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Pulmonary changes and cor pulmonale in mucoviscidosis

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The lungs of eight cases of cystic fibrosis in patients ranging from age 19 days to 23 years were examined by the large-section technique of Gough and Wentworth (Gough, 1960). All cases showed in life a susceptibility to staphylococcal and pseudomonal bronchopneumonia. In all cases the bronchial tree was plugged with mucus. The lungs from the older patients showed diffuse and pronounced bronchiectasis with luxuriant peribronchial granulation tissue and dilatation of the pulmonary arterial system. The distal air spaces in all cases showed only minimal distension and only in the eldest was there any evidence of destructive emphysema. Three cases developed cor pulmonale which we thought was the result of hypoxaemia due to a ventilation–perfusion imbalance.

Infection of the lungs is one of the classic features of mucoviscidosis (cystic fibrosis of the pancreas). Viscid mucus and pus in the bronchial tree cause chronic bronchiolar obstruction. This in turn has been thought to cause destructive emphysema (May and Lowe, 1949; Royce, 1951; Bodian, 1952; Andersen, 1962). This paper describes a morbid anatomical study to determine whether bronchiolar obstruction or emphysema is the more important factor in the pathogenesis of cor pulmonale in mucoviscidosis.

MATERIAL AND METHODS

From August 1965 to August 1966 a special study was made of the lungs of all cases coming to necropsy at the Hospital for Sick Children, Toronto. Each left lung was excised, intact, and distended with a formalin-sodium acetate solution. Large sections were then cut and mounted on paper by the method of Gough and Wentworth (Gough, 1960). We did this because accurate diagnosis of emphysema requires special preparation of the lung, particularly fixation with expansion (Gough, 1964, 1965). Macro-histological slides measuring 3 × 2 in. were also prepared from each lobe. Eight lungs so examined were from patients with mucoviscidosis.

Some of the clinical features and diagnostic investigations in these cases are given in Tables I and II. In particular we were concerned with the levels of the blood gases on the day of death. Lung sections of these cases were compared with sections from patients of approximately the same age in the total series of 345 lungs who did not have cystic fibrosis.

In the eight cases of mucoviscidosis we noted: (1) blockage and distension of the bronchial tree by viscid mucus and pus (Figs 1 to 5); (2) infection of the lung; (3) the bacteriology of the sputum; (4) destructive emphysema (seen in one case only, Fig. 5); (5) right ventricular hypertrophy (seen in three cases only); and (6) the number of branches of pulmonary arteries and radicles of the bronchial tree of various diameters. These were compared with those from control cases of the same age. The findings were similar to those of mucoviscidosis occurring in Cardiff, except that in one of the Cardiff children there were large bullae which had been seen radiographically. In this child the bullae varied in size and number from one day to the next, indicating that the bullae were due to air trapping (Fig. 6).

RESULTS

The morbid anatomical data collected as above are shown in Table III. The pulmonary artery and bronchial tree radicles were dilated in cases 4 to 8.

