

The pathology of the acute and chronic stages of farmer's lung

R. M. E. SEAL, E. J. HAPKE, AND G. O. THOMAS, WITH
J. C. MEEK AND M. HAYES

From Sully and Machynlleth Chest Hospitals

The pathology of five patients who had a biopsy in the acute stage is described; interstitial pneumonia, sarcoid-like granulomata, bronchiolitis, and vasculitis were found. Three of these patients progressed to the chronic stage, when the one with the most extensive bronchiolar involvement had lung function findings of airway obstruction. One progressed to the chronic stage with lung function findings of a transfer defect, and another had radiographic evidence of pulmonary fibrosis with normal lung function tests at rest. The pathology of the chronic stage is described in six patients, with necropsy findings in five. Interstitial pulmonary fibrosis, cystic change, and pulmonary hypertensive changes were the principal findings.

The first account of the condition since called farmer's lung was by Campbell in 1932, who described the acute attack following work with mouldy hay in a group of farm workers. Studdert (1953) reported that one of these farm workers, 18 years later, showed radiographic evidence of some fibrosis and emphysema. At the necropsy on another of Campbell's original group, 'coincidental cystic disease of the lungs' was found.

In 1958 several clinical accounts of farmer's lung appeared together with histological findings following lung biopsy—Dickie and Rankin (1958), Totten, Reid, Davis, and Moran (1958), and Frank (1958) from America, and Riddell and Stewart (1958) from England. These biopsies were usually performed shortly after admission to hospital as the acute symptoms were subsiding. All reports mentioned the presence of an acute interstitial pneumonia and 'sarcoid-like' granulomata.

Seal (1960), in a brief account, recognized the interstitial pneumonitis and sarcoid-like lesions as the pathology of the acute stage following recent exposure, and described the pathology of the chronic end result as severe destruction of pulmonary architecture with fibrosis and collagen-lined cystic areas.

Seal, Thomas, and Griffiths (1963) found lesions in the walls of respiratory bronchioles and an 'arteritis' of related pulmonary arterioles in patients in the acute phase. Page and Hawn (1963) reported a single case with biopsy findings in the

acute attack and also commented on inflammation of small bronchi and bronchioles. Emanuel, Wenzel, Bowerman, and Lawton (1964) described the biopsy findings in 24 patients and emphasized that 25% revealed organizing endobronchial exudate or bronchiolitis obliterans.

As the disease of farmer's lung became scheduled in 1965 under the British National Insurance Act of 1946, a full understanding of the pathology in all stages has become more important.

MATERIAL

Lung biopsy material was obtained during an acute attack from five patients diagnosed as farmer's lung in the Machynlleth Chest Clinic. One of them had a needle biopsy three weeks after the onset of symptoms in 1965 (and was studied in the acute group in the preceding paper in this journal), whilst the other four patients had biopsy material removed by limited thoracotomy after transfer to Sully Hospital in 1959 and 1960, five weeks, nine weeks, 13 weeks, and seven months from the onset of an acute episode. All these patients have been followed up clinically, radiologically, and physiologically. Three of them eventually progressed to the chronic stage of farmer's lung and were assessed in the chronic group in the preceding paper in this issue by the same authors.

The necropsy findings of five chronic farmer's lung patients from the Machynlleth area are described.

An account of the biopsy findings in a sixth chronic patient first seen in this stage at Sully Hospital in 1957 is given.

METHODS

The lung biopsy material obtained by limited thoracotomy was fixed in formol saline. Frozen sections were stained for fat. Paraffin blocks were prepared and sections were stained by haematoxylin and eosin, P.A.S., and special techniques to demonstrate reticulin, collagen, elastic tissue, fungi, and acid-fast bacilli. All sections were examined by polarized light.

Immunofluorescent studies were carried out on the needle biopsy specimen; a paraffin block of the tissue was made by the cold processing technique of Sainte-Marie (1962). Serologically positive serum from a patient suffering from farmer's lung was conjugated with fluorescein isothiocyanate (F.I.T.C.). Conjugation was performed at 0° C. for 15 minutes using 100 mg. F.I.T.C., 2 ml. of antiserum, and an equal volume of carbonate-bicarbonate buffer pH 9.0. The suspension was centrifuged at 3,000 r.p.m. and the supernatant was added to a Sephadex G25 column of 14 mm. diameter and length 180 mm. The conjugated antiserum was eluted with phosphate-buffered saline at pH 7.4. The sections were treated with the conjugate for 10 minutes and then washed thoroughly with the phosphate-buffered saline and mounted in non-fluorescent immersion oil.

A section from the paraffin block was also stained by haematoxylin and eosin.

The lungs obtained at necropsy were inflated with formol saline. Photographs were taken using the barium sulphate impregnation technique (Heard, 1958), and in two patients large paper sections were prepared. Tissue for paraffin blocks was selected and examined after staining by haematoxylin and eosin and the additional staining techniques described above. Blocks were taken from hilar nodes, kidneys, liver, spleen, and myocardium, and were carefully examined for the presence of sarcoid-like granulomata.

CASE HISTORIES

PATHOLOGY IN THE ACUTE STAGE

Farmer's lung in its acute phase is now well recognized as a clinicopathological entity. In the majority of patients clinical and radiological resolution occurs within months, probably assisted by steroid therapy.

In a small proportion of patients, pulmonary fibrosis results, clinically characterized by permanent effort dyspnoea, with a variable profile on lung function testing (Hapke, Seal, Thomas, Hayes, and Meek, 1968). The biopsy findings in the acute phase described here are therefore grouped and presented according to the subsequent clinical progress.

CASE 1 (Biopsy appearances in the acute attack in a patient who subsequently made a complete clinical recovery.)

G.L.I.D., a farm labourer, was first seen in Machynlleth Chest Hospital in February 1958 at the age of 16 years, suffering from an influenza-like illness, with severe dyspnoea following exposure to mouldy hay dust. His chest radiograph revealed marked fine miliary changes. He had received B.C.G. two years previously and his tuberculin test was now negative. Following admission he made a rapid clinical and radiological recovery: no steroids were given. His tuberculin test became positive a year later without B.C.G. revaccination.

He was readmitted to Machynlleth Chest Hospital in March 1960 with a similar influenza-like illness with moderate exertional dyspnoea and 'miliary' radiological signs. There was a slight neutrophilic leucocytosis and an increase in β and γ globulin. He was transferred to Sully Hospital, and on 22 March he had a lung biopsy by limited left thoracotomy, five weeks after the onset of his illness and after three weeks of steroid therapy, when his chest radiograph was almost clear. At thoracotomy the lung was found to be free, somewhat yellowish in colour, induration on palpation involving the lower part of the left upper lobe and the entire lower lobe. A biopsy was taken from the apex of both the upper and lower lobes. The anaesthetist stated that it was a 'difficult lung to inflate'.

Microscopy There was thickening of the inter-alveolar septa largely due to cellular infiltration. Some of these cells were small lymphocytes, but the majority were larger with vesicular convoluted nuclei, probably histiocytes. There was an occasional cell with an elongated nucleus resembling a fibroblast and an occasional eosinophil. Some alveoli contained oedema fluid and foamy macrophages. There was no proliferation of alveolar epithelial cells.

There were numerous 'sarcoid-like' epithelioid tubercles consisting of epithelioid cells and giant cells of Langhans and foreign body type, with a rim of lymphocytes around the periphery. Some tubercles showed central foci of very slight necrosis. Most of the tubercles were located in the centre of the lung lobule near a respiratory bronchiole (Fig. 1). Small intracellular brown particles were seen within epithelioid cells and giant cells. Special stains revealed lipid in the centre of the lesions and intracellular P.A.S. positive granules. No acid-fast bacilli, bacteria or fungal elements were seen. Reticulin stains revealed an increase in reticulin fibres in the inter-alveolar septa and a fine reticulin network within the sarcoid-like granulomata, with more extensive interstitial reticulin formation in the centre of the lobule (Fig. 2). The amount of collagen judged from Van Gieson staining was minimal. Some respiratory bronchioles were occluded, partly by



FIG. 1. Case 1. A peribronchiolar sarcoid-like granuloma consisting of epithelioid cells and giant cells and surrounded by lymphocytes. H. & E., $\times 95$.

inflammatory changes in the walls and partly from an exudate of fluid with neutrophils and phagocytes in the lumen. There was slight thickening of the walls of small pulmonary arteries and arterioles from swelling of muscle fibres and vacuolation of intimal cells. An occasional doubly refractile particle of bacillary size and shape was seen within the macrophages near the small pulmonary vessels. A solitary irregular Schaumann body, measuring $28 \times 20 \mu$, was found in one section surrounded by a giant cell and epithelioid cells. It is of interest to note that there was little difference between the findings from the upper and lower lobe biopsies, although the surgeon considered the lower lobe was more severely

involved. The salient features of both biopsy specimens are summarized and arbitrarily graded in the Table (Case 1).

Subsequent course Progress was uneventful, leading to complete clinical and radiological recovery. The patient gave up farming on medical advice, and when last seen in October 1967 had no symptoms and worked as a manual labourer without any dyspnoea. Findings of detailed lung function tests, including diffusing capacity studies on exercise, were within normal limits. His chest



FIG. 2. Case 1. There is an increase in reticulin in alveolar septa and in the centre of the lobule around arteries and bronchioles. The granulomata have a fine reticulin network. Reticulin stain, $\times 44$.

TABLE
ARBITRARY GRADING OF SEVERITY OF HISTOLOGICAL CHANGES IN THE ACUTE STAGE

Case	Birefringent Material	Sarcoid-like Granulomata	Arterial Lesions	'Interstitial' Mononuclear Infiltration	'Interstitial' Fibrosis	Lymphocytic Foci	Bronchiolar Lesions
1	±	+++	+	+++	-	+	++
2	±	++	+	++	+	++	++
3	-	+	++	++	++	++	++
4	-	+	++	++	++	++	++

radiograph was normal. No precipitin antibodies to mouldy hay dust extract were found in his serum when it was first tested in 1963, five years after the acute attack.

CASE 2 (Biopsy appearances in the acute phase with subsequent clinical progression; radiographic evidence of pulmonary fibrosis and airway obstruction on pulmonary function testing.)

E. M. J., a 53-year-old farmer, was first seen on 23 February 1959, complaining of fever, anorexia, cough, and effort dyspnoea after threshing mouldy grain two weeks previously. He was advised to avoid such exposure, but continued feeding this hay to his cattle. He became severely ill and was admitted to Machynlleth Chest Hospital on 18 March 1959 with fever, severe dyspnoea, cyanosis, and crepitations at both bases. His chest radiograph showed extensive fine mottling with larger confluent opacities. The tuberculin test was negative. After treatment with oxygen, potassium iodide, and prednisone (10 mg. daily), he improved enough to be transferred to Sully Hospital. There a lung biopsy by limited left thoracotomy was carried out on 10 April 1959, nine weeks after the onset of his first symptoms, four weeks after the onset

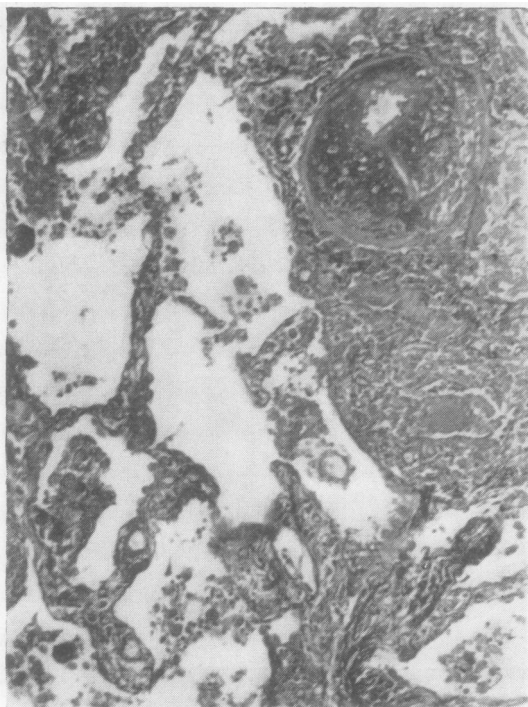


FIG. 3. Case 2. Thickened inter-alveolar septa with large vascular channels cut transversely. There is an ill-defined perivascular granuloma. There is thickening of the wall of the pulmonary artery. Mallory's trichrome, $\times 88$.

