

# Diffuse lymphoid interstitial pneumonia

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**MacFarlane, A., and Davies, D. (1973).** *Thorax*, 28, 768–776. **Diffuse lymphoid interstitial pneumonia.** A woman developed linear shadows in the chest radiograph at the age of 54 years. Over the next 11 years she gradually became thin and breathless. When she died she had clubbing of the fingers and extensive consolidation with some honeycombing in her lungs. Necropsy examination showed large yellowish-brown deposits in the lungs. Microscopically these were composed of sheets of mature lymphocytes. There was complete destruction of the lung architecture and there were deposits of hyaline material. In the less affected areas the distribution was interstitial. Other organs were not involved. There was no evidence that this was a localized tumour of lymphatic origin. The condition is best regarded as a rare variety of interstitial pneumonia, the classification of which is reviewed briefly.

In 1966 Carrington and Liebow described the clinical, radiological, and morphological findings in five adults and one child with an interstitial pneumonia characterized by massive infiltration of both lungs by lymphoid tissue. They called the condition 'lymphocytic interstitial pneumonia'. We describe a patient who appears to fit the original description.

## CASE HISTORY

Mrs. E.M.H., a housewife, was born in 1901. Her health had been good until 1955 when she coughed up a little blood after injuring her nose and face. She had no other symptoms and there was no clinical abnormality. The chest radiograph showed fine linear shadows in the upper half of the right lung and in the lateral part of the left lung (Fig. 1). There were no earlier films.

In December 1955 she fell and injured the left side of her chest. She developed a cough with sputum, spent five weeks in bed, and was treated for pneumonia. When referred to hospital in March 1956 she complained of some residual pain and a slight cough with sputum. There was no abnormality on physical examination. Radiographically the lung fields were unchanged but there were fractures of the left fifth to ninth ribs with very little callus formation.

She presented again in 1960 complaining of epigastric pain of a few months' duration, a slight cough with occasional scanty sputum, and mild dyspnoea on exertion. She looked weary and older than her age and her weight had dropped 8 kg to 48 kg. Apart from a few scattered crepitations over the lungs and epigastric tenderness there was no abnormality. The

radiograph showed considerable extension of the lung shadowing, particularly in the right upper lobe, and there was an area of consolidation in the right middle lobe (Fig. 2). The rib fractures had healed except for a persisting gap in the seventh rib. While being investigated in hospital her general condition improved and the pain disappeared.

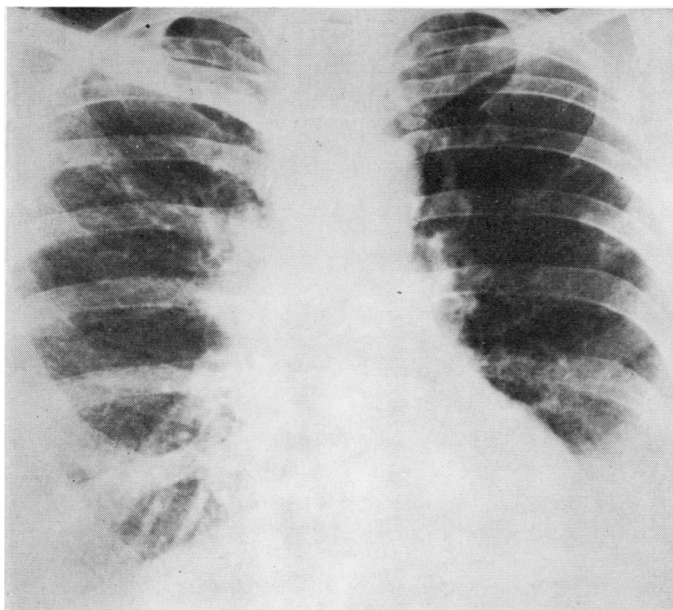
In March 1961 she had a haematemesis, her haemoglobin falling to 5.6 g/100 ml. A barium meal showed a large ulcer in the mid-part of the lesser curvature of the stomach. After blood transfusion she was treated with antacids and a diet, the ulcer gradually decreasing in size. In May 1962, however, she had further bleeding and a partial gastrectomy was done. The resected stomach showed a simple ulcer, 2.5 cm in diameter, without any unusual histological features.