TABLE I

CLINICAL FEATURES

Case	Age	Sex	Main Symptoms	Appearance of Chest Radiograph	Clubbing
1 (B.T.)	19 days	F	Meconium ileus—peritonitis	Pneumonitis in the perihilar area	Absent
2 (B.S.)	26 days	F	Meconium ileus—enterotomy and irrigation	Dense pneumonic consolidation in R. upper lobe—some infiltration in L.L. lobe	Absent
3 (P.F.)	3 mths.	M	Severe respiratory distress—cyanosis—bronchopneumonia	Perihilar interstitial pneumonia—terminal massive bilateral pneumonia. Small R. pneumothorax	Absent
4 (S.T.)	4 yrs.	F	Repeated respiratory infections—terminal severe respiratory distress. Foul, bulky stools	Marked bilateral interstitial and parenchymal inflammatory deposits	Present
5 (C.C.)	7 yrs.	F	Repeated respiratory infections—bronchopneumonia—cyanosis—cor pulmonale	Peribronchial infiltration—bilateral bronchopneumonia. Increasing cardiac shadow (1 week before death)	Present
6 (K.N.)	9 yrs.	M	Repeated episodes of bronchopneumonia. Biliary cirrhosis—oesophageal varices—haematemesis—terminal massive repeated haemoptyses	Bilateral linear fibrotic changes—honeycomb pattern to entire L. upper lobe. Pulmonary arteriogram showed R. pulmonary artery vessels dilated and an early appearance of the venous vessels. Poor pulmonary arterial circulation in upper part of left lung (1 week before death)	Present
7 (K.L.)	10 yrs.	F	Repeated upper R. tract infections and pneumonia. Terminal cor pulmonale	Widespread densities and fibrotic changes. Increasing cardiac shadow terminally	Present
8 (B.C.)	23 yrs.	M	Presented age 12 years with failure to thrive, diarrhoea, and recurrent bronchitis. Repeated episodes of bronchopneumonia. Terminal cor pulmonale	Peribronchial infiltration. Bilateral basal bronchiectasis. Emphysema and extensive interstitial fibrosis. Terminal increase in heart size	Present

TABLE II

LABORATORY INVESTIGATIONS

Case	Pancreatic Proteolytic Enzymes	Intestinal Absorption Tests	Blood Gases Day of Death (mm. Hg)	
			P_{O_2}	P_{CO_2}
1	—	—	—	—
2	—	—	—	—
3	Stool examination, absent proteolytic enzymes	—	74 40	62 100
4	—	Small bowel enema showed puddling of barium	—	—
5	3 u. trypsin/ml. of duodenal juice (normal over 50 u.)	Vitamin A absorption curve flat	—	70 50
6	—	Liver biopsy showed focal biliary cirrhosis	74 63	57 75
7	3 u. of trypsin/ml. of duodenal juice	Vitamin A absorption curve flat Glucose tolerance curve normal	35 43 52	69 73 63
8	No proteolytic enzymes in duodenal juice	Vitamin A absorption curve flat	20 — —	78 90 100

Around the bronchiectatic spaces there was a highly vascular granulation tissue. This was particularly marked in case 6, who had repeated massive haemoptyses terminally (see Fig. 3).

DISCUSSION

This study confirms that in mucoviscidosis the lungs show plugging of the bronchial tree by viscid mucus and purulent exudate (Table III). There is usually associated bronchiectasis and bronchopneumonia. The peculiar proneness of the cystic fibrosis lung to staphylococcal and pseudomonal infections was also confirmed in this investigation (Table III).

In contrast we found no evidence of destructive emphysema in seven of the eight cases of mucoviscidosis. It must be stressed that the dilatation seen in the distal air spaces in the cystic fibrosis lungs is minimal when compared with normal lungs of the same age. Emphysema has been defined as 'a condition of the lung characterized by increase beyond the normal in the size of air spaces distal to the terminal bronchiole either from dilation or from destruction of their walls' (Ciba Guest Symposium, 1959). There is a difficulty in comparing different series of cases because ballooning of the lung due to bronchial obstruction may be reported as emphysema, and such ballooning was present in cases 4 to 8.

The appearance of the mucoviscidosis lungs was reminiscent of that seen in fatal cases of status asthmaticus. These lungs also do not show destructive emphysema but are overdistended, as is seen in drowning. Their bronchi are also plugged with mucus (Williams and Leopold, 1959; Gough, 1961). Subsegmental areas of bronchiectasis are also not unusual in asthma (Gough, 1964).