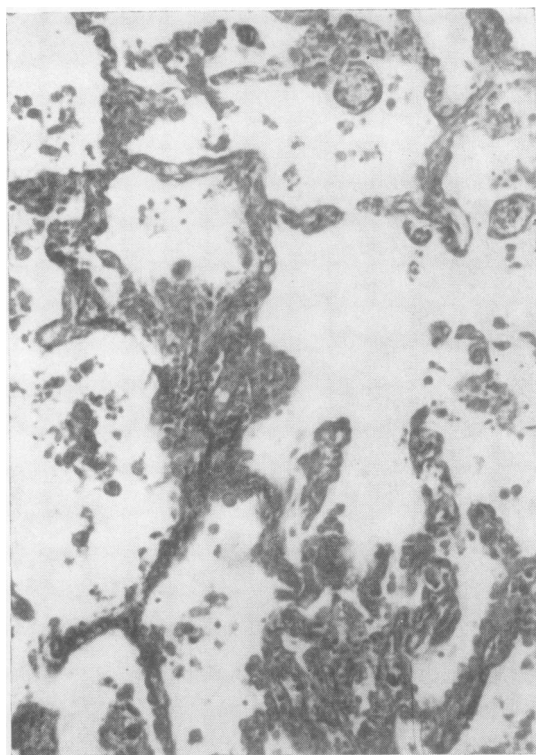


FIG. 4. Case 2. Thickened alveolar septa with small collagenous buds covered by flattened alveolar epithelial cells (above left). Mallory's trichrome, $\times 90$.

of his severe attack, and after three and a half weeks of steroid therapy. At this time his chest radiographs had almost cleared.

The surgeon found apical adhesions; 'the lung felt indurated' but the lingula and the anterior segment of the upper lobe seemed 'somewhat better aerated'. A biopsy was taken from the indurated area above the oblique fissure.

Microscopy There was much thickening of inter-alveolar septa from mononuclear cellular infiltration, consisting of a few lymphocytes, many histiocytes, and a few fibroblasts. In some septa alveolar capillaries were obliterated and in some places there were enlarged vascular channels in the septa cut in transverse section, measuring 15–30 μ in diameter (Fig. 3). The thickening of the septa was also partly due to fibrosis. There were small 'buds' of collagen surrounded by flattened alveolar epithelial cells, projecting from the septa into the alveolar spaces (Masson bodies) (Fig. 4). There were sarcoid-like epithelioid granulomata, many surrounded by a narrow band of collagen fibres. These granulomata were

usually in the centre of the lobule, closely related to bronchioles and pulmonary vessels (Fig. 5). Some alveoli contained oedema fluid and a few alveolar macrophages. The walls of some alveoli were lined by cuboidal epithelial cells.

The walls of pulmonary arteries were thickened from swelling of muscle fibres and intimal proliferation. The lumen of terminal bronchioles was partly obliterated by collections of inflammatory cells in the walls (Fig. 6). These histological features are graded in the Table (Case 2).

A portion of biopsy tissue was ground in a Griffiths' tube, plated on blood agar and Sabouraud's media, and incubated at 22° C. and 37° C. for seven days. No bacteria or fungi were isolated.

Subsequent course There was a gradual improvement in the patient's condition over the next four months. At the end of August 1959 he felt well with no dyspnoea on exertion, and steroid therapy was discontinued. One month later he complained of slight exertional dyspnoea, and so prednisone therapy was reintroduced for a further three months until mid-

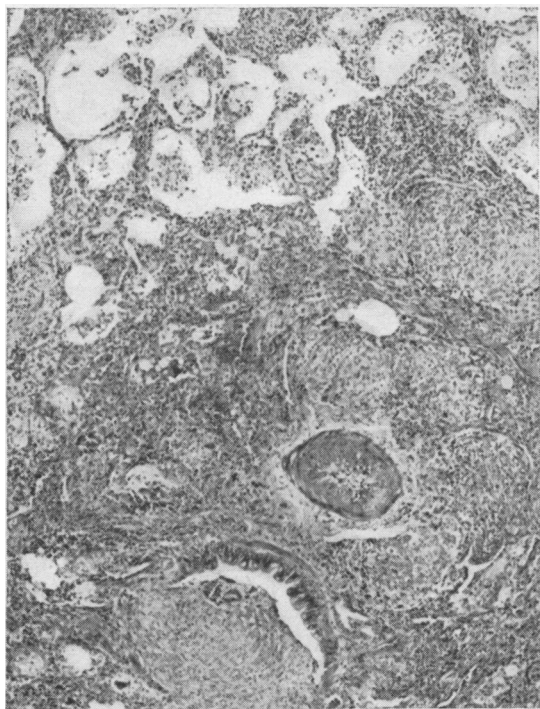


FIG. 5. Case 2. Thickened alveolar septa above. To right of centre and above, a collagen encapsulated granuloma. Below, a thickened pulmonary artery and, below this, a partially occluded bronchiole. Mallory's trichrome, $\times 35$.

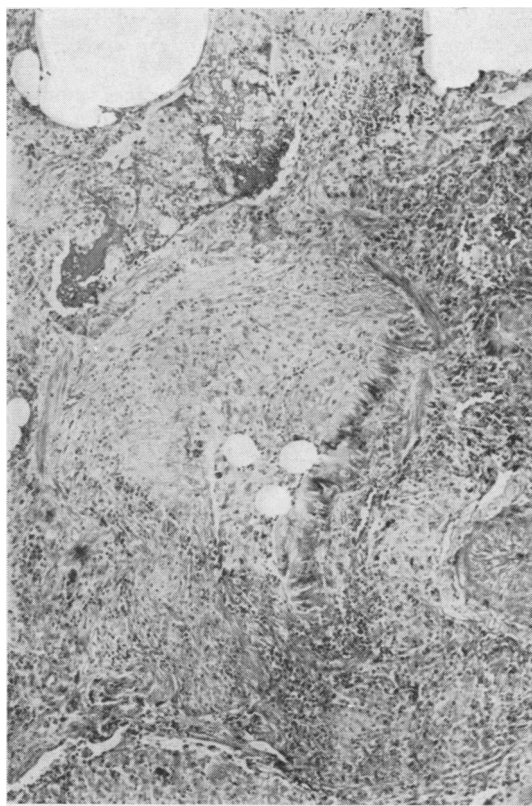


FIG. 6. Case 2. A bronchiole partly occluded by granulomatous lesions in the wall and partly by inflammatory exudate in the lumen. H. & E., $\times 98$.

December 1959. At that time he had not returned to work but had only 'pottered about' on his small-holding, still complaining of slight cough and exertional dyspnoea. A review of follow-up chest radiographs revealed that minimal mottling had persisted for over 12 months from his acute attack.

In May 1960 he attended the M.R.C. Pneumoconiosis Research Unit at Llandough Hospital for lung function studies which showed airway obstruction. At this time his chest radiograph revealed signs of definite early fine fibrosis, and a few months later progression to upper lobe contraction had occurred.

In August 1960 he took a job as a labourer with the local Water Board, and in 1962 he was admitted to hospital for reassessment. His clinical condition, chest radiographs, and lung function findings were found to be unchanged from 1960. His serum, tested for the first time, contained precipitin antibodies to mouldy hay extract.

In December 1963, when he developed a septic finger and was treated with penicillin, he experienced a mild influenza-like illness with increased dyspnoea; recent exposure to any mouldy vegetable matter was

denied, though fine miliary opacities superimposed on fine fibrotic changes were noted on the chest radiograph. He rapidly improved to his former state of slight exertional dyspnoea, but 'occasional' morning cough and sputum 'in cold weather' were mentioned for the first time.

He was reassessed in 1965, among the chronic group reported in the clinical paper in this journal (case 18). Airway obstruction was found on lung function testing.

CASE 3 (Biopsy appearances late in the acute attack in a patient with subsequent clinical progression to radiological fibrosis with a diffusion defect on lung function tests.)

E. J., a farmer aged 48 years, was admitted to Machynlleth Chest Hospital in 1959 with a past history of a 'malaria-like' attack in 1953 following threshing, and an influenza-like illness in 1956 following exposure to mouldy hay dust. The latter illness was characterized by severe exertional dyspnoea and cough, and a chest radiograph revealed miliary mottling. He made a full clinical recovery, but the chest film never completely cleared.

In September 1958, following the stacking of sheaves of mouldy grain, he developed increasing shortness of breath. He was admitted to Machynlleth Chest Hospital on 17 February 1959, having been off work for six weeks: he had been in daily contact with mouldy hay until he was incapacitated. His chest radiograph showed extensive diffuse miliary mottling. He was treated with potassium iodide and prednisone (10 mg. daily for 10 days), was discharged much improved on 28 February 1959, and was able to return to farm work. On 9 March his chest radiograph had only slightly cleared, though clinical improvement had continued. He was readmitted on 27 April with a recurrence of exertional dyspnoea and a 'hard dry' cough. There was slight cyanosis, crepitations were heard at both bases, and a chest film showed miliary changes with superimposed confluent opacities and radiological signs of pulmonary oedema. Prednisone therapy was reinstituted. His general condition and breathlessness improved and he was transferred to Sully Hospital, where a lung biopsy by limited left thoracotomy was carried out on 19 May 1959—seven months after the onset of symptoms, three months after his admission to hospital, and after a total of five weeks' steroid therapy. At this time his chest radiograph still showed definite miliary mottling. At thoracotomy the lung was firm and indurated: biopsies were taken from the lateral basal segment of the lower lobe and the apical segment of the upper lobe. Swabs for culture were taken from the raw areas, but no bacteria or fungi were grown after incubation for seven days at 22° C. and 37° C.

Microscopy There was considerable thickening of inter-alveolar septa, partly from dense lymphocytic and plasma cell infiltration but also from collagen deposition. The pulmonary capillaries in

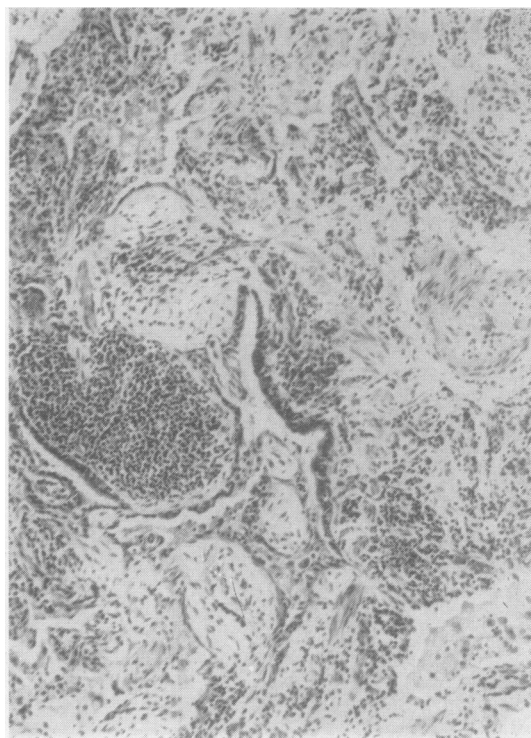


FIG. 7. Case 3. Peribronchial and perivascular fibrosis, lymphocytic foci, and thickening of small pulmonary artery. H. & E., $\times 77$.

many septa were obliterated, whilst in others there were dilated vascular channels. There was extensive fibrosis and large foci of lymphocytes around bronchioles and pulmonary arteries, and Masson bodies were seen in terminal air spaces distal to bronchioles (Fig. 7). There was thickening of pulmonary arterioles and many were surrounded by an infiltrate of lymphocytes and plasma cells. Characteristic 'sarcoid-like' granulomata were not seen, but there were occasional loose collections of epithelioid cells with scattered isolated foreign-body type giant cells. These collections were sometimes surrounded by plasma cells and lymphocytes and were sometimes 'embedded' in fibrous tissue.

