EDITORIAL

Q fever: still a query after all these years

In 1935, Derrick [1] working in Brisbane, Australia, was the first to recognise the infection now known as Q fever. In describing the syndrome he coined the name Q fever as an abbreviation for ‘query’ fever, and 60 years later this name remains well suited to a disease which is still incompletely studied and little understood; all aspects of Q fever and its aetiological agent, the intracellular gram-negative bacterium *Coxiella burnetii*, still require further investigation.

*C. burnetii* infects a wide range of animals other than man, including various mammals, birds and ticks [2]. The bacterium exists as a strict intracellular parasite when infecting its host, but it can also survive in the environment. Early assessments of the epidemiology of Q fever suggested that, like brucellosis, it was acquired through contact with cattle, sheep and goats; however, recent work has shown that it is also associated with domestic cats and dogs, and wild animals such as deer [3]. Infection can also be acquired through transfused blood. The role of ticks in the natural cycle of *C. burnetii* remains uncertain, although they are suspected to be reservoirs or vectors for the organisms. Q fever is usually acquired through the inhalation of infectious aerosols, but infection via the digestive tract, through skin trauma or by sexual contact may also occur [4]. Rarely, the disease can be transmitted from a mother to her fetus [5].

Q fever is prevalent throughout the world with the exception of New Zealand [6]. The incidence varies greatly between different geographical locations, but seems to be highest in regions where there is medical or scientific interest in the disease. The fact that Q fever seems to ‘follow’ rickettsiologists is not altogether surprising; clinical diagnosis is complicated by numerous possible epidemiological conditions and the wide spectrum of clinical presentations, including both acute and chronic forms. The presentations of acute Q fever include a flu-like syndrome, an isolated fever, hepatitis, pneumonia, meningo-encephalitis, myocarditis, pericarditis and exanthema with fever. Chronic forms include endocarditis, osteomyelitis, pseudotumour of the lung and miscarriage [7]. The chronic form of Q fever is more common among immunocompromised patients, thus HIV seropositive or cancer patients, or those receiving steroid treatment are particularly susceptible. The clinical presentation of chronic Q fever is often determined by specific underlying host factors [8]. Endocarditis or vascular infections, for example, are more common in patients with heart disease. All chronic forms of the disease develop slowly with bacteria invading and persisting in host monocytes and macrophages.

The factors that determine the presentation of acute Q fever are even less well understood than those influencing the chronic form of the disease. In some countries, pneumonia is the most common presentation, whereas in others it is hepatitis. Opinion on potential influencing factors is divided. Variation in the virulence of infecting strains of *C. burnetii*, or in the size of the inoculum acquired, or in the route of infection, have been suggested, but no strong evidence for any of these possibilities exists. What is known is that, in keeping with many other intracellular parasites, *C. burnetii* infection induces a non-sterile immunity [8]. Following acute infection, despite the presence of both cellular and humoral immunity, the organisms survive in macrophages, and reactivation of Q fever can be induced by immunosuppression of apparently cured animals [9].

With this immense variation in clinical presentation it is not surprising that many cases are missed or misdiagnosed. However, laboratory diagnosis can be easily performed by the micro-immunofluorescence (MIF) test to determine specific anti-*C. burnetii* antibody levels in serum. The test is straightforward, reliable and specific when purified antigens are used, with only cross-reaction with *Bartonella* spp. being reported. The MIF test also allows differentiation of past and current infections (by determination of IgM levels) and of acute and chronic infections (only patients with the latter form have high IgA and IgG antibody titres to *C. burnetii* phase I antigens). Other serological tests are also available, although the complement fixation tests lack sensitivity and ELISA-based tests lack specificity (personal observations).

Unfortunately, there are few reference laboratories for Q fever. In countries lacking such facilities, the disease is poorly diagnosed and reported incidence is, not surprisingly, low. Indeed, the apparent lack of significant levels of Q fever in many countries probably explains why such laboratories are not
considered necessary! For example, in Marseille in the south of France, the prevalence of Q fever is about 50/100,000 inhabitants, and C. burnetii is responsible for c. 15% of the endocarditis cases diagnosed. Is there really a focus of Q fever here? There are no epidemiological reasons why the disease should be more prevalent here than elsewhere. The real answer probably lies solely in the fact that there is a team here really a focus of Q fever? There are no known increases in the incidence of Q fever in recent years. In California, for example, where the disease was highly endemic during the 1950s [11], cases are no longer reported. Similarly, in the UK, the number of cases of Q fever recognised in the 1970s and early 1980s [12] has fallen. In both locations medical and scientific interest in the disease have also declined; this cannot be coincidence.

Several features of C. burnetii make it a uniquely fascinating organism. This intracellular parasite is also able to exist in a spore-like, highly resistant form in the environment. Its specific targets within the host are monocytic cells. Within infected cells the bacterium survives in a large single vacuole resulting from the fusion of all the lysosomes at a pH of 4.8 [13]. In cell or egg cultures, C. burnetii exhibits the phenomenon of phase variation, equivalent to the rough or smooth variants of enterobacteria. Patients with acute Q fever exhibit antibodies essentially against epitopes expressed by the phase II form, whereas chronically infected patients produce antibodies against both forms. Genomic analysis of C. burnetii reveals that there is a low heterogeneity between strains obtained from different locations and from patients with different presentations of Q fever. Although some strains possess plasmids of various sizes, their presence does not appear to influence virulence [14]. All these observations need further investigation.

A vaccine for Q fever is commercially available in Australia and another is under development in the USA. The target population for such a vaccine needs to be defined. Currently the vaccine is only received by abattoir workers in Australia and laboratory investigators in Russia and Slovakia. As knowledge of the epidemiology of the disease increases, perhaps the vaccination of other recognised at-risk groups should be considered, such as patients with valvulopathy, especially those living in rural areas.

Treatment of Q fever is difficult; although acute forms of the disease are generally self-limiting, chronic forms, specifically endocarditis, are often fatal. Q fever endocarditis has been treated successfully with tetracyclines, either alone or in combination with other agents. Combinations of quinolones and doxycycline have also been shown to be generally efficient, although these regimens may need to be followed for anything between 3 years and a lifetime. The low pH of the intracellular vacuole inactivates many anti-C. burnetii antibiotics, but it has been demonstrated recently that the pH of these vacuoles can be increased from 4.8 to 5.4 by use of chloroquine or hydroxychloroquine, thus enhancing the bactericidal action of doxycycline [15]. The preliminary results of this study suggest that a combination of these two drugs can reduce the duration of treatment, although regimens of 18 months may still be necessary.

Sixty years after their discovery, many aspects of Q fever and its aetiological agent, C. burnetii, remain wide open and young medical and scientific investigators are encouraged to come and join the hunt!

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References