Our findings support the hypothesis that cor pulmonale in mucoviscidosis is due to increased airway obstruction and chronic hypoxia, leading to an elevated pulmonary arterial pressure with-

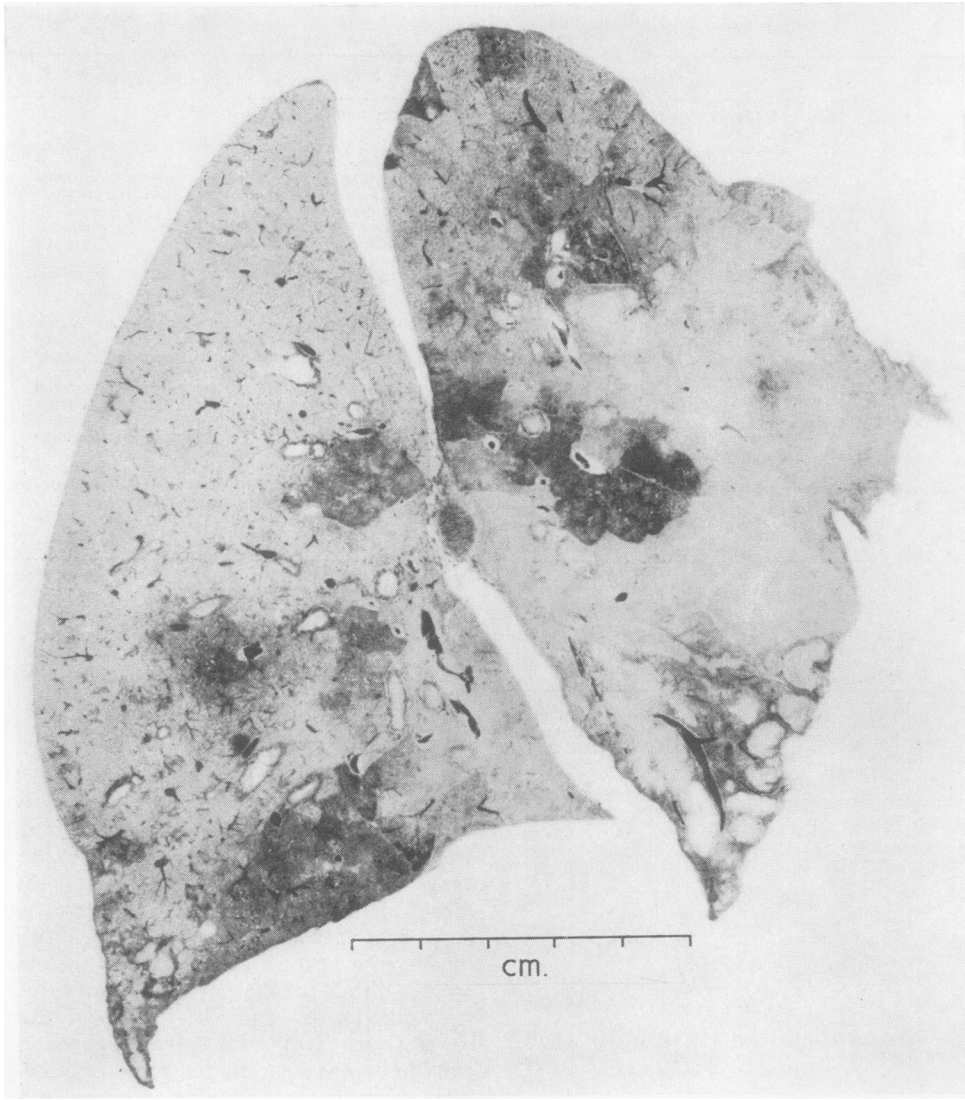

FIG. 1. *Case* 4. *Bronchiectasis and patchy pneumonia. There is no destructive emphysema. Unstained section.*

out any damage to the capillary bed of the lung by destructive emphysema (Bowden, Fischer, and Wyatt, 1965; Coates, 1966; Beier, Renzetti, Mitchell, and Watanabe, 1966). The terminal blood gas levels of some of the patients studied in this paper (Table II) demonstrate the presence in them of hypoxaemia. Goldring, Turino, Andersen, and Fishman (1961) also thought that hypoxia, rather than a specific ventilatory defect or the duration of the disease, was the major determinant of cor pulmonale in cystic fibrosis. Clearly, this hypoxaemia is not due to destructive emphysema, but probably to an imbalance between ventilation and perfusion. Adequate ventilation is prevented by mucous plugs. Excessive perfusion is due to luxuriant peribronchial granulation tissue. Furthermore, the hypoxic state is worsened by repeated attacks of bronchopneumonia.