From then until she died her health deteriorated steadily. She continued to have abdominal pain for about a year after operation but it then abated. She had a few episodes of urinary infection which were mainly symptomless, the organisms involved being *Entamoeba coli* and *Streptococcus faecalis*. General weakness and shortness of breath became the dominant symptoms. She lost more weight but during four hospital admissions between 1964 and her death she always regained a considerable amount and felt better.

Clubbing of the fingers appeared in 1962 and later became marked. Multiple crepitations developed over both lungs at about the same time. During the last year of her life she was short of breath on the slightest exertion and was often mildly cyanosed. She had occasional low-grade fever. Her sputum was mucopurulent and averaged about 20 ml daily, cultures producing *E. coli* and *Bacillus proteus*, and there was no response to antibiotics. Occasional ankle oedema appeared.

The chest radiographs showed progressive disease and by 1965 the right upper lobe showed contraction

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**FIG. 1.** *Chest radiograph in 1955 showing fine linear shadows in the upper half of the right lung and in the periphery of the left mid zone.*

**FIG. 2.** *Radiograph in 1960 showing considerable extension of shadowing in the right upper lobe, moderate extension in the left lung, and consolidation in the middle lobe. Healed fractures of the left fifth to ninth ribs with a gap between the fragments in the seventh rib.*

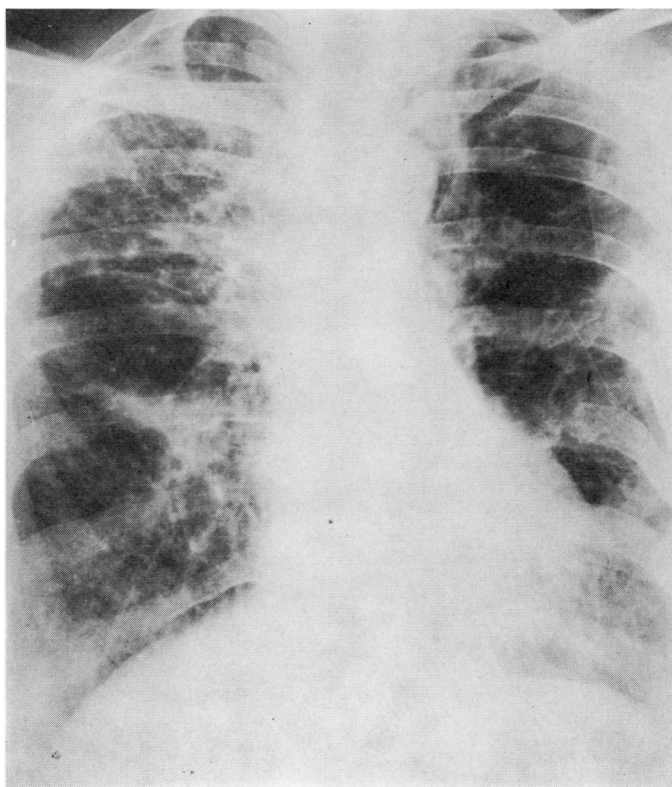




FIG. 3. By 1965 there has been a further increase in shadowing in both lungs. There is honeycombing in the right upper lobe and in scattered areas on the left.

FIG. 4. Sagittal section of right lung showing consolidation of the posterior two-thirds of the upper lobe, almost the whole of the middle lobe, the apex of the lower lobe, and in scattered areas of the remainder. There is honeycombing in some of the affected areas best seen in the posterior part of the upper lobe.

FIG. 5. Sagittal section of the left lung showing consolidation of the posterior third of the upper lobe and in other scattered areas. Honeycombing is present, especially in the apex of the lower lobe.

