The formation of C.F. antibody to Phase 1 antigen by our patient appears to be unique, and, as this finding is most simply explained in terms of prolonged antigenic stimulation, the presence of such antibody clearly deserves further investigation as a possible indicator of chronic infection with *R. burneti*.

Summary

This paper describes the pathological and bacteriological findings in the case of chronic Q fever infection described clinically by Robson and Shimmin.

Examination of the patient's serum at the beginning of his chronic illness revealed high titres of complement-fixing antibody to both antigenic phases of *Rickettsia burneti*. The rickettsia was isolated from the blood stream on two widely separated occasions during the chronic illness. An account of the experiments establishing these points is given in detail.

Examination after death revealed a cerebral haemorrhage, a distorted aortic valve with vegetations, and various secondary changes in other organs resulting from heart failure. Microcolonies of rickettsia-like organisms were seen in histological sections of the aortic-valve vegetations, which were also shown by guinea-pig inoculation to contain *R. burneti* in large numbers. In addition, the rickettsia was isolated from the lung and spleen.

The findings differed in a number of ways from those of subacute bacterial endocarditis, and this point is explored in detail.

We are grateful to Dr. F. H. Scadding for his help and encouragement at all stages of this investigation. We are indebted to Dr. M. G. P. Stoker (Cambridge) for a gift of Phase 1 antigen; to Mr. E. Mitchell (Cambridge) and Mr. M. Turney (Middlesex Hospital) for the illustrations; to Mr. C. E. Trickett (Middlesex Hospital) for technical assistance; and to Mrs. O. Eddison for much secretarial help.

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Two hundred people from European refugee camps and 10 elderly White Russians from China are to be admitted to Great Britain during the autumn under a scheme put forward by the World Refugee Year United Kingdom Committee and approved by the Government. Of these 200, 150 will include single men and women suffering from tuberculosis, or families in which one member, other than the breadwinner, is tuberculous. These patients will go to sanatoria, and their treatment will be the responsibility of the National Health Service. They will then rejoin their families and be resettled in Britain. The other 50 will come from Germany and Austria mainly in family groups which have so far been difficult to settle. (*The World's Children*, vol. 39, No. 3.)

ASSOCIATION OF CARDIAC PULMONARY HAEMOSIDEROSIS AND FIBROSIS

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[WITH SPECIAL PLATE]

The deposition of haemosiderin in the lungs was first commented upon by Virchow in 1858, but it was not until 1928 that Fahr (quoted by his disciple Rosenhagen) appreciated the focal character of this phenomenon in describing the condition of pulmonary haemosiderosis in association with valvular heart disease. His observations were based on three necropsies, the cases including two with mitral stenosis and one with aortic incompetence.

Such endogenous haemosiderin has commonly been supposed to lead to pulmonary fibrosis, and the term "brown induration" has been used to summarize the changes. Zenker (1866) thought that exogenous siderosis was also associated with fibrosis, but this has not been confirmed by later workers. McLaughlin (1951) has contrasted the findings in the industrial siderosis of rouge-workers and arc-welders, where the inhalation of inorganic iron is not followed by fibrosis, with those in endogenous pulmonary haemosiderosis, where fibrosis is reported to be commonly found.

Recent experience with two patients under the care of one of us (P. E.) has led us to believe that endogenous haemosiderin in the lung may be less fibrogenic than has hitherto been supposed. This is in keeping with the findings of Taylor and Strong (1955), who carried out necropsy studies on the lungs in 45 cases of mitral stenosis. They found that the degree of haemosiderin was proportional to the degree of right ventricular hypertrophy, but that there was little evidence of fibrosis or giant-cell reaction in cases showing heavy pulmonary haemosiderosis. Although many textbooks on medicine and pathology mention diffuse pulmonary fibrosis as a result of mitral stenosis with haemosiderosis, Muir (1958) in his textbook notes the microscopic absence of fibrosis, and Lendrum (1950) states that "indeed it is remarkable how normal is the appearance of the lung between the nodules."