The dilatation of the pulmonary arterial system

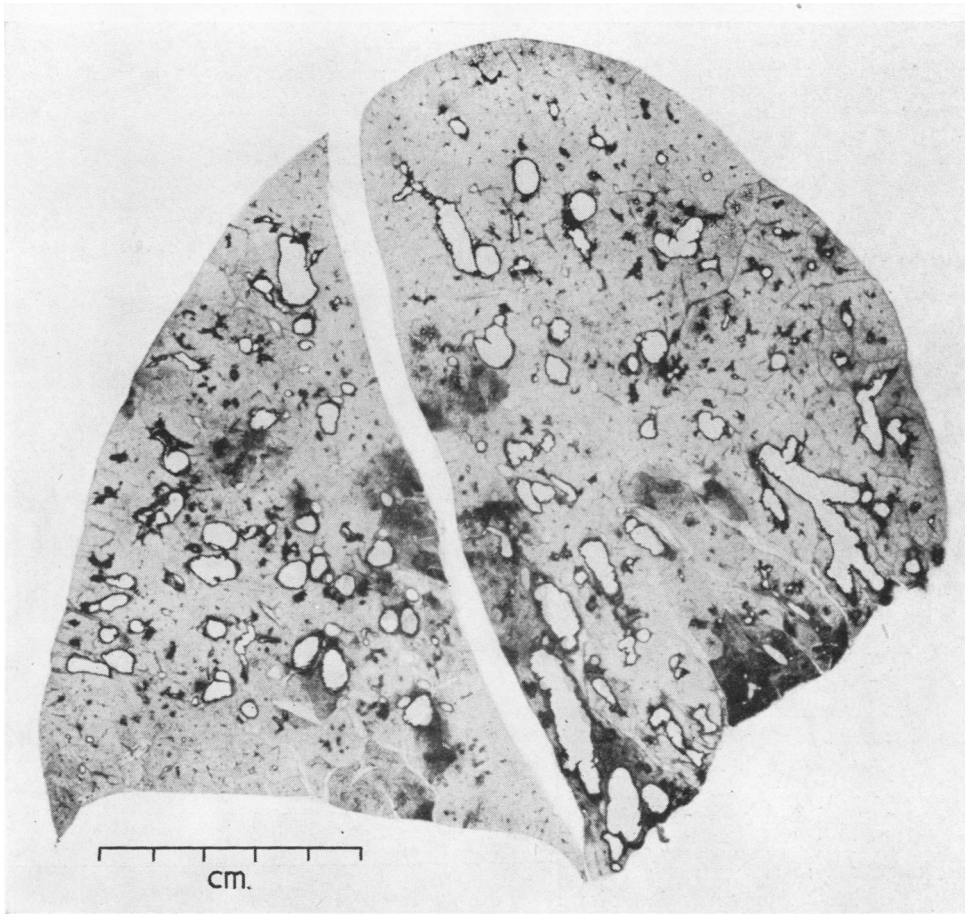

FIG. 2. *Case 5. Diffuse bronchiectasis. The bronchi are more clearly outlined by the haematoxylin and Fett Rot stains.*

TABLE III

MORBID ANATOMICAL DATA

Case	Blockage and Distension of Bronchi with Mucous Secretion	Evidence of Inflammation	Bacteriology of Sputum[1]	Destructive Emphysema	Right Ventricular Hypertrophy	Weight of Heart (g.)	Thickness of Ventricles (mm.)	
							R.V.	L.V.
1	0	Bronchiolitis	P	0	0	17·5	—	—
2	+	Abscess in left lower lobe	S	0	0	—	—	—
3	+	Bronchiolitis and bronchopneumonia	S E	0	0	41	—	—
4	+	Bronchiectasis	P S	0	±	178	5	12
5	+	Bronchiectasis	P S	0	±	202	5	15
6	+	Bronchiectasis	P S	0	+	270	11	11
7	+	Bronchiectasis	P S	0	+	188	7	10
8	+	Bronchiectasis	P S	+	+	964	13	11

