

Q fever in Plymouth, 1972–88

A review with particular reference to neurological manifestations

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(Accepted 25 April 1990)

SUMMARY

Between 1972 and 1988 we have serologically confirmed 103 *Coxiella burnetii* infections: 46 were acute, 5 were chronic, 52 represented past infections. Details of 61 cases are presented.

Of acute cases 80% had respiratory involvement; at least 63% had pneumonias. The incidence (22%) of neurological complications was of particular interest; 40% of these patients had prolonged sequelae. One acutely ill patient died of fulminating hepatitis. Patients with pre-existing pathology or immunosuppression were especially susceptible to *C. burnetii*.

In the absence of acute sera, the complement fixation test alone provided inadequate differentiation between recent and past Q fever: phase II titres persisted at ≥ 80 for more than 1 year after the acute infection in 15 cases; maximum duration of persistence was 14 years. Three patients acquired high phase I titres.

Only 5% of cases had chronic Q fever, but in view of the diverse sequelae observed in this series, we suggest that long-term serological and clinical follow-up of all cases of Q fever is fully justified.

INTRODUCTION

The Plymouth Public Health Laboratory provides a diagnostic serology service for South West Devon and East Cornwall and serves a catchment population of 425 000 of whom 334 000 reside in Devon and 91 000 in Cornwall (1988 estimates). All sera submitted from patients with respiratory infections, pyrexias of undetermined origin (PUOs), culture negative endocarditis and hepatitis (for which there is thought to be an infectious aetiology not explained by hepatitis A or B, cytomegalovirus, Epstein–Barr virus or toxoplasmosis) are tested for complement fixing antibodies to *Coxiella burnetii* in recognition of the prevalence of this infection in the locality. This practice has not changed over the period of the study.

All cases of Q fever diagnosed and monitored by the Public Health Laboratory in Plymouth between 1972 and 1988 have been reviewed and where possible their clinical condition and serological status have been assessed in 1989.

MATERIALS AND METHODS

Serum samples submitted to the laboratory by both general practitioners (GPs) and hospital clinicians were included in the study.

After prior inactivation at 56 °C for 30 min, sera were tested for phase II antibodies to *C. burnetii* by conventional complement fixation (CF) techniques, allowing overnight complement fixation at 4 °C. (The antigen supplied by the Division of Microbiological Reagents and Quality Control, Central Public Health Laboratory, London, was derived from the Nine Mile strain of *C. burnetii* passaged in eggs to obtain the phase I antigen from which the phase II antigen was prepared by periodate treatment.) Sera were tested in doubling dilutions starting at 1 in 10. Some were referred to the Regional PHLS Virology Laboratory, Bristol for confirmatory serology and phase I titres. (Bristol used a starting dilution of 1/8 or 1/16 which explains the difference in titres quoted in the text.) Indirect immunofluorescence (IF) for *C. burnetii* specific IgM and IgG was carried out in Bristol on selected cases. Liver biopsies and post-mortem material were examined by the Department of Histopathology in Plymouth. Guinea-pig inoculation for *C. burnetii* was undertaken at the PHLS Special Pathogens Laboratory, CAMR, Porton Down.

Acute Q fever was diagnosed serologically by either a fourfold or greater rise in the phase II titre or by a stable phase II titre ≥ 80 if there was strong clinical evidence of acute Q fever. In one case this was supported by the presence of *C. burnetii* specific IgM. Chronic Q fever was diagnosed serologically when both phase I and phase II titres were high (> 512) at presentation and persisted for several months into the illness. The appearance of phase I antibodies during an acute infection was carefully monitored over time in order to detect persisting infection.

Wherever possible patients were followed up clinically by their GPs or hospital physicians and serologically by the Plymouth microbiologists for some months after presentation. This has been continued on a long-term basis by one of the authors (S.R.) in close collaboration with the relevant GPs. By this means the clinical outcome and antibody status of some of the cases have been followed for several years after the initial infection and is still in progress.

RESULTS

Between 1972 and 1988 103 patients were identified with serological evidence of *C. burnetii* infection, 89% of whom were diagnosed from 1980 onwards and 36% were detected in the last 2 years of the study period. An additional two cases (spouses of confirmed cases) had illnesses indistinguishable from acute Q fever but serological confirmation was not requested.

Sixty patients had phase II CF titres ≥ 80 . One further patient had a rise in titre from < 10 to 40 associated with acute Q fever but left the area before his peak titre could be estimated. These 61 cases have been divided into three clinical categories depending upon their presentation and serological response: acute infections (46), recent/past infections (10) and chronic infections (5). There were an additional 42 cases with serological evidence of past exposure to *C. burnetii* as shown by single or sustained phase II titres in the range ≥ 10 to ≤ 40 . In these

