

A COMPARISON OF PHYSIOLOGICAL AND PATHOLOGICAL FINDINGS IN CHRONIC BRONCHITIS AND EMPHYSEMA, WITH SPECIAL REFERENCE TO RESPONSE TO EXERCISE

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Any senior medical student is expected to recognize the picture of clinical emphysema, though many authors, such as Fletcher (1952), feel that it is an unreliable diagnosis. Within the last 20 to 30 years radiological emphysema has been added to the syndrome (Simon and Galbraith, 1953), and in the last 15 years the emphasis has been on the associated disorders of pulmonary physiology. Such factors as defects in forced ventilation, high functional residual capacity, low mixing efficiency, arterial oxygen desaturation on exercise, and sometimes reduced pulmonary diffusing capacity for oxygen and carbon monoxide have been described. Whether the three pictures of clinical, radiological, and physiological emphysema always represent the same pathological state, however, is very doubtful. At the Ciba Symposium, reported in 1959, emphysema was 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 dilatation or from destruction of their walls." It will be seen that not everyone includes alveolar destruction in the definition.

We think that studies of the effects of exercise may help to distinguish those patients in whom alveolar structure is lost, and in this paper we show the correlation between our physiological and pathological findings.

METHODS

Over 300 patients have been studied who suffered from dyspnoea, non-tuberculous bronchial or diffuse pulmonary disorders, and some from coronary or left heart disease presenting with dyspnoea. None were included who had phthisis or bronchial carcinoma or acute pulmonary inflammatory disease or pleural effusions.

EXERCISE.—The standard exercise was three minutes pedalling on an exercycle with a set resistance. A steady state is normally shown at this time by the simultaneous tracing of ventilation and oxygen uptake; Donald, Bishop, and Wade (1954) had found this by other methods.

We have investigated the effect of exercise on (a) arterial oxygen, and (b) ventilation equivalent for oxygen. Since we think that the relationship of forced ventilation tests to the stresses of real life is slight, we believe that the effects of muscular exercise should present a much truer idea of the patients' functional ability.

Arterial oxygen saturation was measured at rest and after exercise, with the patient breathing room air. Blood was taken either by arterial puncture using an indwelling Riley needle, or by taking arterialized blood from the ear lobe (Lilienthal and Riley, 1944; Gilson and Hugh-Jones, 1955). Estimations were made by the Roughton-Scholander technique (1943) or by the colorimetric method of Molyneux and Pask (1955), these methods being frequently checked against each other. Arterial oxygen desaturation on exercise was taken as less than 92% (cf. Grade 2 emphysema of Baldwin, Courmand, and Richards, 1949).

Ventilation Equivalent for Oxygen.—This is the amount of air breathed to yield 100 ml. of oxygen to the blood (Anthony, 1930). We found that a few patients became seriously anoxic when they exercised while breathing room air from a spirometer, so we used a spirometer containing oxygen-enriched air (about 60% O₂) with the mixture kept stable throughout the test by an automatic oxygen adder (Grove and McNab, 1959). Using high oxygen mixtures presumably ensures high alveolar oxygen tension and—except in the presence of very gross diffusion defects—permits the oxygen uptake to correspond to the oxygen utilization, thus making the test a much truer one of ventilatory efficiency.

The minute volume of respiration was derived from the respiratory tracing and the oxygen consumption was recorded by a pen attached to the oxygen reservoir (Grove and McNab, 1959).

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RADIOLOGICAL EMPHYSEMA.—This was assessed after consideration of the level of the diaphragm and its contour (postero-anterior and lateral view), the rib contour, the presence or absence of radiotranslucency below the heart, and by fluoroscopy.

DEFICIENT FORCED VENTILATION.—A recording spirometer embodying the principles of Bernstein, D'Silva, and Mendel (1952) was used (Grove and McNab, 1959). Patients with a forced expiratory volume of less than 60% of the inspiratory capacity (F.E.V./I.C.<60%) were considered as having moderate deficiency.