[1]P = *Pseudomonas aeruginosa*
S = *Staphylococcus pyogenes*
E = *Escherichia coli*

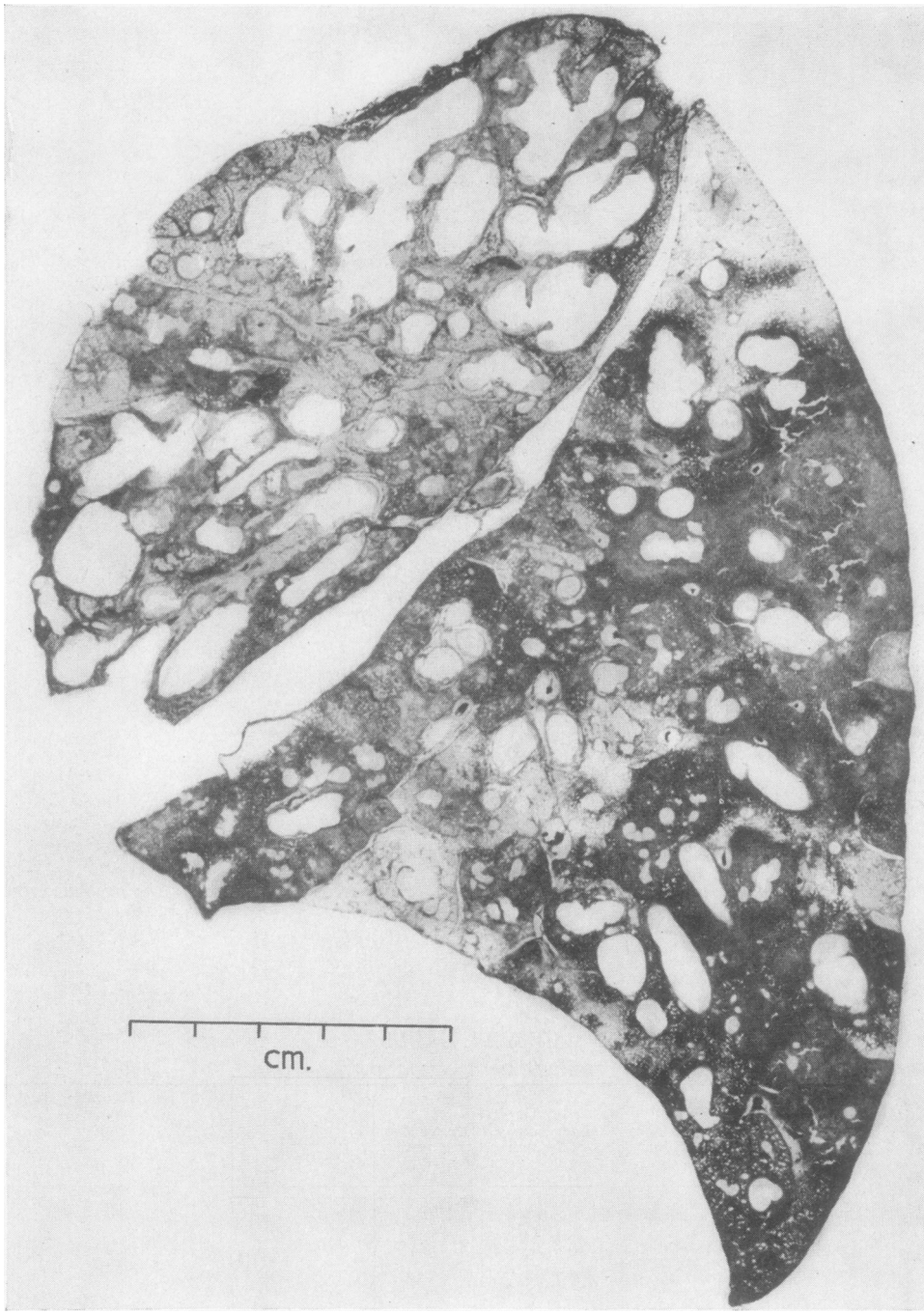

FIG. 3. *Case 6. Pronounced bronchiectatic cavity formation. The cavities are lined by highly vascular granulation tissue. Unstained section.*