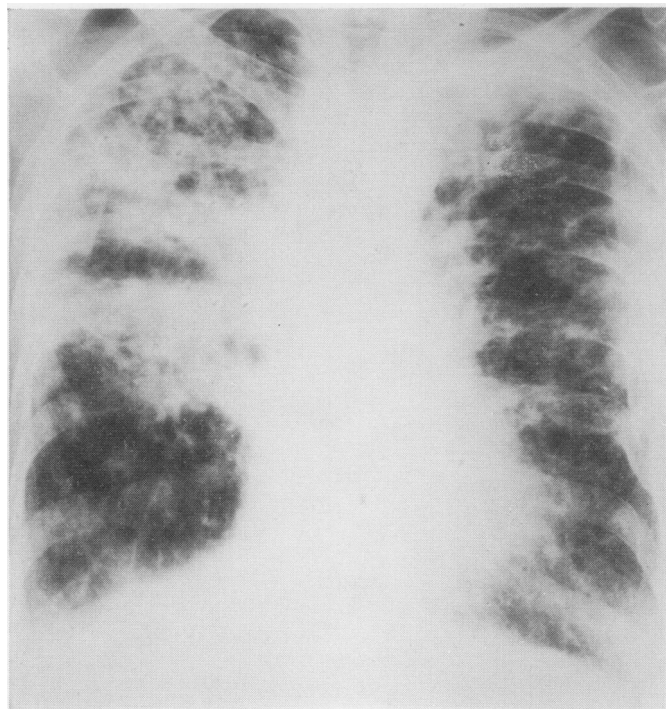


FIG. 3

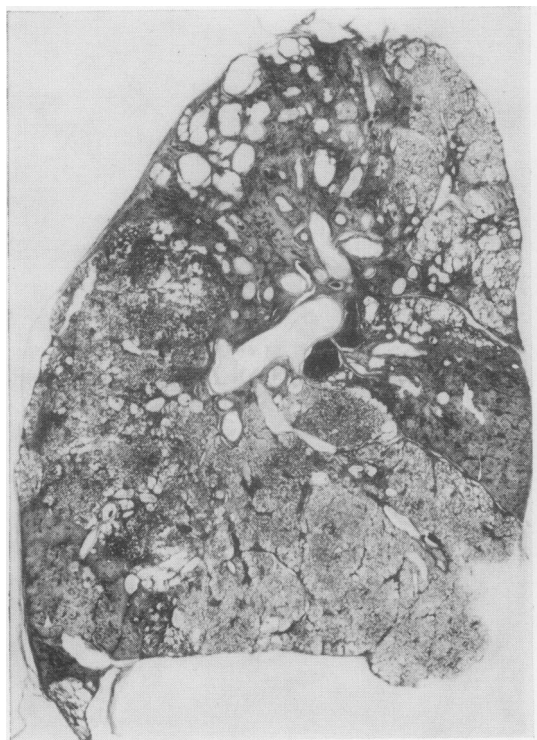


FIG. 4

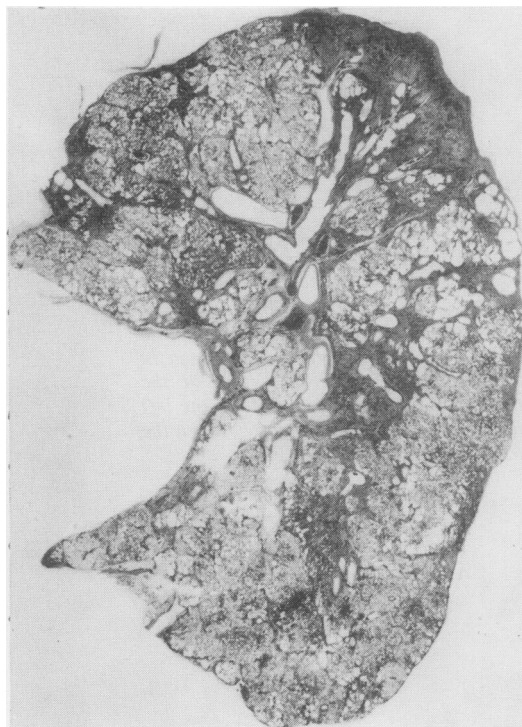


FIG. 5



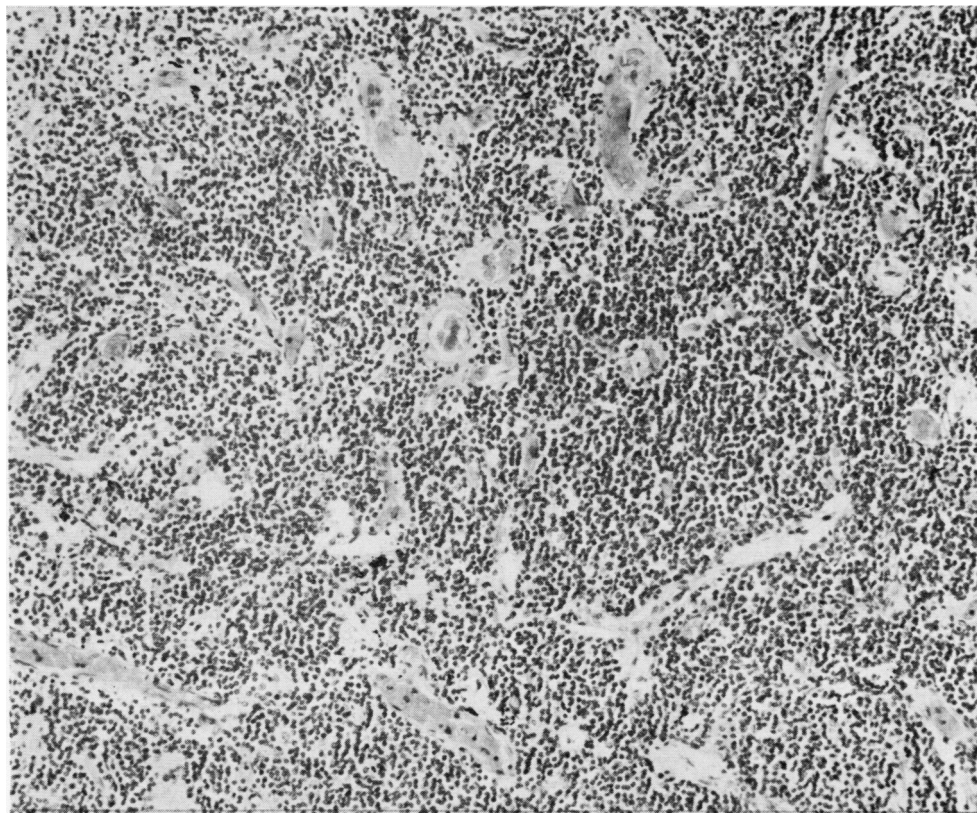


FIG. 6. Sheets of small lymphocytes in a vascular framework ( $\times 50$ ).

with extensive fibrosis and honeycombing. There was dense consolidation of the middle lobe and some cloudy shadows in the remainder of the right lung. The left lung was less involved but there was scattered fibrosis and honeycombing (Fig. 3). The heart remained normal in size.

The patient died at home in January 1966 from general weakness and respiratory insufficiency.

#### SUMMARY OF INVESTIGATIONS

The following investigations were carried out.

*Blood group* O Rhesus positive. *Haemoglobin* varied from 11 to 16 g/100 ml except during gastrointestinal bleeding. *White blood count* varied from 6,500 to 12,300 per  $\mu$ l, with normal differential counts; last count of December 1965 was 11,800 per  $\mu$ l with 69%

neutrophils and 31% leucocytes. *Platelets* always normal. *ESR*—all tests from 1960 varied between 15 and 32 mm in one hour (Westergren). *Blood urea and electrolytes*: all readings normal. *Serum calcium*: 9.5 mg/100 ml in 1965. *Serum proteins*: albumin 3 to 4.3 g; globulin 2.7 to 2.8 g/100 ml. *Rheumatoid latex fixation test*: four out of five positive between 1963 and 1965. *Rose Waaler test* repeatedly negative. *Tuberculin skin test* weakly positive in 1960 and 1964 (Heaf, grade 1). *Tubercle bacilli* were never found in the sputum. *Electrocardiograms*: rather low voltage only. *Scalene lymph node biopsy* in 1964 normal.

The results of *lung function* are shown in the Table.

*Pathological findings.* The body was thin. There were dense fibrous adhesions in both pleural sacs.