FUNCTIONAL RESIDUAL CAPACITY AND MIXING EFFICIENCY.—These were estimated by the katharometer technique of McMichael (1939) and Bates and Christie (1950). Functional residual capacity was accepted as large if over 60% of the total lung capacity: Whitfield, Waterhouse, and Arnott (1950) had found occasional normals up to 70% T.L.C. Mixing efficiency was considered low if less than 38% of predicted normal.

CHRONIC BRONCHITIS.—The presence of chronic bronchitis was assessed carefully on the history, and roughly included all patients with chronic or recurrent cough with sputum, for which no other cause could be found.

RESULTS

PHYSIOLOGICAL FINDINGS.—There are several features which are commonly accepted as characteristic of more than a slight degree of emphysema, and these are: radiological emphysema, deficient forced ventilation, large functional residual capacity, arterial oxygen saturation on exercise below 92%, low mixing efficiency, and increasing dyspnoea on exertion.

Table I shows the percentage of patients in various groups who show oxygen desaturation and fall of ventilation equivalent on exercise.

These findings mean that in bronchitic patients the combination of oxygen desaturation on exercise when breathing air, together with a fall of

TABLE I
PERCENTAGE OXYGEN DESATURATION AND FALL OF VENTILATION EQUIVALENT ON EXERCISE

A. In 120 unselected "chest" patients	20%
B. In 87 of these with chronic bronchitis	22%
In 38 of these with radiological emphysema	34%*
" 49 " " without " "	16%
" 60 " " with poor forced ventilation	28%*
" 27 " " without " "	16%
" 70 " " with large functional residual capacity	26%*
" 17 " " without " "	18%
" 48 " " with low mixing efficiency	25%
" 39 " " without " "	23%
" 66 " " with increasing exertion dyspnoea	26%
" 21 " " without " "	19%
C. In 33 of these without chronic bronchitis	9%

* These percentages are "significantly" greater than the series, though we realize that one must be guarded in considering "significance" in the numbers with which we are dealing.

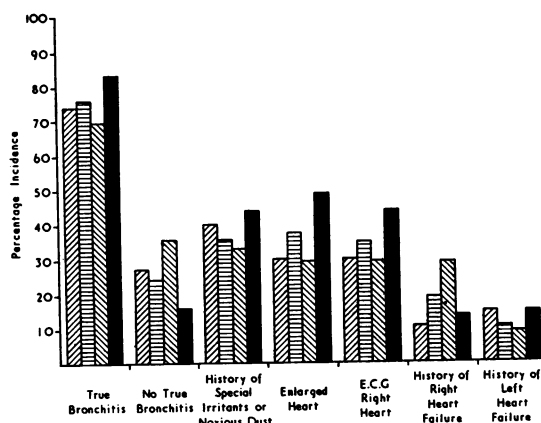


FIG. 1.—Incidence of various clinical features in patients who have arterial desaturation on exercise breathing air, with and without a fall in the ventilation equivalent on similar exercise breathing oxygen-enriched air.

▨ % in series of 120 non-cancerous and non-tuberculous "chest" cases.

■ % in all patients with arterial oxygen less than 92% on exercise.

▨ % in patients with arterial oxygen <92% on exercise plus failure of ventilation equivalent to fall on exercise.

■ % in patients with arterial O₂ <92% plus fall in ventilation equivalent on exercise.

ventilation equivalent on similar exercise (but when breathing oxygen-enriched air), is slightly more likely to occur in patients who have the previously stated features in keeping with pulmonary emphysema. These features, however, could be present in the absence of extensive alveolar destruction.

A similar analysis to that shown in Table I was made of a considerable number of other clinical and physiological findings. None of these gave the same consistent picture which is shown by Table I for the effects of exercise.

Fig. 1 shows that other clinical manifestations supposed commonly to occur in patients with severe destructive emphysema were in fact more common in our 24 patients who showed the combination of arterial oxygen desaturation with fall in ventilation equivalent on exercise. A surprising anomaly was that a history of right heart failure was less commonly noted in such patients, but this is in keeping with the figures of Baldwin and others (1949) for Grade 4 emphysema.