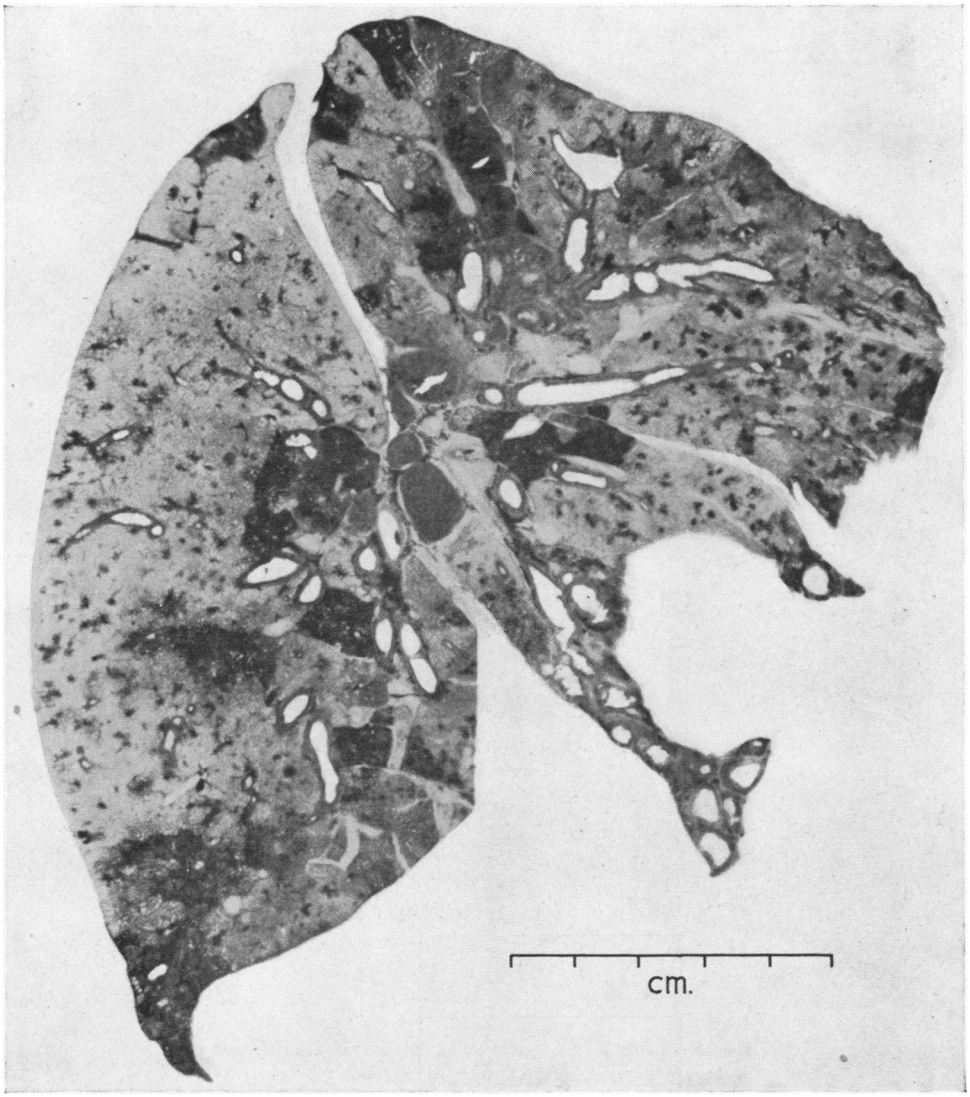

FIG. 4. *Case 7. Diffuse bronchiectasis and bronchopneumonia. The hilar lymph nodes are prominent. (H-F stain.)*

seen in this series confirms the work of Bowden *et al.* (1965), who interpreted the change as evidence of antemortem pulmonary hypertension.