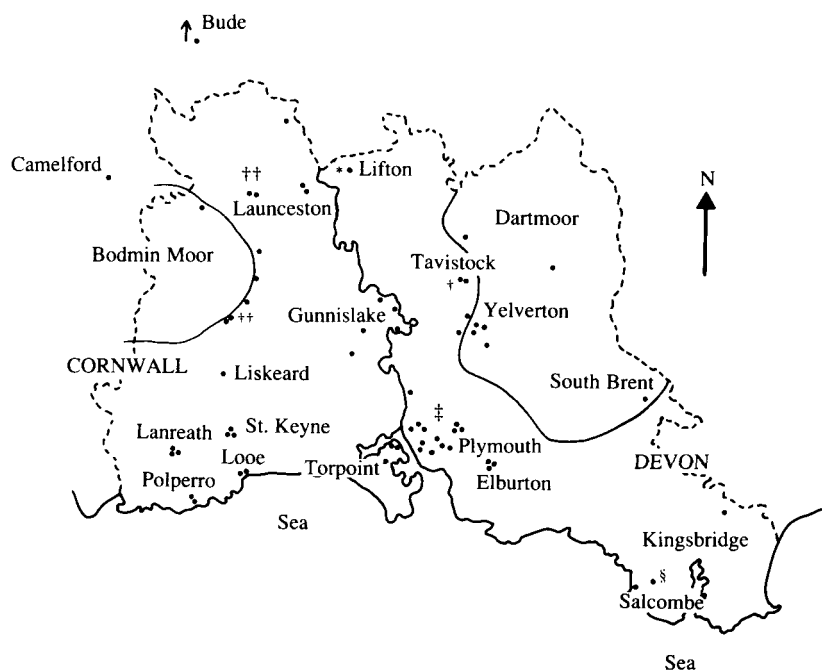


Fig. 1. Q fever: geographical distribution of cases.

Key: - - - Plymouth Health Authority (managed); †, handled carcasses from North Devon;
 *, ex Ilfracombe; ‡, ex Somerset;
 †, ex Spain; ††, clinical diagnosis only.

patients Q fever was not considered to be causally related to the presenting complaint.

The 61 clinically significant patients ranged in age from 6-75 years (mean 43 years). Males exceeded females by 45:16. Figure 1 shows their geographical distribution.

Acute infections

Forty-one per cent of the acute cases presented in the three spring months of March, April and May. Only 17% were in occupations which have been traditionally associated with Q fever: butcher (2), abattoir worker (2), farm worker (1), farmer's wife (2), part-time farmer (1). However eight patients had recently undertaken building alterations, renovated former farm buildings or were painters/decorators, and five kept pet animals or birds. One patient worked in a dairy, one was a salesman for animal feedstuff and one a student of environmental sciences. Four patients admitted to regularly drinking raw milk but they were each frequently exposed to other environmental sources of *C. burnetii*. Only four patients were able to identify the occasion on which infection had probably occurred: a physician who had been clearing out straw and rubble from his new moorland home, two members of a film crew who were exposed to wind-dispersed

Table 1. *Acute Q fever*

No. cases	46*	
Male	35	
Female	11	
Age (years)		
Range	6-75	
Mean	43	
Clinical features		(%)
Pneumonia, radiologically proven	29	(63)
Neurological	10	(22)
Chest infection, not pneumonia	8	(17)
PUO	4	(9)
Hepatitis	3	(7)
Arthralgia/arthritis	3	(7)
Pericarditis	1	(2)
Outcome		
Uncomplicated	26	(57)
Underlying malignancy	5	(11)
Neurological sequelae	4	(9)
Persistent chest symptoms	4	(9)
Hepatic dysfunction	4	(9)
Prolonged fatigue	2	(4)
Death		
Acute	1	(2)
Within 3 years	2	(4)

* Two more cases (spouses of index cases) had no serological investigations.

particles from bales of straw and peat while filming on Dartmoor, and a prison officer who had recently assisted with an aborting cow.

With the exception of the film crew incident, all were sporadic infections, but at least four family outbreaks were identified. The first involved a mother and her 6-year-old son, who lived across the road from a working farm. Both parents were zoologists. The son had pneumonia, the mother a 'flu-like illness. In both cases Q fever was serologically confirmed, but the father and two other children were asymptomatic. The second family outbreak involved a husband and wife who were concurrently admitted to hospital: the wife had pneumonia, meningism and a rash attributable to serologically confirmed acute Q fever; the husband had milder symptoms but serology was not undertaken. In the third instance the wife of a patient with granulomatous hepatitis due to Q fever had a 'flu-like illness similar to her husband's 2 weeks earlier, but unfortunately serum was not submitted from the wife. The fourth family outbreak involved a father and his two young sons; he had recently renovated farm buildings for self-catering accommodation and had also acquired a smallholding prior to his pneumonia. His sons were asymptomatic but had low titres to Q fever when tested 4 months later. His wife and daughter were seronegative. A guest who had stayed in the holiday cottages acquired Q fever on returning home from his holiday in Devon.

Twenty-two per cent of acute infections were in newcomers to the area. Some of those normally resident in Devon and Cornwall may have acquired their infections while visiting outlying areas: one, a slaughterman handled carcasses

from North Devon; one became ill on returning from holiday in Ilfracombe and one may have been infected in Spain.

In total 63% of cases were in either current or past smokers. Twenty-eight per cent had pre-existing, or subsequently developed, complicating pathology: liver disease (4), carcinoma of breast (2), non-Hodgkin's lymphoma (2), carcinoma of bronchus (1), bronchiectasis (1), systemic lupus erythematosus (1), previous polio (1), severe mental subnormality (1). Thirteen per cent admitted to excessive alcohol consumption.

Clinical features

Respiratory

Seventy-six per cent had coughs of which over a half were productive (most were current or past smokers) and 20% had one or more episode of haemoptysis. Abnormal chest signs were detected in 56% of cases and 29/39 (74%) of those who had chest X-rays had radiological evidence of pulmonary consolidation, which involved the left lower lobe in 41% of cases. Two cases had pleural effusions. Two cases had complicating pulmonary pathology: bronchiectasis (1) and carcinoma (1).