The various histological features are graded in the Table (Case 3). It is probable that some of the fibrosis seen in this biopsy was present before the severe attack in 1958–9, especially as his chest radiograph had never completely cleared after the episode in 1955.

Subsequent course There was slow improvement on steroid therapy, but some effort dyspnoea remained, and in September 1959 he was only fit for light work when his chest films showed radiographic changes suggesting pulmonary fibrosis. In 1963 his serum contained precipitins to mouldy hay and *Thermopolyspora polyspora* (*T. polyspora*).¹ In June 1964 his lung function tests at the M.R.C. Pneumoconiosis Research Unit showed mild airways obstruction and a low diffusing capacity. In February 1965 his lung function tests were repeated in Machynlleth (case 23 in preceding paper), with similar findings.

CASE 4 (Biopsy appearances in an acute attack in a patient who eventually progressed to the chronic stage with normal lung function tests at rest.)

G. C., a farmer aged 42 years, had a past history of an acute attack of farmer's lung in the spring of 1955 after exposure to mouldy hay, characterized by fever, cough, effort dyspnoea and weight loss, and a miliary appearance on the chest radiographs. Recovery was complete clinically and radiologically after three months. Shortly before Christmas 1959, following two days of turkey feathering, he noticed morning tightness relieved by the coughing of mucoid sputum. There was severe effort dyspnoea. He continued working and was exposed to mouldy hay; his condition deteriorated and he was admitted to Machynlleth Chest Hospital on 1 March 1960. There were fine crepitations at both bases and the chest films showed more extensive changes than in the first attack five years previously. He was treated with prednisone in a dose of 15 mg. daily for three days, and then 10 mg. daily. He improved rapidly and was transferred to Sully Hospital on 15 March 1960, where his condition continued to improve. Lung function studies (M.R.C. Pneumoconiosis Research Unit) on 22 March 1960 showed that his spirometric values, lung volumes, and diffusing capacity at rest were normal, though the PaO_2 was a little low (75 mm. Hg). He hyperventilated on exercise (70 l./min.) and the PaO_2 was reduced (70 mm. Hg). Alveolar to arterial O_2 tension differences were 19 and 35 mm. Hg at rest and on exercise respectively.

He had a minimal thoracotomy on 30 March 1960 for biopsies of the left upper and left lower lobes, 13 weeks after the onset of symptoms and after four weeks of steroid therapy, when the miliary opacities had almost cleared.

Microscopy There was a diffuse thickening of alveolar walls from mononuclear infiltration with more extensive infiltration in the centre of pulmonary lobules. Many of these mononuclears were large (25 μ) with foamy cytoplasm; similar cells were seen in small numbers within the alveolar spaces. There were sparse 'sarcoid-like' granulomata. Marked vascular involvement with intimal proliferation was observed in small muscular pul-

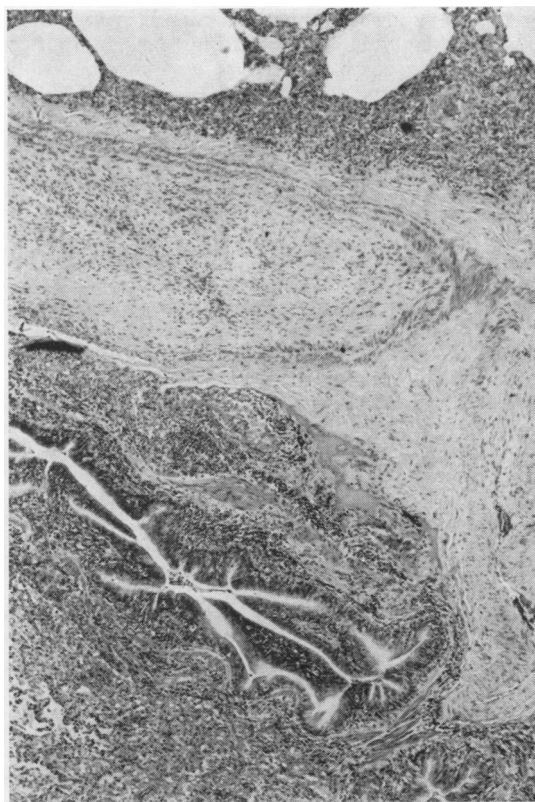


FIG. 8. Case 4. Thickening of inter-alveolar septa. Peribronchial and perivascular inflammatory changes with fibrosis. The pulmonary artery shows intimal hyperplasia and some muscle hypertrophy. H. & E., $\times 55$.

monary arteries with hypertrophy of the media (Fig. 8), and elastic stains revealed reduplication of the internal elastic lamina. There was little evidence of bronchiolar involvement. Occasional doubly refractile particles were seen. Foci of lymphocytes could be found around vessels and bronchioles, but no evidence of established fibrosis of the alveolar walls, though there was some perivascular fibrosis and fibrosis of interlobular septa.

The findings are summarized in the Table (Case 4).

Subsequent course There was continuous improvement, but the slight fine miliary appearance in the chest film remained. Steroid therapy was continued until mid-June 1960. On follow-up visits the patient complained of tiredness and lassitude after work and the chest radiograph continued to show minimal residual opacities. In 1962 his serum contained precipitin antibodies to mouldy hay extract. Lung func-

¹ This organism has now been renamed *Micropolyspora faeni*

tion studies showed no material change in ventilatory capacity, lung volumes, or diffusing capacity, but the ventilatory response to exercise was now materially less (45 l./min.).

When seen in 1965 he complained of moderate dyspnoea on effort, but lung function tests at rest in Machynlleth Chest Hospital (case 3, chronic group, in previous paper in this issue) were still within normal limits.

CASE 5 (Needle biopsy appearances with immuno-fluorescent studies early in the first acute attack in a patient who made a complete recovery.)

W. H. J., a 44-year-old farmer, was admitted to Machynlleth Chest Hospital on 10 May 1965 with a three-week history of effort dyspnoea, headache, and anorexia. He had been feeding mouldy hay to his 12 cows for much of the winter. On examination there were fine crepitations at both lung bases and the chest radiographs revealed the fine miliary appearance of an acute attack of farmer's lung. Precipitin antibodies were present in his serum to *T. polyspora*. A needle biopsy of the lung was carried out on 13 May 1965.

Microscopy There were sarcoid-like granulomata, thickened pulmonary arterioles, and thickening of interalveolar septa by a mononuclear infiltrate. There was no increase in collagen.

The same material treated with F.I.T.C.-conjugated serum and examined under ultraviolet light revealed bright fluorescence in the walls of arterioles and some fluorescence in the cells of the granulomata.

Subsequent course Under steroid therapy there was a return to normal of radiological and lung function findings within three months, at which time he was asymptomatic (see W. M. J., acute group, in previous paper).

PATHOLOGY IN THE CHRONIC STAGE

The chronic stage of farmer's lung may follow a succession of acute attacks or a single severe attack, or may develop insidiously and present to clinicians for the first time in the chronic stage.

CASE 6 (Pathology of a patient in the chronic stage with clinical progression after two acute attacks and lung function findings of a transfer factor defect.)

G. A. M., a farmer aged 42 years, was seen in 1955 with his first chest illness, an acute attack of farmer's lung, characterized mainly by respiratory symptoms after exposure to mouldy hay. He had a normal M.M.R. chest radiograph in 1951. In 1957 he had a further attack, after which, despite avoiding further exposure, he became progressively breathless on exertion.

In March 1960 he was found to be cyanosed at rest. There was poor air entry on auscultation but no

adventitious sounds. There was moderate right ventricular hypertrophy with a loud P₂ and gallop rhythm.

β- and γ-globulins were increased. Serial radiographs revealed progression from the acute miliary appearances of 1955 to moderate signs of pulmonary fibrosis with early contraction of the upper lobes in 1960. Lung function tests revealed a much decreased diffusing capacity and a significant fall in Pao₂ on exercise. A lung biopsy was performed by limited right thoracotomy on 30 March 1960. All lobes felt finely granular on palpation.

Microscopy The architecture of the lung was relatively undisturbed, but there was a 'fine' interstitial fibrosis with collagenous thickening of inter-alveolar septa and a light lymphocytic infiltrate in places. There was also collagenous thickening of interlobular septa (Fig. 9), and there were perivascular collections of lymphocytes. There were occasional areas of fibrosis up to 1 × 2 mm., and in these areas there were collections of lymphocytes and plasma cells. Some alveoli contained brown pigment-laden macrophages. The pulmonary arteries showed changes of pulmonary

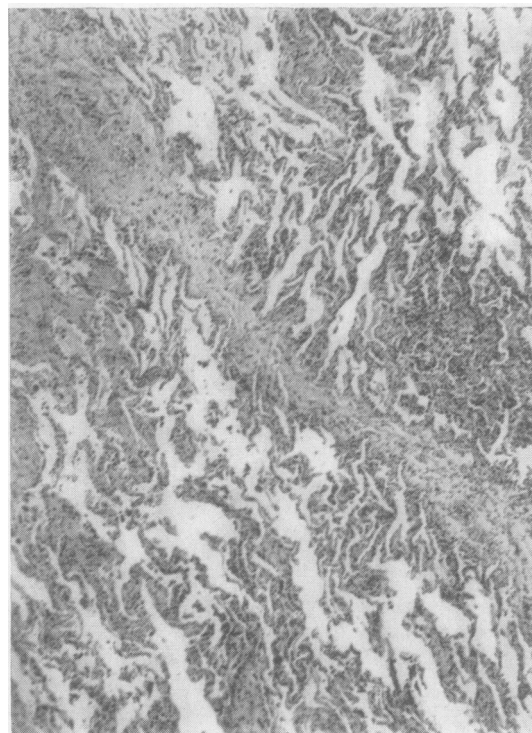


FIG. 9. Case 6. Fibrosis and lymphocytic infiltration of inter-alveolar septa and collagenous thickening of interlobular septum. H. & E., ×33.

hypertension with much intimal fibroelastosis of muscular pulmonary arteries. There were no granulomata. The larger areas of fibrosis contained several small, bacillary sized and shaped, doubly refractile particles.

Subsequent course Steroid therapy was started, but his condition deteriorated and he died in respiratory and congestive cardiac failure on 15 May 1960, five years after the first of his two acute attacks.

Necropsy Both lungs revealed a fine, diffuse, interstitial fibrosis with a fine cystic appearance and a few cystic spaces measuring up to 2.0 cm. The cystic change was more marked in the upper lobe (Fig. 10). The pulmonary arteries were dilated. The heart showed marked right ventricular hypertrophy, up to 9.0 mm. in thickness. There was slight atheroma of the right coronary artery. There was moderate chronic venous congestion of the liver and spleen.