Vigorous bronchial drainage and prophylactic antibiotics would seem the best way of prolonging life in mucoviscidosis, although Coates (1966) has suggested that patients who survived to adulthood had an inherently benign disease.

We think that the luxuriant peribronchial granulation tissue in the areas of bronchiectasis would make broncho-pulmonary vascular communications a relatively common late development in cases of cystic fibrosis. However, we did not think that these were the main cause for the cor pulmonale which developed in cases 6, 7, and 8.

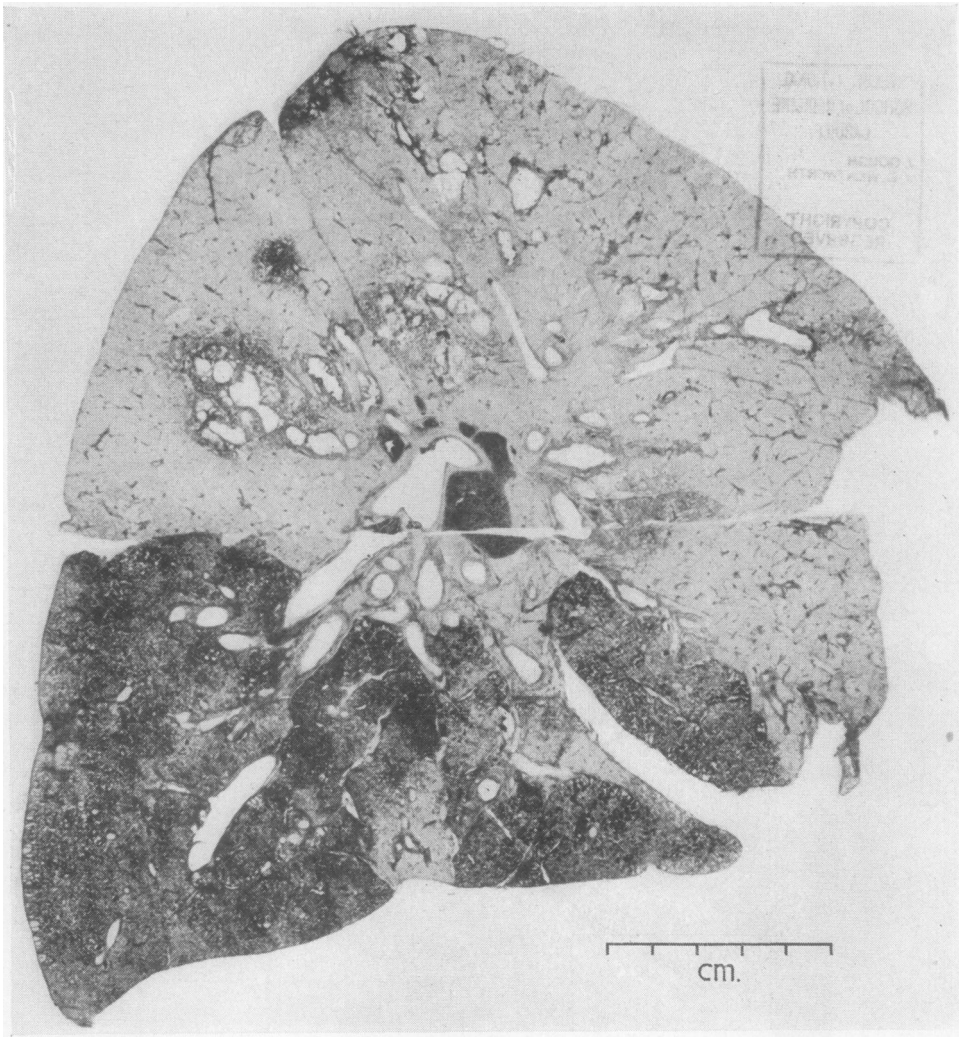

FIG. 5. *Case* 8. *Severe bronchiectasis and hilar lymph node enlargement. There is also some panacinar destructive emphysema, particularly in the upper half of the lung. Perl's stain for iron.*