Neurological

Forty-six per cent complained of headache; in 15 patients this was severe. Nine cases had additional neurological features at presentation and a further one developed transient neurological complications during his illness. These 10 cases are compared in Table 2. All of the neurological cases met the serological criteria for acute Q fever.

Gastrointestinal

Mild gastrointestinal features were common, in particular weight loss and anorexia (26% each), vomiting (15%), diarrhoea (13%), abdominal pain (7%). Two cases were jaundiced at presentation: one had alcoholic liver disease, gallstones and subsequently pancreatitis, the other presented with jaundice after a 'flu-like illness (she was diagnosed as having chronic active hepatitis although a liver biopsy was omitted and she responded well to steroids). A third case, with non-Hodgkin's lymphoma, became jaundiced in the terminal stages of her illness.

On examination 9/41 (22%) cases had hepatomegaly, and 6/41 (15%) had splenomegaly. The latter was usually minimal but in one case 8 cm spleen was palpable. Gallstones were detected in two cases. Only two cases had liver biopsies: one case (H.M.) had typical granulomas surrounded by a fibrinoid ring and centred on empty vacuoles.

Musculoskeletal

Thirty-five per cent had generalized myalgia; 7% had acute arthralgia. One case had a flitting polyarthralgia which localized to his ankles; at presentation he had a very tender, swollen left ankle with lesser involvement on the right.

Rashes

Four patients had skin rashes; two may have been antibiotic related (ampicillin

Table 2. Neurological manifestations of acute Q fever

Case (onset)	Sex	Age	Clinical features	(SF findings)	EEG	Serology (Phase II)	Outcome
G. H. (1975)	M	47	Pneumonia (Confusion, meningism, leg weakness, bitemporal hemianopia)	1975: Protein = 0.55 g/l (no cells)	ND	1975: 4-fold rise (< 10 to 320)	1975-82: Mental slowness, leg weakness left $>$ right 1982: Increasing leg weakness, left facial asymmetry, left homonymous field loss. 1989: Residual leg weakness, dizziness, otherwise well
M. G. (1977)	M	47	Pneumonia Headache, photophobia, visual hallucinations (taking pentazocine)	1982: Protein = 0.64 g/l (no cells)	1982: Abnormal ?degenerative	1989: Ph II = 96	Recovered
D. W. (1977)	M	45	Backache, night sweats, loss of weight, breathless, leg weakness, paraesthesiae hands	ND	ND	1977 4-fold rise (< 10 to 160) 1989: Ph II = 48	Recovered
P. S. (1978)	M	43	Pneumonia Headache, neck stiffness, motor neuropathy (legs $>$ arms)	Normal	ND	1977 4-fold rise (< 10 to 160) 1989: Ph II = 32	Recurrent headaches, shoulder pains, numbness left leg until 1982
J. H. (1980)	F	52	Pneumonia Meningism, drowsy	Normal ($\times 2$)	?encephalitis	4-fold rise (< 10 to 40)	Lost to follow up
V. B. (1980)	F	51	Pneumonia	Normal	Encephalitis (resolved 5 months later)	4-fold rise (< 10 to 640)	Recurrent meningism, tender arms, blurred vision, periorbital pain (continued for 3 years) Lost to follow up
H. M. (1981)	M	75	Pneumonia PUO, granulomatous hepatitis. 1 week later: confused, disorientated	Normal	ND	4-fold rise (< 10 to 640)	Recovered, then lost to follow up
D. H. (1981)	M	18	Chest infection (educationally subnormal) (Collapse (?cause), decerebrate)	Normal	Grossly abnormal ?cerebral infarction or encephalitis	High stable (= 4096)	Recovered
M. A. (1987)	M	32	Lower limb peripheral neuropathy (wasted, flaccid, paraesthesiae) Jaundice,	Normal	ND	4-fold rise (< 10 to 80)	Minimal leg weakness and wasting at 1 year (alcoholic)
F. G. (1988)	M	61	hepatosplenomegaly Pneumonia Painful paraesthesiae (arms $>$ legs)	ND	ND	High stable (> 4096)	Residual paraesthesiae at 6 weeks. Emigrated 1989

ND, not done; Ph II, phase II titre.

Table 3. *Serological diagnosis of acute Q fever*

No. cases (%)	Phase II titre at presentation, <i>N</i> (%)		
	< 10	≥ 10 to < 512	≥ 512
	19 (41)	15 (33)	12 (26)
	Diagnostic criteria		
No. cases (%)	Fourfold rise	Single/stable phase II titre, <i>N</i> (%)	
		≥ 80 to < 512	≥ 512
	23 (50)	11* (24)	12 (26)

* Also IgM positive (1).

and trimethoprim), the other two were not. The first, a naval recruit, had erythema multiforme on his chest and anterior abdominal wall. The second case (V. B.) had a purpuric rash on her legs and buttocks; her husband (a serologically unconfirmed case) had a widespread pruritic papular rash.

Laboratory investigations

With two exceptions total white cell counts ranged from $4.5-16.1 \times 10^9/l$. Two patients had very low counts due to underlying pathology: $1.1 \times 10^9/l$ (SLE on immunosuppressive therapy) and $0.9 \times 10^9/l$ (non-Hodgkin's lymphoma). Three patients were anaemic: iron deficiency anaemia (1), macrocytic anaemia (1), lymphoma (1).

