Thorax (1968), **23**, 316.

A case of non-bacterial endocarditis due to Q fever

D. J. WOODGATE[1], TEN FEIZI[1], R. G. SOMMERVILLE[2], P. J. SCHEUER[1], AND J. R. McDONALD[3]

From the Royal Free Hospital, London[1], Belvedere Hospital, Glasgow[2], and the Central Public Health Laboratory, London[3]

A case of chronic Q fever is described, presenting as a problem of endocarditis of six years' duration with negative blood cultures. The Q-fever endocarditis was superimposed on pre-existing rheumatic mitral valve disease. In spite of four months' treatment with tetracycline the patient died of intractable cardiac failure. At necropsy, inclusion bodies were found in macrophages in the mitral valve, and an organism, probably a strain of *Rickettsia burneti*, was isolated from post-mortem material. A review of eight previously reported cases of chronic Q-fever endocarditis from this country has shown that in the majority of patients the diagnosis was made months or years after the onset of infection by this organism. With the exception of a case diagnosed after 10 months of illness and treated with tetracycline for eight weeks, these patients received either no specific treatment or a short course of tetracycline or chloramphenicol. It is suggested that the failure of antibiotic therapy in this and other reported cases may be, in part at least, due to a delay in diagnosis and in initiation of prolonged specific therapy.

The suggestion that a cardiac abnormality might predispose to a chronic endocarditis with *Rickettsia burneti* was first made by Marmion, Stoker, McCoy, Malloch, and Moore (1953). The first report of Q fever as a cause of fatal non-bacterial endocarditis was by Robson and Shimmin (1959). To date eight such cases have been reported from this country (Robson and Shimmin, 1959; Evans, Powell, and Burrell, 1959; Smith and Evans, 1960; Ferguson, Craik, and Grist, 1962; Postgraduate Medical School, 1963; and Mitchell, Grist, Bazaz, and Kenmuir, 1966). We report another case of chronic Q fever which presented a problem of endocarditis with negative blood cultures.

CASE REPORT

A 43-year-old postal worker was admitted to hospital in 1959 complaining of a sore throat and cough associated with a purpuric rash on the legs. He gave a history of rheumatic fever at the age of 17 and of having been turned down by the Forces on account of 'heart trouble'. On admission in 1959 he was noted to have atrial fibrillation and clinical signs of mitral stenosis. He had always lived in England. His chest radiograph was reported as showing a shadow at the right hilum extending into the mid-zone. The haemoglobin was 12·1 g./100 ml. and W.B.C. 6,000/c.mm. with a normal differential. Two blood cultures yielded no bacterial growth. A diagnosis of rheumatic heart disease and bronchopneumonia was made and he was given 1 g. of tetracycline daily for five days. He was discharged 10 days later.

For the next two years he complained of intermittent cough and moderate shortness of breath.

In December 1962 he was readmitted to hospital complaining of several months' increasing malaise, and pain in the legs of one week's duration. He had an intermittent pyrexia up to 102° F., a purpuric rash, hepatosplenomegaly, and clubbing of the finger-nails. Investigation at this time revealed a haemoglobin of 12·3 g./100 ml., W.B.C. 3,000/c.mm. with a normal differential, platelet count 92,000/c.mm., E.S.R. 78 mm. in one hour (Westergen), serum albumin 3·1 g./100 ml. and globulin 6·1 g./100 ml. A liver biopsy showed only slight fibrosis and non-specific inflammatory infiltration of the portal tracts and parenchyma. Nine blood cultures gave no bacterial growth. He was treated with 4 million units of penicillin daily for six weeks. The pyrexia resolved but the E.S.R. did not fall below 42 mm. in one hour. During 1963–64 he had four further admissions with a similar clinical picture and persistently negative blood cultures. On each occasion he was treated with a short course of either penicillin or tetracycline.

