REVIEW ARTICLE

PULMONARY LYMPHANGIOMYOMATOSIS

Pulmonary Lymphangiomyomatosis

A Review

Bryan Corrin, MD, Averill A. Liebow, MD and Paul J. Friedman, MD

Anatomic and clinical observations of 28 cases, including 23 previously unpublished, of pulmonary lymphangiomyomatosis are recorded and discussed. This brings the total reported to 57. All patients were women in the reproductive age group with the major complaint of breathlessness. This was usually progressive, and death from pulmonary insufficiency resulted within 10 years. Functional changes were obstructive or restrictive, or both. Pneumothorax, chylous effusions and hemoptysis were frequent complications. Radiographically the lesions initially appear as fine, linear and nodular, predominantly basal densities, and progress to a pattern of bullous change, or honeycombing, involving all portions of the lungs, not sparing the region of the costophrenic sinuses as is typical of eosinophilic granuloma. There may be associated pleural effusions. A progressively increasing lung volume is characteristic. The lesions consist of an irregular, nodular or laminar "irrational" proliferation of smooth muscle within all portions of the lung, with loss of parenchyma leading to honeycombing. Proliferated muscle can obstruct bronchioles (with air trapping and formation of bullae often complicated by pneumothorax), venules (with pulmonary hemorrhage and hemosiderosis accompanied clinically by hemoptysis) and lymphatics (with chylothorax or chyloperitoneum). Both thoracic and abdominal lymph nodes and the thoracic duct can also be involved in the myoproliferative process with formation of subsidiary minute channels and obstruction. Renal or perirenal angiomyolipomas can also occur, as exemplified by 2 patients in the present series. Identical pulmonary lesions occasionally occur in tuberous sclerosis. Especially since these patients usually have no neurologic disturbances and are almost always women, the possibility of a relationship between tuberous sclerosis and lymphangiomyomatosis must be considered. One feature of note in pulmonary lesions of tuberous sclerosis is the presence of adenomatoid proliferations of epithelium. Such changes were also observed in 2 patients of the present series, and it is remarkable that both of these women had "retarded" children. At present the question of whether lymphangiomyomatosis is a *forme fruste* of tuberous sclerosis must be considered as unresolved. It may yield to further investigation, possibly including chromosomal studies. (Am J Pathol 79:347–382, 1975)

THERE EXIST thirty-four published reports [1–30] of a rare but distinctive disease of the lungs, marked by widespread smooth muscle proliferation, which is generally termed pulmonary lymphangiomyo-

From the Departments of Pathology and Radiology, University of California, San Diego, School of Medicine, La Jolla, Calif.

Supported in part by Grants HL-12373 and HL-14169 from the National Institutes of Health.

Accepted for publication January 4, 1975.

Address reprint requests to Dr. Averill A. Liebow, Department of Pathology, University of California, San Diego, School of Medicine, La Jolla, CA 92037.

matosis. Earlier reports have been largely sporadic, and few physicians will have the opportunity to become familiar with the disease by personal experience. That this disease is more common than has been realized is suggested by our experience of 28 cases mainly referred for consultation, 23 of which have not been reported previously. This report on the clinical, radiologic and pathologic features of this disease is made to provide better recognition of this entity and to present some new observations that explain certain of its anatomic and clinical features.

Pulmonary lymphangiomyomatosis is part of a more inclusive syndrome in which muscle associated with extrapulmonary lymphatics is excessive. When present, pulmonary involvement is a prominent feature of the lymphangiomyomatosis syndrome, but there exist instances where the lungs are spared and the lesions are confined to extrapulmonary sites, notably lymph nodes and lymphatics. Such cases have been reviewed by Cornog and Enterline [16] and, more recently, by Wolff [25] and are outside the scope of this report. So too are those cases of tuberous sclerosis (epiloia, Bourneville's disease) in which the lungs are affected, for although the pulmonary lesions in that condition may be similar to those reported here [31,32] and although some features suggest the possibility of a relationship between the two processes, there are also certain differences in their natural history.

Clinical Features

The patients were predominantly Caucasian, but included one Negro, one Chinese and one Filipino. In common with those previously reported, they were all female. Their ages at the onset of symptoms ranged from 17 to 47 years (Table 1).

In none of the patients was there a history of epilepsy or mental retardation. Two patients, Cases 27 and 28, each had a "retarded" child, but it was not possible to establish whether either had manifestations of tuberous sclerosis although it was suspected in one.

The presenting symptom was either breathlessness (13 patients) or was referable to one of three complications: pneumothorax (6 patients), chylous effusion (2 patients), or pulmonary hemorrhage (2 patients, in one of whom breathlessness was also a major presenting complaint). Ten patients experienced hemoptysis at some time in their illness. Pneumothorax, frequently recurrent, occurred in a total of 12 women. Chylous effusions were found in 11 and were generally confined to the pleural cavities, but 2 patients were found to have chylous ascites and another had chyluria.

Red blood cell counts and hemoglobin levels were usually within

Table 1—Lymphangiomyomatosis: Clinical Data

Case	Sex	Age at onset	SOB	Cough	Pneumo-thorax	Chylous effusion	Hemop-tysis	Hemo-sider-osis	Presenting symptoms	Course	RV strain	Thoracic duct & lymph node involvement	Renal angiomyo-lipomas	Uterine fibroids
1	F	37	+	+	+	Thorax	+	+++	SOB	D 4½ yrs	+	Hilar, cervical, retroperitoneal	+	+
2	F	47	+	+				+++	SOB, cough	D 1 yr	+			+
3	F	30	+	+		Thorax	+	+	Pain in chest	D 3 yrs		Thoracic nodes Thoracic duct		
4	F	26	+			Thorax		+	SOB	D <1 yr		Scalene		
5	F	45	+			Thorax	+	+++	Hemoptysis, SOB, chest pain	?				
6	F	40						—		?				Broad ligament ?
7	F	18	+	+	—	Thorax	+	+++	"Chylothorax"	D 10 yrs		Retroperitoneal		
8	F	33	+	+				+++	SOB, cough	A 3 yrs				
9	F	34	+	+	+			++	Pneumothorax	D 6 yrs	+			
10	F	28	+	+		Thorax		+++	Chylothorax	A 3 yrs		Scalene	Translucent areas in kidneys (72)	
11	F	40	+	+	—	—	—	—	SOB, cough	A 3 yrs				
12	F	30	+	+		—	Min.	—	Pneumothorax	D 5 yrs	+	—	—	
13	F	33	+					—	Minimal SOB	A 11 yrs				
14	F	19			+			+++	Pneumothorax	A 2 yrs				

15	F	28	+	+		Thorax	Pink sputum	+++	SOB	A 3½ yrs				
16	F	47	+	+	+		+	+++	SOB, cough	D 1 yr		Aortic, hilar, axillary		+
17	F	40	+	+	+	Chyluria		+++	SOB	D 7 yrs		Retroperitoneal	—	+
18	F	20	+	+	+	Thorax, abdomen		+++	SOB	D 3½ yrs	+	Supraclavicular mediastinal, thoracic duct	+	
19	F	36		+				—	Muscle pain, fever	?				
20	F	30	+	+	+			+++	Pneumothorax	?				
21	F	47	+		+			?		D 8 yrs				
22	F	41	+					—		?				
23	F	43	+			Thorax	—	—	SOB	A 1½ yrs		Thoracic duct region		
24	F	30		+	—	Thorax		?	Malaise, cough	A 1 mon		Scalene		
25	F	27	+		+	—	+	+	Pneumothorax	A 7 yrs				
26	F	26	+	+	+	—	+	+	SOB	A 3 yrs	+			
27	F	20	+		+			+	Pneumothorax	A 1 mon				
28	F	41	+	+		Thorax	+	—	Hemoptysis	A 17 yrs				

SOB = shortness of breath, A = alive, D = died.

normal limits or somewhat elevated. Except for the patient with chyluria, the urinalysis showed nothing of significance. It is noteworthy that in this patient there was a 4+ proteinuria and reduction of blood albumin to a level of 1.9 g/100 ml. The chylous pleural fluid obtained in Case 3 had a total protein content of .75 g/100 ml and in Case 15, 6.3 g/100 ml; the respective specific gravities of the fluids were 1.020 and 1.042. Total lipids levels were as follows: Case 1, 1500 mg/100 ml; Case 2, 1255 to 3013 mg/100 ml; and Case 15, 2600 mg%. In Case 15 the triglyceride level concurrently was 2400 mg/100 ml and the cholesterol level, 132 mg/100 ml.

Some functional changes associated with lymphangiomyomatosis are recorded in Table 2. Vital capacity was usually diminished and tended to fall progressively. Both functional residual capacity and residual volume were generally increased, but total lung capacity was not far from normal. There was marked reduction in maximal breathing capacity and in the forced expiratory volume at both 1 and 3 seconds, as well as a striking reduction in maximal midexpiratory flow rate. Diffusion capacity for CO was usually diminished. In almost all patients the pO_2 and pCO_2 were considerably lower than normal, and blood pH was within the normal range or elevated. Only in 1 patient, Case 28, was there CO_2 retention and acidosis.

Breathlessness gradually increased in severity, but there was considerable variation in its rate of progression. Death was usually due to respiratory failure, which was known to have occurred in 11 patients 1 to 10 years after the onset of symptoms. Other patients, however, are still alive up to 17 years later. One exceptional patient (Case 13) was discovered when a chest film was made for slight shortness of breath, but she has remained virtually asymptomatic for 9 years, with no progression of the radiologic changes.

We were able to review full-size chest films or copies in 15 patients and slides in another. Several distinct patterns and features were demonstrated, with overlap or progression among them. The clinical severity of the disease in general correlated well with the degree of involvement as assessed radiographically.

A reticular pattern was seen in over half the cases; in some this was a blurred or indistinct pattern (Figures 1 and 2) which looked slightly nodular or miliary on initial inspection, much like the indistinct small vessel prominence of congestive heart failure (Figures 3 to 6). In several the reticulation was very delicate or sharp (Figures 7 and 8). Coarse reticular markings, similar in appearance to interstitial fibrosis, were noted in the lower lung field in several instances. Septal lines

Table 2—Lymphangiomyomatosis: Physiologic Data

Case	Date	Lung volumes (% normal)				Flows (% normal)				Diffusion capacity (CO)	Arterial blood gases		
		VC	FRC	RV	TLC	MVV	FEV_1	FEV_3	MMEFR		pO_2	pCO_2	pH
1		34	100	165	76								
4	10/66	128	82				58				72→42	30→25	
	9/68	55	168				39						
	6/67			57	93	86	66	87		12.6	64	33	7.32
6	5/69			121	104		60	77		10.3	53	30	7.44
	6/71			88	100		66	84		8.3			
7	1/67	99			119					10.1	66	30	
	2/68	47			131	25					52	37	
9		71				61	66				42	39	
10		70	89	105	81		83						
12	12/70	68	138	218	107	20	23	52	7	86%	76	31	7.45
	9/71	49											
13							63			6.9			
15		58	172	255	100	32	44	68		36%	63	21	7.40
16		82	124	148	102	54			20		58	42	7.39
17		<70		>140					49		72	33	
18		54					38						
20											46	27	7.51
26	7/73	34	223	387	141	12	9	15	2		42	78	7.30
28	10/73	<86	97	106	93	53	41		11	7.4%	58	25	7.4

VC = vital capacity, FRC = functional residual capacity, RV = residual volume, TLC = total lung capacity, MVV = maximal breathing capacity, FEV_1, FEV_3 = forced expiratory volume at 1 and 3 seconds, MMEFR = maximal midexpiratory flow rate.

(Figure 8) were seen less commonly; they were fuzzy in three cases, suggesting edema at the lung base, but very sharp and distinct in three others. In the latter group it was difficult to distinguish septal lines from the edges of lung cysts or bullae, which were demonstrated in half the patients. Lung volume was conspicuously increased (Figure 7) in nearly half the patients, suggesting an important bronchial obstructive component. Abnormal markings were seen throughout the lungs in half the cases, although in some of these, as in those with partial involvement, changes were most marked at the bases. Appreciable asymmetry was noted only once.

Pleural effusion was demonstrated at some stage in the course of the disease in two-thirds of the patients whose chest films were available (Figure 6); in 2 patients chylothorax followed lung biopsy. Pneumothorax (Figure 9) was demonstrated in 5 of the 16 patients whose radiographs we reviewed and in at least 12 of the whole group at some time. No mediastinal tumor was demonstrable, although central pulmonary artery dilatation was observed in one instance.

Serial films were available in 9 cases. Progression was evident in nearly all of these, with a tendency to change from indistinct reticular markings to sharp lines. In addition there was an increase in lung size with time (Figures 10–14) demonstrated in 5 patients.

Ventilation and perfusion scans (Figures 15 and 16) were available for 1 patient in whom radiographic involvement was essentially uniform throughout, at that time. Perfusion was shown to be diminished more at the bases, with additional heterogeneity noted in one upper lobe. Pulmonary angiography confirmed the better perfusion of the upper lobes; the vessels to the rest of the lung appeared stretched or attenuated, with slower circulation of contrast material.

Lymphangiography in another patient (Case 4), performed at a time in which the only definite chest film abnormality was bilateral pleural effusion, showed abnormal lymphatic channels, presumably collaterals, in the upper abdomen. Large and small lymph cysts were demonstrated along the iliac and paraaortic chains and in the mediastinum. No normal lymph nodes were seen above the level of the pelvis. In none of the cases was a lymphangioma of the thoracic duct demonstrated on plain films of the chest.

Intravenous urograms of 2 patients were reviewed. In one (Case 17) the only abnormality was pyelolymphatic backflow involving normal calyces. The lymphatic channels thus seen did not appear dilated. In the other case (lymphangiogram described above) there were many round defects seen in the parenchymal contrast phase, with some efface-

ment of the collecting system. These may have represented cysts or possibly angiomyolipomas.

Pathology

The essential lesion in the lungs was focal proliferation of smooth muscle that involved all parts. It infiltrated the pleura, septa and walls of alveoli, which were consequently thickened, sometimes in nodular fashion. In all instances there was some loss of alveoli, with "honeycombing" as an end result (Figures 17–21). The septa among the revised distal air spaces were at least focally thickened by the proliferated smooth muscle, often in many layers (Figures 21 and 22), and with massive local accumulations or intrusions into the lumen (Figure 23). In some foci there were masses of large rounded or ovoid cells with hyperchromatic nuclei interpreted as immature myocytes (Figure 24). Irregular muscular hyperplasia also involved walls of bronchioles (Figures 25 and 26). Focal hyalinization or collagenization of the muscle was sometimes in evidence within bronchioles as well as more distal air spaces (Figures 26 and 27). Focal emphysema resulting from over-distension of distal air spaces with breakdown of septa among them was also observed, with bullous change (Figure 27). At least a partial explanation of the emphysema was the marked narrowing of certain small conducting airways by burgeoning masses of muscle in their walls (Figures 25 and 26), a change conducive to air trapping. Air trapping also accounted for the frequency of pneumothorax in this condition. Thus the gross appearance was that of bullous change as well as honeycombing, the latter distinguished by the thick walls of some of the large spaces.