Liver function tests were abnormal in 16/27 (59%) cases. One patient who presented with pericarditis had grossly elevated cardiac enzymes (aspartate aminotransferase, 83 IU/l (< 40); creatine kinase, 925 IU/l (< 195); CKMB, 136 (2-9); CKMB/CK index, 9.3% (< 4) indicative of myocardial damage.

Serological response

In most cases a serological diagnosis could be made by CFT 3 weeks after the onset of symptoms. In 24% of cases for whom convalescent serology only was available and who had single or stable phase II titres in the range ≥ 80 to < 512 , they were judged clinically to have had acute infections and appropriate therapy was recommended. IgM detection was not consistently available. Earlier experience in Plymouth had shown that stable phase II titres in the range ≥ 10 to < 80 represented infection at some time in the past and treatment was not usually recommended. However such a decision depended upon sequential serological results.

Fifty-four per cent of acute cases had at least three serum samples submitted during their illness. Figure 2 shows the phase II antibody distribution at 3-monthly intervals from presentation. In 52% of acute infections phase I serology was also undertaken, in 33% of which phase I antibodies were detected (range 10 to > 512) usually after 3 months into the illness. In general phase I antibodies were found in association with high phase II titres (Fig. 3). Prolonged serological follow-up was essential to ascertain the significance of phase I antibodies. Three

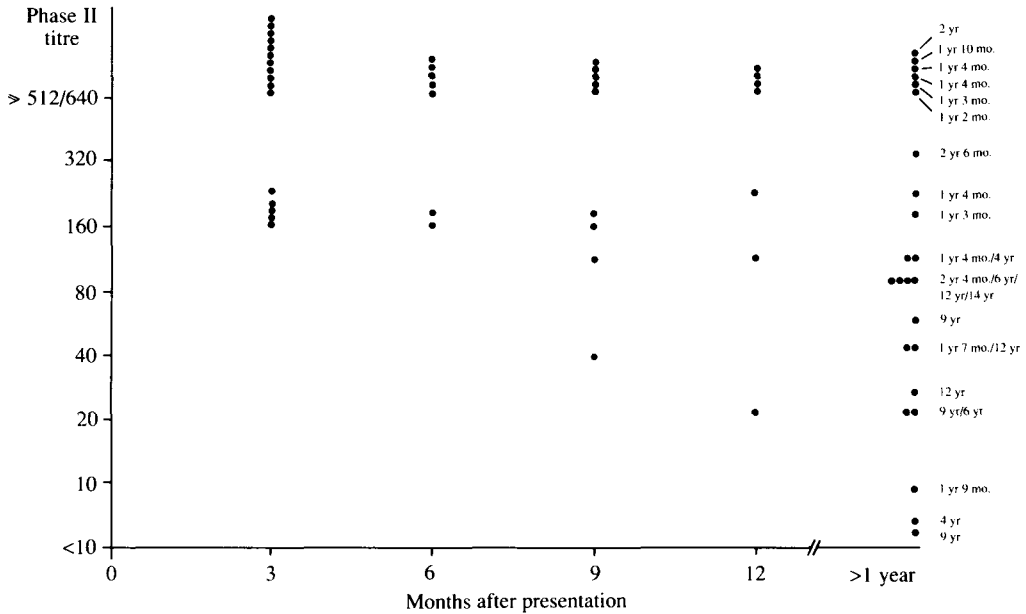


Fig. 2. Phase II CF response after acute Q fever.

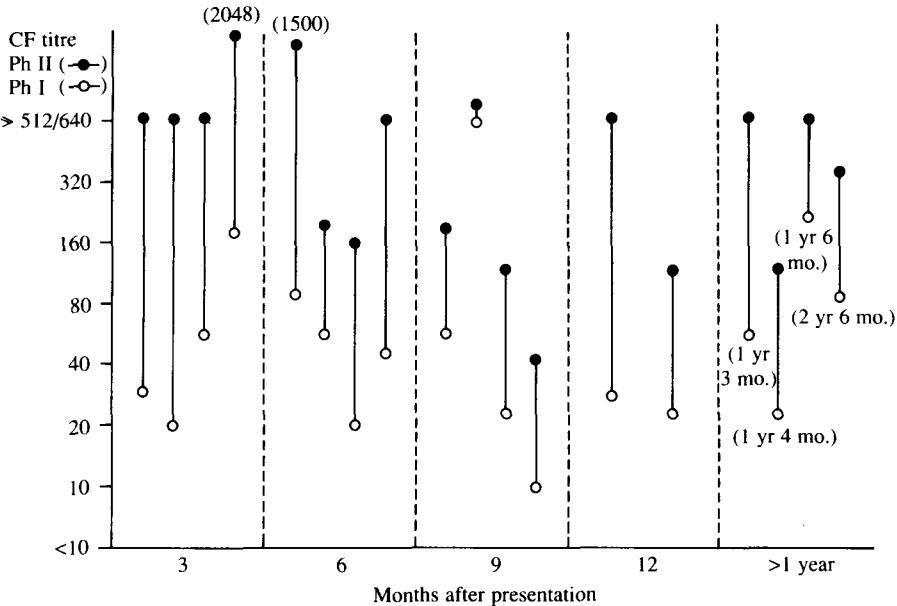


Fig. 3. Correlation between phase I and phase II titres after acute Q fever.