On microscopical examination there were

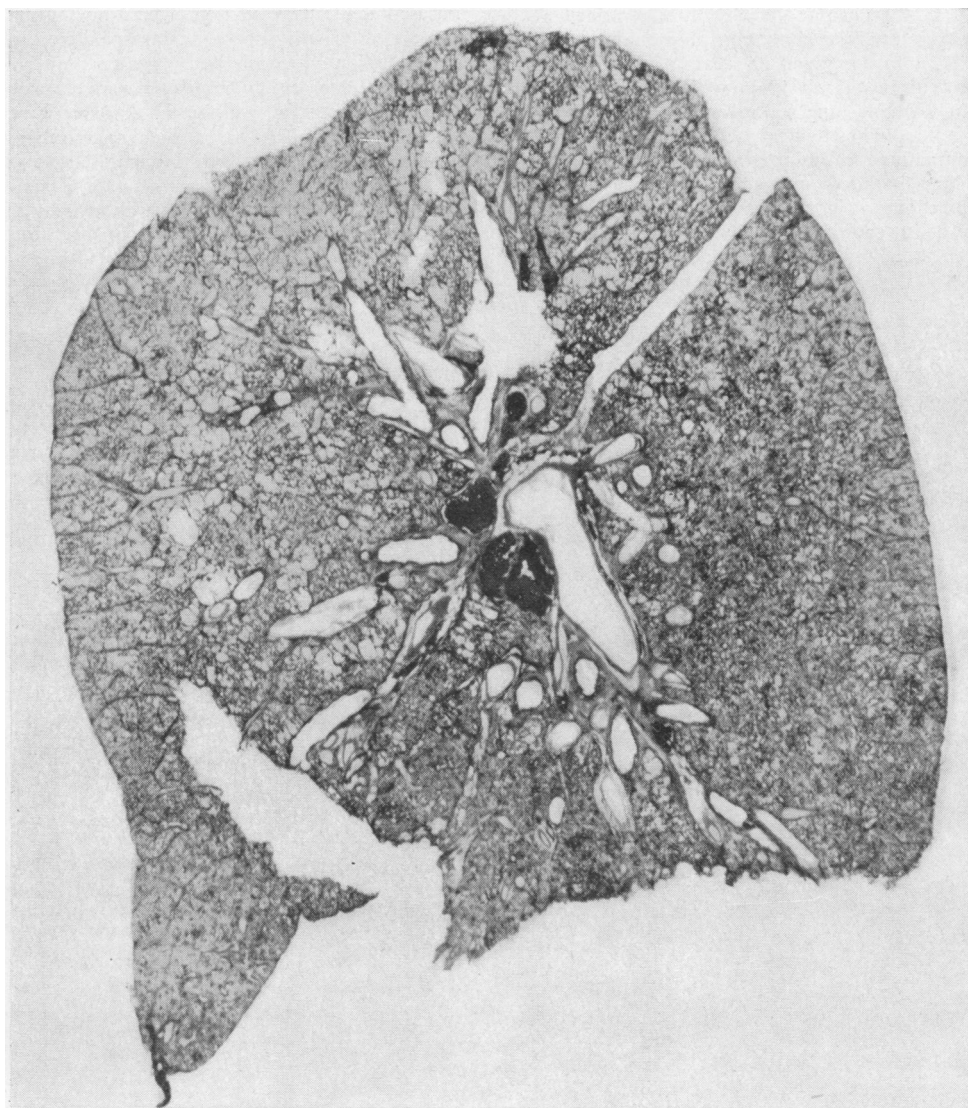


FIG. 10. Case 6. Gough-Wentworth thick paper section showing interstitial fibrosis with a fine cystic change in the left upper lobe. $\times \frac{1}{2}$.

changes essentially similar to those seen on biopsy, except that distended air spaces were seen, which were related to focal areas of fibrosis and are considered areas of irregular emphysema (Fig. 11). In some places the spaces resembled centrilobular emphysema but with slight fibrosis of the walls (Fig. 12). No sarcoid-like granulomata were seen. Some blocks revealed relatively normal parenchyma. Hilar nodes contained several foci of plasma cells in the medulla.

CASE 7 (Post-mortem findings in a patient who first presented in the chronic stage with superadded acute changes, and progressed to cor pulmonale.)

D. G. T., a farmer aged 28 years, was first seen as an outpatient in March 1960, with a past history of attacks of farmer's lung for several winters, for which he had not sought medical aid.

He complained of increasing effort dyspnoea and recently had handled very mouldy hay. There were fine crepitations at both lung bases on auscultation, and the chest radiographs revealed miliary change characteristic of an acute episode superimposed on

chronic changes, seen as moderate contraction of both upper lobes. A calcified lymph node was present at the right hilum, and the trachea deviated to the right. He refused treatment and returned to his farm.

In January 1961 he was admitted to Machynlleth Chest Hospital, having been well during the summer and autumn, but for the past two weeks he had become increasingly dyspnoeic with a cough productive of a small amount of mucopurulent sputum. Slight cyanosis, early finger clubbing, a tachycardia of 120 min., and basal crepitations were present. The chest radiograph showed honeycomb changes and contraction of the upper lobes as in 1960, without superimposed acute type changes. Sputum culture yielded a heavy growth of coagulase-positive, penicillin-resistant staphylococci, but repeated sputum cultures for *Mycobacterium tuberculosis* were negative. There was an increase in γ -globulin. The serum contained precipitin antibodies to extracts of mouldy hay. He was treated with antibiotics, steroids, and digoxin.

Clinical improvement was slow, and he was discharged on 21 March 1961, still on 5 mg. steroids daily, which was continued for a total of nine months. The radiographic appearance remained unchanged.

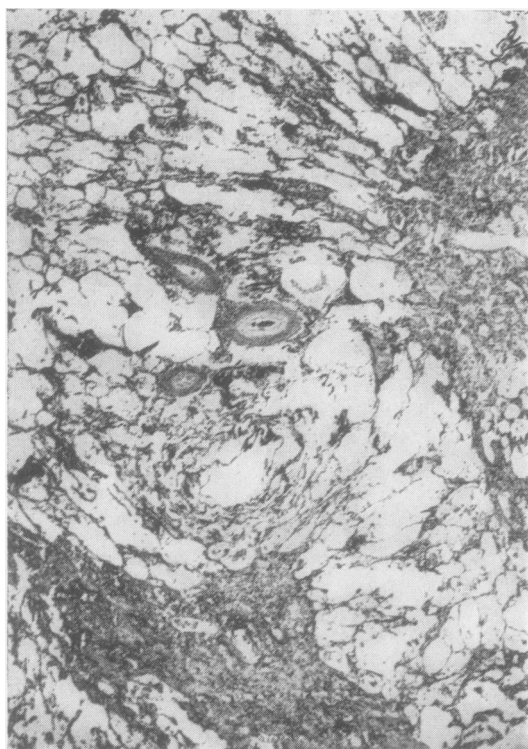


FIG. 11. Case 6. Two focal areas of fibrosis with related irregular emphysema. Changes of pulmonary hypertension. H. & E., $\times 11$.

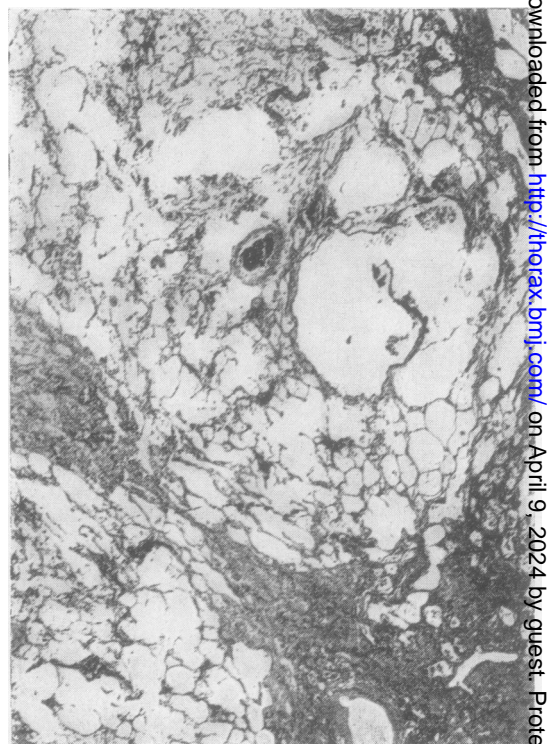


FIG. 12. Case 6. Focal area of fibrosis with related emphysema and a cystic space resembling centrilobular emphysema. H. & E., $\times 11$.

On follow-up in February 1962 he stated that he 'had had quite a good winter'. His general condition was good and his chest radiograph was unchanged.

He was readmitted on 20 May 1963, complaining of dyspnoea which had increased during the winter, a cough productive of only small amounts of sputum, and 'quite a bit' of weight loss.

His chest film revealed increased diffuse fibrosis of both lungs and an increase of the fine cystic change. The cardiac shadow was now enlarged with a prominent right outflow tract. The E.C.G. showed an occasional ventricular extrasystole but no evidence of cor pulmonale. On discharge on 5 June 1963 he was much improved.

He was readmitted on 8 January 1964 with severe dyspnoea and a cough productive of purulent sputum. There was no cyanosis, but there was tachypnoea, tachycardia, crepitations at both bases, and a bounding apex beat with a loud P₂. Sputum culture yielded a growth of coagulase-positive staphylococci. The chest radiograph revealed little change in the appearance of gross interstitial fibrosis with cystic change and cardiac enlargement of the right ventricular type.

He was treated with ampicillin, 250 mg. six-hourly, but his condition deteriorated, he became cyanosed with marked tachypnoea, and died in respiratory failure on 10 January 1964.

Necropsy General nourishment was poor, there being some evidence of recent loss of weight. There was slight finger clubbing.

There was a small bilateral straw-coloured, 150 ml. pleural effusion. The right lung weighed 740 g. and the left 780 g. Both lungs were congested and there was extensive interstitial fibrosis of the lower lobes with fine cystic change (1–3 mm.); in the right posterior basal segment there were larger focal areas of fibrosis with a coarser cystic change (up to 2 cm.). The upper lobes were extensively fibrosed with numerous large related cystic spaces up to 1.5 cm. The major bronchi were not ectatic. The hilar nodes were grey in colour and there were old calcified caseous lesions in one right hilar node. The macroscopic appearances of the cut surface of the left lung are illustrated in Figure 13.

The heart weighed 460 g. The tricuspid and mitral valve orifices were dilated and both ventricles were dilated. The right ventricle was considerably hypertrophied. The pericardium, endocardium, and myocardium appeared normal. The aorta showed only a few foci of atheroma.

Microscopy The lungs revealed a diffuse interstitial fibrosis. The cystic spaces were lined with collagen. In the cystic areas there was extensive fibrosis with much lymphocytic infiltration and sparse plasma cells. No granulomata were seen. There was cuboidal cell metaplasia in some areas

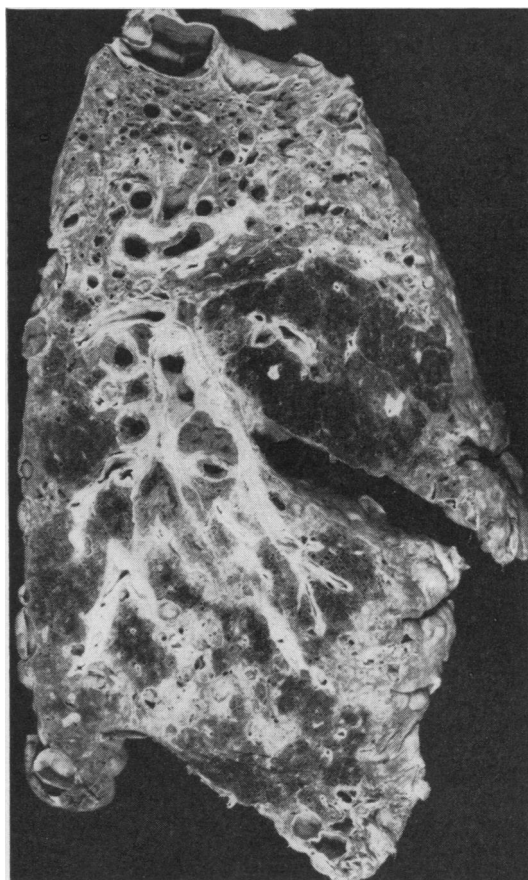


FIG. 13. Case 7. Left lung with extensive fibrosis and honeycomb change more marked in the upper lobe. Barium sulphate impregnation, $\times 2/3$.

and minimal exudation of mononuclear cells into the alveolar spaces. The pulmonary arteries showed changes of pulmonary hypertension; some larger vessels were occluded by organizing antemortem thrombus. Occasionally multinucleate cells were seen in interstitial tissues and alveolar spaces. The hilar lymph nodes revealed collagenous foci with spindle-shaped cells containing much refractile particulate matter. Examination under polarized light showed these particles to be doubly refractile; some were irregular in shape, measuring up to 2 μ in diameter, but the majority were bacillary in shape and size. Similar doubly refractile material was found in the fibrotic areas in the lung parenchyma, more marked in the areas of confluent fibrosis. There was slight hyperplasia of the mucous glands of major bronchi.