Proliferated smooth muscle also accompanied, and sometimes thickened, both pulmonary arteries (Figure 28) and veins. In some patients the latter were actually totally obliterated by intrusive masses of muscle tissue, but they could nevertheless be easily identified in elastic stains (Figures 29–31). This venoocclusive process provided an explanation for pulmonary hemorrhage and hemosiderosis (Figure 32) and was manifested clinically by hemoptysis. Occasionally this was sufficiently severe to produce iron encrustation of vascular elastic tissue, as seen in other forms of pulmonary venoocclusive disease. Encrusted elastica typically produced a foreign body reaction and became fragmented (Figure 33).

Justification for the designation lymphangiomyomatosis was evidence of involvement of both intra- and extrapulmonary lymphatics in the myoproliferative process (Figures 34–37). Such lymphatics were often

dilated and accompanied by masses of lymphocytes (Figure 34), as well as by strands of free-lying muscle, especially prominent in the septa and pleura. Lymphatics normally are associated with small strands of smooth muscle cells in these sites. The presence of valves was useful in identifying lymphatics (Figure 36). They were sometimes prominent in the parietal as well as visceral pleura. In one instance the alveoli at necropsy contained a protein-rich fluid similar to that within the lymphatics, and this was interpreted as lymphedema (Figure 36). This followed ligation of the thoracic duct. Obstruction of lymphatics by the proliferated muscle was the probable mechanism for the frequently observed chylothorax. Mediastinal and retroperitoneal lymphatics in several patients were also embedded in thick cord-like structures or distended by milky fluid.

In 3 patients the thoracic duct was a resilient, firm, spongy, sausage-like structure, many times its usual external diameter (Figure 38). Microscopically it was subdivided into myriads of subsidiary channels by a meshwork of smooth muscle fibers enclosing masses of lymphocytes.

Lymph nodes were known to be involved in the myoproliferative process in nine patients. The affected nodes included the axillary, cervical, subclavian, mediastinal and paraaortic and pelvic chains. Grossly they were spongy, resilient and pale tan or white (Figure 39). The muscle was associated with lymph channels which were thus subdivided in plexiform fashion, as in the thoracic duct. In some nodes, only the lymphatics as they entered the subcapsular system were involved, but in others a part or even most of the node was replaced by a meshwork of smooth muscle through which the lymph was made to follow a devious course (Figure 40). It was especially in patients with such lymph node involvement that chylous effusions were found in serosal cavities.

Evidence of continuing proliferative activity was not only the progression of the disease clinically, but also the presence of masses of rounded anaplastic cells, in which mitotic activity was prominent (Figures 40 and 41). These we have interpreted as myoblasts, the conclusion also ultimately reached by Cornog and Enterline [16] although they earlier entertained the possibility that they represented "lymphangiopericytes." Such anaplastic cell masses have also been observed in pulmonary lesions of tuberous sclerosis.[31,32] They were also noted in lymphangiomyomatosis by Inglis [10] and were observed in a cytologic smear of pleural fluid as free clumps of cells that were suspected of being neoplastic. Valensi [27] called them "glomus-like structures."

In 2 patients there were peculiar acinar atypical adenomatoid pro-

liferations of epithelium which were supported by what appeared to be uniformly and only slightly thickened interalveolar septa (Figures 43–45). Such focal proliferations (Figure 49) we had previously observed in a 17-year-old girl who was presumed to have a *forme fruste* of tuberous sclerosis because of the presence of "sebaceous adenomas," and who had pulmonary lesions otherwise similar to those of our other patients with lymphangiomyomatosis (Figure 48). Of further note is that each of the women with the adenomatoid atypical proliferation had a child described as "retarded," with no stigmata of tuberous sclerosis, except that the child of Case 27 was suspected of having this condition.

Two patients were found at necropsy to have renal tumors (Figure 46), which proved to be angiomyolipomas (Figure 47). None of the patients examined post mortem had any cerebral, retinal, cutaneous or cardiac lesions of the type found in tuberous sclerosis. Five patients had clinical, cardiographic or necropsy evidence of right-sided cardiac hypertrophy. Other findings included uterine fibroids (5 patients), liver cysts (1 patient), unexplained filling defects in the liver scan and a scalp tumor (1 patient), diabetes (1 patient) and adrenocortical adenoma (1 patient).

Discussion

The 23 new cases reported here represent a major increment over the 34 previously published. Most of these have been referred from other centers over a 20-year period. In one instance the diagnosis was made by biopsy following discovery of an abnormal chest film in an almost asymptomatic woman who for at least 9 years thereafter experienced only transient mild dyspnea (Case 13). This case is exceptional but suggests the existence of mild and stable or slowly progressive forms that may remain undiscovered.

The previously reported cases are comparable to ours, and the following syndrome emerges: The disease is confined to women but shows no familial tendency. Symptoms first appear at any time during the reproductive years, and the disease is marked by breathlessness of increasing severity, usually leading to death from respiratory failure in from 1 to 10 years. Pneumothorax and chylous effusions are common, and there is a hemorrhagic tendency which is confined to the lungs. Our studies have helped to explain both the mechanisms of the hemoptysis and the pneumothorax.

When pneumothorax develops, the site of rupture may be presumed to be one of the numerous thin-walled bullous structures that eventually

come to replace much of the lung. Examination of the fine airways suggests that there is not only loss and reconstruction of original parenchyma, but also air trapping resulting from muscular proliferation with narrowing of conducting airways. Such an exuberant growth of muscle is frequently found within the walls of bronchioles. The lumen is then narrowed, and dilatation of air spaces immediately beyond the obstruction is often seen. The reported incidence of pneumothorax in 12 of 34 patients is comparable to that in our series. It should be noted that other diseases with bronchiolar obstruction, such as eosinophilic granuloma and sarcoidosis, may also be complicated by pneumothorax probably consequent to air trapping.

In 34 previously published cases of lymphangiomyomatosis, chylous effusions were encountered in 27; in 8, chylous ascites was also present. This incidence of chylothorax is considerably greater than in the present series, probably because many of our patients were in a relatively early stage, with the diagnosis made at biopsy rather than at necropsy. Chyloptysis was reported in 1 previous case, and chyuria was reported in 1 patient; it also occurred in 1 of the present group.

Chylous effusions are evidently the consequence of proliferation of muscle with obstruction of lymphatics and replacement of lymph nodes. Distended collateral vessels are then found, and rupture of these leads to chylothorax or chylous ascites. Lymphaticovenous anastomoses in the renal pelvis have previously been described by Collard and associates,[33] in a patient with lymphangiomyomatosis in whom pulmonary involvement was not established with certainty. Chyluria as in Case 17 was reported by Frack *et al.*[20] That pulmonary lymphedema and chyloptysis may also develop following surgical interruption of the thoracic duct is suggested by our Case 3, in which the alveoli were flooded by protein-rich fluid subsequent to such ligature. Increased parenchymal congestion has also been observed after therapeutic obliteration of the pleural space.[29] This has suggested to some that the pleural cavity may serve as a sump that protects the lung against lymphedema. In some patients, however, pleural symphysis achieved mechanically or by such means as instillation of nitrogen mustard may have an important effect in preventing accumulation and ultimate loss by drainage of chylous fluid.[30,34]

Little attention has been given in the past to the presence, and even less to the pathogenesis, of hemoptysis. With the use of elastic stains we have demonstrated, within the masses of muscle tissue, the outlines of small veins partly or fully occluded by the myoproliferative process. Other veins showed interruption of their elastic laminae by the infiltrating muscle cells and all degrees of this destructive process were found,

to a stage where the vascular origin of an elastic arc was equivocal. This feature deserves more emphasis, as we found evidence of associated hemorrhage in over half of our cases. Thus three major complications, pneumothorax, chylous effusion and hemoptysis, are attributable to an obstructive effect of the muscle proliferation affecting bronchioles, lymphatics and venules, respectively.

The functional effects of the process in the lungs may now be considered in the light of anatomic findings. Published data concerning disturbances in pulmonary physiology accompanying lymphangiomyomatosis are scanty. These correspond, however, to the finding in the present series. For example, in patients reported by Silverstein and others [29] there was reduction in vital capacity, in FEV_1, and in arterial pO_2. Ventilatory obstruction correlates well with our observations on bronchiolar narrowing, air trapping and emphysema. Compliance has been examined by relatively few investigators, and their results are contradictory: whereas Vadas and colleagues [17] found increased compliance (our Case 1), others [11] report a "restrictive" pattern indicative of stiffening of the lung. The explanation for this may be that while a diffuse massive muscular infiltration of the alveolar walls would tend to decrease lung compliance, focal involvement of bronchioles would cause air trapping leading to atrophy and loss of alveoli and, thus, increased compliance. With both airway and vascular obstruction frequently present, it is not surprising that ventilation–perfusion relationships were disturbed, and "alveolo-capillary block" and "diffusion abnormalities" were noted in our patients as well as in others.[11,21] Cardiac catheterization studies have only rarely been performed. In Case 17 the mean pulmonary arterial pressure was 25 mm Hg. In many other cases there was clinical, cardiographic or necropsy evidence of right heart strain.

In Malik's [35] patient with tuberous sclerosis and pulmonary lesions, although vital capacity was normal and maximal voluntary ventilation only slightly less than normal, the midexpiratory flow rate was reduced, and D_{CO} was also diminished, as was arterial pO_2. The pCO_2 was within the normal range. During 6 years of observation, although D_{CO} continued to decline steadily, there was little progression of dyspnea.

In explaining the distinctive patterns seen on chest radiography in lymphangiomyomatosis, several pathophysiologic features of the disease must be considered. First is the actual abundance of smooth muscle. This was more marked in some cases than others, but might account for the accentuation of markings and the delicate reticular pattern seen in a few cases. In most instances the secondary consequences of the

myomatosis determined the gross morphology. Lymphatic obstruction and engorgement, venous obstruction, and interstitial edema probably accounted for the fuzzy reticular patterns or septal lines seen in several cases. It is of interest that in one instance (Case 3) the patient was reported to have developed miliary mottling after ligation of the thoracic duct, suggesting lymphatic dilatation in the lung as lymph was diverted from mediastinal channels. Prominent lymphatics and lymphedema were indeed found in the lung (Figures 36 and 37). In 3 other patients there was a degree of improvement during the course of the disease that strongly suggested that the clearing densities must have corresponded to accumulations of fluid, rather than proliferated muscle or scar tissue. Sharp septal lines may have represented dilated lymphatic channels without significant edema or hemorrhage, or may have been confused with the edges of bullae or blebs. Bronchiolar obstruction with air trapping was the physiologic basis for the appearance of blebs, bullae and general enlargement of the lungs as well as of the pneumothorax.

There was not a good correlation between the initial appearance of the chest film and the likelihood of progression of the disease to respiratory insufficiency. Pleural effusion was also found independently of the outcome. On the other hand, radiographic demonstration of increased lung volume was of prognostic value: It was found in 5 of 6 patients who died, whereas normal lung volume was found in 6 of 8 long-term survivors. The other 2 in the radiologic series had inadequate films.

The differential diagnosis of obstructive airway disease, with nonproductive cough and possibly repeated pneumothoraces, will certainly include emphysema, but the increased markings in the roentgenograms in general will suggest other conditions. The exception, so-called increased markings emphysema,[36] is characterized clinically by severe chronic bronchitis and pulmonary hypertension, occurs much more often in men and has irregular densities on the radiograph which are usually coarser than the reticular markings of lymphangiomyomatosis. Eosinophilic granuloma is often manifested by repeated pneumothoraces, but in this condition the costophrenic angles are usually clear because of the relative sparing of the basal segments of the lower lobe, a distribution opposite that of lymphangiomyomatosis.

Breathlessness combined with basal mottling or honeycombing on the chest film may suggest idiopathic interstitial fibrosis, though cases in which lung volume is seen to increase are readily distinguished. Biopsy should be diagnostic, but the unwary pathologist may well miss the characteristic muscular proliferation of lymphangiomyomatosis, espe-

cially when it is diffuse rather than nodular or has a collagenous admixture, or if there is extensive honeycombing. Awareness of the condition, close scrutiny of the infiltrate and the use of trichrome stains will help safeguard against interpreting the interstitial spindle cells as fibroblasts. Pleural effusion also is rare in chronic interstitial pneumonia, except when associated with rheumatoid disease.

It is well recognized that hypertrophy and hyperplasia of smooth muscle occur in many types of chronic pulmonary disease.[37] Prominent among these are interstitial fibrosis and emphysema. In the latter the walls of large bullae often contain masses of muscle derived from residue of bronchi, vessels, and from lymphatic and perilymphatic strands normally found in the septa and pleura. In interstitial fibrosis this process may be so extensive that the terms "muscular cirrhosis" or "bronchiolar emphysema"[38] have been applied. These designations are not justified if they are meant to indicate special diseases, since they represent merely an extreme degree of a process present to some extent in all cases of interstitial fibrosis.[39] The probable stimulus to the hypertrophy and hyperplasia of smooth muscle in these conditions is the increased tension imposed by the fibrosis, or by the stretching of bullae consequent to air trapping. In lymphangiomyomatosis, however, the myoproliferation is "irrational," in that it may be unassociated with fibrosis, and it is often focal or nodular rather than uniform, and far in excess of what is observed in an ordinary bulla.

Once the proliferative process is recognized as muscular, it may be asked whether it could represent a "metastasizing leiomyoma" derived from the uterus.[40,41] This is a seemingly attractive hypothesis to explain the lymphangiomyomatosis syndrome, especially since the condition is confined to adult women. In several of our patients and in a number reported by others, uterine fibroids were present or had been excised. To date we have seen 17 examples of metastasizing leiomyomas. In all instances the patient was known to have had leiomyomata of the uterus. We have concluded, on both clinical and pathologic evidence, however, that the two conditions are quite different, notably in the distribution of the muscular tissue. Radiographically, in metastasizing leiomyoma there are distinctly outlined spherical nodules usually exceeding 1½ cm in diameter and often larger. It is true that cyst formation can occur rarely in such intrapulmonary metastases. This is the result of entrapment of epithelium with secretion of a mucoid fluid. In lymphangiomyomatosis, however, the cysts contain gas. Microscopically, lung tissue intervening among the metastatic nodules is quite normal, whereas in lymphangiomyomatosis the interalveolar septa and other tissues are

more diffusely and irregularly involved. In no instance have the lymph nodes or the thoracic duct been involved in metastasizing leiomyoma. Neither pneumothorax nor chylothorax have been observed. Thus there should be no difficulty in differential diagnosis of these two diseases, nor is there any sound basis for considering lymphangiomyomatosis to be related to uterine myomata.