TABLE

	Vital Capacity (litres)	FEV <sub>1</sub> (litres)	Peak Exp. Flow Rate (l/min)	Transfer Factor (ml/min/mmHg) (steady state)	Arterial O <sub>2</sub> Sat. (%)	Arterial PCO <sub>2</sub> (mmHg)
Expected 1961 ..	2.9	2.55	415	14.3		
May 1961	2.0	1.0				
September 1963	1.45	1.0	175	11.4	87	44
April 1964	1.45	1.0	155	10.4	81	
March 1965	1.40	0.9	150	9.0	85	
December 1965 ..	1.05	0.75				

The trachea and main bronchi were filled with tenacious mucus. Both lungs were distended through the main bronchi with 10% buffered formalin and sectioned a week later. Paper-mounted whole lung sections were prepared by the Gough-Wentworth technique.

There was extensive deposition of a firm, rubbery homogeneous yellow-brown tissue in both lungs. Honeycombing was present in some of the affected areas. In the right lung (Fig. 4) the parts

involved were the posterior two-thirds of the upper lobe, almost the whole of the middle lobe, the apex of the lower lobe and, in scattered foci, the posterior half of the lower lobe.

In the left lung (Fig. 5) the posterior third and anterior rim of the upper lobe and the apical and central parts of the lower lobe were similarly involved. There was extensive purulent bronchitis and bronchopneumonia in both lower lobes.

The heart weighed 340 g and showed right ventricular hypertrophy and minimal coronary atheroma.

The hilar lymph nodes showed only carbon pigmentation. No infiltrations were seen in any tissues other than lungs. The lymph nodes and spleen looked normal.

Microscopically the solid areas in the lungs were composed of sheets of mature small lymphocytes with complete destruction of normal lung architecture (Fig. 6). There was no mitotic activity in these cells and only occasional plasma cells and large mononuclear cells were present. Blood vessels were abundant in most areas. At the margins of the solid areas the lymphocytic infiltra-

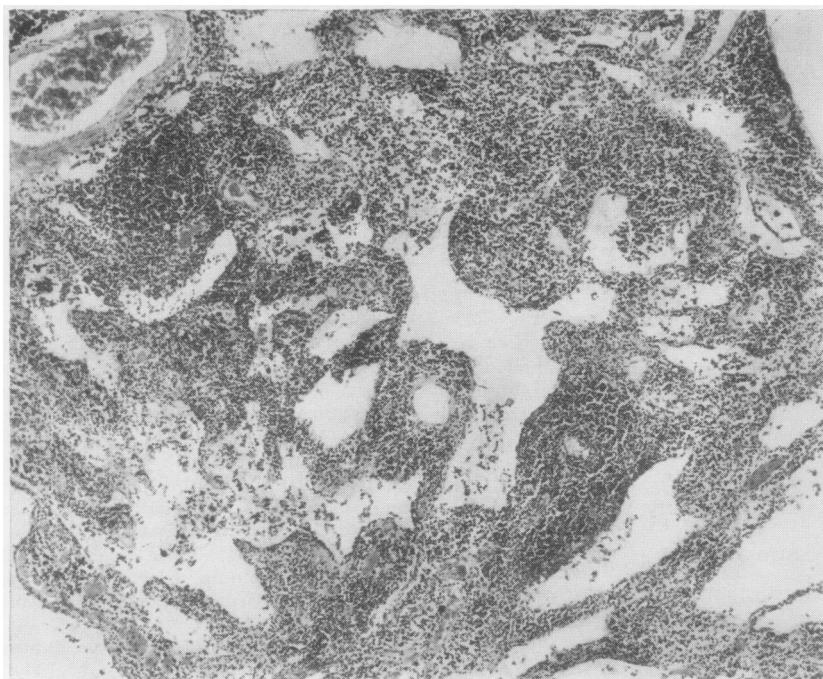


FIG. 7. Interstitial distribution of the infiltrate at the margins of the solid areas ( $\times 50$ ).



tion was seen to be interstitial with partial retention of lung architecture (Fig. 7). In macroscopically normal lung the earliest lymphoid infiltrations were seen around bronchioles and accompanying branches of the pulmonary arteries (Fig. 8). No follicular arrangement with or without germinal centres was seen.

In many areas there were large masses of a hyaline material among the sheets of lymphocytes (Fig. 9). With a haematoxylin and eosin stain this looked like amyloid but gave negative reactions with the usual special stains, Congo Red and methyl violet. It gave the staining reactions of collagen, however.