PATHOLOGICAL FINDINGS.—In 18 cases where complete investigation had been carried out, the

TABLE II
RELATION OF ANATOMICAL CHANGES IN LUNG TO OTHER FINDINGS
(In cases referred to or diagnosed as emphysema)

Findings at Necropsy or Operation	Patient	Reasonably Diagnosed as Emphysema	Combined Finding*	Lungs Examined and/or Specimens Obtained at	Additional or Anomalous Findings
Lungs showed generalized severe parenchymal damage (emphysema)	W.Sw.	Yes	Yes	Operation	—
	O.W.†§	—
	E.B.†§	Operation and necropsy	—
	C.H.†	..	Desaturation intermittent	Necropsy	Prominent peripheral vessels atypical on radiograph
	J.W.	..	Yes	..	F.R.A. and mixing fair
	H.L.	Bullae both sides
Lungs showed local emphysema with bullae. No generalized emphysema	W.L.	Enlarged heart, aortic stenosis
	J.G.	—
	W.St.	Operation	Bulla at apex
	J.M.†§	Yes	No: (No desaturation V.E. +)	Operation	Fair F.E.V.
	H.K.G.	No	No: (V.E. +)	..	Local bulla, rest of lung ? normal, Fair mixing efficiency
	F.S.	Yes	Fair mixing efficiency
Lungs showed no generalized emphysema, or very slight centrilobular change	A.S.	..	No: (No desaturation)	..	Normal mixing efficiency
	H.C.	..	Yes	..	Gross replacement of lung, e.g., widespread bilateral bullae
	F.S.†	Yes	No: (V.E. +)	Necropsy	Scar of old cardiac infarct
	T.S.†	..	No: (No desaturation)	..	Mixing efficiency normal; lung markings increased
	J.C.†	..	No: (V.E. +)	..	Fair mixing efficiency, radiograph atypical
	P.S.†§	..	No: (No desaturation)	..	Old healed tuberculosis with scarring and bullae at apex

* Arterial oxygen desaturation on exercise + fall of ventilation equivalent on exercise

† Lung sections prepared by the technique of Heard (1958)

§ Illustrative cases

lungs or parts of lungs have been studied at or after operation or necropsy. The findings are summarized in Table II according to the degree of damage to the lung parenchyma which was established. All 18 of these patients had been considered to have true emphysema before admission.

Of these 18 cases details and photographs are given of two from the first group in Table II and one each from the second and third groups (Figs.

4 to 15). Photographs of naked-eye and microscopic appearance of normal lung prepared by the same technique are also shown (Figs. 2 and 3). In each case the microscopic appearances are of the least affected parts of the specimens, as the grosser damage is revealed in the macroscopic pictures. The presence of red cells in the alveoli in some of the sections is the result of the method of preparation of the lung and is not pathological

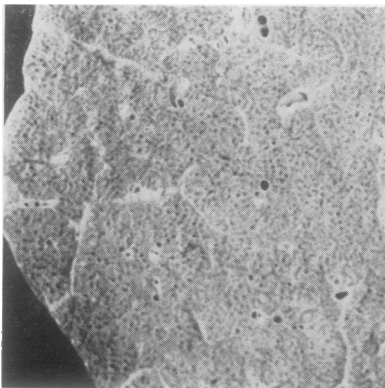


FIG. 2.—Normal lung.

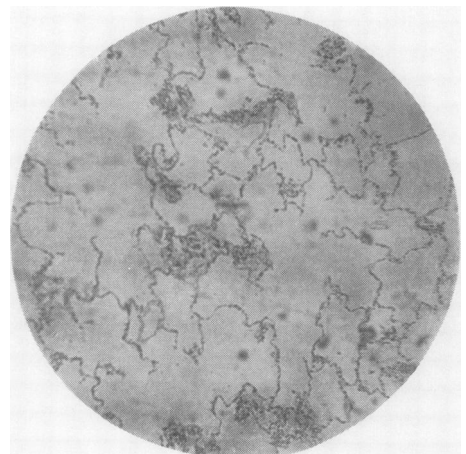


FIG. 3.—Normal lung.