Because of similarities of the pulmonary lesions of lymphangiomyomatosis and those of tuberous sclerosis known since their description by Berg and Vejlens,[31] the question of a possible relationship between the two conditions has properly arisen. In fact Valensi [27] has considered lymphangiomyomatosis to be a *forme fruste* of tuberous sclerosis. The classic triad of tuberous sclerosis consists of "sebaceous adenomas," usually of the face, epileptic seizures, and mental retardation. Not all elements of this triad are present in all cases. The cerebral lesions, described in detail by Bourneville [42] after their discovery by von Recklinghausen, consist of focal gliosis, often with giant glial cells. These lesions tend to become calcified. Cutaneous lesions were originally described by Pringle [43] as sebaceous adenomas, and this interpretation has been repeated in many publications since that time. Nickel and Reed,[44] however, have shown them to be composed predominantly of angiofibromatous proliferations, although some may have a neurilemmomatous component, as in von Recklinghausen's neurofibromatosis. Other skin lesions are described as "shagreen patches."

Angiofibrolipomas of the kidney and perirenal tissues are common in tuberous sclerosis, as are "phakomas" in the eye grounds. These also represent focal gliosis. Sclerosing periosteal or deossifying "cystic" bone changes occur, and rarely rhabdomyomas of the heart, as described by von Recklinghausen,[45] can be seen. These changes occur with approximately equal frequency in men and women. Patients with stigmata of tuberous sclerosis who have pulmonary lesions, however, are almost all women, and more often are of normal intelligence.

Histologically the lesions in the lung indeed are identical in many respects to those in lymphangiomyomatosis. For example, in biopsy tissue from the lungs of a 17-year-old girl with sebaceous adenomas (angiofibromas) of the face, but apparently normal in intelligence and other characteristics, there was proliferation of smooth muscle, with rarefactive changes. There was, however, no clear evidence of involvement of intrapulmonary lymphatics, nor has this been described in other such cases. Nevertheless, myomatosis of lymph nodes with lymphatic obstruction does occur in tuberous sclerosis, having been demonstrated in 6 of 31 patients with tuberous sclerosis reviewed by Valensi.[27] Radio-

graphically, as might be expected, the appearance is identical with that described in the present review for lymphangiomyomatosis. Chylothorax is relatively uncommon in tuberous sclerosis; it was reported in 2 of 31 patients with pulmonary lesions in that condition.[27]

In our patient with tuberous sclerosis we have observed multiple peculiar adenomatoid proliferations in the lung (Figure 48). These have also been illustrated by Spencer.[46] We have also observed these in 2 of our patients with lymphangiomyomatosis (Cases 27 and 28), each of whom had a "retarded" child, but in whom tuberous sclerosis was not established.

Valensi [27] made a detailed comparison of other associated findings in 18 patients with lymphangiomyomatosis and in 31 with pulmonary lesions in tuberous sclerosis; in the latter group of patients cerebral lesions were known to exist in 17. Sebaceous adenomas were observed in 26 of the 31, and 24 of the group were known to have renal lesions. In our series of 28 patients with lymphangiomyomatosis, 2 were known to have renal lesions similar to those of tuberous sclerosis. These, however, occur occasionally as incidental findings at necropsy in persons of either sex.

Tuberous sclerosis is considered to be inherited through a dominant gene with variable or incomplete expression. A positive family history was recorded in approximately 25% of patients in the group reviewed by Valensi.[27] No relevant family history was found in lymphangiomyomatosis except possibly for the mental deficiency of the offspring of 2 of our patients. Valensi [27] states that it is not valid to exclude tuberous sclerosis for lack of a family history of the disease and that lymphangiomyomatosis and the pulmonary lesions in tuberous sclerosis represent "opposite ends of a sepectrum" of presentation of tuberous sclerosis. He points out that the complete triad of tuberous sclerosis was present in only 6 of 31 cases when pulmonary involvement existed. It is by no means certain in our present state of knowledge, however, that Valensi's conclusion is warranted.

As an explanation of lymphangiomyomatosis some have turned to the possibility of a hormonal imbalance, and recent pregnancy or gonadotrophin therapy has been noted in a few cases.[25] One of our patients was receiving progesterone for endometriosis. It is of interest that fibromyomas can be produced in castrated guinea pigs treated for 3 months with estradiol benzoate and that these regress when the administration of estrogen is discontinued.[47] They develop in the uterus and throughout the peritoneum but not in the thorax. This process may have no relevance to lymphangiomyomatosis. Nevertheless, in studying future

cases of this condition particular attention should be paid to the possibility of endocrine abnormality or hormone treatment.

Considering the age distribution and the fact that all known patients are female, the possible therapeutic value of male sex hormone or castration has been considered, although no evidence has been adduced of beneficial effects from such therapy. A course of androgens was in fact tried, by Bush and associates,[21] with no apparent effect on the course of a patient with already advanced pulmonary disease. It may, however, be justifiable to administer androgens at an earlier stage in the evolution of the disease.

Various attempts at therapy have been made by surgical intervention when lymph node masses or the thoracic duct were involved. Removal of the former has resulted in at least temporary arrest of chylothorax. There has been some success also in treatment of that condition by poudrage of the pleural space with talc and, recently, with nitrogen mustard [30,34] or irradiation[34]; obliteration of the pleural space can offer some relief for severe chylothorax as well as troublesome recurrent episodes of pneumothorax. Removal of lymphangiomyomas of the thoracic duct, ligation of the duct and its anastomosis with the venous system have also been performed, but none of these procedures has been uniformly successful. In fact, ligature of the thoracic duct was followed by massive flooding of the lungs with protein-rich fluid in Case 3 of the present series. Irradiation of lymph node masses also has been performed, but without significant result. Control of the pulmonary lesions has not been accomplished by any means of therapy.

References

1. Burrell LS, Ross HM: A case of chylous effusion due to leiomyosarcoma. Br J Tuberc 31:38–39, 1937
2. Rosendal T: A case of diffuse myomatosis and cyst formation in the lung. Acta Radiol 23:138–146, 1942
3. Roujeau J, Delarue J, Depierre R: Lymphangiectasie pulmonaire diffuse, pneumonie chyleuse et chylothorax, après thrombose puerpérale de la veine sous-clavière gauche. J Fr Med Chir Thorac 4:488–503, 1950
4. Inglis K: Neurilemmoblastosis: The influence of intrinsic factors in disease when development of the body is abnormal. Am J Pathol 26:521–549, 1950
5. Brandt M: Über Angiomyomatose der Lungen mit Wabenstruktur. Virchows Arch [Pathol Anat] 321:585–598, 1952
6. Loeffler VW, Jaccard G: Über einen Fall von Chyloptoe mit pseudomiliarem Lungenbild. Schweiz Med Wochenschr 84:1335–1336, 1954
7. Heppelston AG: The pathology of honeycomb lung. Thorax 11:77–93, 1956
8. Laipply TC, Sherrick JC: Intrathoracic angiomyomatous hyperplasia associated with chronic chylothorax. Lab Invest 7:387–400, 1958

9. Henke D, Hecht A: Chylothorax und Ascites chylosus bei neurinomatöser Hamartie im Bereich des Ductus thoracicus. Thoraxchirurgie 6:564–587, 1959
10. Inglis K: The nature and origin of smooth muscle-like neoplastic tissue in the lungs and corresponding lymph nodes in a case of so-called "honeycomb lungs". Arch De Vecchi Anat Patol 31:179–209, 1960
11. Fraimow W, Cathcart RT: Clinical and physiological considerations in pulmonary muscular hyperplasia. Ann Intern Med 56:752–764, 1962
12. Correll N, Fischer C: Lymphangioma of the thoracic duct. JAMA 182:1136, 1962
13. Justin-Besançon L, Péquignot H, Galey JJ, Renault P, Even Ph: Lymphangiectasies pulmonaires diffuses acquises avec insuffisance respiratoire et chylothorax. Sem Hop Paris 39:1179–1190, 1963
14. Pachter MR, Lattes R: Mesenchymal tumors of the mediastinum. III. Tumors of lymph vascular origin. Cancer 16:108–117, 1963
15. Rienhoff WF III, Shelley WM, Cornell WP: Lymphangiomatous malformation of thoracic duct associated with chylous pleural effusion. Ann Surg 159: 180–184, 1964
16. Cornog JL Jr, Enterline HT: Lymphangiomyoma, a benign lesion of chyliferous lymphatics synonymous with lymphangiopericytoma. Cancer 19:1909–1930, 1966
17. Vadas G, Paré JA, Thurlbeck WM: Pulmonary and lymph node myomatosis: Review of the literature and report of a case. Can Med Assoc J 96:420–424, 1967
18. Wuketich S: Angioleiomyomatose der Lunge und der Lymphknoten. Verh Dtsch Ges Pathol 51:333–338, 1967
19. Pamukcoglu T: Lymphangiomyoma of the thoracic duct with honeycomb lungs. Am Rev Resp Dis 97:295–301, 1968
20. Frack MD, Simon L, Dawson BH: The lymphangiomyomatosis syndrome. Cancer 22:428–437, 1968
21. Bush JK, McLean RL, Sieker HO: Diffuse lung disease due to lymphangiomyoma. Am J Med 46:645–654, 1969
22. Ardichvili D, Colard M, de Windt J: Syndrome de lymphangiomyomatose. Ann Anat Pathol (Paris) 15:307–320, 1970
23. Cabanne F, Renault P, Michiels R, Dusserre P, Justrabo E, Bastien H: Lymphangiomyome ou lymphangiopéricytome: a propos d'une néoformation pelvienne kystique infectée. Laval Med 42:431–437, 1971
24. Jelihovsky T, Nicks R, Stephen D: Lymphangiomyomatosis with chylothorax. Aust NZ J Med 1:333, 1971
25. Wolff M: Lymphangiomyoma: Clinicopathologic study and ultrastructural confirmation of its histogenesis. Cancer 31:988–1007, 1973
26. Joliat G, Stalder H, Kapanci Y: Lymphangiomyomatosis: A clinicoanatomical entity. Cancer 31:455–461, 1973
27. Valensi QJ: Pulmonary lymphangiomyoma, a probable *forme fruste* of tuberous sclerosis: A case report and survey of the literature. Am Rev Resp Dis 108:1411–1415, 1973
28. Leeds SE, Benioff MA, Ortega P: Pulmonary lymphangiomyoma with renal angiomyolipomas. Calif Med 119(2):74–78, 1973
29. Silverstein EF, Ellis K, Wolff M, Jaretzki A III: Pulmonary lymphangiomyomatosis. Am J Roentgenol Radium Ther Nucl Med 120:832–850, 1974

30. Lieberman J, Agliozzo CM: Intrapleural nitrogen mustard for treating chylous effusion of pulmonary lymphangioleiomyomatosis. Cancer 33:1505–1511, 1974
31. Berg G, Vejlens G: Maladie kystique du poumon et sclérose tubéreuse du cerveau. Acta Pediatr Scand 26:16–30, 1939
32. Dawson J: Pulmonary tuberous sclerosis and its relationship to other forms of the disease. Q J Med 23:113–145, 1954
33. Collard M, Fievez, M, Godart S, Toussaint JP: The contribution of lymphangiography in the study of diffuse lymphangiomyomatosis: Report of a case with anatomic observations. Am J Roentgenol Radium Ther Nucl Med 102: 466–470, 1968
34. Miller WT, Cornog JL Jr, Sullivan MA: Lymphangiomyomatosis: A clinical-roentgenologic-pathologic syndrome. Am J Roentgenol Radium Ther Nucl Med 111:565–572, 1971
35. Malik SK, Pardee N, Martin CJ: Involvement of the lungs in tuberous sclerosis. Chest 58:538–540, 1970
36. Fraser RG: The radiologist and obstructive airway disease. Am J Roentgenol Radium Ther Nucl Med 120:737–775, 1974
37. Liebow AA, Loring WE, Felton WL: The musculature of the lungs in chronic pulmonary disease. Am J Pathol 29:885–911, 1953
38. Siebert FT, Fisher ER: Bronchiolar emphysema: So-called muscular cirrhosis of the lungs. Am J Pathol 33:1137–1161, 1957
39. Meyer EC, Liebow, AA: The relationship of interstitial pneumonia honeycombing and atypical epithelial proliferation to cancer of the lung. Cancer 18:322–351, 1965
40. Steiner PE: Metastasizing fibroleiomyoma of the uterus: Report of a case and review of the literature. Am J Pathol 15:89–110, 1939
41. Spiro RH, McPeak CJ: On the so-called metastasizing leiomyoma. Cancer 19:544–548, 1966
42. Bourneville D: Sclérose tubéreuse des circonvolutions cérébrales: Idiotie et épilepsie hémiplégique. Arch Neurol 1:81–91, 1880–1881
43. Pringle JJ: A case of congenital adenoma sebaceum. Br J Dermatol 2:1–14, 1890
44. Nickel WR, Reed WB: Tuberous sclerosis. Special reference to the microscopic alterations in the cutaneous hamartomas. Arch Dermatol 85:209–226, 1962
45. Von Recklinghausen FD: Ein Herz von einem Neugeborenen. Gesellschaft Geburtshülfe Berlin Verh 15:73–74, 1863
46. Spencer H: Pathology of the Lung, Second edition. London, Pergamon Press, 1968
47. Lipschütz A, Vargas L: Experimental tumorigenesis with subcutaneous tablets of oestradiol. Lancet 236:1313–1318, 1939