The honeycomb cysts were usually lined by cubical epithelium and some contained pus. Enderteritis obliterans was present in the affected zones (Fig. 10).

#### DISCUSSION

The patient was almost symptomless when the abnormal shadows were discovered. Shortness of breath gradually developed as the disease progressed. At no time was there any evidence of collagen disease. She had been treated with antacids and oral iron and received several courses of antibiotics (not nitrofurantoin) but not drugs that are known to produce lung changes. Likewise, she had not kept birds nor been exposed to organic antigens known to cause disease.

The diagnosis during life was idiopathic diffuse fibrosing alveolitis but there were some atypical features. The early ventilatory tests showed evidence of air flow obstruction, but as the disease progressed there was a much greater fall in vital capacity than in the forced expiratory

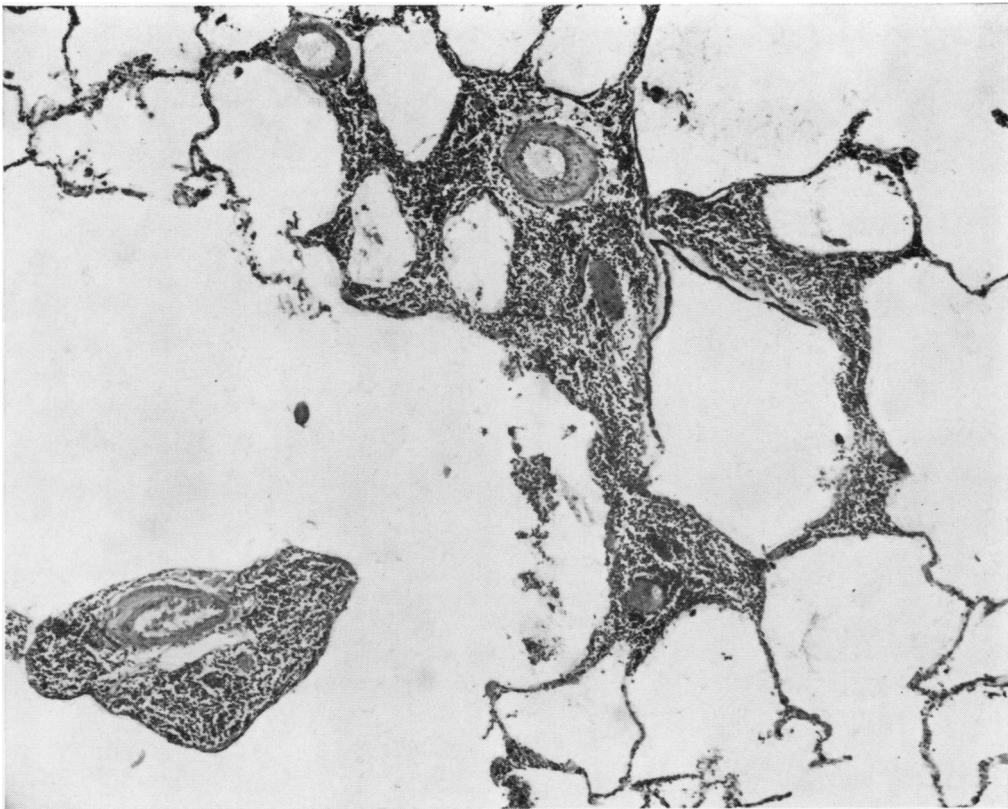


FIG. 8. *Peribronchiolar and perivascular infiltration by small lymphocytes in a macroscopically normal area ( $\times 50$ ).*

volume in one second (FEV<sub>1</sub>) (Table). Hyperventilation was not as marked as usual in the late stages but there was more purulent sputum than expected. These findings could be explained by postulating the coexistence of chronic bronchitis. The radiographic changes were asymmetrical and there was a preponderance of disease in the upper zones. Consolidation in the right middle lobe was also a prominent feature and at necropsy it showed homogeneous lymphoid infiltration.