CASE 8 (Necropsy findings in a patient who first presented with acute on chronic symptoms of farmer's lung. The lung function findings were of 'gas transfer' defect. Death was sudden.)

W. W. G., a farmer aged 38 years, was admitted to Machynlleth Chest Hospital in March 1961, in an attack of acute farmer's lung characterized by an increase in dyspnoea on exertion and cough productive of some mucoid sputum. He admitted similar attacks during previous winters related to the handling of mouldy corn. His chest radiograph at this time showed considerable pulmonary fibrosis with contraction of the upper lobes. There were no recognizable superimposed miliary opacities, though there were crepitations at both bases. There was an increase in β - and γ -globulin and his fingers were clubbed. He was treated with steroids, his condition improved, and he was discharged in May 1961.

He was seen from time to time as an outpatient. In 1962 his Kveim test was negative, and the serum contained precipitins to mouldy hay and to *T. polyspora* in 1964 and 1965. His chest radiograph remained unchanged from 1961 to 1965. He was reassessed with the chronic group in the preceding paper of this journal (case 16). It will be noted that his respiratory function tests revealed a defect in gas transfer.

He was readmitted in November 1965 with an increase in cough productive of mucoid sputum and dyspnoea following a 'cold on the chest' with hoarseness of voice. On examination he was slightly cyanosed and normotensive. The cardiovascular system revealed no abnormal findings. Seven days after admission, when he was apparently beginning to improve, he died suddenly.

Necropsy The lungs revealed considerable pulmonary fibrosis, which was 'fine interstitial' (Fig. 14) but with larger foci, both linear and stellate, in the upper lobes. Some of these foci appeared to be peri-bronchial, others involved the interlobular septa (Fig. 15). On several cut surfaces of the lower lobes there was an occasional caseous nodule, 1 to 2 mm. in diameter. There was moderate right ventricular hypertrophy but no coronary artery disease.

There was evidence of congestive failure in small bilateral pleural effusions, a little ascites, and moderate chronic venous congestion of the liver.

Microscopy There was an interstitial fibrosis manifested by collagenous thickening of the interalveolar septa and fibrosis around smaller vessels and conducting air passages, with only slight mononuclear infiltration and little evidence of exudation of mononuclears into the alveolar spaces. In the larger areas of fibrosis seen macroscopically there were foci of lymphocytes, occasional multinucleate giant cells, and a few elon-

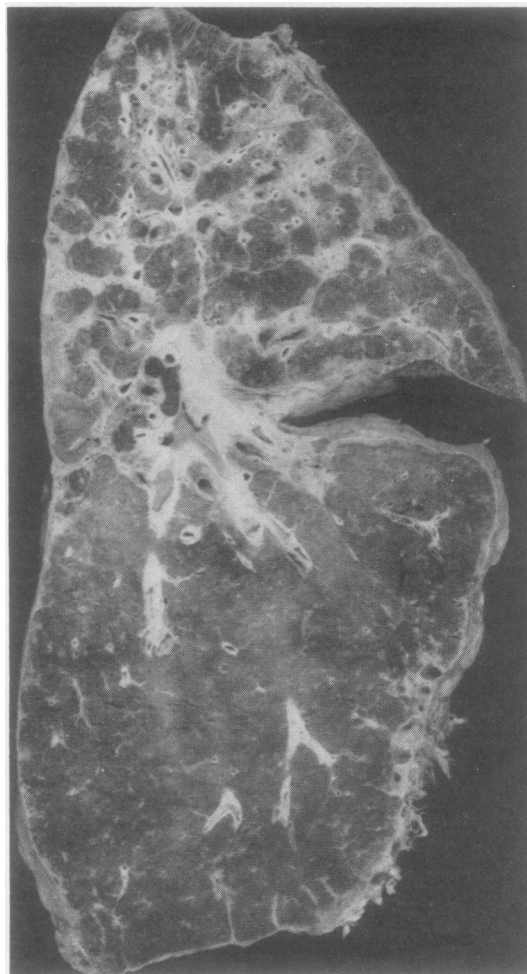


FIG. 14. Case 8. Left lung showing interstitial fibrosis with large focal areas of fibrosis in the upper lobe. Barium sulphate impregnation, $\times 2/3$.

gated doubly refractile particles, 4 to 6 μ by 1 μ . There were small cystic spaces lined by respiratory epithelium, probably representing dilated respiratory bronchioles. The walls of the muscular pulmonary arteries were thickened, mainly from hypertrophy of the media. There was marked hyperplasia of the mucous glands of the major bronchi.

The small caseous foci revealed a necrotic centre bounded by a capsule of epithelioid cells and multinucleate giant cells of both Langhans and foreign body type with fibroblasts and lymphocytes but without a well-developed collagenous capsule. The P.A.S. and Gomori stains revealed

small fragments of fungal mycelium, and Ziehl-Neelsen stains failed to show acid-fast bacilli.

The hilar nodes showed prominent lymph follicles and in the medulla a marked increase in plasma cells, with an occasional multinucleate giant cell but no sarcoid-like tubercles.

CASE 9 (Rapid progression to the chronic stage after a solitary severe acute attack.)

A. T., aged 28 years, was admitted to Sully Hospital in March 1957 for investigation of effort dyspnoea with a slight cough and sputum of six months' duration. He also complained of a slight 'wheeze' on walking and on 'sitting about'.

He gave a past history of an attack of 'double pneumonia' three years previously. He had been a farm worker in Gloucestershire for nine years.

On examination he was found to have widespread medium crepitations, but no other significant abnormalities were found. Chest radiographs showed coarse fibrosis with early contraction of the upper lobes. His tuberculin test was positive at 1 in 100. Repeated cultures of sputum for fungi were negative, but coagulase-positive staphylococci were grown. The serum calcium was raised to 12 mg./100 ml. The differential diagnosis considered was sarcoidosis and

tuberculosis, and he was discharged home to await the result of nine sputum cultures for *Myco. tuberculosis*. These proved to be negative.

He was readmitted in June 1957 for a scalene node biopsy which was normal. He was treated as sarcoidosis with anti-tuberculosis drugs and prednisone. In November 1957 he was allowed to return to light farm work, but by April 1958 he had to stop work owing to increasing effort dyspnoea and was readmitted to Sully Hospital. At that time he had developed slight finger clubbing and in August 1958 signs of pulmonary hypertension with E.C.G. changes. At lung biopsy on 27 September 1958 the pleural cavity was found to be obliterated by easily broken down adhesions. The right upper lobe was found to be small and firm and slightly nodular on palpation: the lower lobe was rubbery. A mediastinal node and a small portion of the upper and the most normal portion of the lower lobe were removed.

Microscopy The biopsy from the 'normal' lower lobe revealed a normal pulmonary architecture, but there was collagenous thickening of the alveolar walls and a slight infiltrate of lymphocytes. The interlobular septa showed collagenous thickening and there was a big increase in connective tissue

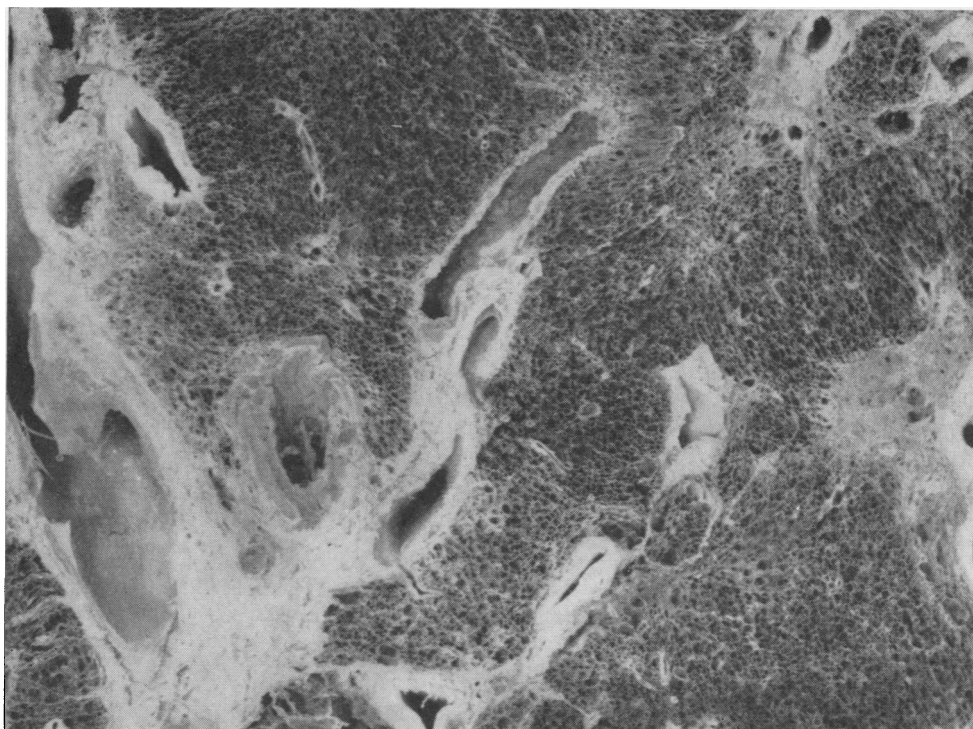


FIG. 15. Case 8. Fine interstitial fibrosis with small peribronchial focal area to the right. Barium sulphate impregnation, $\times 3$.

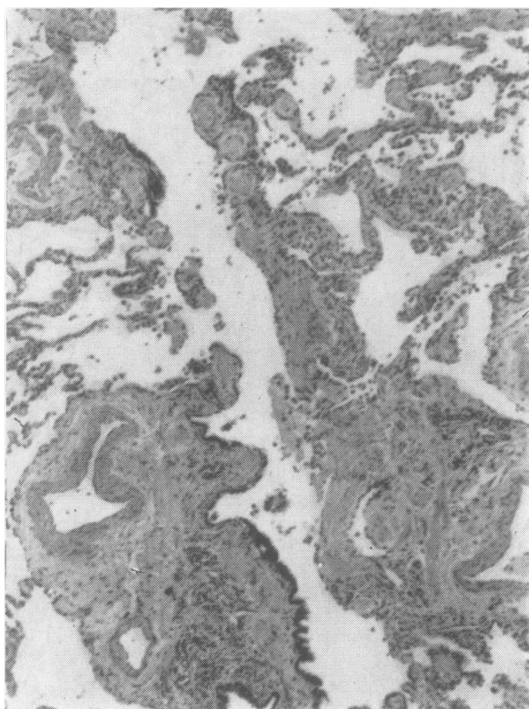


FIG. 16. Case 9. Interstitial fibrosis involving inter-alveolar septa, and peribronchial and perivascular areas. H. & E., $\times 38$.

around respiratory bronchioles and pulmonary vessels, the walls of the latter being thickened (Fig. 16). In some alveoli there were a few large mononuclears containing many P.A.S.-positive granules.