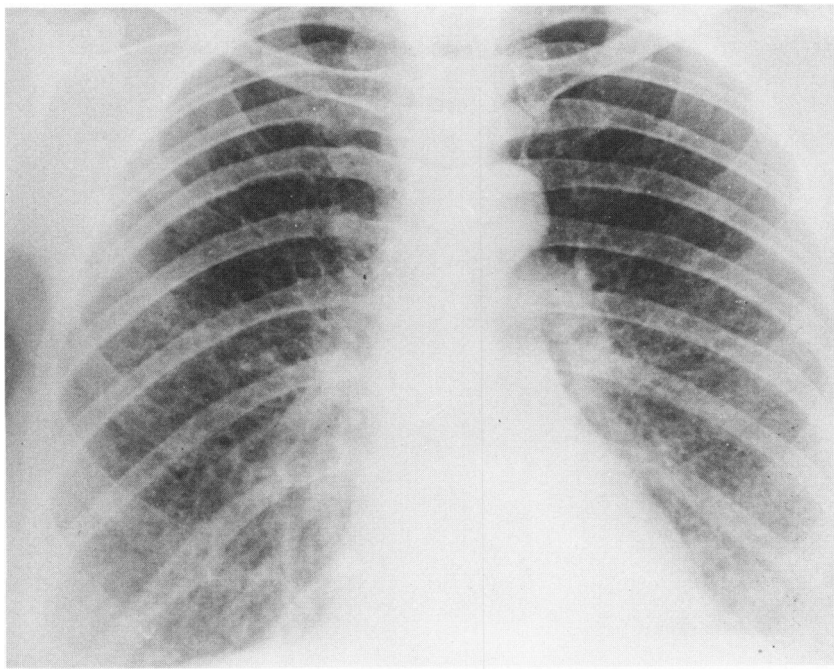
Acknowledgments

The writers are indebted to the following physicians, many of whom not only supplied the clinical data with the material referred for consultation but were most gracious in providing follow-up information, often at considerable expense of time and effort. Case 1: W. M. Thurlbeck, then of Montreal, Quebec[17]; Case 2: S. Hanson, Edmonton, Alberta, Canada; Case 3: J. L. Thornton, Richmond, Va; Case 4: J. F. Funder, Melbourne, Aus-

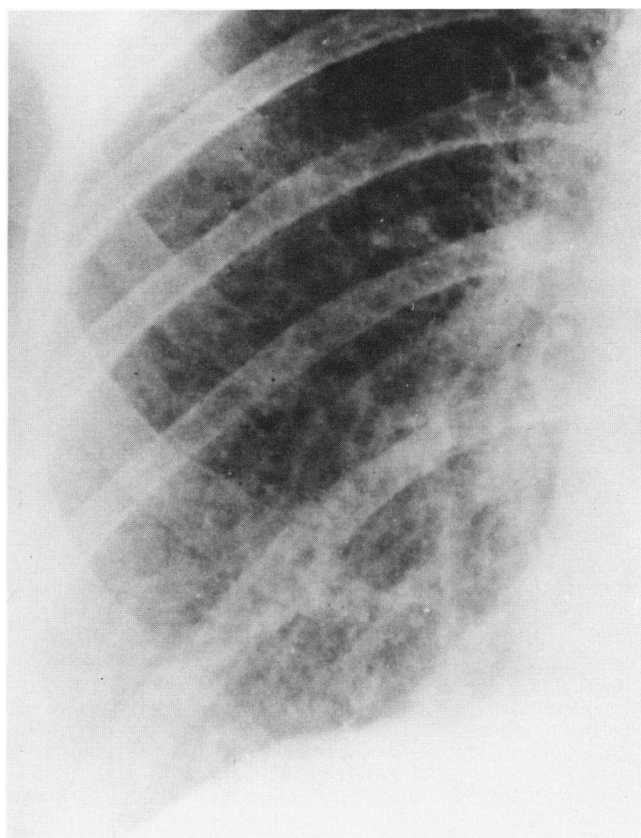
tralia; Cases 5 and 24: Y. K. Paik, Honolulu, Hawaii; Case 6: G. M. Greenberg, Brooklyn, NY; Case 7: W. R. Benson and W. Weatherly, Chapel Hill, NC; Case 8: E. A. Gall, Cincinnati, Ohio; Case 9: P. M. Pacheco, Bogota, Colombia; Case 10: T. Jelihovsky, Camperdown, Australia[10]; Case 11: Q. Valensi, New York, NY; Case 12: W. L. Jensen and H. Froeb, La Jolla, Calif; Case 13: E. H. Smith, Omaha, Nebr; Case 14: S. K. Battacharji, Harrisburg, Pa; Case 15: C. M. Agliozzo, Duarte, Calif[30]; Case 16: A. W. Morris, Anniston, and D. P. Courington, Birmingham, Ala; Case 17: C. B. Carrington, New Haven, Conn (In press, Cancer); Case 18: K. Mottet, Seattle, Wash (In press, Cancer); Case 19: J. B. Ellis, Columbia, SC; Case 20: M. S. N. Murthy, Columbus, Ohio; Case 22: L. G. Hefter, Los Angeles, Calif; Case 23: W. Burgert, Tallahassee, Fla; Case 25: K. G. Bensch, Palo Alto, Calif; Case 26: G. G. Burton, Loma Linda, Calif; Case 27: D. H. McCowan, Coos Bay, Ore.

Dr. Corrin was on study leave supported by St. Thomas' Hospital and Medical School, SE1 7EH, England.

[*Illustrations follow*]

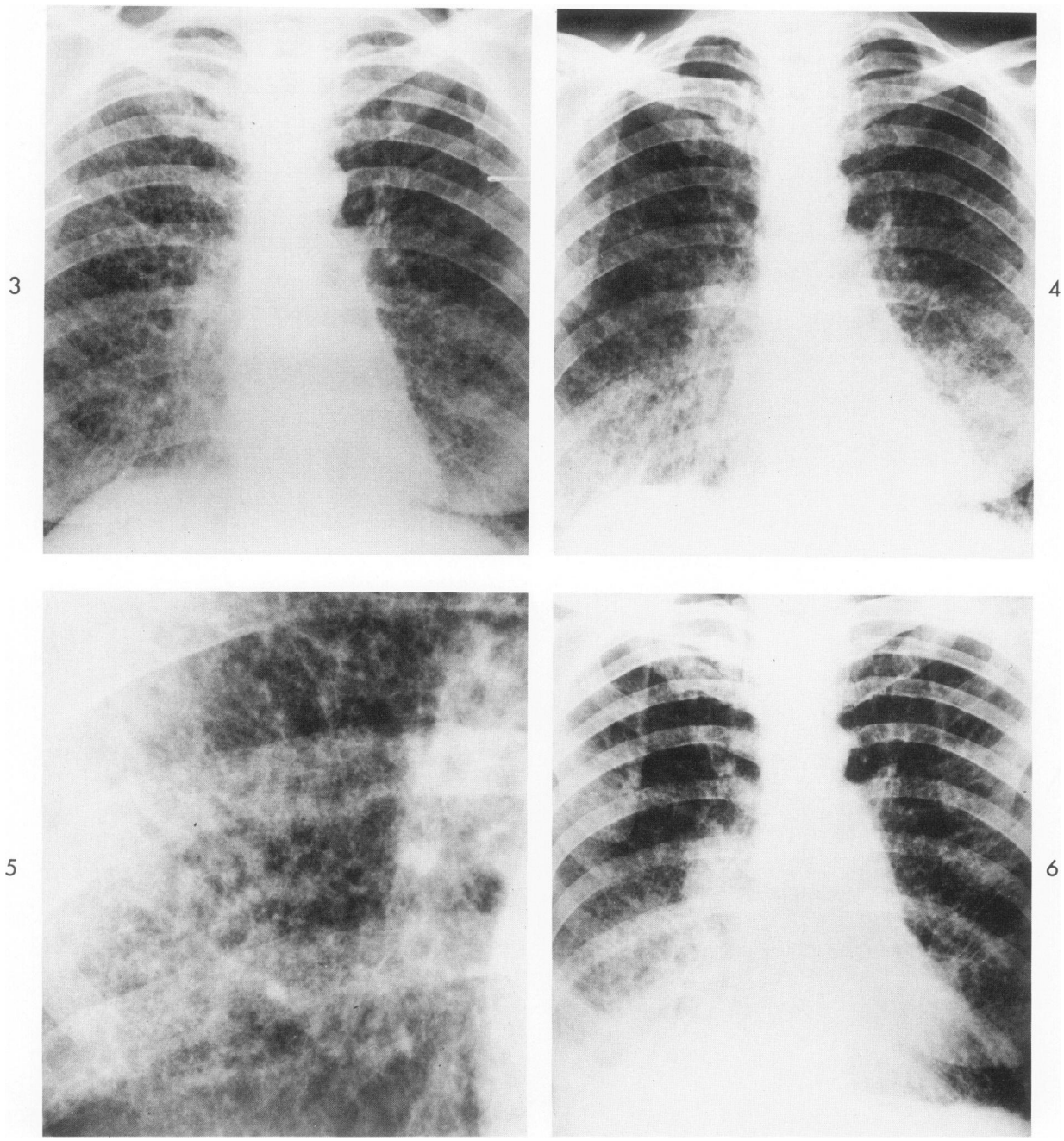


1

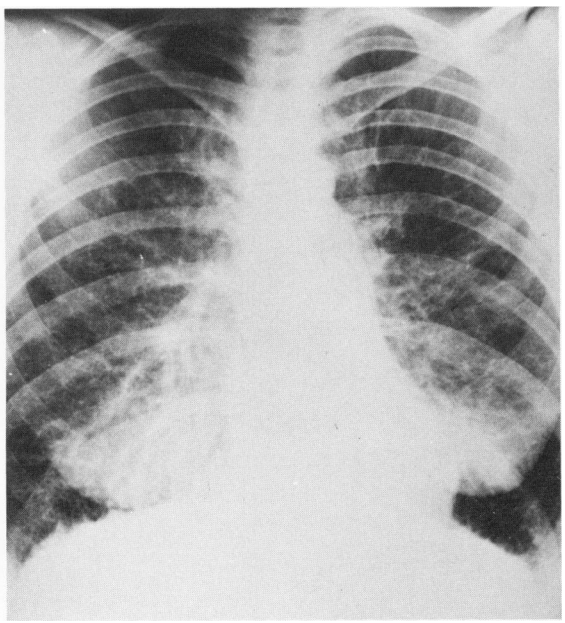


2

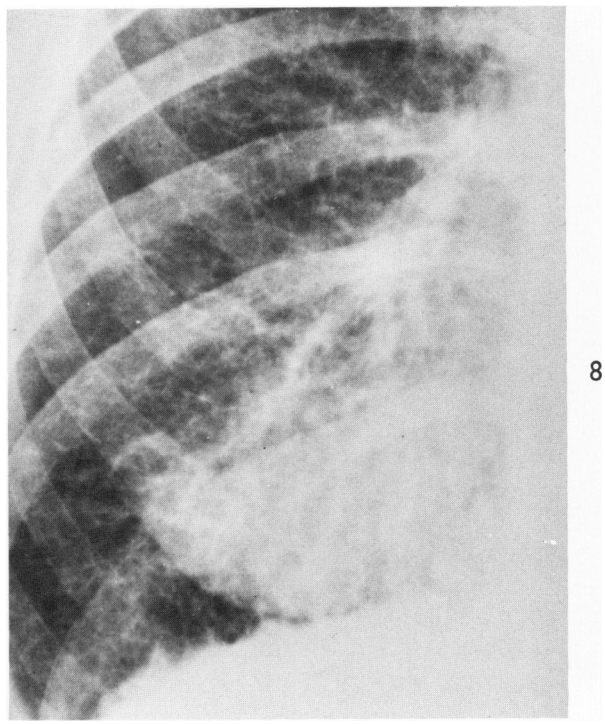
Fig 1—Case 6. Posteroanterior radiograph of a 40-year-old woman illustrating a soft reticular pattern, somewhat accentuated at the lung base. **Fig 2**—Detail of Figure 1.



Figs 3-6—Radiographs in Case 17. **3**—Posteroanterior view of the chest. There is a diffuse reticular pattern and small pleural effusions are present at both bases. **4**—Six months later. The reticular pattern is more dense and irregular, with greater accentuation at the lung bases. **5**—A detail from a magnification film made at about the same time as Figure 4. Fine nodular and reticular markings are clearly shown. The normal vascular pattern is almost completely obliterated in the lung periphery. **6**—Posteroanterior radiograph made 6 years later. The upper lung fields show fewer markings, with a configuration suggesting emphysema. Some of the rounded radiolucencies in the mid lung fields are also larger than previously. Overall lung volume has increased, with flattening of the diaphragm. The right pleural effusion has increased, as has the density of parenchymal markings at the right base.



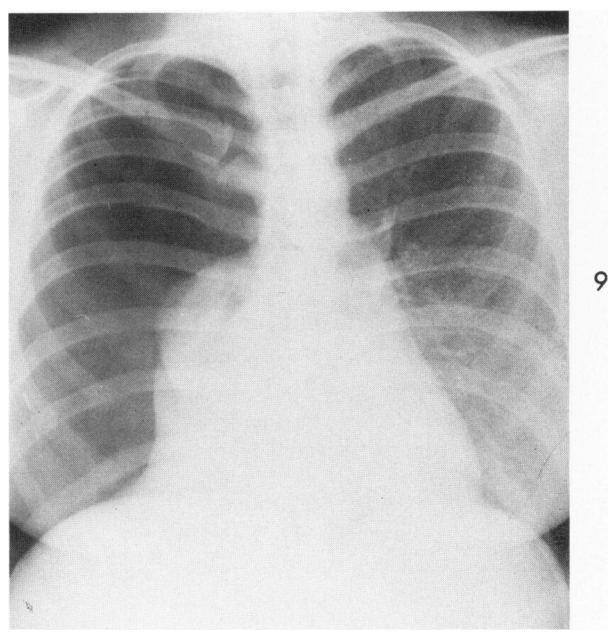
7



8

Fig 7—Posteroanterior radiograph showing hyperinflation and a diffuse reticular pattern in Case 7.

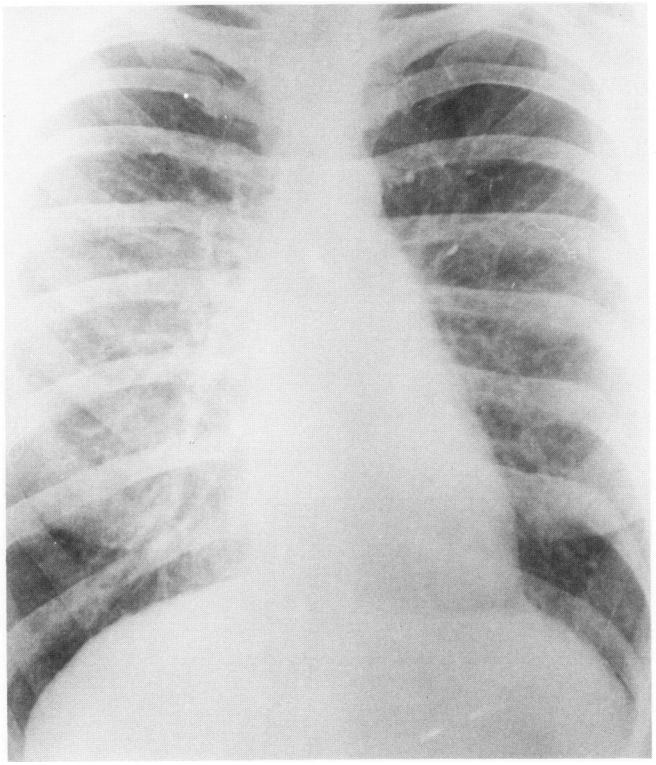
Fig 8—This detailed view shows septal lines at the costophrenic angle as well as the distinctive honeycomb pattern of this disease, formed by delicate lines in the midlung zone. (See also Figure 33 from same case).