Pathologically the lesions appeared to have started interstitially but there were two features which distinguished them from those in idiopathic fibrosing alveolitis, *viz.*, the distribution in the lungs and the almost monotonous uniformity of the cellular infiltrate. In fibrosing alveolitis the changes are predominantly basal and subpleural whereas in our patient the upper lobes were mainly involved. The inflammatory infiltrate in fibrosing alveolitis is more varied, and para-amyloid

material is not a prominent feature. However, honeycombing, as a final common pathway, is seen in both.

Enlargement of lymph nodes, spleen, or liver was not evident at any time. Blood counts over the years did not show a lymphocytosis. She was not therefore suffering from chronic lymphatic leukaemia. Differentiation from pseudolymphoma and malignant lymphoma was more difficult. The term pseudolymphoma is best reserved for a localized mass of well-differentiated lymphocytes with an admixture of other inflammatory cells and containing follicles with germinal centres (Saltstein, 1963). It could be argued that this was a well-differentiated lymphocytic lymphosarcoma involving both lungs only. All the lymphocytes, however, were small and there were no primitive forms and no mitotic activity. The distribution was unlike that of primary pulmonary lymphoma and there was no involvement of the hilar lymph nodes.

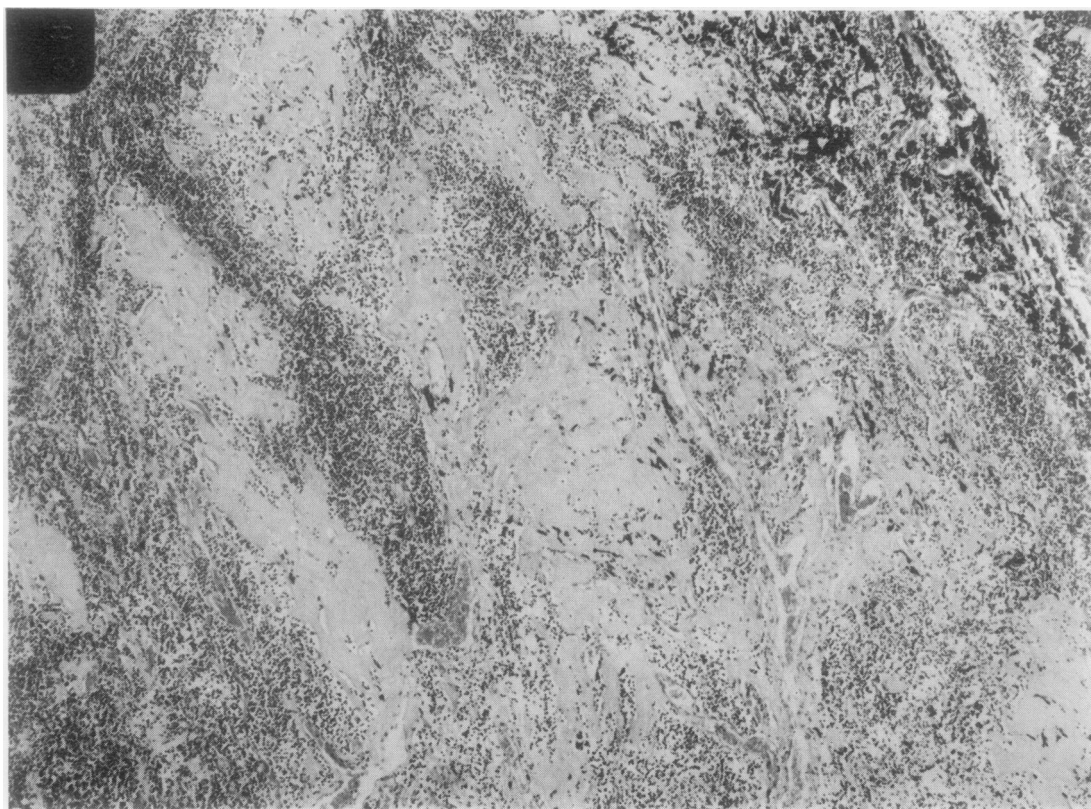


FIG. 9. Hyaline collagen (para-amyloid) among the lymphocytes. There is some carbon deposition at top right ( $\times 50$ ).



Likewise, the condition was clearly not that described as lymphomatoid granulomatosis (Liebow, Carrington and Friedman, 1972).