patients developed high phase I titres: all were males, mean age 69 years, with moderately heavy alcohol consumptions and two had established liver disease; all were smokers. The first case (H. M.) with Q fever granulomatous hepatitis, had a phase I titre of 192 at 3 months, which declined to 96 at 5 months, but further serology was not undertaken. The second case (V. D.) with chronic liver disease, had a phase I titre of 48 at 7 months, which rose to 256 at 14 months and remained

stable until just prior to his death 2 years later. The third case (G. R.) had a phase I titre > 512 at 8 months; this declined to 64 at 15 months, at which it remains 19 months after his acute illness. The last case is well at the time of writing.

So far 50% of acute cases have been followed up serologically for 1 year or more (range 1–14 years). Six cases, all male, mean age 56 years, have phase II titres \geq 512 more than 1 year after their acute infections. Two cases, both males, have phase II titres of 96, 14 years and 12 years respectively after their acute Q fever. This supports the view that it is almost impossible to predict the exact onset of infection in a patient who presents well into the convalescent period with a CF titre of this order.

Treatment

Many patients were commenced on ampicillin/amoxycillin or broad-spectrum antimicrobials pending serological results. Fifty-two per cent ultimately received either tetracycline or doxycycline. Thirty-three per cent received a course of oral erythromycin at some time during their illness. It was not possible to say whether early treatment of acute Q fever with tetracycline hastened recovery or prevented long-term sequelae.

Outcome

Fifty-seven per cent made uneventful recoveries. The remainder had either prolonged symptoms of their Q fever or complicating pathology (Table 1). Only two of the eight patients who developed phase I antibodies remain well to date.

Three patients died. Case M. S., who had non-Hodgkin's lymphoma, died before the diagnosis of acute Q fever was made and before she could receive appropriate antibiotic therapy. Ante mortem liver biopsy was unhelpful and led to severe bleeding. At necropsy the liver was much enlarged with gross fatty change, the spleen was enlarged and haemorrhagic, both lungs were oedematous, and there was abdominal lymphadenopathy. There was no histological evidence of Q fever in any organs, presumably due to her immunocompromised state. A full report of this case is in preparation.

Case V. D. had a fatal myocardial infarction 2 years after his acute Q fever. The lungs were congested with numerous firm, dark-red palpable nodules up to 0.3 cm diameter, histologically confirmed as granulomas. The liver and spleen were both enlarged but showed no focal lesions. Direct immunofluorescence of the liver, spleen and lung for *C. burnetii* was negative. Guinea-pig inoculation of the same material was non-contributory.

Case F. B., who had cerebral lupus erythematosus, had a fatal pneumonia 3 years after her Q fever. There was no necropsy.

Recent/past infections

Ten cases had serological evidence of Q fever sometime in the past (phase II titres, 80–512 either as single or stable titres).

Three patients lived on farms and one kept horses. None could identify the incident at which infection had occurred. One did recall an illness, 3 years before, which had all the features of acute Q fever – a PUO which persisted for 3 weeks despite simple analgesics and standard antibiotics (probably amoxycillin) but which was never investigated serologically.

Table 4. *Patients with recent or past infection*

No. cases	10	
Male	6	
Female	4	
Age (years)		
Range	17–65	
Mean	40	
Clinical features		(%)
Non-specific (malaise, headache, myalgia, shortness of breath)	9	(90)
Persistent cervical lymphadenopathy	1	(10)
Outcome		
Uncomplicated	3	(30)
Sarcoidosis	2	(20)
Polyarteritis nodosa	1	(10)
Prolonged fatigue	1	(10)
Depression	1	(10)
Persistent lymphadenopathy	1	(10)
Lost to follow up	1	(10)

Chest symptoms were not prominent. Only 40% had chest X-rays; two were normal but the other two had radiological evidence of pulmonary sarcoidosis.

Three cases had high phase II titres (256–512): case P.W. – a schizophrenic patient who had a past history of attempted suicide necessitating a splenectomy and who had had a repair of an atrial septal defect in adulthood – presented with intermittent cervical lymphadenopathy which remains undiagnosed despite node biopsies 2.5 years later. She has had repeated courses of doxycycline. Her phase II titre has remained stable at 512 for 1 year but showed a fourfold decline in 1990.

Case T.R. had deranged liver function (obstructive pattern), a raised white cell count ($18 \times 10^9/l$ with 20% eosinophilia) and impaired renal function. He was commenced on doxycycline but developed worsening arthralgia, vasculitic lesions at the fingertips and deteriorating renal function. A renal biopsy confirmed the diagnosis of polyarteritis nodosa (PAN). His phase II titre remained stable at 256 for a year after presentation but with the benefit of hindsight this probably represented past infection.

Case A.G. also presented with a phase II titre of 256. Living on a smallholding she has continual exposure to sources of *C. burnetii*. Despite repeated courses of oral tetracycline her symptoms of tiredness and depression have continued and she is currently being investigated for post-viral debility.

Three cases had low phase I titres (range 8–16) but no high titres were observed. Such low titres are probably of no diagnostic significance.

Chronic infections

All five patients presented with both phase I and phase II CF titres > 512.