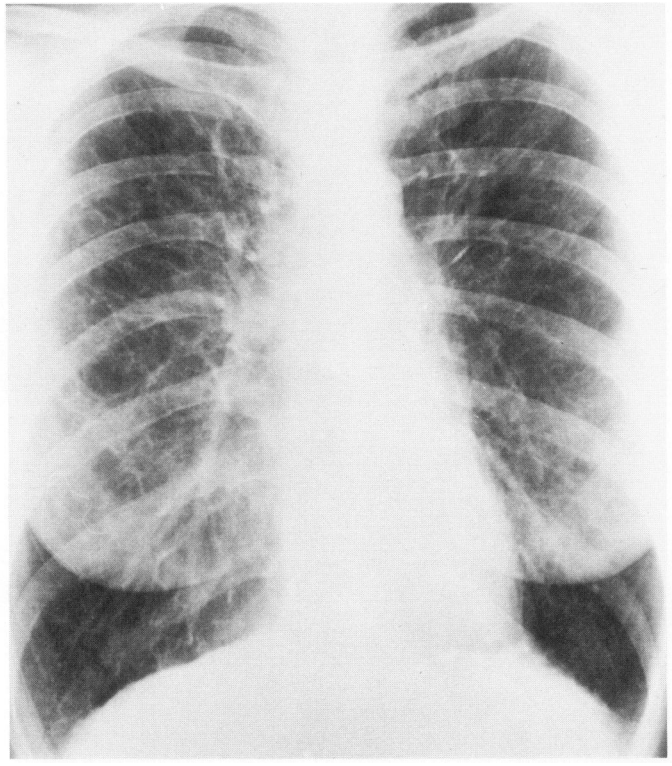


9

Fig 9—Case 14 Posteroanterior radiograph showing massive collapse of the right lung due to total pneumothorax. Except for minimal prominence of the vascular markings, attributable to diversion of blood flow, the left lung appears essentially normal.

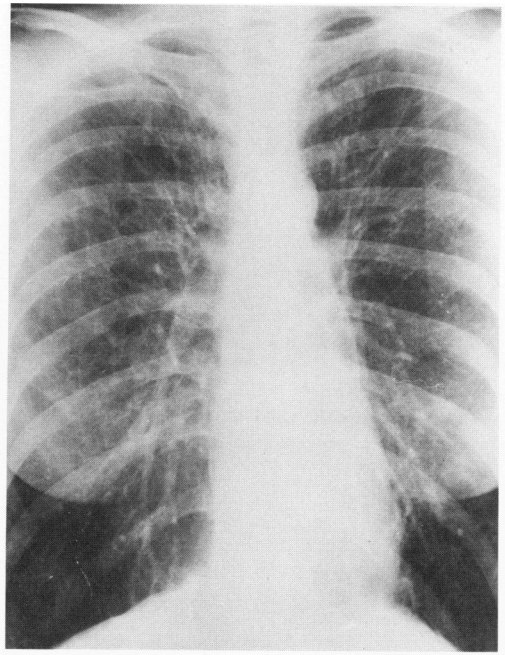
10

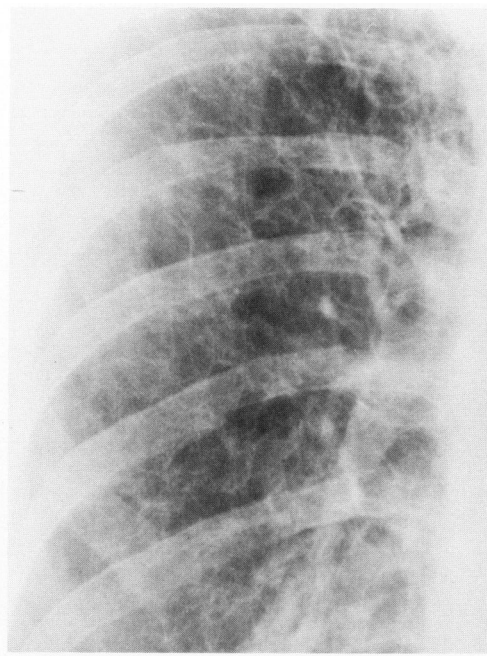


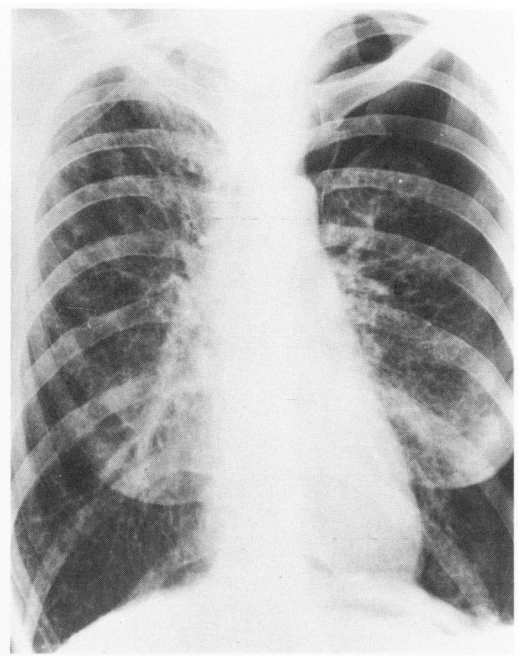


11

12



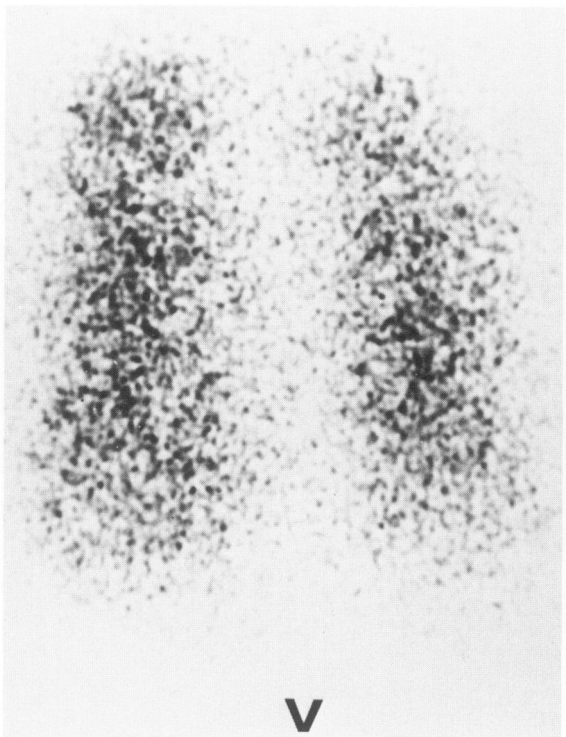




13,14

Figs 10–14—Radiographs of Case 12. **10**—Posteroanterior radiograph made in 1968, probably showing an indistinct reticular abnormality at the lung bases with some abnormal linear markings in the upper lung fields as well. **11**—In November 1971 a posteroanterior radiograph shows significant increase in lung volume, with corresponding narrowing of the heart and flattening of the diaphragm. At this time, septal lines are noted at both lung bases, and there are sharply defined ring shadows in the upper lung zones, as well as irregular markings scattered throughout the periphery. **12**—This radiograph made in October 1972 appears to show a diminution in the intensity of irregular markings in the lung, possibly due to a reduction in the amount of interstitial edema. The delicate-walled honeycomb or ring shadows are again best seen in the upper lobes; see a detailed view in Figure 13. **13**—Detail of the radiograph of October 1972, showing the characteristic sharply defined ring shadows that make up this unusual honeycomb pattern. **14**—In March 1973 there is further flattening of the diaphragm and enlargement of the lungs, with spontaneous pneumothorax on the left. Except for some irregular densities at the right apex, the right lung shows no significant change from the earlier study. The enlargement of the heart is consistent with the development of cor pulmonale.

15



16

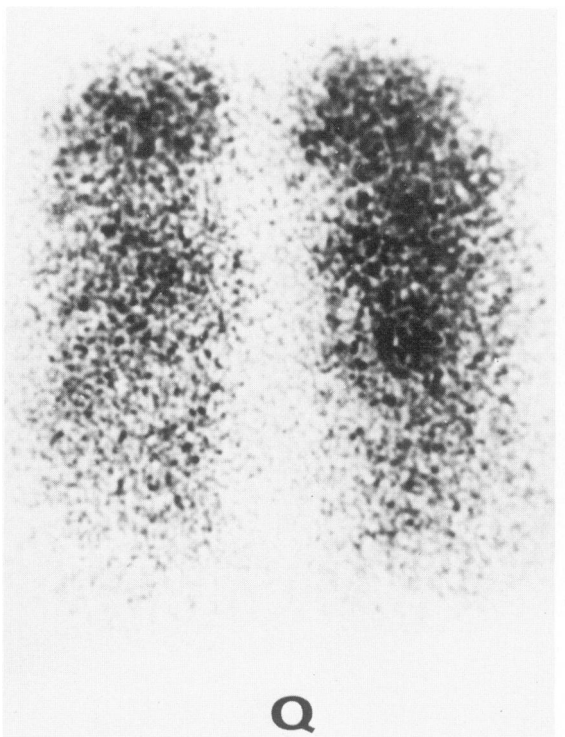
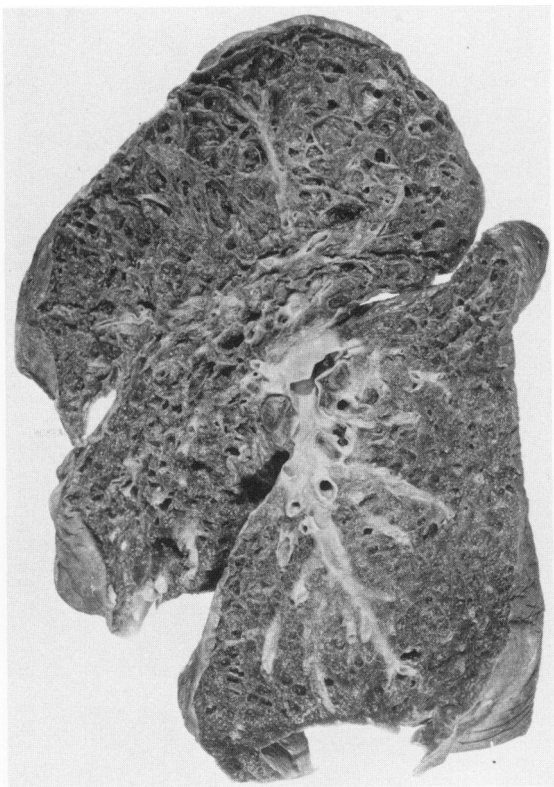
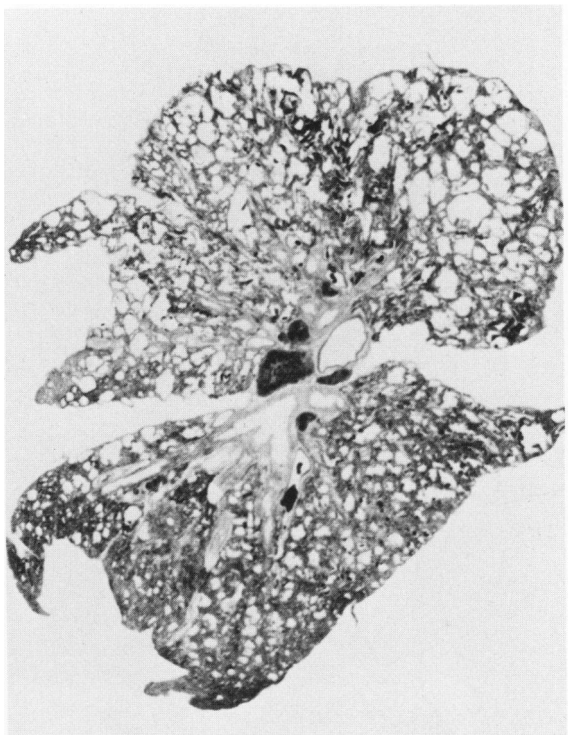


Fig 15—Scintillation scans of ventilation (*V*) made in February 1971 on the same patient as in Figures 10–14 (Case 12). Note the relatively uniform distribution of ventilation, with some diminution at the apices and bases. **Fig 16**—The perfusion scan (*Q*) in Case 12, on the other hand, shows a more irregular distribution with a subtle matched defect in the right subapical region (note the site of the largest bullous lesions in Figure 13), but overall a marked diminution at the over-expanded lung base. The upper lobe ventilation-perfusion inequality, especially the disproportionate perfusion of the left upper lobe, is suggestive of obstructive airway disease, with insufficient parenchymal destruction in this region to prevent perfusion. The diminution in ventilation and perfusion at the lung bases is consistent with loss of parenchyma.