The biopsy from the upper lobe revealed loss of normal pulmonary architecture, there being dense fibrosis with small cystic spaces lined by cuboidal cells. The smaller pulmonary arteries and the pulmonary arterioles were thickened mainly from hypertrophy of the media. The hilar nodes contained several focal collections of plasma cells.

At the time of biopsy it was thought that the changes indicated chronic idiopathic interstitial fibrosis. However, a review of the clinical notes at the time of the 'double pneumonia' in December 1953 showed that the episode had followed threshing, and the radiographs were characteristic of a severe attack of farmer's lung, leaving little doubt that he was now in the chronic stage of this disease.

Subsequent course The patient was maintained on steroid therapy and was found a light job not on a

farm. At the follow-up in 1950 pulmonary function tests revealed a big reduction in lung volume and a substantial drop in PaO_2 during exercise, suggesting oxygen transfer difficulties. Signs of cor pulmonale became more obvious: he eventually deteriorated and died at home in November 1960, seven years after a severe attack of farmer's lung and only two years after the diagnosis had been established. There was no necropsy.

CASE 10 (Pathology of chronic farmer's lung after repeated acute attacks with persisting miliary radiological opacities.)

A. E., a farmer aged 54 years, had his first typical acute attack of farmer's lung in February 1953, after threshing. The onset was sudden, with respiratory and constitutional symptoms. There was a similar episode in 1957, also after threshing, when his chest radiograph had shown characteristic miliary mottling. This cleared slowly under steroid therapy. In 1960, after having been exposed to mouldy hay, he complained of severe headaches and exertional dyspnoea. His chest radiograph revealed miliary opacities, which remained unchanged for several years after this episode. Though he had left farming for a clerical job he complained of frequent headaches, slight effort dyspnoea, and occasionally a dry and unproductive cough.

In March 1962 he had a needle biopsy, as the miliary opacities had persisted for two years. The biopsy specimen showed fibrosis of the alveolar septa—a fine diffuse interstitial fibrosis. No sarcoid-like granuloma was seen and there was no exudation of large mononuclears into the alveolar spaces. The serum contained precipitins to mouldy hay extract. In March 1965 he was reassessed with the chronic group reported in the preceding paper (case 9). On pulmonary function testing an interstitial disease pattern was found, the principal abnormality being a reduced compliance. The serum contained precipitin antibodies to *T. polyspora*.

In September 1965 an undescended right testicle was removed which contained a seminoma. In February 1966 he developed bilateral hilar lymphadenopathy; the Kveim test was negative. The mediastinum was irradiated, following which he developed post-irradiation fibrosis of the lung with the characteristic radiological linear demarcation vertically on each side. In spite of steroid therapy his condition deteriorated and he died in respiratory failure in July 1966.

Necropsy There was evidence of recent loss of weight.

There were small bilateral clear pleural effusions with a fibrinous exudate over both lower lobes. The lungs were firm and rubbery on palpation (right 850 g., left 740 g.). The cut surface of all lobes of both lungs revealed medially yellowish consolidated areas; laterally, there was only a fine interstitial fibrosis. The diagnostic significance of

the medially located pathology would probably have been missed but for the clinical and radiological evidence. Similarly, the fibrosis in the lateral portions could easily have been missed macroscopically if the lungs had been examined uninflated in the post-mortem room. The right ventricle was slightly hypertrophied² and there was chronic venous congestion of the liver and spleen.

Microscopy Section taken from the lateral part of the lung revealed collagenous thickening of alveolar septa with small foci of lymphocytes around smaller blood vessels. There were small areas of fibrosis in the centre of the lobules with dilatation of related respiratory bronchioles. In these focal areas of fibrosis there were a few dust-laden macrophages containing doubly refractile particles, mostly bacillary in size and shape. There was perivascular fibrosis but only slight thickening of intimal and muscular layers.

Tissue from the medial regions of the lung differed considerably. The architecture was more disturbed, the interstitial fibrosis more severe. There was an exudate of amorphous eosinophilic material into the alveolar spaces, occasionally mimicking the appearance of hyaline membrane disease. Some alveoli also contained many neutrophil polymorphonuclear leucocytes, a few collections of plasma cells, and an occasional giant cell of foreign body type containing large spear-like clefts. Other alveoli contained an exudate of large foamy macrophages, and in places there was much hyperplasia of bronchiolar epithelium. Hilar nodes revealed extensive fibrosis and dense plasma cell infiltration. No tumour deposits were recognizable.

Comment Without the clinical facts the pathology of these lungs would be virtually impossible to interpret. In the light of the clinical and radiological information, however, the lateral parts of both lungs present the pathology of chronic farmer's lung, whereas the medial portions present superimposed radiation lung damage with organizing pneumonic and proliferative changes. This radiation lung damage must be considered the principal cause of death.

CASE 11 (Pathology of interstitial fibrosis with cor pulmonale in a farmer's wife, illustrating the difficulties of diagnosis.)

A. J. J., a farmer's wife aged 57 years, was admitted to Machynlleth Chest Hospital on 8 April 1963, complaining of progressive dyspnoea and a cough produc-

tive of whitish sputum for the past month. Owing to her husband's illness three months previously she had taken over the feeding of the cattle and had continued until she was incapacitated. She had had a partial thyroidectomy seven years before.

On examination she was afebrile, orthopnoeic, and cyanosed: her blood pressure was 140/90 mm. Hg. There were showers of crepitations at both bases. The chest radiograph showed an enlarged heart shadow, with pulmonary plethora and nodular shadows in the lung fields.

A differential diagnosis of bronchopneumonia, silent myocardial infarction, and farmer's lung was considered. The E.C.G. showed right ventricular strain only, while serial blood pressure readings did not change. She was given oxygen, prednisone (20 mg. daily), digoxin (0.25 mg. daily), and mercurial diuretics.

She had a mucoid sputum with occasional purulent flecks, and on culture *Candida albicans* was always the predominant organism, though on one occasion *A. fumigatus* was also grown.

On electrophoresis there was an increase in γ -globulin, but the serum contained no precipitin antibodies when tested at both Sully and the Brompton Hospitals using different antigens. The tuberculin test was negative.

She improved clinically and was discharged on 16 April 1963, when the only change in her chest radiograph was a noticeable decrease in the size of the cardiac shadow.

She was seen frequently as an outpatient, still complaining of slight effort dyspnoea and a cough which only produced a little clear mucus. Her chest radiograph taken in December 1963 was unchanged with persistent slight cardiac enlargement and some dilatations of the main and medium-sized pulmonary arteries. The constant peripheral lung changes suggested an established pulmonary fibrosis.

She was readmitted to Machynlleth Chest Hospital on 28 February 1965 with an increase in effort dyspnoea following upper respiratory tract infection. She denied any recent exposure to mouldy hay dust.

On examination she was found to be in congestive cardiac failure. A systolic murmur conducted to the axilla and a basal diastolic murmur were heard. This was thought to represent pulmonary incompetence consequent upon pulmonary hypertension rather than an aortic leak. There was electrocardiographic evidence of cor pulmonale. The chest radiograph showed the lung fields to be unchanged, but there was an increase in the cardiothoracic ratio.

After treatment for cardiac failure she was discharged on 22 March 1965 much improved clinically, but the chest radiograph failed to improve.

She continued to complain of dyspnoea on exertion and in June 1965 she was readmitted in congestive cardiac failure, and died in cor pulmonale four years after the onset of effort dyspnoea—when chest radiographs already revealed evidence of established pulmonary fibrosis.

² After removing excess fat, the heart weighed 310 g., the left ventricle with the septum 160 g., and the free part of the right ventricle 80 g.

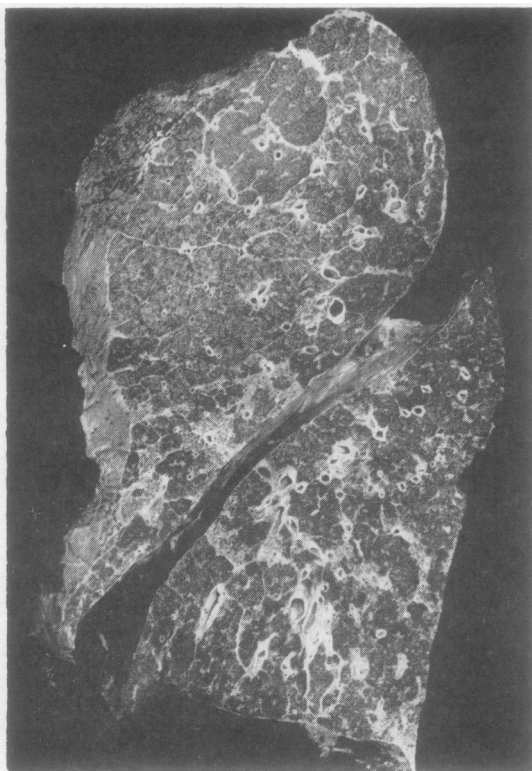


FIG. 17. Case 11. Interstitial fibrosis with focal areas but without cystic changes. Barium sulphate impregnation, $\times 5/7$.

Necropsy The general nourishment was poor, there being some evidence of recent loss of weight.

The lungs revealed a patchy diffuse interstitial fibrosis with many focal areas of fibrosis around the bronchi and related pulmonary vessels. No haemosiderin foci were seen and there was no obvious emphysema or cystic change (Fig. 17).

There was much right ventricular hypertrophy and dilatation. There was severe atheromatous narrowing of the lumen of the anterior descending branch of the left coronary artery, but the myocardium appeared normal. There was severe atheroma of the aorta with narrowing of the origin of the left renal artery. There was evidence of congestive cardiac failure in that there was a small bilateral straw-coloured pleural effusion and chronic venous congestion of the liver and spleen.

Microscopy There were some areas of normal lung except for considerable dilatation of alveolar capillaries; other areas revealed a fine interstitial fibrosis with dense lymphocytic infiltration. The

confluent areas of fibrosis were also heavily infiltrated with lymphocytes.

DISCUSSION

MORBID ANATOMICAL AND HISTOLOGICAL FEATURES OF ACUTE ATTACK

Granulomata Sarcoid-like granulomata were seen in the lung tissue of all our acute patients except case 3, where the biopsy material was obtained much later in the attack and after more prolonged steroid therapy than in the other patients. Dickie and Rankin (1958) also found granulomata in biopsy material examined early in an attack, but not in another patient who had a biopsy some four months after admission to hospital. Similarly, Baldus and Peter (1960) reported sarcoid-like granulomata in two patients who had biopsies in an acute attack, while Page and Hawn (1963), reporting on lung tissue from a patient taken many months after the onset of symptoms, described rare focal granulomas only. Rankin, Kobayashi, Barbee, and Dickie (1967) reported numerous pulmonary granulomata in a 17-year-old farmer five months after the onset of symptoms. Laubach (1965) described sarcoid-like granulomata in a patient with a two-month history of farmer's lung of insidious onset. Emanuel *et al.* (1964) reported on the biopsy histology of 24 patients with farmer's lung, though in only three patients were case histories given. In nine patients there was obvious granuloma formation; a further eight had questionable granuloma formation only. Obvious granulomata were present in two patients with a two-month history of illness. The third patient with a case history was a chronic case who died of respiratory insufficiency and cor pulmonale, and, as in our chronic patients, no granulomata were seen. These authors listed the duration of steroid therapy prior to lung biopsy, and it is evident from the data that granulomata were seen in nine of 11 patients who had biopsies performed after less than five months' steroid therapy, in four of seven with more than five months' therapy, and in four of six patients who had not been treated with steroids. The authors did not consider granulomata essential for the diagnosis of farmer's lung to be made.