In September 1965 the patient was again admitted to hospital because of further deterioration, with general malaise, night sweats, loss of weight, and diminishing effort tolerance. Physical examination showed that he was ill and wasted, with an intermittent pyrexia up to 100·6° F., finger-nail clubbing and palmar erythema. There was purpura on the legs and scapular regions, and a non-tender haematoma, 2 mm.

in diameter, was present on the pulp of the right index finger. There were signs of mitral stenosis and incompetence, tricuspid incompetence, and pulmonary hypertension. He was in congestive cardiac failure. The liver was enlarged, extending to the right iliac crest, and was pulsatile. The spleen extended 5 cm. below the left costal margin. Investigation showed haemoglobin 12·2 g./100 ml., W.B.C. 3,500/c.mm. and a normal differential count, platelet count 133,000/c.mm., E.S.R. 50 mm. in one hour, serum albumin 2·2 g./100 ml. and globulin 4·5 g./100 ml. A chest radiograph revealed generalized cardiac enlargement and pulmonary congestion. Eleven blood cultures yielded no bacterial growth. Because of this, evidence of Q fever was sought. Complement-fixing antibody against *R. burneti* phase 1 antigen was present at a titre of 1:4,096 and against phase 2 antigen at a titre of 1:64,000. Negative results were obtained with influenza A, B, and C, psittacosis, adenovirus, parainfluenza 1 type sendai, parainfluenza 3, respiratory syncytial virus, and *Mycoplasma pneumoniae* antigens. Bone marrow aspirate and 1 ml. of the saline extract from macerated blood clot were each inoculated by the intraperitoneal route into two guinea-pigs. After three weeks the guinea-pigs were bled by heart puncture and the serum was examined, simultaneously with pre-inoculation serum specimens obtained from each pig, for antibody to *R. burneti* by complement fixation test. Negative results were obtained from all sera.

The serum antibody findings, and in particular the presence of antibody against phase 1 antigen, strongly suggested a diagnosis of Q-fever endocarditis (Marmion, Higgins, Bridges, and Edwards, 1960). The patient was therefore treated with 2 g. of tetracycline daily. The fever subsided after 11 days and the spleen diminished in size. The E.S.R. fell to 2 mm. in one hour after 18 days of therapy and remained at this level. The heart failure, however, was resistant to treatment; the signs of valvular incompetence became more marked and he died in February 1966 after four months' therapy with tetracycline.

NECROPSY FINDINGS In view of the diagnosis of Q fever the necropsy was performed with full antiseptic precautions as described by Andrews and Marmion (1959). Subsequent examination of the blood of the pathologist and necropsy attendant, as well as of the bacteriology technicians who had handled material from the patient, revealed no significant titres of complement-fixing antibodies to *R. burneti*, and no cases of Q fever occurred. Specimens from the heart valves, lung, spleen, and bone marrow were delivered to the Virus Reference Laboratory, Colindale, for investigation. Otherwise all organs were put into formalin and were handled as little as possible prior to fixation.

Macroscopic findings The pericardial cavity was totally obliterated by thin adhesions. The heart was enlarged and after fixation weighed 800 g. The chambers, particularly the left atrium and the left ventricle, were dilated. The mitral valve circumference was reduced to 6 cm., the valve was moderately thickened by fibrous tissue, and there were ill-defined irregularities of the surface. Fibrosis extended into the posterior wall of the left atrium. The chordae tendineae were shortened and thick and there was fibrosis of the papillary muscles. The appearances were typical of old rheumatic disease. No lesions were seen in the other valves.

The spleen, which was of approximately normal size, contained an infarct. Its capsule showed old fibrous thickening. The lymph nodes were of normal size and appearance. The kidneys contained several recent infarcts. The liver was slightly enlarged and showed changes of chronic venous congestion.

Microscopic findings The mitral valve was scarred and vascularized and contained foci of calcification. Towards the edge of the valve there were scanty small collections of neutrophils and macrophages. The latter contained numerous inclusions which, in their size and positive staining by Macchiavello and Giemsa methods, resembled Rickettsiae (see Figure). No Aschoff bodies were found in sections of the heart.

In the lungs there were changes of chronic venous congestion as well as of bronchopneumonia with early abscess formation. Interstitial pneumonia, as seen by infiltration of thickened alveolar walls by acute and chronic inflammatory cells, was noted in a few areas. No Rickettsiae were, however, demonstrable. Infarcts in the spleen and kidneys were judged to be several weeks or months old. The liver was congested, fibrotic, and fatty.