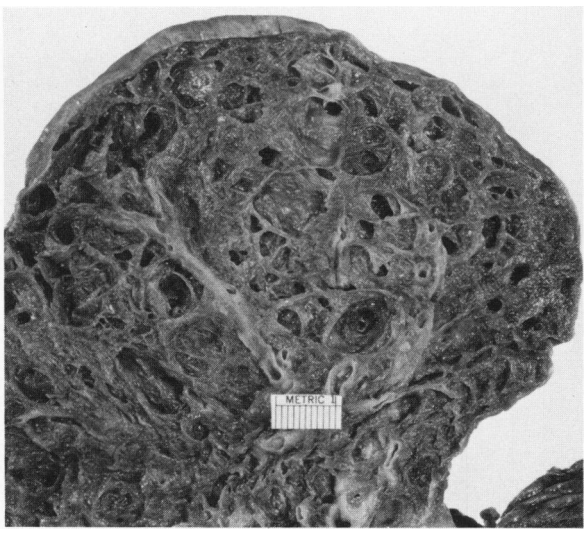
17

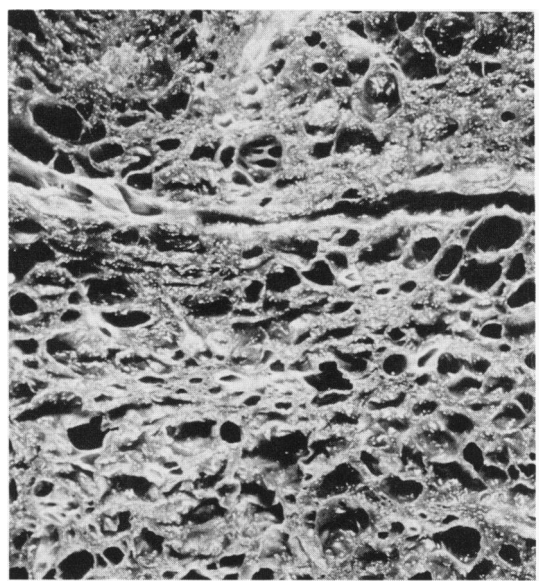




18

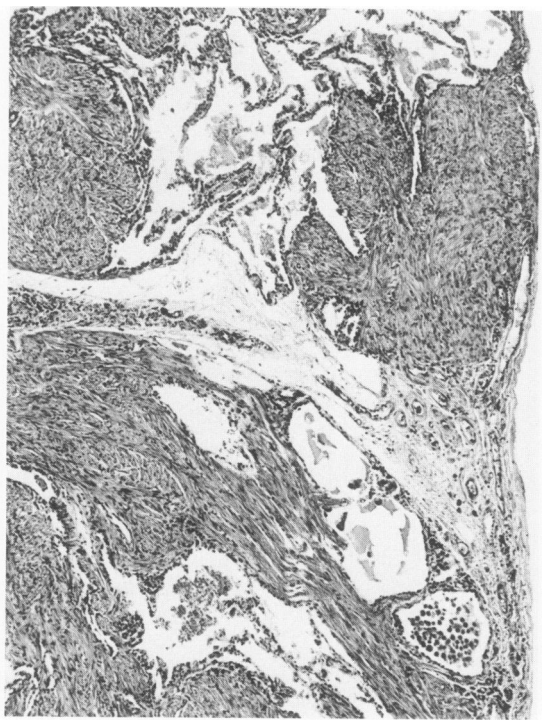
19

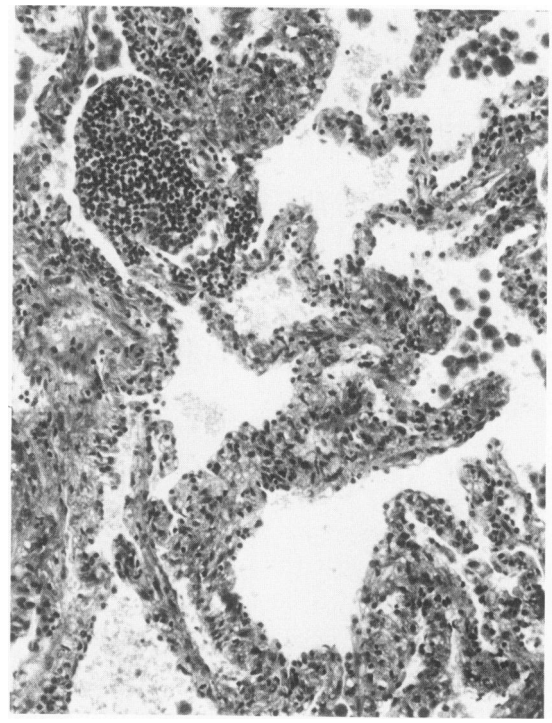


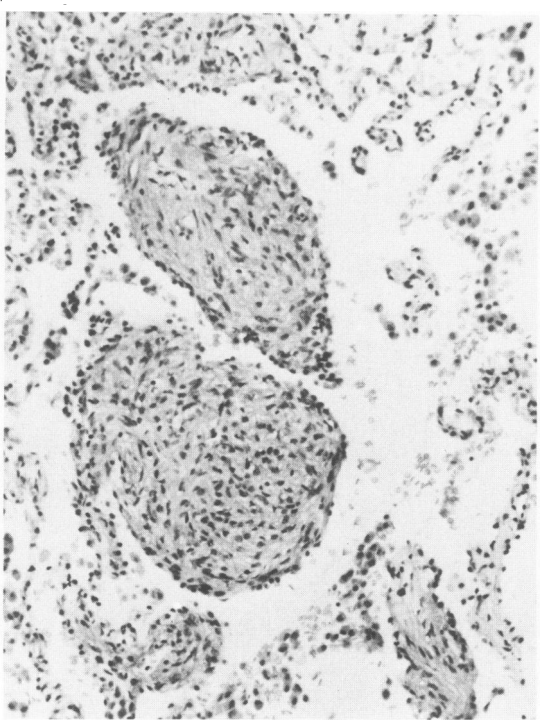


20

Fig 17—Lymphangiomyomatosis, gross specimen (Case 16). A section of the right lung demonstrating honeycombing most extensive in the upper and middle lobes. (See Figures 29–31 and 39 from same case). **Fig 18**—Gough-Wentworth section of same specimen showing that honeycombing in fact extends even to the basal portion of the lower lobe. **Fig 19**—Same case as in Figure 17. Close-up of right upper lobe showing coarse "honeycombing." Most of the spaces are lined by smooth muscle, and in this instance do not represent emphysematous bullae. **Fig 20**—Honeycombing involving both upper and lower lobes, from another patient (Case 18). The spaces also are lined by flattened epithelial cells underlying masses of smooth muscle. (See Figures 32, 38, 46 and 47 from same case.)







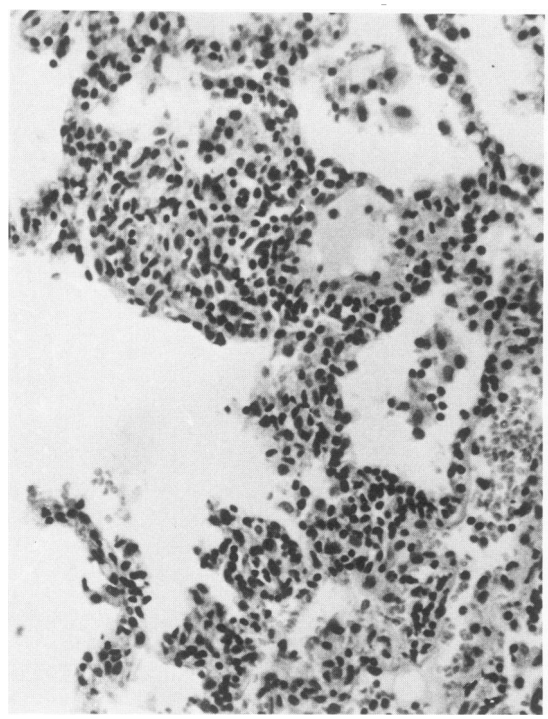
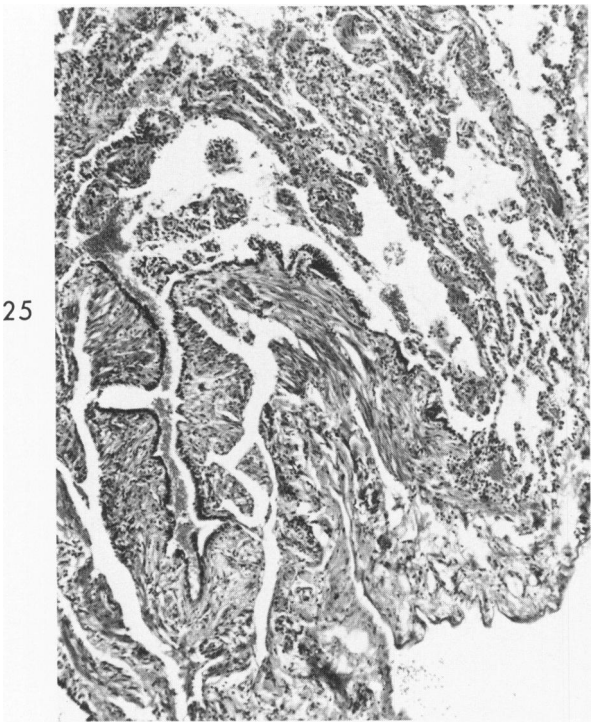
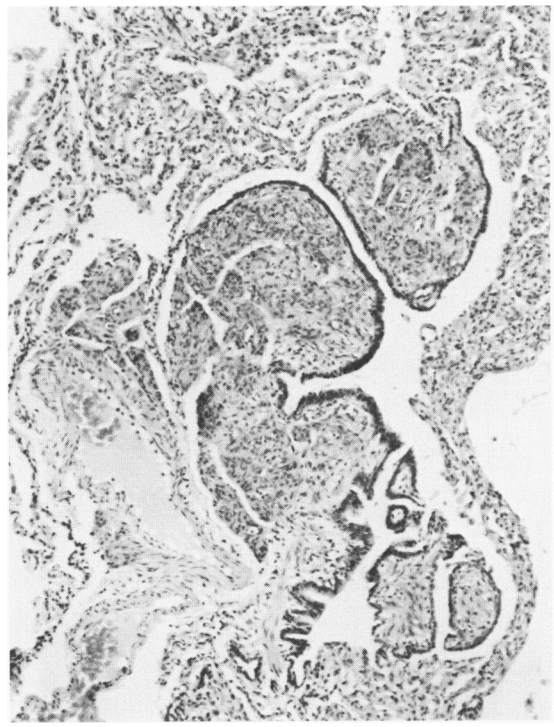


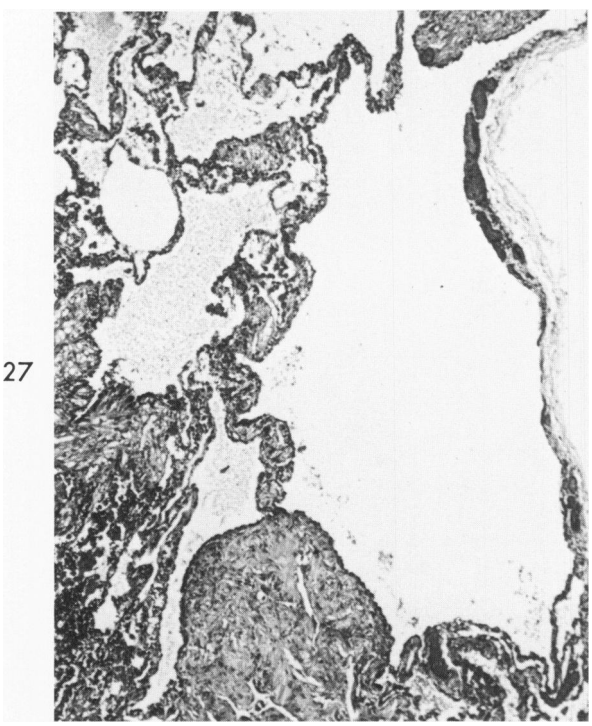
Fig 21—A focus of extensive leiomyomatosis (Case 22). The section shows evidence of honeycombing. Revised and enlarged distal air spaces are lined by flattened epithelial cells. One such space at right below the septum contains masses of hemosiderin-laden phagocytes. Others are filled with proteinaceous material. The pleura and a septum are greatly thickened and contain several dilated lymphatics and many small vessels, probably collateral venules, following occlusion of some intrapulmonary veins. **Fig 22**—Interalveolar septa thickened by intrusive masses of smooth muscle, among which there are focal masses of lymphocytes (Case 11). (See Figure 27 from same case.) **Fig 23**—Nodular accumulations of smooth muscle extending into distal air spaces from interalveolar septa infiltrated by muscle cells (Case 4). (See Figures 26, 34 and 35 from same case.) **Fig 24**—Focus of rounded, little differentiated cells, interpreted as immature myocytes, within interalveolar septa (Case 28). (Compare with Figures 34 and 35). Such "primitive" foci, or "glomus-like structures" have also been described in tuberous sclerosis. (See Figures 44 and 45 from same case.)



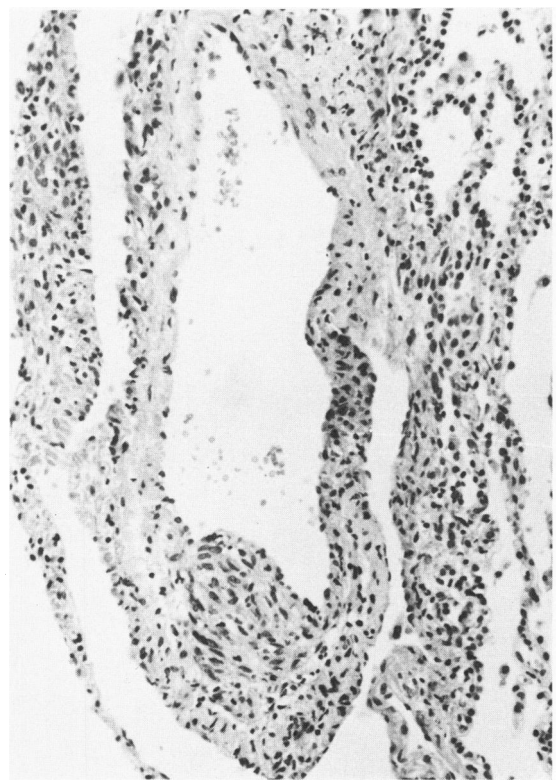
25



26

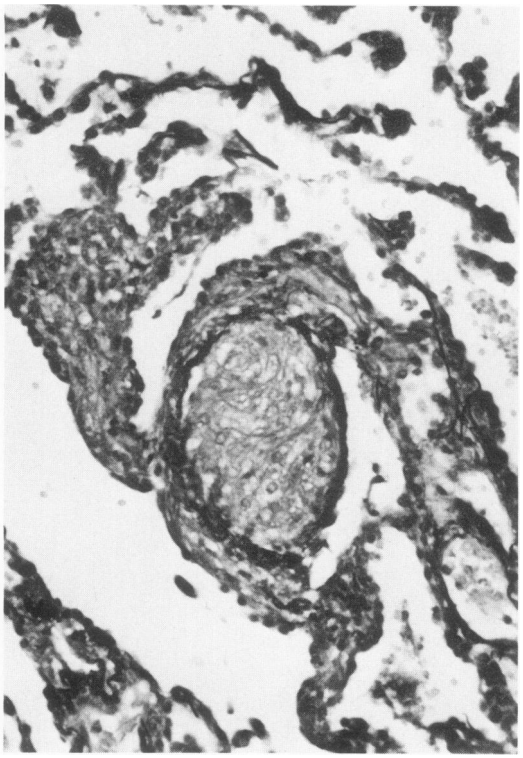


27

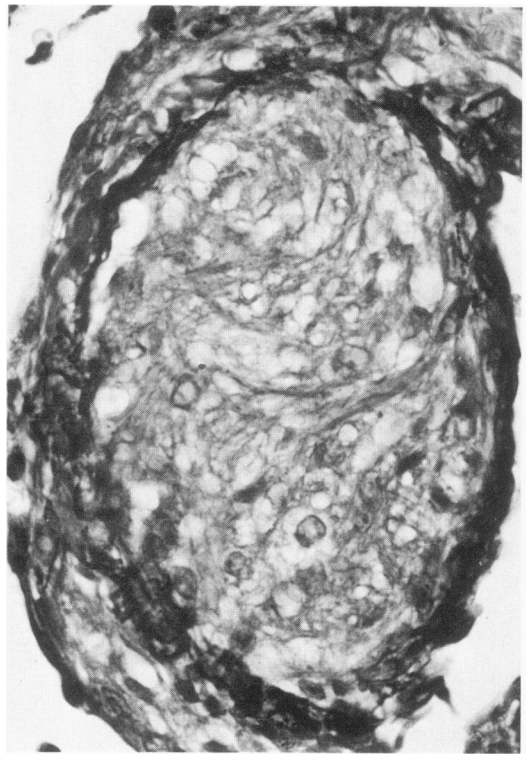


28

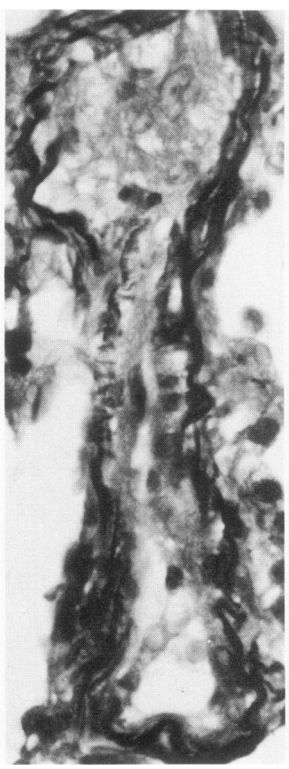
Fig 25—Bronchiole with intrusive masses of smooth muscle that have caused marked narrowing and deformity of this conducting airway (Case 20). The latter expands into a large space lined by flattened epithelial cells with a wall composed predominantly of smooth muscle. **Fig 26**—Bronchiole deformed as in Figure 25, with focal hyalinization of smooth muscle (Case 4). (See Figures 23, 34 and 35 from same case.) **Fig 27**—Dilated distal air space lying beneath the pleura (at right) (Case 11). The pleura is thickened by strands of smooth muscle; elsewhere, the wall of this space contains smooth muscle which has in part become hyalinized. (See Figure 22 from same case.) **Fig 28**—Irregular nodular thickening of wall of small artery by smooth muscle resembling that which lines an adjacent air space (Case 27). (See Figure 43 from same case.)



