsbee, and C. L. Wisseman, Jr.** 1979. Antibody response in man following a small intradermal inoculation with *Coxiella burnetii* phase I vaccine. Acta Virol. **23:**73–81.
53. **Peacock, M. G., R. N. Philip, J. C. Williams, and R. S. Faulkner.** 1983. Serological evaluation of Q fever in humans: enhanced phase I titers of immunoglobulins G and A are diagnostic for Q fever endocarditis. Infect. Immun. **41:**1089–1098.
54. **Pellegrin, M., G. Delsol, J. C. Auvergnat, J. Familiades, H. Faure, M. Guiu, and J. J. Voigt.** 1980. Granulomatous hepatitis in Q fever. Hum. Pathol. **11:**51–57.
55. **Peter, O., G. Dupuis, D. Bee, R. Luthy, J. Nicolet, and W. Burgdorfer.** 1988. Enzyme-linked immunosorbent assay for diagnosis of chronic Q fever. J. Clin. Microbiol. **26:**1978–1982.
56. **Peter, O., G. Dupuis, M. G. Peacock, and W. Burgdorfer.** 1987. Comparison of enzyme-linked immunosorbent assay and complement fixation and indirect fluorescent-antibody tests for detection of *Coxiella burnetii* antibody. J. Clin. Microbiol. **25:**1063–1067.
57. **Pinsky, R. L., D. B. Fishbein, C. R. Greene, and K. F. Gensheimer.** 1991. An outbreak of cat-associated Q fever in the United States. J. Infect. Dis. **164:**202–204.
58. **Powell, O.** 1960. "Q" fever: clinical features in 72 cases. Australas. Ann. Med. **9:**214–223.
59. **Powell, O. W.** 1961. Liver involvement in "Q" fever. Australas. Ann. Med. **10:**52–58.
60. **Qizilbash, A. H.** 1983. The pathology of Q fever as seen on liver biopsy. Arch. Pathol. Lab. Med. **107:**364–367.
61. **Raoult, D., P. Brouqui, B. Marchou, and J.-A. Gastaut.** 1992. Acute and chronic Q fever in patients with cancer. Clin. Infect. Dis. **1:**127–130.
62. **Raoult, D., H. Torres, and M. Drancourt.** 1991. Shell-vial assay: evaluation of a new technique for determining antibiotic susceptibility, tested in 13 isolates of *Coxiella burnetii*. Antimicrob. Agents Chemother. **35:**2070–2077.
63. **Ruppanner, R., D. Brooks, C. E. Franti, D. E. Behymer, D. Morrish, and J. Spinelli.** 1982. Q fever hazards from sheep and goats used in research. Arch. Environ. Health **37:**103–110.
64. **Salmon, M. M., B. Howells, E. J. G. Blencross, A. D. Evans, and S. R. Palmer.** 1982. Q fever in an urban area. Lancet **i:**1002–1004.
65. **Samuel, J. E., M. E. Frazier, M. L. Kahn, L. S. Thomashow, and L. P. Mallavia.** 1983. Isolation and characterization of a plasmid from phase I *Coxiella burnetii*. Infect. Immun. **41:**488–493.
66. **Samuel, J. E., M. E. Frazier, and L. P. Mallavia.** 1985. Correlation of plasmid type and disease caused by *Coxiella burnetii*. Infect. Immun. **49:**775–779.
67. **Sawyer, L. A., D. B. Fishbein, and J. E. McDade.** 1987. Q fever: current concepts. Rev. Infect. Dis. **9:**935–946.
68. **Schachter, J., M. Sung, and K. F. Meyer.** 1971. Potential danger of Q fever in a university hospital environment. J. Infect. Dis. **123:**301–304.
69. **Simor, A. E., J. L. Brunton, I. E. Salit, H. Vellend, L. Ford-Jones, and L. P. Spence.** 1984. Q fever: hazard from sheep used in research. Can. Med. Assoc. J. **130:**1013–1016.
70. **Spelman, D. W.** 1982. Q fever: a study of 111 consecutive cases. Med. J. Aust. **1:**547–553.
71. **Srigley, J. R., H. Vellend, N. Palmer, M. J. Phillips, W. R. Geddie, A. W. P. Van Nostrand, and V. D. Edwards.** 1985. Q-fever: the liver and bone marrow pathology. Am. J. Surg. Pathol. **9:**752–758.
72. **Tigertt, W. D., A. S. Benenson, and W. S. Gochenour.** 1961. Airborne Q fever. Bacteriol. Rev. **25:**285–293.
73. **Tobin, M. J., N. Cahill, G. Gearty, B. Maurer, S. Blake, K. Daly, and T. R. Hone.** 1982. Q fever endocarditis. Am. J. Med. **72:**396–400.
74. **Turck, W. P. G., G. Howitt, L. A. Turnberg, H. Fox, M. Longson, M. B. Matthews, and R. Das Gupta.** 1976. Chronic Q fever. Q. J. Med. **45:**193–217.
75. **Urso, F. P.** 1975. The pathologic findings in rickettsial pneumonia. Am. J. Clin. Pathol. **64:**335–342.
76. **Varma, M. P. S., A. A. J. Adgey, and J. H. Connolly.** 1980. Chronic Q fever endocarditis. Br. Heart J. **43:**695–699.
77. **Watt, A. H., A. G. Fraser, and M. R. Stephens.** 1986. Q fever endocarditis presenting as myocardial infarction. Am. Heart J. **112:**1333–1335.
78. **Welsh, H. H., E. H. Lennette, F. R. Abinauti, and J. F. Winn.** 1951. Occurrence of *Coxiella burnetii* in the placenta of naturally infected sheep. Public Health Rep. **66:**1473–1477.
79. **Wilson, H. G., G. H. Neilson, E. G. Galea, G. Stafford, and M. F. O'Brien.** 1976. Q fever endocarditis in Queensland. Circulation **53:**680–684.
80. **Worswick, D., and B. P. Marmion.** 1985. Antibody responses in acute and chronic Q fever and in subjects vaccinated against Q fever. J. Med. Microbiol. **19:**281–296.
81. **Yeaman, M. R., and O. G. Baca.** 1991. Mechanisms that may account for differential antibiotic susceptibilities among *Coxiella burnetii* isolates. Antimicrob. Agents Chemother. **35:**948–954.
82. **Yeaman, M. R., L. A. Mitscher, and O. G. Baca.** 1987. In vitro susceptibility of *Coxiella burnetii* to antibiotics, including several quinolones. Antimicrob. Agents Chemother. **31:**1079–1084.