The pathology of our material, and a review of the literature where information is available giving the duration of the illness prior to biopsy, lead us to believe that granulomata are a feature of the acute stage, appearing within three weeks and slowly resolving over 12 months. This resolution may be hastened by steroid therapy.

These granulomata are not to be confused with the larger 1 to 2 mm. necrotic lesions seen in chronic case 8, where much central necrosis and fragments of branching mycelium were seen.

Histologically, many of the 'sarcoid-like' granulomata showed microscopic foci of central necrosis rich in fat. No bacteria or fungal elements were seen in any of our cases, but only small brown particles and P.A.S.-positive granules, located in the granulomata but also seen elsewhere. These small particles are not exogenous from inhaled dust, as they are frequently seen in granulomata of other aetiology. They probably represent residual bodies, the end result of incomplete lysosomal digestion in phagocytic cells (Williams and Williams, 1967).

A thin collagenous capsule surrounding 'sarcoid-like' granulomata was seen only in case 2, while in case 3 the loose collections of epithelioid cells were frequently associated with fibrosis. Both cases progressed to the chronic stage.

We suggest that resolution of granuloma in some cases is accompanied by fibrous replacement, contributing to the end result of pulmonary fibrosis. The presence of granulomata, however, also is compatible with resolution without fibrosis, as evidenced in case 1, where granulomata were numerous and complete clinical and radiological resolution has occurred.

Interstitial inflammatory changes There was invariable cellular infiltration of the inter-alveolar septa in all our acute patients. In case 1, where later complete resolution occurred, the cellular infiltrate consisted mainly of histiocytes. Case 3, with the longest duration of illness preceding biopsy and, eventual progression to chronic pulmonary fibrosis, was the only case in which lymphocytes predominated and in which plasma cells were seen in large numbers. Our small series of patients from whom biopsy material was obtained at varying times after the onset of symptoms suggests that the early cell infiltrate is predominantly large mononuclear of histiocyte type, while small round cell infiltration occurs at a later stage and may be associated with the development of interstitial fibrosis. In case 4 large foamy mononuclear cells were seen in the inter-alveolar septa and around bronchioles and vessels, but it is significant that only in this patient is there a clinical suggestion that bird protein might be a contributing antigen (his illness prior to biopsy included exposure to turkey feathers). These large foamy histiocytes have been observed in biopsy material in two patients with bird fancier's lung seen by us.

The only biopsies with little or no interstitial fibrosis were in cases 1 and 5, where complete resolution occurred. It is also interesting to note that in case 1 the considerable increase in interstitial reticulin resolved without progression to collagen formation. Fibrosis was definite in cases 2 and 4 and considerable in case 3.

In the latter three patients the disease had been present for a longer period before the biopsy, and these patients progressed to the chronic stage of irreversible pulmonary fibrosis. It is difficult to be sure how much of this fibrosis seen at the time of the biopsy had developed during the illness preceding the biopsy and how much was already present from previous episodes, as each patient had suffered attacks prior to the occasion when lung biopsy was performed.

Bronchiolar lesions Apart from case 5 (a needle biopsy), obstructive lesions of bronchi were seen in all the acute cases. These lesions were usually found in areas of lung with much confluent disease affecting the surrounding parenchyma. The failure to demonstrate airways obstruction on lung function tests in the acute attack is presumably because the occasional obstructed airways supply consolidated and therefore unventilated lung tissue. It is significant that case 2, with the severest bronchiolar involvement, eventually progressed to pulmonary fibrosis with obstructive airways disease on lung function testing, although case 3 also revealed organizing bronchiolitis but progressed to pulmonary fibrosis with transfer factor defect. That such obstructive lesions may resolve is suggested by case 1, in whom bronchiolar lesions were found at biopsy and resolution appeared complete with normal lung function tests. Emanuel *et al.* (1964) found organizing endobronchial exudate in six of their 24 patients. Although no follow-up pulmonary function tests were carried out they stated that four of these 'recovered', one patient continued to have 'active disease', and one patient after further acute attacks died of cor pulmonale. At necropsy extensive pulmonary fibrosis with bullous emphysema was found.

Vascular lesions Acute inflammatory lesions in the walls of blood vessels were not seen in our acute patients, which is surprising in a condition regarded as largely representing a pulmonary Arthus reaction. Some changes, consisting of proliferation of intimal cells and swelling of muscle fibres, were, however, found in all cases, whilst in two patients eventually progressing to chronic disease additional hypertrophy of the

media was seen, suggesting pulmonary hypertension. As these patients had suffered severe previous episodes, it cannot be concluded that the hypertensive changes had occurred within a few months.

There was also evidence of obliteration of capillaries in the septa of those patients in whom collagen deposition had occurred. Electron microscopy would throw more light on the nature of these capillary changes and the mode of obliteration.

'Foreign material' The presence of foreign body giant cells, sometimes with clefts and birefringent material, was seen in many of our cases. It is surprising that only in case 1, who had a biopsy early in his second attack and was completely recovering, was a Schaumann body seen. Emanuel *et al.* (1964) found foreign body type giant cells in 78% of their biopsies, and 58% contained foreign material, much of which was doubly refractile. They thought that these findings were of diagnostic significance. We feel that the significance of foreign body giant cells and particulate matter needs further investigation.

MORBID ANATOMICAL AND HISTOLOGICAL FEATURES OF THE CHRONIC STAGE

Diffuse interstitial fibrosis The lungs of all six patients examined in the chronic stage revealed areas of fine interstitial fibrosis without any sarcoid-like granulomata, but in all patients there were also focal areas of fibrosis of variable size, often peribronchial. Emanuel *et al.* (1964), in biopsy material, also noted confluence of the fibrosis to produce focal masses. These focal masses were the predominant macroscopic feature in cases 8 and 11. A big increase in smooth muscle was not a feature of the chronic stage of farmer's lung, contrasting with some examples of diffuse idiopathic pulmonary fibrosis.

Cellular infiltration Lymphocytic infiltration of the collagen-thickened inter-alveolar septa was present to a variable degree in all cases and also focal collections of lymphocytes, sometimes with plasma cells, particularly around bronchioles and small pulmonary vessels. Collections of dust-laden phagocytes in alveolar spaces were seen frequently, but in no instance was there extensive exudation of pale, slightly eosinophilic cells so frequently seen in idiopathic pulmonary fibrosis and desquamative interstitial pneumonia (Liebow, Steer, and Billingsley, 1965). Scattered giant cells,

often of foreign body type, were frequently seen and intracellular doubly refractile particles, as described by Emanuel *et al.* (1964), were encountered in all patients.

'Honeycomb' or cystic changes and emphysematous changes Cystic change was an obvious macroscopic feature of the cut surface of the lungs in cases 6 and 7, the cysts varying from a millimetre or so to several centimetres. Microscopically, they were usually lined with collagen. These cystic areas were always found in densely fibrotic zones and are clearly similar to cystic change found in a variety of pulmonary conditions associated with fibrosis described by Heppleston (1956) and Anderson and Foraker (1960).

All our patients in the chronic stage of farmer's lung had obvious pulmonary fibrosis on macroscopic examination of the lung, which was also apparent radiologically. In case 6 there were areas of thin-walled distended air spaces distal to terminal bronchioles which merited being considered emphysematous by definition (Ciba Symposium, 1959), but these areas were always related to small foci of fibrosis and therefore, under the present international classification, are best considered to be examples of irregular emphysema. Emanuel *et al.* (1964) described 'bullous emphysema' in the necropsy findings in association with extensive pulmonary fibrosis in a patient with chronic farmer's lung who died in cor pulmonale.

The development of destructive centrilobular or pan-acinar emphysema without obvious fibrosis is difficult to conceive as an end result of the acute stage of farmer's lung. However, resolution of all interstitial inflammatory damage without fibrosis is a theoretical possibility except for localized inconspicuous bronchiolar post-inflammatory bronchiolar strictures in centrilobular emphysema (Leopold and Gough, 1957). That this may rarely occur is suggested by a case report by Colp, Coppola, and Buchberg (1967) of a patient with non-obstructive interstitial pulmonary disease of unknown aetiology progressed to 'generalized emphysema' with airways obstruction without any fibrosis being found at necropsy.

Predominant involvement of upper lobes with contraction The upper lobes were more severely involved by confluent fibrosis in cases 7 and 11 and by honeycomb or cystic change in cases 6 and 8, confirming the radiographic appearances during life. This pattern of upper lobe predominance in the chronic stage is somewhat surprising

as in the acute stage the lower lobes appeared to be more involved radiologically and also on palpation at thoracotomy.

Cor pulmonale All our chronic cases (except case 8) revealed clinical evidence of cor pulmonale, and histologically changes of pulmonary hypertension were seen. The five cases in whom necropsy was performed revealed considerable right ventricular hypertrophy, and in case 7 the antemortem thrombus of a medium-sized vessel probably represented primary thrombosis frequently seen in pulmonary hypertension from any cause.

MORBID ANATOMICAL AND HISTOLOGICAL DIAGNOSIS OF FARMER'S LUNG

Acute stage In the early acute stage the combination of non-caseating granulomata, diffuse interstitial inflammatory changes, bronchiolitis, and arterial lesions should suggest farmer's lung or one of the other diffuse pulmonary diseases resulting from inhalation of antigenic material, such as bird fancier's lung. The diffuse involvement of inter-alveolar septa, the bronchiolitis, and vascular changes are not seen in sarcoidosis. Later in the severe acute attack, when granulomata have resolved but considerable interstitial lymphocytic cellular infiltration and lymphoid follicles remain and some collagen deposition may have occurred, the picture is far less specific and difficult to distinguish from diffuse fibrosing alveolitis (Hamman-Rich syndrome) and collagen disease.

Chronic stage The combination of a diffuse interstitial fibrosis, focal peribronchial confluent areas of fibrosis, a variable degree of cystic change, and maximal involvement of the upper lobe with contraction should suggest the possibility of farmer's lung or closely related conditions such as bird fancier's lung. The presence of focal collections of plasma cells and the absence of granulomata in hilar nodes and other organs exclude chronic sarcoidosis. Schaumann bodies are common in chronic sarcoidosis but are rare in farmer's lung. The diagnosis in the chronic stage, however, can only be made with certainty by taking account of the clinical history. Patients seen in the acute stage and followed into the chronic stage will present no diagnostic difficulty; others presenting in the chronic stage with super-added acute manifestations are more likely to be misdiagnosed. Case 9 seen in the chronic stage illustrates the importance of obtaining details of

previous 'pneumonic' episodes; without this care such patients would probably be considered examples of diffuse fibrosing alveolitis (Hamman-Rich disease, diffuse idiopathic pulmonary fibrosis). The necropsy diagnosis of the aetiology of the fibrosis found in a farmer after an insidious onset of symptoms without a history of classical acute attacks and possibly with negative serology gives rise to the greatest difficulty. In the present state of our knowledge we think it would be wise to consider such patients as having farmer's lung, particularly for the purposes of industrial benefit.

Correlation of pathology and radiology In four of our five acute patients sarcoid-like granulomata and extensive diffuse interstitial inflammatory changes were found when there were only minimal miliary changes on the chest radiograph. Similar radiographic changes persisting for over 12 months were due to interstitial disease only. We therefore think that radiographic clearing is only a crude index of resolution and that fine miliary appearances are significant and may indicate the presence of granulomata or of interstitial pathology only.

In the late chronic stage there was good correlation between radiology and pathology, the chest films indicating the fibrotic nature of the disease, the predominance of upper lobe pathology, and the development of cor pulmonale.