DISCUSSION

The ventilation equivalent for oxygen can vary with the nervous state of the patient, which may cause overbreathing without changing oxygen uptake and so give a high reading. In our experience the "overbreathing" difficulty can be overcome if carefully handled by practised workers. We accept a value of up to 3.5 litres as "normal" (Mead, Lindgren, and Gaensler, 1955). The ventilation equivalent has not been studied much during exercise, when it becomes less than at rest in normals. Failure to fall, or an increase, after exercise is usually interpreted as a significant abnormality, and even after pneumonectomy the value falls on exercise (Cournand and Berry, 1942).

In Table III we have summarized the findings of various authors who have estimated ventilation equivalent on exercise.

TABLE III

Author	Patients	Ventilation Equivalent at Rest	Ventilation Equivalent on Exercise (l.)
Baldwin and others (1948)	Normal	—	Value falls
Bruce and others (1949)	Normals	—	" "
Kaltreider and McCann (1937)	"	—	" "
Cournand and Berry (1942)	Pneumonectomy	—	" "
Baldwin and others (1949)	Pneumoconiosis	—	" "
Kaltreider and McCann (1937)	Normals, fibrosis (tuberculous but not interstitial), emphysema, asthma Mitral valve disease	—	" "
*Knipping and Moncrieff (1932)	Heart failure	Raised approximately in proportion to degree of failure Not estimated	Value rises " "
McIlroy and Bates (1956)	Pneumonectomy	—	Over 3.5
Harris and Thomson (1958)	Normals of varying ages	Older had higher V.E. than younger	In older patients V.E. falls

* Oxygen-enriched air.

We had anticipated that the loss of total diffusing surface associated with alveolar destruction would produce a rising ventilation equivalent on exercise, and in our experience this happens in patients suspected of alveolo-capillary block. However, we found that the combination of arterial oxygen desaturation on exercise while breathing air, combined with a fall of ventilation equivalent on similar exercise (while breathing oxygen-enriched air), occurred more often in patients likely to have pathological emphysema. We suspect that this finding results from mechanical inability to increase ventilation in proportion to oxygen requirements. Oxygen uptake probably

increases relatively more in these patients because of increased cardiac output and decrease of mixed venous oxygen tension on exercise (Riley, Shepard, Cohn, Carroll, and Armstrong, 1954).

Bates, Knott, and Christie (1956) showed that patients with chronic bronchitis, deemed not to have emphysema, had gross ventilatory defect (M.V.V.) and low mixing efficiency, but their diffusing capacity for carbon monoxide (D_{co}) did not differ greatly from that in old normals. Bates (1958) suggested that the functional distinction is primarily one between a normal alveolar bed in chronic bronchitis and its destruction as emphysema progresses.

Work done in this laboratory had suggested that quite severe physiological defects might be due to chronic bronchitis without destructive emphysema, and Ogilvie (1959) emphasized this point. He quoted pathological and physiological evidence that the clinical state of severe emphysema can exist in the absence of detectable damage to the alveolar or diffusing surface of the lung.

Table II and the details of certain cases tend to confirm the suggestion that arterial oxygen desaturation on exercise combined with a fall in ventilation equivalent on exercise in a patient who has other evidence of emphysema may indicate the presence of widespread destructive change in the lung parenchyma. They suggest also that, in many patients thought to be emphysematous, gross physiological defects may be present in the absence of generalized or localized anatomical emphysema of any severity, and that a rise of ventilation equivalent on exercise makes marked generalized emphysema unlikely to be present, even when other factors have pointed strongly to its presence.

Much more extensive comparison of physiological and pathological findings than we can offer here would, however, be necessary before any proof or disproof of the truth of this could be obtained.

Centrilobular destruction of alveoli in our cases was associated with gross physiological defects, despite the presence of relatively large amounts of apparently normal lung parenchyma in the periphery of the lobules.