We therefore regard this as a variety of interstitial pneumonia. Liebow and Smith (1968) classified these cases as (1) usual or classical (this would be described as the mural form of fibrosing alveolitis in Britain); (2) bronchiolitis obliterans and diffuse alveolar damage; (3) desquamative; (4) lymphoid; and (5) giant cell.

He described the earlier radiographic appearances of lymphoid interstitial pneumonia as feathery septal infiltration with linear branching peripheral shadows. Later they tended to become confluent. Histologically all showed condensations of lymphocytes resembling normal lymphoid follicles, and in half there were germinal centres. In our case the infiltrations were diffuse and deposition of hyaline para-amyloid material was

prominent, as it was in two of Carrington and Liebow's (1966) cases.

Since the original publication a case associated with monoclonal gammopathy and myasthenia gravis was reported by Montes, Tomasi, Noehren, and Culver (1968) and two cases with a marked increase in gamma globulins were reported by Moran and Totten (1970). In these cases plasma cells were a prominent feature of the infiltrate and they might be more appropriately classified as a sixth type, plasma-cell interstitial pneumonia. The case described by Young, Tillman, Burton, and Sampson (1969) appears to be one of lymphoid interstitial pneumonia with minor increases in immunoglobulins.

Eosinophilic pneumonia (Liebow and Carrington, 1969) may be added as a seventh type of interstitial pneumonia.

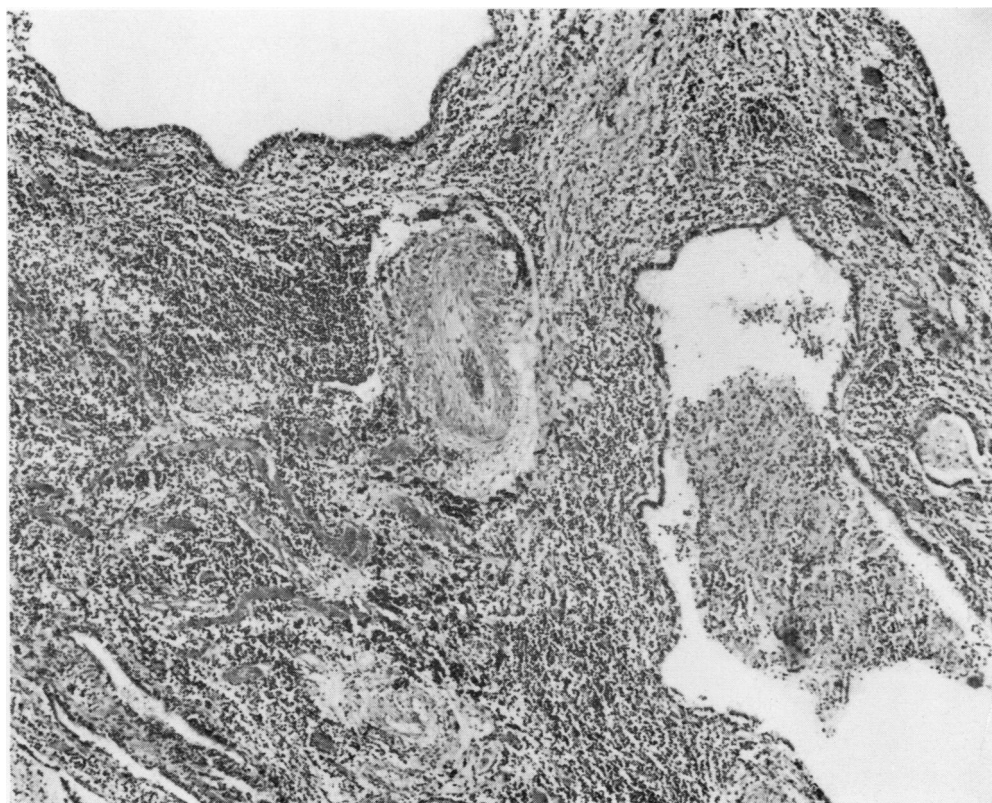


FIG. 10. Honeycomb cysts partly lined by cubical epithelium, one containing pus. The interstitial tissue shows lymphocyte infiltration and streaks of para-amyloid. Endarteritis is present ( $\times 50$ ).



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