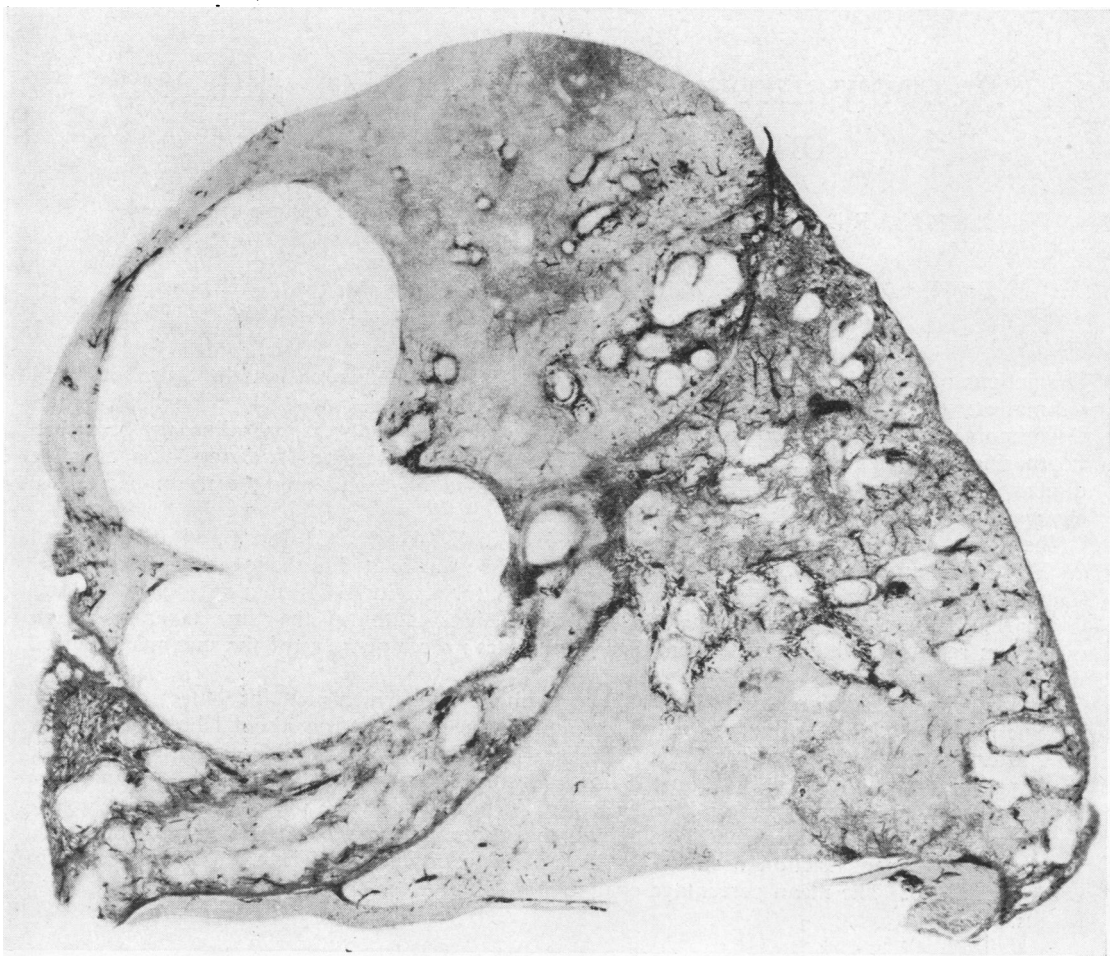

FIG. 6. *Bullae and bronchiectasis in a Cardiff case.*

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