It seems to us that it would be of great clinical importance to be able to determine the presence or absence of true alveolar destruction during life. Four apparently emphysematous patients who had gross physiological defects and clinical disability died while still in possession of almost intact lung parenchyma, and this might have been deduced from the anomalous physiological findings. The knowledge that normal parenchyma was available might have justified even more strenuous efforts

to assist more adequate ventilation and to prevent or postpone the fatal termination. Such methods might well include otherwise unjustifiably risky surgical procedures or prolonged steroid therapy (combined with antibiotics) even in the presence of infection.

SUMMARY

Some of the results obtained in this hospital by routine physiological examination of chest patients, with and without chronic bronchitis, have been mentioned.

The literature on the ventilation equivalent for oxygen is briefly reviewed and the application of this test in our laboratory described.

Six features generally considered to be characteristically present in emphysema have been chosen, and we have discussed the occurrence in association with these features of changes in ventilation equivalent resulting from exercise.

The ventilation equivalent actually falls on exercise in patients who may have true emphysema, and this is presumably due to inability to increase ventilation because of mechanical difficulties.

Eighteen cases are quoted, and four fully described, where clinical and physiological findings suggestive of emphysema were made and where pathological or operative findings are available. Comparison of these with the results of routine physiological testing suggests that study of the effects of exercise on arterial oxygen saturation and on ventilation equivalent for oxygen may show whether anatomical emphysema is present or not.

We wish to express our indebtedness to Mr. Trevor James, our laboratory technician, who prepared the specimens of lung by Dr. Heard's technique and photographed the impregnated slices and histological sections; to Miss F. M. Putland for preparation of figures and tables; and to Mrs. D. Gibbs for patience over typing and re-typing.

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Appendix

ILLUSTRATIVE CASE SUMMARIES

CASE 1.—O. W., aged 50. Mild chronic bronchitis with minimal spasm. Twenty-one years of increasing dyspnoea on exertion attributed to an episode of exposure to coke fumes. Severely disabled: Grade 4 (Gilson and Hugh-Jones, 1955).

In June, 1959, blood pressure was 135/80 mm. Hg, Hb 17.4 g.%. An E.C.G. showed p. pulmonale, right ventricular hypertrophy and strain. Radiological emphysema present, more marked at right base (Fig. 4).

Physiology	1956		June, 1959	
F.E.V./I.C. (%) ..	46		38	
F.R.C./T.L.C. (%) ..	62		80	
Mixing efficiency (%) ..	—		33	
	Rest	Exercise	Rest	Exercise
Art. O ₂ saturation (%) ..	88	85	88	79
V.E. (l.) ..	5.0	2.8	3.2	1.9

Bronchspirometry was performed under "pethilorphan" and "largactil," using our special bronchospirator (McNab, 1954), with the following results:

	Right	Right, Mid and Lower	Left	Left Lower
I.R.V. (l.) ..	0.5*	0.2	0.85	?
Tidal air (l.) ..	0.2	0.03	0.35	0.2
O ₂ uptake (l./min.) ..	0.2	?	0.18	0.12

* These figures are only approximate.

Right lower lobe (removed July, 1959) showed diffuse emphysema with little or no normal parenchyma (Fig. 5). Histology confirmed this (Fig. 6).

At operation the right upper lobe was seen to be affected by a similar process to the lower lobe, though less severely. In view of the radiograph and bronchospirometry it was felt that the left lung was also involved.

The history, radiological, and all physiological findings favoured destructive emphysema, which was found in the lobe removed. There was O₂ desaturation, and the ventilation equivalent fell on exercise.

CASE 2.—E. B., aged 50. "Known emphysema," history of five years' chronic bronchitis following acute illness. Severe continuous bronchospasm, and severely disabled by increasing dyspnoea on exertion (Grade 5, Gilson and Hugh-Jones, 1955).