Case 1

This patient, a man aged 43—already reported by Ellman and Gee (1951), but further elaborated here in the light of subsequent progress—was first seen in 1939 at the age of 23. He gave a history of acute rheumatic fever with joint involvement at the age of 7. He had two episodes of pneumonia when aged 13 and 16. At the age of 22 he noticed breathlessness and recurrent haemoptyses. Examination showed a thin man with a sallow complexion, but no cyanosis. There was no dyspnoea at rest. There were physical signs of a tight mitral stenosis with auricular fibrillation at this time. In 1943 he had a severe haemoptysis of about 1 pint (0.6 litre) and his dyspnoea increased. A chest radiograph showed gross miliary mottling throughout both lungs; there was moderate enlargement of the left auricle, with some systolic pulsation visible on screening; the right auricle was considerably enlarged and formed the right border of the cardiac silhouette. Cardiac catheterization at Hammersmith

Hospital showed a right ventricular pressure of 20 cm. saline with a pulmonary arterial pressure of 30 cm.

Mitral valvotomy was carried out on March 5, 1952, when the mitral opening was found to be very small (8 × 4 mm.) with little regurgitant stream. Commissures were split to the ring with a valvotome, leaving an opening about 4 cm. in diameter. Lung biopsy showed pulmonary haemosiderosis with thickening of arterioles but no fibrosis (Special Plate, Fig. 1). After operation his improvement was dramatic. His exercise tolerance increased from 10 yards to 3 miles (9 m. to 5 km.). He went back to full-time work and took up dancing. Sputum disappeared and there was no recurrence of haemoptysis. Clinically to date, the physical signs in the heart are within normal limits, and no apical murmur can be heard. Radiologically, the cardiac outline had now returned to normal, and the striking miliary mottling in the lung fields (Special Plate, Fig. 2) began to clear gradually over the course of the next three years (Special Plate, Fig. 3). When last seen in October, 1958, he was entirely free from symptoms, no haemoptysis had occurred since the valvotomy, and on x-ray examination of the chest the lung fields were virtually clear.

Case 2

In this case, that of a man of 41, mitral stenosis was first diagnosed at the age of 11. There was no definite history of preceding rheumatic fever and no disability at that time. Mitral stenosis was confirmed when he was rejected at an Army medical examination at the age of 24. He continued at work as a van-driver without obvious disability. In the course of the next 10 years he had several episodes of bronchitis with increasing exertional dyspnoea and recurrent haemoptyses. The physical signs were: collapsing pulse; sinus rhythm—jugular venous pulse not raised; apex beat 4 in. (10 cm.) to left of mid-sternal line; signs of right ventricular enlargement; apical diastolic thrill, apical systolic and diastolic murmurs, and aortic diastolic murmur. Blood pressure 130/65 mm. Hg. A chest radiograph showed evidence of enlargement of left auricle and right ventricle and a characteristic pulmonary haemosiderosis (Special Plate, Fig. 4). Tomography revealed definite calcification of the mitral valve. Cardioscopy showed jerky wide-amplitude pulsation. Systolic expansion of the left auricle and right ventricle was confirmed and marked calcification of the mitral valve noted.

On April 28, 1954, because of his symptoms of progressive breathlessness and haemoptysis, mitral valvotomy was performed at Hammersmith Hospital. There was a normal-sized auricular appendage, with a large pulmonary artery and veins. The mitral valve measured 9 × 4 mm. There was gross calcification of the mitral valve, which was rigid. In view of the rigidity of the valve a small split was made in the lateral commissure in order to avoid increasing the mitral incompetence. The final valve size was 1.5 cm. The post-operative course was uneventful. The dyspnoea was greatly improved for three years, there were no further haemoptyses, and the patient was able to return to work for three years.

In January, 1957, the dyspnoea returned, and in March the sputum was blood-streaked. Later the haemoptysis recurred and it was obvious that the mitral valve had restenosed. In view of the gross calcification of the valve and signs of mitral incompetence, it was felt that further valvotomy was contraindicated, and his symptoms, despite symptomatic treatment, became progressively worse.

In December, 1957, at the age of 41, he developed a sudden left hemiplegia due to a cerebral embolus. On his final admission to hospital on December 19, 1957, there was residual weakness of the left arm, face, and leg, together with obvious signs of mitral stenosis with incompetence. Chest radiographs showed the generalized miliary mottling of the lung fields to be unchanged. Following upon an episode of acute pulmonary oedema he died on January 28, 1958.