Clinical features

All had been symptomatic for some months prior to their presentation. However, none had been previously diagnosed as having acute Q fever. Brief case histories follow.

Table 5. Patients with chronic Q fever

No. cases	5	
Male	4	
Female	1	
Age (years)		
Range	33–58	
Mean	48	
Clinical features		(%)
Subacute endocarditis	3	(80)
Cardiac failure, meningism	1	
PUO (pre-existing chronic renal failure)	1	
Surgical intervention		
Valve replacement	3	
Renal transplantation	1	
Outcome		
Survive to date	3	(60)
Refused cardiac surgery, secondary <i>S. epidermidis</i> endocarditis, died 11 y after presentation	1	
Renal failure, secondary <i>Strep. faecalis</i> endocarditis, died	1	

Case L.D. A 52-year-old building supervisor presented in 1972 with an 18-month history of recurrent rigors, malaise, aching legs, weight loss and worsening headaches. Cardiac catheterization confirmed aortic incompetence. *C. burnetii* titres were: phase I, 1024; phase II, 8192. He was treated with tetracycline, to which co-trimoxazole was later added and his serology responded (phase I, 160; phase II, 640 at 1 year). He declined cardiac surgery in 1977 despite deteriorating cardiac function. In 1978 he had a *Staphylococcus epidermidis* endocarditis which was successfully treated. His *C. burnetii* titres were then low (phase I, < 10, phase II, 80). He survived on long-term doxycycline for a further 5 years, albeit in a poor cardiac condition.

Case R.N. A 54-year-old engineering inspector with a past history of rheumatic fever, presented with an 18-month history of lethargy and tired legs. He had undergone investigations for anaemia and recurrent petechiae over the preceding year. His presenting *C. burnetii* serology showed: phase I, 4096; phase II, > 8000. Echocardiography demonstrated vegetations on the mitral and aortic valves and incompetence of both valves. Renal biopsy confirmed an immune complex nephritis. He was treated with doxycycline, to which co-trimoxazole was added for 2 years. Clinical deterioration ensued on stopping antibiotics and he was maintained on co-trimoxazole and rifampicin for a further 2 years. His serology stabilized (phase I, 256; phase II, 2048). In 1985 he developed renal failure and worsening cardiac function. He had mitral and aortic valve replacements, but died soon after. *Streptococcus faecalis* was grown from the excised valves.

Case T.S. A 33-year-old Australian butcher, arrived in Plymouth in 1978 with a Goretex graft in his leg (the previous year he had been diagnosed as having chronic renal failure). *C. burnetii* serology had not been performed. Over the subsequent 4 years he had recurrent graft site infections. In 1982 he commenced regular haemodialysis, following which he had several episodes of fever, headache,

sore throat, dry cough and shortness of breath. *C. burnetii* serology showed: phase I, 1500, phase II, 1024, and he commenced doxycycline. In 1985 the original Goretex graft was removed due to ischaemia of the leg (unfortunately it was not examined for *C. burnetii*). Echocardiography showed no cardiac vegetations. His *C. burnetii* titres remained high (phase I, 1000; phase II, 1000) until mid-1985. In 1986 he had a successful renal transplant. This was followed by a dramatic decline in CF titres (phase I, 96, phase II, 96), for which cyclosporin may have been partly responsible. It is not possible, in the absence of serology prior to 1982, to date the acute infection. He could have been infected in Plymouth (he remained in the butchery trade for 6 months after his arrival). The possibility remains that his infection was acquired in Australia and that the Goretex graft became chronically infected. Nevertheless doxycycline therapy was stopped in 1988 and he remains well at the time of writing.

Case M.H. A 42-year-old garage proprietor presented in 1986 with a sudden right-sided cerebrovascular accident (CVA) and signs of endocarditis. He gave a past history of bacterial endocarditis in childhood associated with congenital aortic stenosis, and in 1981 had undergone aortic valve replacement. Presenting serology showed: phase I and II titres > 512. He was commenced on doxycycline and clindamycin and the prosthetic aortic valve was replaced. His serology was unchanged in 1988. Treatment was changed to minocycline and rifampicin. He has since moved and has been lost to follow-up.

Case H.K. A 58-year-old hospital domestic with a past history of rheumatic fever, presented in 1988 with cardiac symptoms attributable to mixed aortic and mitral valve stenosis, which settled on conventional therapy. Three months later she developed a severe headache with scalp tenderness, photophobia and fever. CSF showed a raised protein (0.7 g/l), and increased polymorphonuclear leucocytes ($9 \times 10^6/l$) and lymphocytes ($15 \times 10^6/l$) but no bacterial growth. Although serology was compatible with chronic Q fever (phase I and II titres > 512) she had no clinical stigmata of endocarditis and was managed on tetracycline and rifampicin. Aortic and mitral valve replacements were carried out 8 months after her presentation due to deteriorating cardiac function. The excised valves were heavily calcified but there were no vegetations. Subsequent guinea-pig inoculation of the valve remnants (CAMR) failed to produce a seroconversion. Her *C. burnetii* titres have remained very high (512) for 18 months, but she is clinically well and is maintained on doxycycline to date.

DISCUSSION

It has long been recognized that Q fever is endemic in Devon [1, 2]. This has been substantiated in recent years by laboratory notifications to the PHLS Communicable Disease Surveillance Centre (CDSC), London: between 1975 and 1987 25% of cases of Q fever were reported from the South West of England [3]. Nevertheless few of these cases have been published [4–7]. Currently the incidence of sporadic cases in Plymouth stands comparison with Exeter, Taunton or Bristol. Hence a review of our experiences in Plymouth was deemed opportune.