In July, 1959, blood pressure, 100/70 mm. Hg. Hb 16.5 g.%, P.C.V. 54.5%. E.C.G., right atrial hypertrophy with right ventricular strain. Radiological emphysema present, much more marked at right base (Fig. 7).

The patient was not fit for bronchospirometry.

Physiology	14.7.59	4.8.59	28.8.59		28.10.59	
Paco ₂ (mm. Hg) ..	90	80	63		58	
F.E.V./I.C. (%) ..			60		85	
F.R.C./T.L.C. (%) ..			82		26.3	
Mixing efficiency (%) ..			16.5			
	Rest	Rest	Rest	Exercise	Rest	Exercise
Art. O ₂ Sat. (%) ..	90	85	96	84	90	88
V.E. (l.) ..			3.5	2.3	3.0	1.8

In November, 1959, bullae removed from the right lower lobe, which had presumably taken little if any part in ventilation, were tense and remained so for weeks after removal. Patient improved following operation until infection supervened.

In December, 1959, at necropsy both lungs showed centrilobular emphysema (Fig. 8). Right lung also had pneumonic and abscessed areas. Fig. 9 shows slight alveolar enlargement in the periphery of the lobule.

The history, radiographic, and all physiological findings are in keeping with destructive emphysema. O₂ desaturation and fall of the ventilation equivalent on exercise were found. The specimen shows marked centrilobular emphysema although there is still much normal parenchyma.

CASE 3.—J. M., aged 56. Attacks of bronchitis for two years, no spasm. Dyspnoea on exertion, not severe (Grade 2 of Gilson and Hugh-Jones, 1955) and only slowly increasing.

In February, 1959, blood pressure was 180/96 mm. Hg, Hb 15 g.%, P.C.V. 48%, E.C.G. normal.

Radiological emphysema present to the extent that diaphragms were low, and there was marked translucency in the upper part of the right lung with obvious bullous formation in apex. Vessels crowded

Physiology	February, 1959	
F.E.V./I.C. (%) ..	67	
F.R.C./T.L.C. (%) ..	66	
Mixing efficiency (%) ..	36	
	Rest	Exercise
Arterial O ₂ saturation (%) ..	95	97
V.E. (l.) ..	2.8	2.8

Bronchspirometry	Right	Left
T.L.C. (l.) ..	1.9	1.95
I.C. (l.) ..	0.7	0.6
Tidal air (l.) ..	0.2	0.2
F.R.C. (l.) ..	1.2	1.35
Min. vol. resp. (l.) ..	3.2	2.8
O ₂ uptake (l.) ..	0.22	0.22
V.E. (l.) ..	1.5	1.3
Mixing efficiency (%) ..	55	51