Post-mortem Findings (R. A. M. O.).—The body was that of a wasted male with a healed scar over the left lower ribs. The heart weighed 500 g. The pericardium was adherent over the surface of the heart. There was striking enlargement of the right ventricle and left auricle. The mitral valve was stenosed, just admitting the tip of the little finger. The cusps were grossly calcified, thickened, and rigid. The other heart valves appeared normal. The myocardium appeared normal macroscopically. Microscopy showed pericardial thickening and fibrosis with scarring at the base of the mitral valve cusps. No Aschoff nodules or cellular infiltration were seen. The right lung weighed 1,015 g. and the left 775 g. The surface of both lungs was strikingly yellowish-brown in colour. Fine adhesions partially obliterated the fissures and the pleural cavities. The lung parenchyma was firmer than was usual, particularly in the upper lobes, but the changes appeared to be due to oedema rather than fibrosis (Special Plate, Fig. 5). Quantities of oedema fluid were expressible from the cut surface. Histologically the striking change was the large amount of haemosiderin present. Groups of 10–20 alveoli were filled with macrophages containing golden-brown pigment granules, which gave a strongly positive prussian-blue reaction for iron. As had been previously remarked by Lendrum (1950), peribronchial lymphatics and hilar lymph nodes were relatively free from iron. Apart from some thickening of the pleura, reticulin and Van Gieson stains showed no significant increase of fibrous tissue. The alveolar walls appeared thickened in the lower lobes posteriorly, but this seemed to be due to swelling and separation of reticulin fibrils by oedema and dilatation of capillaries rather than to a definite increase of collagen. In the remainder of the lung tissue, despite the focal collections of haemosiderin-laden macrophages filling the alveoli, the alveolar walls appeared normal. Fragmentation of elastica and the cellular reaction described in some cases of idiopathic pulmonary haemosiderosis (Wyllie *et al.*, 1948) were absent. Intra-alveolar capillaries were dilated, with diapedesis and leakage of red cells into many of the alveoli. The pulmonary arterioles appeared thickened, but without sclerosis or fibrinoid change. The brain weighed 1,260 g. There was a recent localized infarct 4 cm. in diameter involving the right lentiform nucleus. The cerebral vessels were free from atheroma.

Discussion

In the two cases described above a miliary pattern in the chest radiographs was known to have been present for 18 years in Case 1; in Case 2 it was found on examination in 1954, when the patient first came to our notice. Both patients had suffered recurrent haemoptyses for twenty and six years respectively. It is therefore of interest that in the first case the miliary pattern disappeared gradually after successful mitral valvotomy, while in the second, where successful valvotomy was not possible owing to calcification of the valve, the long-standing pulmonary haemosiderosis and unchanged miliary radiological pattern were not associated with significant pulmonary fibrosis at necropsy.

It must be concluded that the miliary radiological pattern in Case 1 was due mainly to the focal deposition of haemosiderin, which can certainly be removed from the tissues, as has been described in arc-welders (Doig and McLaughlin, 1948) and during the treatment of haemochromatosis (Davis and Arrowsmith, 1952). This concept is confirmed by radiology of whole-lung sections prepared by the Gough technique in Case 2. It was thus possible to reproduce the miliary pattern exactly, the opacities on the radiograph corresponding with the focal haemosiderin deposits in the lung section (Special Plate, Figs. 6 and 7).

While the exact pathogenesis is still in doubt, it seems generally agreed that the deposition of haemosiderin results from pulmonary capillary hypertension, leading to repeated intra-alveolar haemorrhages or diapedesis of red cells, possibly from varicosities in the anastomosis between bronchial vessels and pulmonary arterioles (Ferguson *et al.*, 1944). Wood (1954) found that a history of sudden profuse haemoptysis of 1 pint (0.6 litre) of blood or more ("pulmonary apoplexy") occurred in 55% of cases showing pulmonary haemosiderosis, and in only 12% of cases without haemosiderosis.

Additional factors must also play a part in haemosiderosis, since haemoptyses in cardiac disorders are common, whereas a miliary pattern in chest radiographs is rare (Ellman and Gee, 1951). The question is probably one of speed, there being a dynamic equilibrium between the rate of formation and removal of haemosiderin. Stagnation and pulmonary oedema probably play an important part in delaying the removal of iron, as shown by Strassmann (1944).

Whether iron in the tissues is inert or fibrogenic is controversial. In the lungs it is interesting to recall that iron oxide was the first dust shown experimentally to have a restraining influence on the fibrogenic properties of free silica (Kettle, 1932). It seems probable that iron produces fibrosis in the liver in the idiopathic (endogenous) type of haemochromatosis, but it must be recalled that in this condition it is present in the tissues for 40–50 years before cirrhosis manifests itself. In the transfusional (exogenous) type of siderosis the hepatic fibrosis produced is minimal, and Cappell *et al.* (1957) believe that iron derived from the breakdown of haemoglobin is less fibrogenic than that absorbed from the intestine.