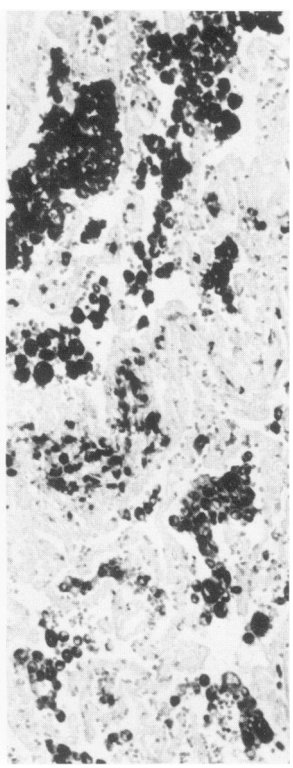
29

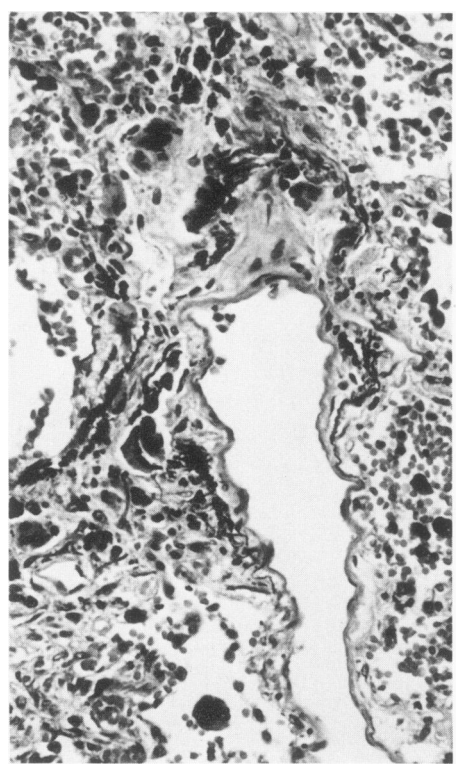


30



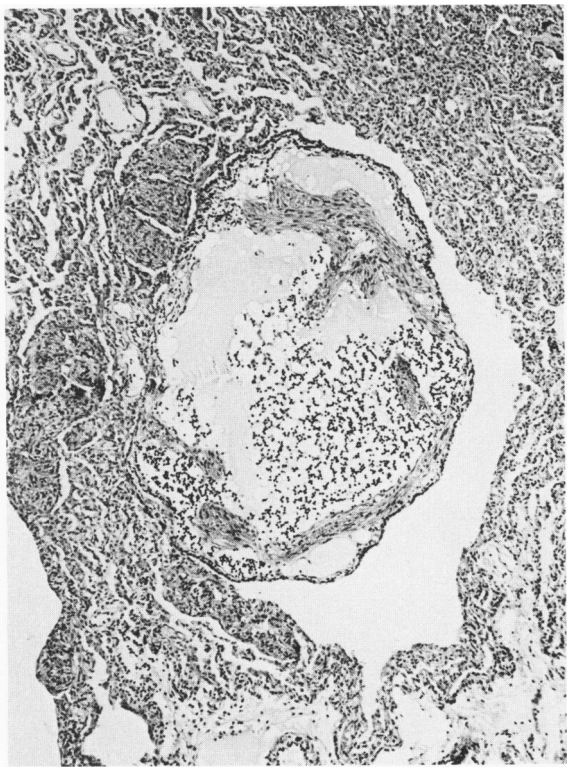
31,32



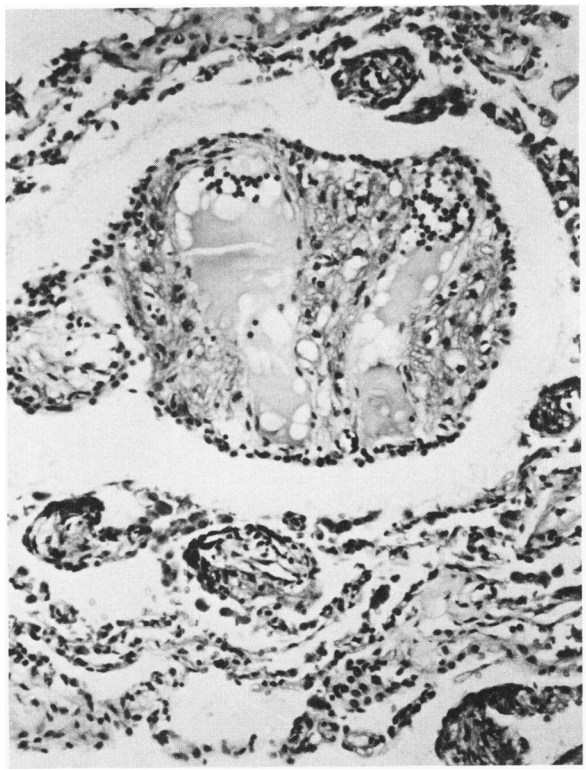


33

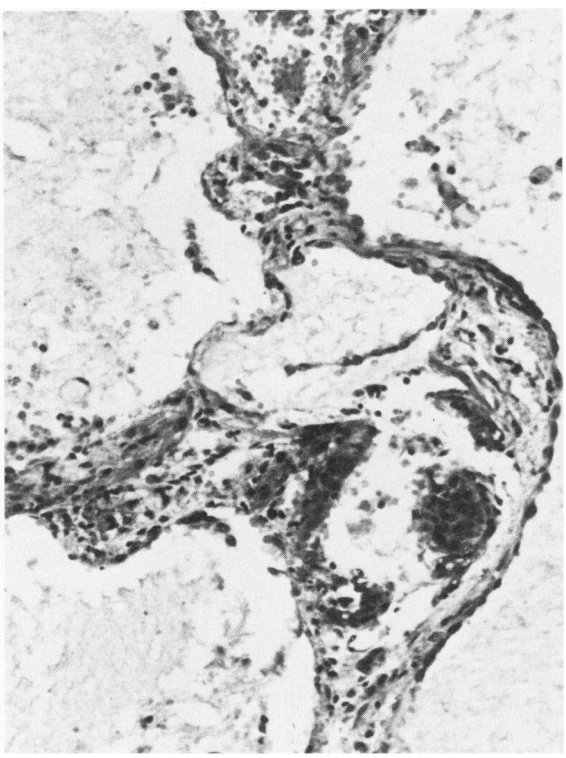
Fig 29—Total occlusion of vein by an intrusive mass of smooth muscle, which also greatly thickens the walls of adjacent distal air spaces (Case 16). (See also Figures 17–19 and 39 from same case.) **Fig 30**—Close-up of vein shown in Figure 29. The lumen is totally occupied by masses of smooth muscle cells. **Fig 31**—Another small vein with partial obliteration by intrusive smooth muscle (Case 16). **Fig 32**—Extensive hemosiderosis seen in an iron-stained section from Case 18. Distal air spaces are filled with large mononuclear cells, the cytoplasm of which is replete with hemosiderin. (See Figures 20, 38, 46 and 47 from same case.) **Fig 33**—Small vein, the elastica of which has been encrusted with iron (Case 7). The elastic tissue is in thick, fragmented strands about some of which a foreign body reaction is occurring. There is extensive hemosiderosis, presumably from occlusion of other venules. (See Figures 7 and 8 from same case.)



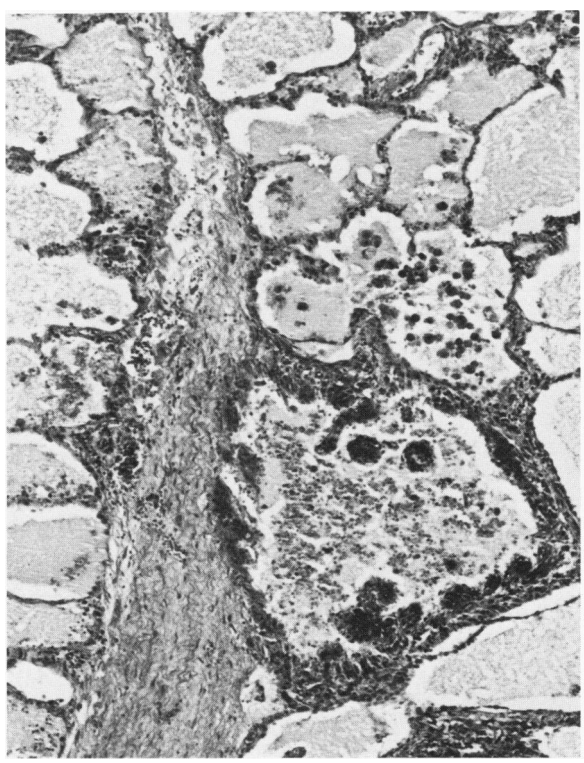
34



35



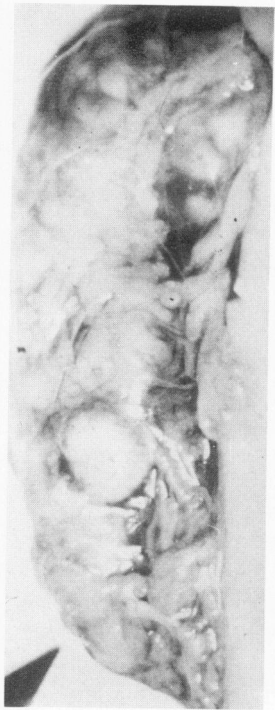
36

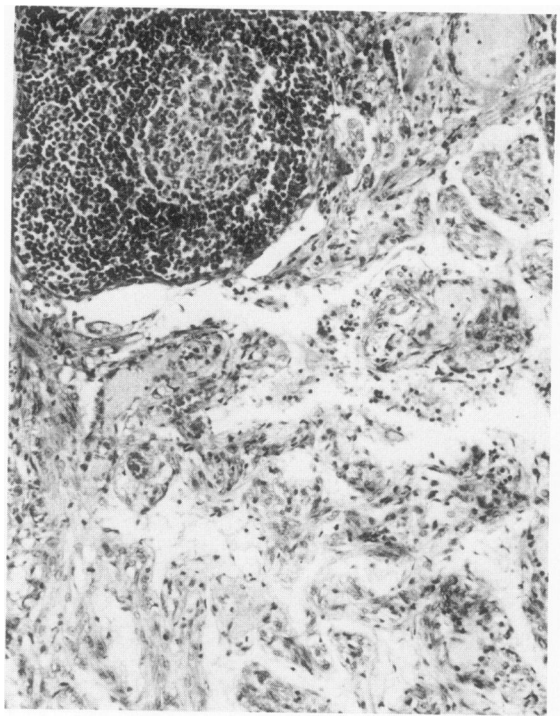


37

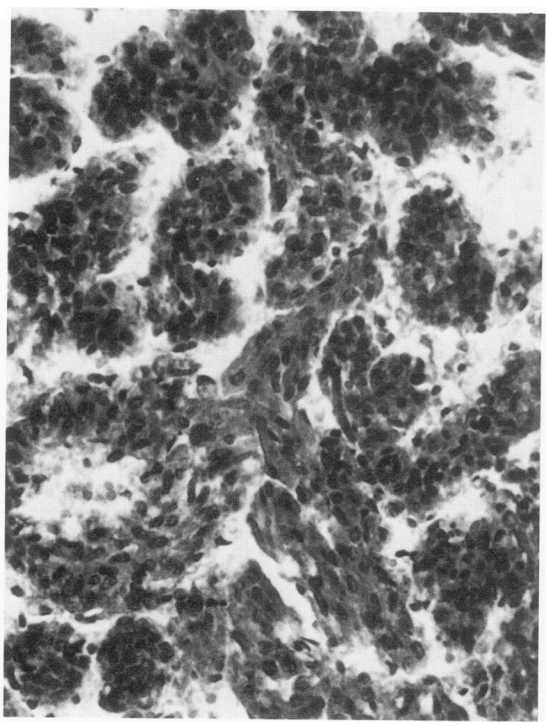
Fig 34—An enormously enlarged lymphatic intrudes into a dilated distal air space (Case 4). This lymphatic is traversed by trabeculae of smooth muscle and contains numerous lymphocytes and a proteinaceous fluid. (See also Figures 23 and 26 from same case.) **Fig 35**—Two enlarged lymphatics with thick muscular walls (Case 4). These structures are traversing an air space from which they are separated by a layer of flattened epithelial cells. **Fig 36**—Dilated lymphatic, identified by the presence of a valve (Case 3). Its wall contains not only mature muscle, but also deeply staining myoblastic foci. Adjacent distal air spaces are filled with a proteinaceous fluid, presumably representing lymphedema. (See also Figures 41 and 42 from same case.) **Fig 37**—An enormously dilated lymphatic with a thick muscular wall, within which are numerous myoblastic foci (Case 3). This lies adjacent to a greatly thickened pulmonary septum. The alveoli contain intensely staining granular eosinophilic proteinaceous material, presumably lymphedema.