The overall seroprevalence in the Plymouth series since 1980 was 0.5% (range: 0.1% in 1982 to 0.8% in 1987); this is undoubtedly an underestimate of the

prevalence of Q fever in this locality. A retrospective review carried out between 1962 and 1966 by five Public Health Laboratories in North West England and North Wales [8] found phase II CF antibodies in 2.6% of sera, of which 22% were possibly recent infections. Underdetection may be due to the fact that mild respiratory symptoms or lymphadenopathy may not warrant serological investigations. Active case finding in the present series revealed additional cases, particularly in relation to family outbreaks, which would have been otherwise missed. Infection within families has been previously described [9–13].

Local residents may have some immunity to *C. burnetii* [2], which is not necessarily detectable by CFT. The increased incidence of symptomatic infection in newcomers to endemic areas was recognized in 1958 [14]. Q fever should be included in the differential diagnosis of a PUO, respiratory or unexplained neurological illness in holidaymakers returning from the South West of England.

Childhood infection is uncommon [8, 9, 15–18]. The youngest child in the Plymouth series to have *C. burnetii* antibodies (phase II, 40) was a 3-year-old girl with aplastic anaemia. There is a potential risk to children of infection with *C. burnetii* by those who visit farms, zoos or building sites.

An unexpectedly large proportion of cases had underlying pathology. There may be several reasons for this: increased susceptibility to infection, tendency to overt infections or increased awareness on behalf of their physicians. The susceptibility of immunosuppressed patients to *C. burnetii* has received attention in recent years [19, 20]. Concomitant liver disease appeared to predispose towards persistent infection as shown by the appearance of phase I antibodies. Weir and colleagues [21] reported two cases of Q fever with granulomatous hepatitis, one of whom acquired phase I antibodies. Both were middle-aged males with moderately heavy alcohol consumptions. It is possible that whereas the liver is covertly involved in the majority (if not all) cases of Q fever [18, 22–26], those patients with pre-existing liver damage, particularly alcohol-induced, are at increased risk of progressing to the chronic state. Prospective studies are necessary to establish this.

The clinical features of acute Q fever in the Plymouth series were broadly comparable with previous reports [18, 22–24, 26–28]. However some differences are noteworthy. The majority (80%) had some respiratory involvement and at least 63% had pneumonias, but in only four cases were the rounded ground-glass opacities, described by Millar [29] as being typical of Q fever, observed.

Five cases had rashes – the rarity of a rash has been regarded as a feature which differentiates coxiella infections from rickettsial infections [22], but Spelman [26] recorded a 7.2% incidence in Australia.

Probably the most significant finding of the Plymouth series was the range of neurological manifestations involving 22% of acute cases and one of the chronic cases. Although recognized for over 40 years, neurological features are not readily attributed to Q fever. Masbernard [30] reviewed the early literature and recounted instances of meningitis, encephalitis (with EEG disturbance), cerebellar symptoms, cranial nerve involvement, confusional states, psychoses, and motor and sensory neuropathies persisting well into convalescence. Twenty-seven per cent of the cases reported from northern England and Wales [8] had neurological involvement (meningism, meningitis or cerebellar ataxia); one case had increased

white cells in the CSF, but long-term follow-up was not recorded. Schwartz [31] described a 40-year-old prisoner who developed a manic psychosis after acute Q fever. Ladurner and colleagues [32] described an 18-year-old girl with fever, headache, nausea and vomiting followed by a depressed level of consciousness, disorientation in time and space and weakness of the right side of her body; she had papilloedema, an abnormal EEG and the CSF had increased lymphocytes, a raised protein and a low glucose. She improved by the eighth day. Marrie [33] described a 35-year-old man with pneumonia and meningoencephalitis due to acute Q fever. Schuil and colleagues [34] ascribed bilateral optic neuritis with lasting unilateral blindness in a 59-year-old farmer to Q fever. Brooks and colleagues [35] recounted the case of a 34-year-old man who developed an acute encephalitis 6 weeks after an attack of Q fever which relapsed but subsequently responded to a course of doxycycline. Shaked and colleague [36] described a female soldier with meningoencephalitis, bilateral optic neuritis and abducens nerve paralysis; CSF showed a lymphocytosis and increased protein.

Indeed all of the neurological features observed in the Plymouth series have been described in the literature, which lends weight to the fact that Q fever played a causal role. The CSF findings (only two raised protein values) were in accord with previous reports which conclude that the CSF is often normal but may show a minimally raised white cell count or protein [26]. Few reports make special mention of the EEG changes in acute Q fever, but Carausu [37] carried out 37 EEGs on 14 cases of acute Q fever (none of whom had major neurological signs): in three cases the EEG was normal, six had gross pathological abnormalities and five had borderline abnormalities. Wallace and colleague [15] in a study of 78 febrile children included two children each of 1-year-old who had serological evidence of acute Q fever and had fits: one had a pre-existing left hemiplegia which became worse during the febrile fit and slow wave activity, focal abnormalities and epileptic bursts of activity were shown on the EEG. The other child remained neurologically normal during the febrile fit and had a normal EEG. Both had raised polymorph counts in the CSF.