Diffuse interstitial fibrosis of the lung parenchyma is said to be a feature of idiopathic pulmonary haemosiderosis (Wyllie *et al.*, 1948). However, in fulminating cases of the condition, such as those described by Ceelen (1931) and Nancekieveil (1949), fibrosis is minimal or absent. Moreover, the aetiology of the condition is still obscure, so that fibrosis may well be due to factors other than haemosiderosis.

Alternatively, the breakdown products of the erythrocytes may be slowly fibrogenic (Lendrum—personal communication). Lendrum points out that it may well be the lipid constituents, and not haemosiderin, that produce fibrosis. Where pure iron oxide is deposited in the lungs, as in arc-welders and silver-finishers, there is a wealth of evidence to show that the pulmonary siderosis leads to little or no disability and no fibrosis (Harding, 1945; McLaughlin *et al.*, 1945; Barrie and Harding, 1947). Where fibrosis does occur in these occupations it is due to mixed dusts, usually silica (Harding, 1948). Stewart and Faulds (1934) ascribed fibrosis in haematite workers to mixture of the iron ore with silica and termed the process sidero-silicosis. Finally, experimental work on the lungs of animals has shown that iron does not cause fibrosis of the lungs (Harding, 1945; Harding *et al.*, 1947).

In the past many pathologists regarded "brown induration" as a diffusely fibrosed lung. Kaufmann (1929) pointed out that this fibrosis was most marked in foci of iron deposition. Lendrum (1950) confirmed that small foci of intensive connective-tissue damage could occur, but that between these the alveolar walls showed a remarkably unaltered appearance.

We have shown here that a case with obvious radiological haemosiderosis not only showed a good clinical response to mitral valvotomy, but also gave radiological evidence of the gradual clearing of the shadows, presumably due to dispersal of the iron. The fatal case confirms that there may be little fibrotic or granulomatous reaction in spite of radiological and necropsy evidence of heavy focal pulmonary haemosiderosis.

Summary and Conclusion

In the past endogenous pulmonary haemosiderosis was commonly supposed to lead to pulmonary fibrosis ("brown induration").

Two cases of mitral stenosis described here failed to develop significant pulmonary fibrosis. In one case a miliary pattern on the chest radiographs was known to have been present for 18 years, and, since the lung fields cleared gradually after successful mitral valvotomy, it was concluded that the opacities were due to haemosiderin unassociated with fibrosis. In the other there was a six-year history of haemoptyses, and a miliary radiological pattern in the chest was present when the case was first seen in 1954. A satisfactory valvotomy could not be performed owing to calcification of the mitral valve. Following upon a cerebral embolism the patient died from pulmonary oedema. The lungs showed heavy focal haemosiderosis, but no significant fibrosis, either macroscopically or microscopically. It was possible to reproduce the miliary pattern exactly by radiography of a whole-lung section after inflation and fixation.

In our view, mitral pulmonary haemosiderosis, seen radiologically, is no contraindication to mitral valvotomy. Indeed, successful valvotomy may be followed by gradual disappearance of the miliary lung infiltration.

We are indebted to Sir Russell Brock and Dr. Paul Wood for their help in relation to Case 1, and to Mr. W. P. Cleland and Dr. J. F. Goodwin in relation to Case 2. We are particularly indebted to Professor A. C. Lendrum for his helpful advice in the preparation of this paper.

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FIG. 1.—Case 1. Section of lung stained Prussian blue, showing occasional macrophages laden with haemosiderin. ($\times 320$.)

FIG. 2.—Case 1. Radiograph of chest showing characteristic mitral heart and miliary infiltration of lungs.

FIG. 3.—Case 1. Radiograph of chest 5½ years after valvotomy, showing complete resolution of miliary infiltration.

FIG. 4.—Case 2. Radiograph of chest showing mitral heart and miliary infiltration of lungs.

FIG. 5.—Case 2. Section of lung stained by Prussian blue, showing numerous macrophages laden with haemosiderin. The alveolar walls show slight thickening due to oedema. ($\times 90$.)

FIG. 6.—Case 2. Radiograph of left upper zone of lung. (Natural size.)

FIG. 7.—Case 2. Photograph of whole lung section taken from left upper zone. Note miliary opacities in radiograph correspond exactly with focal haemosiderin deposits in lung section from same area. (Natural size.)