38, 39

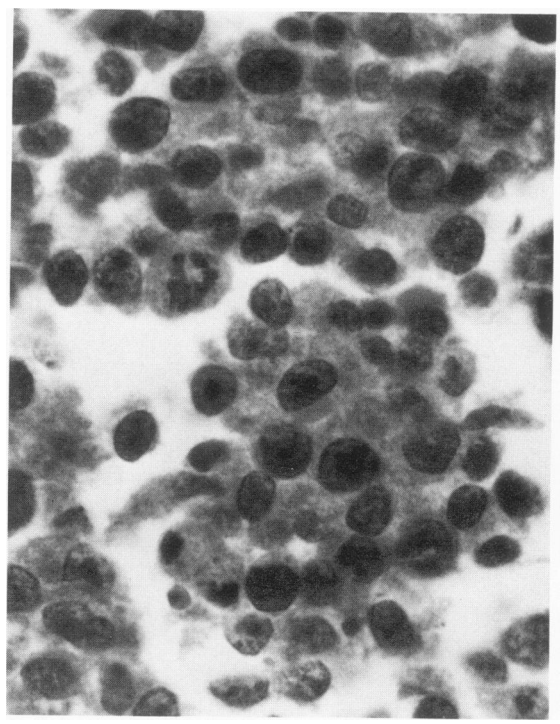




40

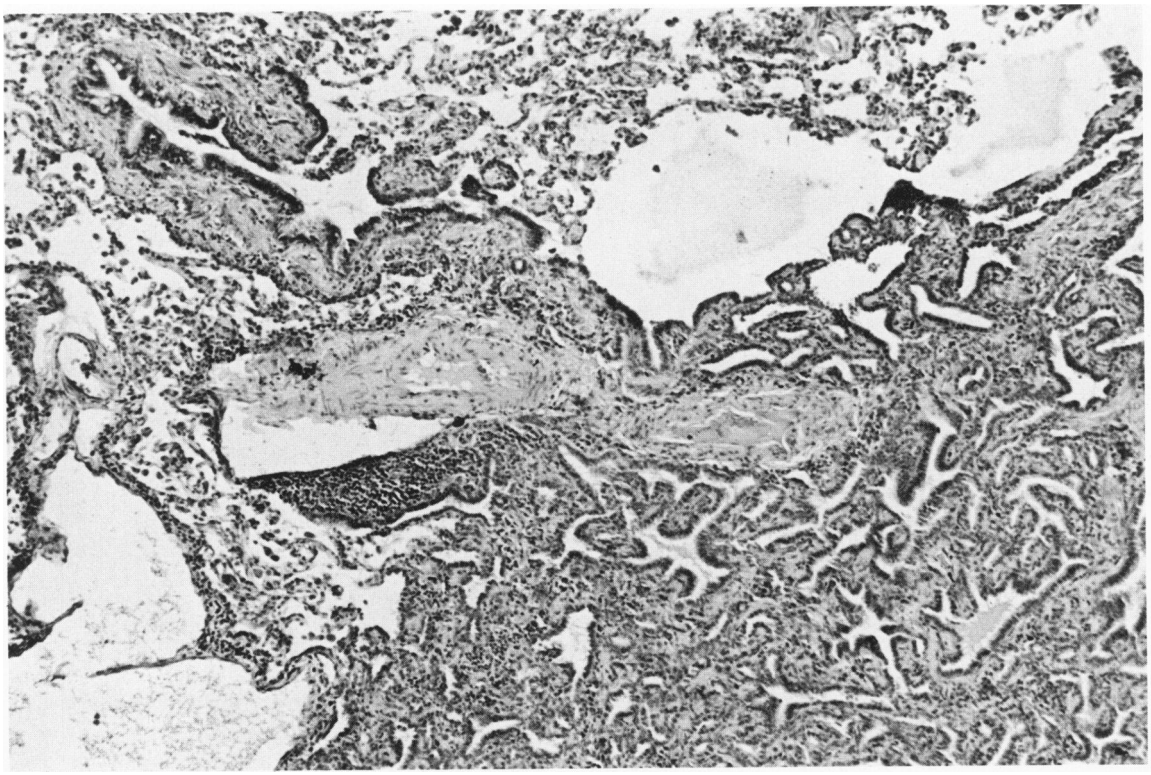


41

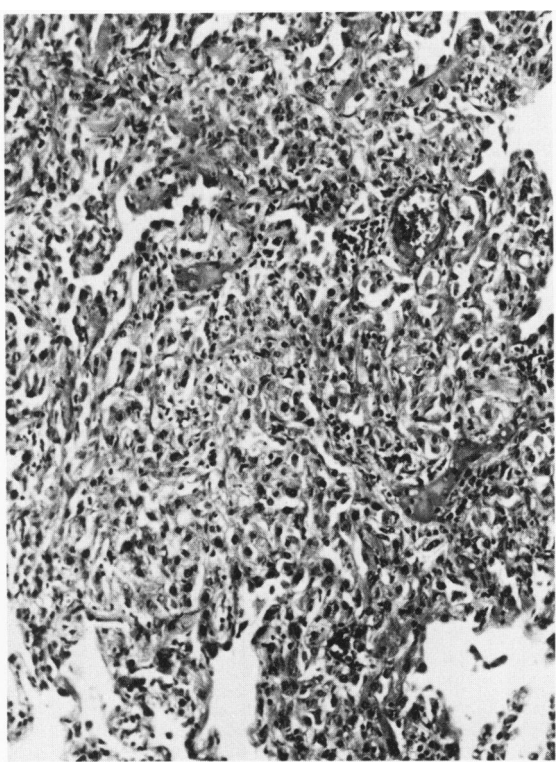


42

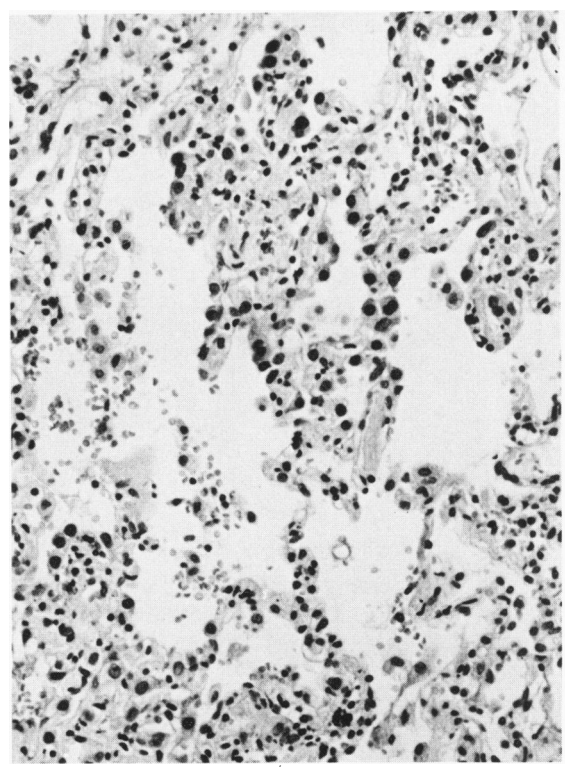
Fig 38—Thoracic duct involved in myomatous proliferation (Case 18). The duct is firm and of sausage-like shape and consistency. It has been subdivided into innumerable small channels by masses of smooth muscle, similar to those within a lymph node (compare with Figure 43; See also Figures 20, 32, 46 and 47 from same case.) **Fig 39**—Enlarged para-aortic lymph node (Case 16). At the right and above particularly are seen thick-walled lymphatics of varicose appearance. Others are seen elsewhere at the right margin of the node which is firm, spongy and white in color. (See Figures 17–19 and 29–31 from same case.) **Fig. 40**—Section of lymph node involved in lymphangiomyomatosis (Case 10). The lymphatic channels are subdivided in labyrinthine fashion by masses of smooth muscle. A secondary follicle is seen above and to the left. **Fig 41**—"Myoblastic focus" (Case 3). There are transitions from elongated myocytes to more rounded myoblastic cells with pyknotic nuclei. (See also Figures 36 and 37 from same case.) **Fig 42**—Anaplastic focus of myoblasts (Case 3). These have a rounded shape, and many are in mitosis. The appearance suggests malignant neoplasm, but this is belied by the behavior of the lesion.



43

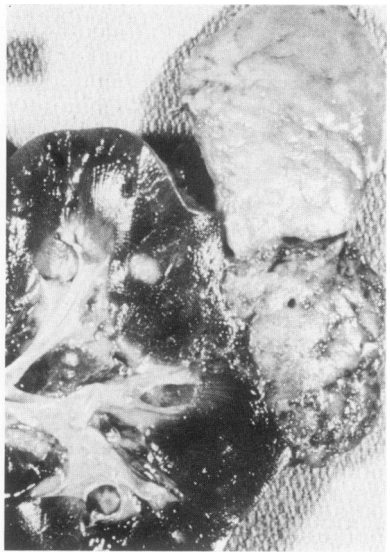


44

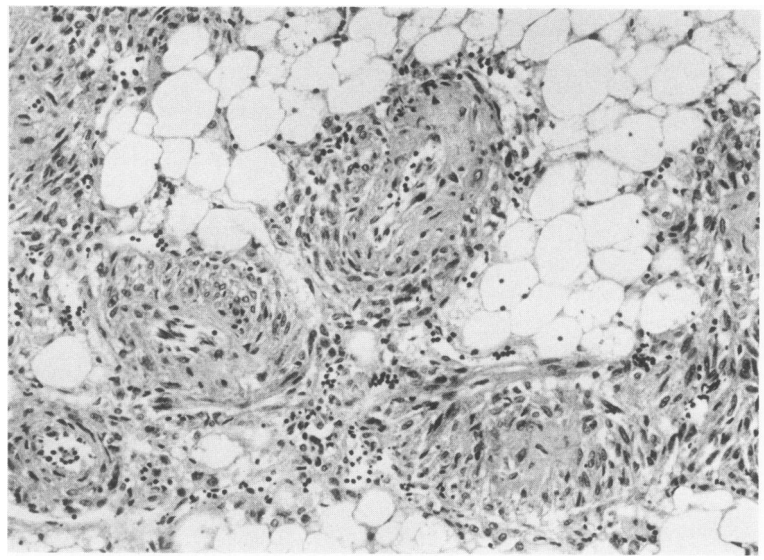


45

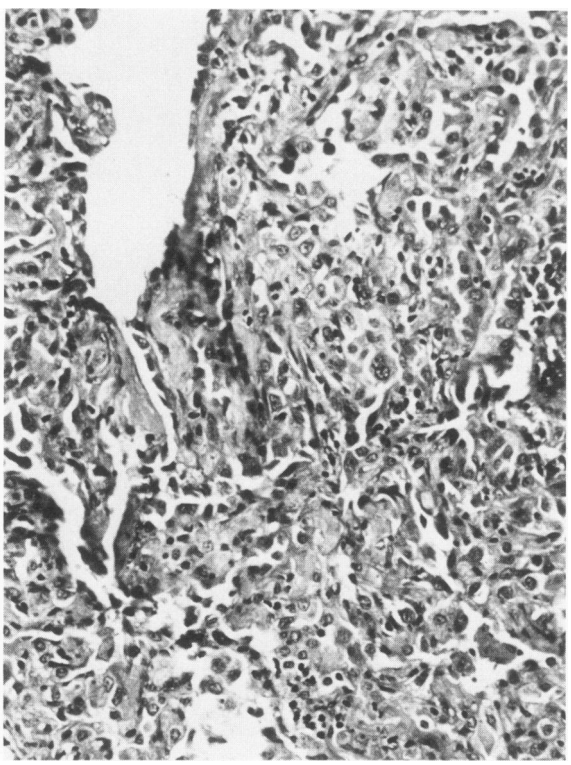
Fig 43—"Adenomatoid focus" (Case 27). In the upper left hand corner of the photograph is a bronchiole, with a narrow lumen and a thick muscular wall. Masses of low columnar or cuboidal epithelium are supported by thick septa of connective tissue. The epithelium has a papillary arrangement. (See Figure 28 from same case.) **Fig 44**—"Adenomatoid focus" (Case 28). Distal air spaces are lined by atypical epithelial cells with pyknotic nuclei. These are supported by thick irregular trabeculae of connective tissue. (See Figure 24 from same case.) **Fig 45**—Another field from same case, at higher magnification, demonstrating rounded epithelial cells with hyperchromatic nuclei.



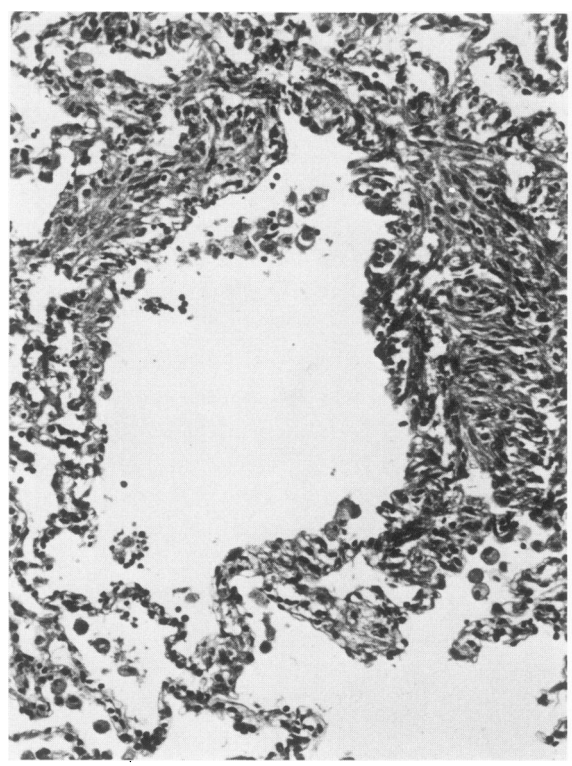
46



47



48



49

Fig 46—Kidney with several foci of angiomyolipomas (Case 18). Two of these are seen in the parenchyma as white nodules. The third, and by far the largest, focus extends into the perirenal fat. (See Figures 20, 32 and 38 from same case.) **Fig 47**—Section of angiomyolipoma (Case 18). Muscle cells of the media are proliferated and extend in irregular fashion into masses of adipose tissue. **Fig 48**—Tuberous sclerosis, "adenomatoid focus." Atypical epithelial cells supported by a stroma of connective tissue line irregular small spaces (compare with Figures 43 and 44). **Fig 49**—Tuberous sclerosis. One of the honeycomb spaces is lined by masses of smooth muscle.