Investigation of necropsy material Suspensions of the heart valve, lung, spleen, and bone-marrow specimens were prepared. A pool of these was inoculated intraperitoneally into two guinea-pigs and into the yolk sacs of four 7-day fertile hen's eggs. The guinea-pigs remained afebrile throughout a 3–4 weeks post-inoculation period and neither pre- nor post-inoculation serum samples reacted with a phase 2 Q-fever antigen. An agent was isolated from the inoculated yolk sacs on the first passage. It was found to be more sensitive to streptomycin than to penicillin and, when stained by the Macchiavello method, had an appearance consistent with a strain of *R. burneti*. There was no growth when the yolk sac suspension was subcultured on mycoplasma medium. Confirmation that it was a strain of *R. burneti* proved difficult because of its strict specificity in early passes. By the sixth pass a complement-fixing antigen prepared from infected yolk sacs reacted with a rabbit antiserum containing both phase 1 and 2 antibodies, with the homologous guinea-pig antisera and with the patient's serum to a low titre but not with purely phase 2 Q-fever antiserum. Finally, confirmation of its being a strain of *R. burneti* was obtained with antigens prepared from the eighth yolk sac pass material. These reacted strongly with a phase 2 Q-fever antiserum.

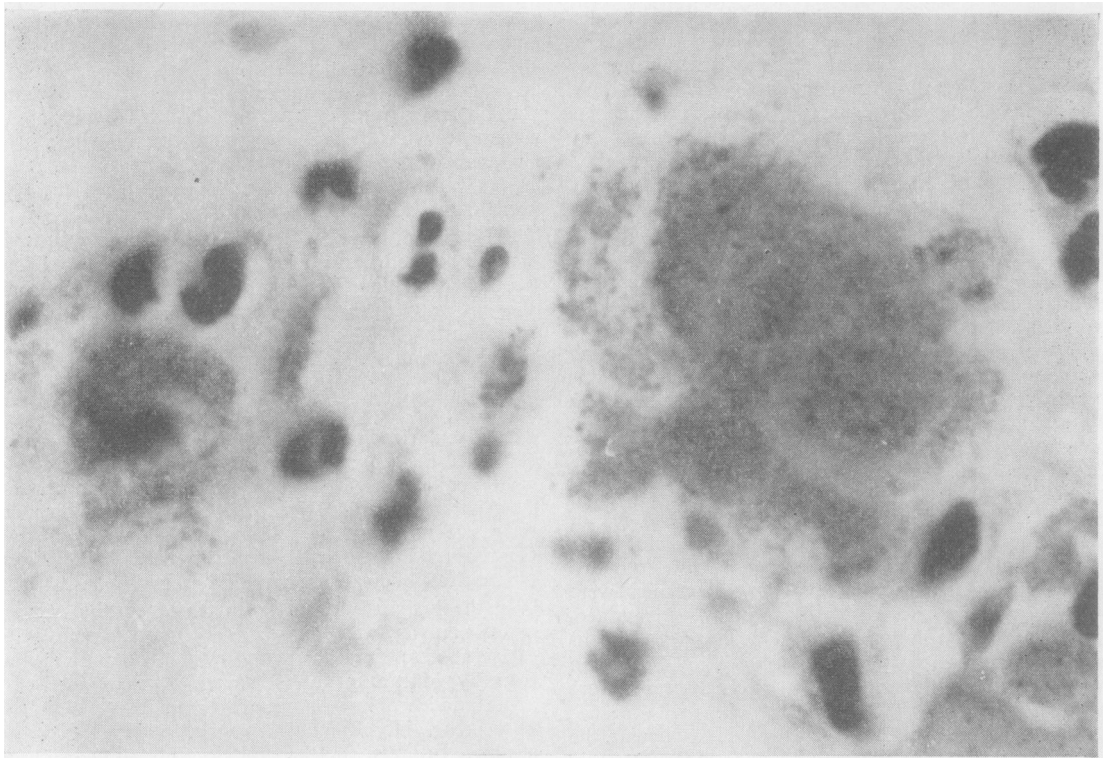

FIGURE. *Mitral valve. The phagocytes are filled with inclusion bodies. Macchiavello stain.* ×1,200.

Attempts to determine the precise source of the Rickettsiae by culture of the individual suspensions were unsuccessful, but we think that they came from the heart valve.