Correlation of pathology and lung-function tests In the acute stage the pulmonary function findings of a decrease in compliance and a reduction in vital capacity, with a greater proportional defect of gas transfer, is adequately explained by the diffuse inflammatory involvement of the alveolar septa. There is also adequate explanation for ventilation and perfusion inequalities. The failure of bronchiolar obstructive lesions to produce an obstructive element on lung function testing has already been discussed.

In the chronic stage lung function tests during life have yielded a variable picture, ranging from a defect in gas exchange to pure obstructive airways disease, in patients having radiological evidence of pulmonary fibrosis (Hapke *et al.*, 1968). Only in four of our chronic patients were pulmonary function tests performed, and in each case the findings were of a transfer factor defect: it is not surprising that extensive diffuse interstitial fibrosis dominated the histological picture. Neither some fibrotic narrowing of respiratory bronchioles in one patient nor much hyperplasia of mucus-secreting apparatus in another was reflected in the

lung function findings. It is significant that the one patient who had a biopsy in the acute attack and who progressed to the chronic stage with airway obstruction was the patient considered to have the severest degree of bronchiolar involvement. Biopsy appearances in case 4 revealed considerable interstitial damage, vascular and bronchiolar changes, and many granulomata, though lung function findings one week previously had revealed only a minimal abnormality at rest: in this patient blood gas studies on exercise were required to demonstrate the defect.

We have not yet had the opportunity of examining the lungs of a chronic patient with or without radiographic evidence of fibrosis who has airways obstruction on lung function testing. It will be interesting to see whether mucous gland and goblet cell hyperplasia or fibrotic narrowing of terminal airways is encountered in such cases.

Factors associated with progression to fibrosis It is significant that of the nine patients clinically seen in the chronic stage, six had exposure whilst threshing, suggesting that such heavy exposure is more likely to lead to permanent pulmonary fibrosis. It is also interesting to note that in some patients the radiological signs of fibrosis developed whilst the clinical condition remained unchanged. A comparison of the histology in the acute stage at differing intervals from the onset of the attack suggests that the fibrosis begins within the first few months. It is difficult to decide whether the fibrosis is an inevitable consequence of severe inflammatory damage, or whether the fibrotic process is more gradual, consequent upon a chronic persisting inflammation. The presence of excess antigen in case 5, three weeks after the onset of an attack, the continued presence of lymphocytes and plasma cells at later stages, and the persistence of antibodies in chronic patients all suggest the latter.

A reappearance of symptoms, signs, and radiological miliary opacities in case 2 without further exposure, when suffering from a staphylococcal infection, raises the possibility that other infections may cause a recrudescence of hypersensitivity lung damage, presumably from a change in the level of circulating antibodies. This observation (also noted by other clinicians) suggests that the fibrosis is a slow continuing process.

Pathology and pathogenesis No bacteria or fungi were isolated from the tissues obtained at lung biopsy of our patients when cultured at 22° and

37° C. Wenzel and Emanuel (1965), however, recovered *T. polyspora* from biopsy material incubated at 60° C. but did not regard the organism as an infective agent.

The absence of any histological evidence of proliferation of bacteria or fungi within the lesions supports the view that the lesions are largely the result of hypersensitivity to inhaled antigenic material. An Arthus (type III) reaction has been considered the most likely explanation in view of the time from exposure to symptoms (8 to 12 hours) related by patients, and the similar interval from exposure to symptoms and signs in inhalation tests (Williams, 1963). The demonstration of precipitin antibodies to *T. polyspora* is also in keeping with an Arthus (type III) allergic reaction to this thermophilic actinomycete. The histological features of vascular changes in all cases with concentration of antigen in and around vessels demonstrated by immuno-fluorescent study of case 5 and the fibrosis around small arteries and arterioles together with the interstitial pneumonitis support this concept. The presence of classical epithelioid tubercles in the early stage suggests a delayed tuberculin (type IV) component, and the presence of numerous foreign body type giant cells raises the possibility of a non-allergic foreign body inflammatory component also.

A comparison of the histological changes in the rabbit induced by repeated endotracheal instillation of heterologous serum, mouldy hay dust, and spores of *T. polyspora* reveal differences (Edwards, Hayes, Jenkins, and Seal, 1968). This also suggests that the lesions in farmer's lung are not entirely explained by a pure pulmonary Arthus reaction.

The histological appearances in farmer's lung in the acute stage certainly have much in common with the histology of the segmental lesions of childhood tuberculosis, where an intra-alveolar oedema with macrophages and interstitial pneumonitis and an increase in reticulin in alveolar septa with numerous non-caseating tubercles can be found. Miller, Seal, and Taylor (1963), and Pepys in Gell and Coombs (1964) however, have pointed out that in such a reaction an Arthus component may also be present attributable to the polysaccharide fraction of *Myco. tuberculosis*.

It can therefore be concluded from the histology that farmer's lung is largely a pulmonary hypersensitivity reaction, but that there may be a component, or components, in addition to an Arthus reaction.

Pathology and terminology Dickie and Rankin (1958) summarized the pathology of farmer's lung as an interstitial granulomatous pneumonitis. Spencer (1967), in a review article on interstitial pneumonia, included farmer's lung and bird fancier's lung as examples of allergic conditions giving rise to this pathology. Pepys (1967) realized the need for a generic term to embrace the several similar clinicopathological entities and suggested the term *extrinsic allergic alveolitis*. We feel, however, that though the use of 'extrinsic allergic' together is a helpful way of bracketing these similar conditions with a similar aetiology, the term 'alveolitis' to pathologists at least will prove confusing as it will not reflect the concentration of damage in and around respiratory bronchioles in the centre of the lobule—an important concept in farmer's lung.

Further, the term 'alveolitis' is now established as including fibrosis in the interstitial tissue around alveoli in diffuse fibrosing alveolitis (Scadding and Hinson, 1967) and cryptogenetic fibrosing alveolitis (Scadding, 1967), which are terms replacing diffuse idiopathic interstitial fibrosis and Hamman-Rich disease. In this condition there is a transfer defect with no obstructive features on lung function tests. Farmer's lung in a proportion of cases may well have obstructing fibrosis of terminal conducting airways as a major factor. We think, therefore, that *extrinsic allergic pneumonia* or *bronchopneumonia* would prove more acceptable.

We wish to thank Professor J. Gough for helpful criticism and advice and for preparing large paper sections, and Dr. W. H. Beasley for helpful co-operation in performing necropsies and submitting inflated lungs and tissues for our examination. We are grateful to Professor Lynne Reid for an opinion on the mucus-secreting apparatus of the major bronchi of necropsy material. We thank Mr. F. Midgeley for the photography and Miss E. M. Jackson for the typing.

This work was supported by a grant from the Welsh Hospital Board.

REFERENCES

- Anderson, A. E., and Foraker, A. G. (1960). Morphological aspects of interstitial pulmonary fibrosis. *Arch. Path.*, 70, 79.
- Baldus, W. P., and Peter, J. B. (1960). Farmer's lung: report of two cases. *New Engl. J. Med.*, 262, 700.
- Campbell, J. M. (1932). Acute symptoms following work with hay. *Brit. med. J.*, 2, 1143.
- Ciba Symposium (1959). Terminology, definitions, and classification of chronic emphysema and related conditions. *Thorax*, 14, 286.
- Colp, C., Coppola, A., and Buchberg, A. S. (1967). Diffuse emphysema as a result of nonobstructive interstitial pulmonary disease. *Amer. Rev. resp. Dis.*, 96, 788.
- Dickie, H. A., and Rankin, J. (1958). Farmer's lung: an acute granulomatous interstitial pneumonitis occurring in agricultural workers. *J. Amer. med. Ass.*, 167, 1069.
- Edwards, J. H., Hayes, M., Jenkins, P. A., and Seal, R. M. E. (1968). To be published.
- Emanuel, D. A., Wenzel, F. J., Bowerman, C. I., and Lawton, B. R. (1964). Farmer's lung: clinical, pathologic and immunologic study of twenty-four patients. *Amer. J. Med.*, 37, 392.
- Frank, R. C. (1958). Farmer's lung: a form of pneumoconiosis due to organic dusts. *Amer. J. Roentgenol.*, 79, 189.
- Grabar, P., and Williams, C. A. (1953). Méthode permettant l'étude conjuguée des propriétés électrophorétiques et immunochimiques d'un mélange de protéines. Application au sérum sanguin. *Biochim. biophys. Acta. (Amst.)*, 10, 193.
- Gell, P. G. H., and Coombs, R. R. A. (1964). *Clinical Aspects of Immunology*. Blackwell Scientific Publications, Oxford. Revised reprint.
- Hapke, E. J., Seal, R. M. E., Thomas, G. O., Hayes, M., and Meek, J. C. (1968). Farmer's lung: a clinical, radiographic, functional, and serological correlation of acute and chronic stages. *Thorax*, 23, 451.
- Heard, B. E. (1958). A pathological study of emphysema of the lungs with chronic bronchitis. *Ibid.*, 13, 136.
- Heppleston, A. G. (1956). The pathology of honeycomb lung. *Thorax*, 11, 77.
- Laubach, C. (1965). Farmer's lung: disease in Eastern Pennsylvania. *N.Y. St. J. Med.*, 65, 3020.
- Liebow, A. A., Steer, A., and Billingsley, J. G. (1965). Desquamate interstitial pneumonia. *Amer. J. Med.*, 39, 369.
- Leopold, J. G., and Gough, J. (1957). The centrilobular form of hypertrophic emphysema and its relation to chronic bronchitis. *Thorax*, 12, 219.
- Miller, F. J. W., Seal, R. M. E., and Taylor, Mary D. (1963). *Tuberculosis in Children*. Churchill, London.
- Page, M. I., and Hawn, C. Van Zandt (1963). Farmer's lung: report of a case, with lung biopsy. *Amer. Rev. resp. Dis.*, 87, 576.
- Pepys, J. (1967). Hypersensitivity to inhaled organic antigens. *J. roy. Coll. Physn (Lond.)*, 2, 42.
- Rankin, J., Kobayashi, M., Barbee, R. A., and Dickie, H. A. (1967). Pulmonary granulomatosis due to inhaled organic antigens. *Med. Clin. N. Amer.*, 51, 459.
- Riddell, R. W., and Stewart, G. T. (1958). *Fungous Diseases and their Treatment*. Butterworth, London.
- Sainte-Marie, G. (1962). A paraffin embedding technique for studies employing immunofluorescence. *J. Histochem. Cytochem.*, 10, 250.
- Scadding, J. G. (1967). Antigen-antibody reactions in bronchopulmonary disease. *J. roy. Coll. Physn (Lond.)*, 2, 35.
- and Hinson, K. F. W. (1967). Diffuse fibrosing alveolitis. *Thorax*, 22, 291.
- Seal, R. M. E. (1960). Farmer's lung. *J. clin. Path.*, 13, 274.
- Thomas, G. O., and Griffiths, J. J. (1963). Farmer's lung. *Proc. roy. Soc. Med.*, 56, 271.
- Spencer, H. (1967). Interstitial pneumonia. *Ann. Rev. Med.*, 18, 423.
- Studdert, T. C. (1953). Farmer's lung. *Brit. med. J.*, 1, 1305.
- Totten, R. S., Reid, D. H. S., Davis, H. D., and Moran, T. J. (1958). Farmer's lung. *Amer. J. Med.*, 25, 803.
- Wenzel, F. J., and Emanuel, D. A. (1965). Experimental studies of farmer's lung. *N.Y. St. J. Med.*, 65, 3032.
- Williams, J. V. (1963). Inhalation and skin tests with extracts of hay and fungi in patients with farmer's lung. *Thorax*, 18, 182.
- Williams, W. Jones, and Williams, D. (1967). 'Residual bodies' in sarcoid and sarcoid-like granulomas. *J. clin. Path.*, 20, 574.