Long-term follow-up of neurological cases does not appear to have been reported, but this would seem to be prudent in the light of the Plymouth series.

Chronic Q fever accounted for only 5% of the Plymouth cases; 4% had major cardiac involvement. This compares with an estimated figure of 11% derived from a retrospective analysis of 839 cases of Q fever reported to CDSC between 1975 and 1981 [38]. More recent estimates from CDSC [3] concur with the Plymouth figure. One chronic case had no evidence of valvular endocarditis. This is in accord with Ellis and colleagues [39] who described vertebral osteomyelitis, endocarditis of an abdominal aortic Dacron graft, sudden infant death syndrome and death of a premature baby born to a mother who had a history of infertility and miscarriage – all in association with high phase I titres. Although unproven, it is tempting to postulate that in case T.S. the infected Goretex graft served as a persistent focus of *C. burnetii*.

Throughout the study the CFT was the mainstay of diagnosis, as it is in the majority of UK laboratories to the present day. Its limitations are twofold: inability to provide any early diagnosis and lack of discrimination between recent and past infections when convalescent serum only is available. In the UK there is

a need for complimentary serological techniques, IFA and enzyme-linked immunosorbent assays (ELISA) for phase I and II antibodies and their component immunoglobulin classes, to allow earlier and more precise diagnoses [40–43].

The phase I CF response in acute Q fever is not well defined [26, 44]. Winner and colleagues [45] found a 56% incidence of phase I CF antibodies in postal workers in Oxfordshire who were followed up for 15 months after an outbreak of Q fever; CF titres ranged from 8–64. Spelman [26] proposed that only high or persistent phase I antibodies may be clinically relevant. The Plymouth results would concur with this, with the caveat that phase I titres are sufficiently uncommon to warrant detailed clinical examinations and repeated serological assessments especially if patients have pre-existing hepatic or cardiac abnormalities. Turck and colleagues [46] in their review of chronic Q fever alluded to the fact that persistent infection with *C. burnetii* may occur despite the phase I titre being < 200, the threshold traditionally accepted as being indicative of Q endocarditis [47]. These diagnostic dilemmas may be resolved by the adoption of more sensitive serological techniques: detection of high phase I IgA titres by IFA has been proposed as the optimum method for the serological diagnosis of endocarditis [48–50], but unfortunately this test is not available in the UK. Impairment of the host's cell-mediated immune response to *C. burnetii* in cases of endocarditis warrants detailed evaluation [48, 51].

Standard antimicrobial therapy for Q fever was used throughout the study. Tetracyclines, although only rickettsiostatic, have long been regarded as optimal therapy for both acute and chronic Q fever [46, 52, 53] especially if treatment is commenced early on in the illness. Satisfactory clinical response has been attributed to erythromycin [10, 54], rifampicin, clindamycin and co-trimoxazole [39, 53, 55], but none has undergone controlled clinical trials. Currently in Plymouth all acute cases receive at least a 10-day course of oxytetracycline or doxycycline but if they have already responded to a course of amoxycillin and erythromycin, further tetracycline is generally not indicated unless there is clinical or serological evidence of persisting infection. Recent *in vitro* work using L929 fibroblast cells persistently infected with *C. burnetii* has demonstrated excellent cidal activity from the quinolones [56] but clinical trials in humans are awaited.

There was no evidence from the Plymouth series for the superiority of one particular regimen of combination chemotherapy for chronic Q fever, indeed the impression gained was that after a short course of combination therapy, doxycycline alone was probably adequate but this was usually continued for many years. The longest survivor (11 years) was maintained solely on doxycycline for the last 6 years and had no cardiac surgery. The CFT response was not a useful guide to the duration of therapy – additional prognostic indicators are therefore required.

In conclusion, although it is now 40 years since the first human cases of Q fever were described in England [1], it remains a most unpredictable infection, as evidenced by the continued occurrence of sporadic cases and unexpected outbreaks [45, 57, 58]. Its predilection for immunosuppressed patients, its diverse neurological manifestations and its propensity to follow a protracted course mean that Q fever is much more than an esoteric cause of culture negative endocarditis. We

suggest prolonged serological and clinical surveillance of all cases of Q fever so that the true incidence of persistent infection may be determined and the complex host–parasite interaction may be further understood.

ACKNOWLEDGEMENTS

We should like to thank the many General Practitioners who assisted in following up their patients; the following Consultants for allowing us to report cases under their care: Dr J. A. Coppleson, Dr J. Cowie, Dr J. D. Gibson, Dr M. J. Grayson, Dr K. R. Hunter, Dr H. M. Leather, Dr A. J. Marshall, Dr C. R. McGavin, Mr J. Mohan, Dr P. D. Mulcahy, Dr A. G. Prentice, Mr C. Teasdale, Surgeon Commander J. G. Williams R. N.; Dr E. M. Allen, Consultant Neurophysiologist, for critical evaluation of the EEGs; Dr D. A. Rutter, Head, Coxiella Reference Laboratory, CAMR, PHLS Porton Down, Salisbury, Wilts., for guinea-pig inoculation; Dr R. J. C. Hart, Exeter Public Health Laboratory, for the serology on case J.H.; Dr M. Zeller and Mrs A. O'Connor for assistance with translations; Mrs S. Waring for her skilful artwork; Mrs L. Rowland for her painstaking preparation of the manuscript.

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