DISCUSSION

It is most probable that this patient's *R. burneti* infection dates from the episode of broncho-pneumonia in 1959. The past history of rheumatic fever and of subsequent heart trouble suggests that the Q-fever endocarditis was superimposed on a heart previously affected by rheumatic valvular disease, a feature in common with at least four out of the eight previously reported cases; the remaining four cases also had pre-existing valve disease compatible with either rheumatic or calcific valve disease (see Table).

To date a diagnosis of Q-fever endocarditis seems to be of academic interest only, for its fatal course has not been affected by tetracycline or chloramphenicol. On reviewing in detail the previously reported cases from this country, it seems that the unsatisfactory response to these two antibiotics may have been due not merely to their having a bacteriostatic (rather than rickettsicidal) action but also to the long duration of illness prior to therapy. The probable duration of illness in these cases ranged from 3 months to 2 years and 8½ months (see Table) and only two of these patients had received prolonged specific treatment. In our patient there was probably a six-year interval prior to diagnosis of Q fever. The four-month course of tetracycline resulted in a subsidence of pyrexia, reduction of the splenic size, and lowering of the E.S.R. to normal, but the patient died of intractable heart failure, and viable rickettsial organisms were still present at necropsy. The presence of buried and presumably inaccessible organisms may be explained by the long delay before diagnosis and initiation of specific therapy. The negative results obtained from the guinea-pigs which were inoculated with ante-mortem material were not altogether unexpected in view of the very high serum antibody levels to both antigenic phases of *R. burneti* encountered in this patient.

While awaiting a more effective antibiotic, better results may well be expected with an increased

TABLE

Case	Author	Past History of Rheumatic Fever	Symptoms Compatible with Acute Q Fever	Probable Duration of Q Fever Prior to Diagnosis	Antibiotic Treatment	Probable Duration of Q Fever Prior to Death	Post-mortem Evidence of Chronic Heart Valve Disease
1	Robson and Shimmin (1959)	−	Pneumonia	6 months	Tetracycline, 2-week course during 6th month of illness. Chlortetracycline during 11th–17th months of illness	2 years	R
2	Evans *et al.* (1959)	−	'Flu-like illness	2 weeks	No chloramphenicol or tetracycline	5 months	C
3	Smith and Evans (1960)	+	'Influenza'	2 years and 7 months	Tetracycline 7 days followed by erythromycin and chloramphenicol from time of diagnosis till death	2 years and 8½ months	R
4	Marmion *et al.* (1960)	Suggestive	?	2 years	No tetracycline or chloramphenicol	2 years	R
5	Ferguson *et al.* (1962)	+	'Flu-like illness	10 months	Tetracycline 8 weeks	13 months	R
6	Postgraduate Medical School (1963)	+	−	2 years	Chloramphenicol for last 25 days of life	2 years	R
7	Postgraduate Medical School (1963)	−	−	3 months	'A course of chloramphenicol'	1 year and 3 months	R
8	Mitchell *et al.* (1966)	−	Febrile illness with cough	4 months	Massive doses of antibiotics including oxytetracycline and chloramphenicol	4 months	C

+=Positive history; −=negative history; R=heart valve changes compatible with rheumatic heart disease; C=changes compatible with calcific aortic valve disease.

awareness of Q-fever endocarditis, early diagnosis, and prolonged therapy with tetracycline.

We are grateful to Dr. F. Lee-Lander for his permission to publish this case, to Dr. N. Crowley for the bacteriological cultures, to Dr. A. D. Macrae for his help with the viral studies, and to Dr. Bradstreet for providing Q-fever antigens and antisera. We thank Professor B. P. Marmion for his advice and encouragement.

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ADDENDUM

Since this paper was submitted for publication, Kristinsson and Bentall (*Lancet*, **2**, 693, 1967) have described 6 (5 certain and 1 presumptive) cases of Q-fever endocarditis. Of the unequivocal cases 4 had sufficient disorganization of the aortic valve to necessitate valve replacement on haemodynamic grounds. All 4 have survived. All have received tetracycline since operation and the disease has remained under control. The fifth case was diagnosed within one month of the onset of endocarditis. Surgery was not needed and the disease appears to have been controlled by prolonged tetracycline therapy.