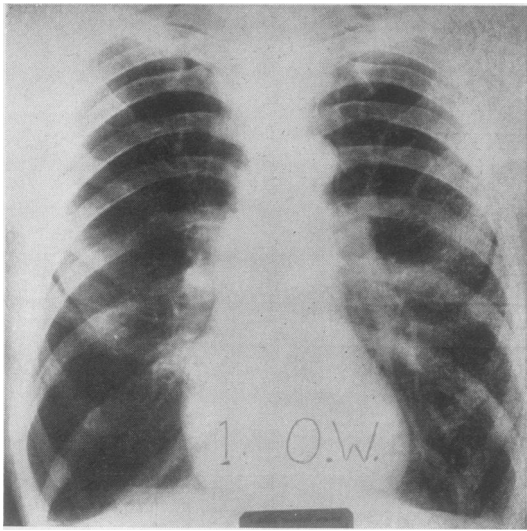


FIG. 4

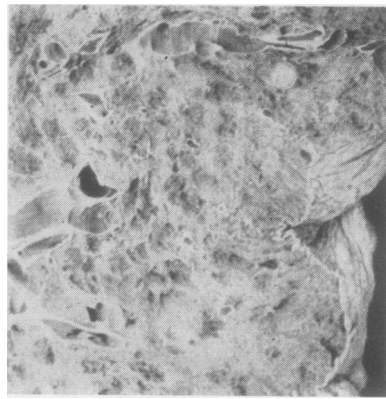


FIG. 5

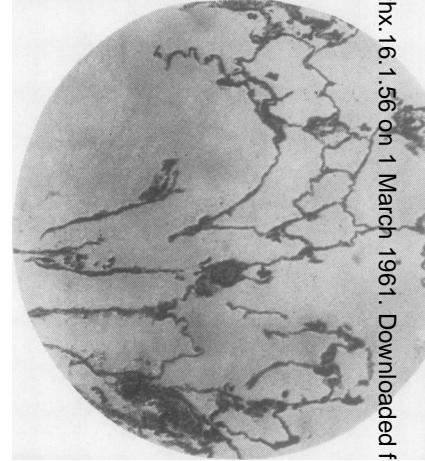


FIG. 6

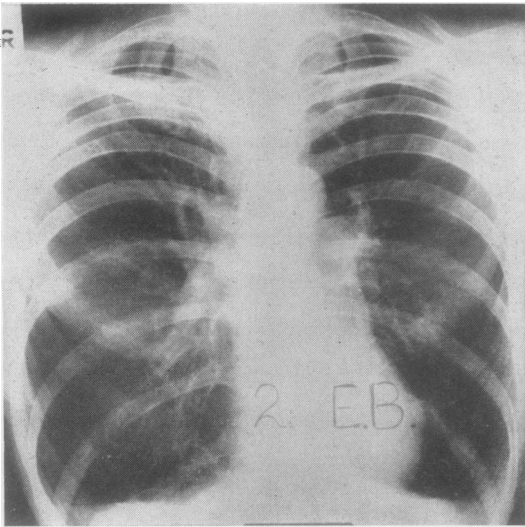


FIG. 7

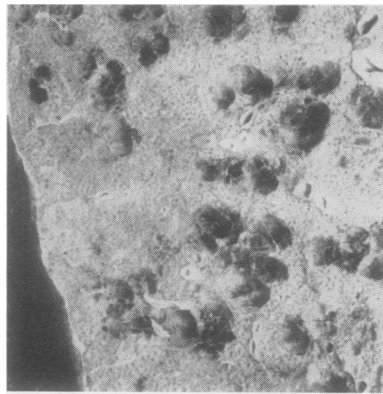


FIG. 8

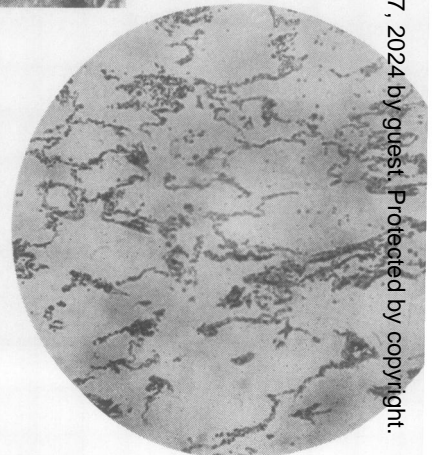


FIG. 9

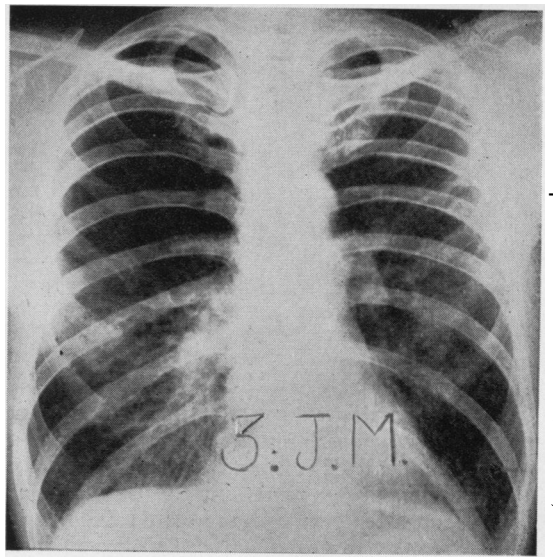


FIG. 10

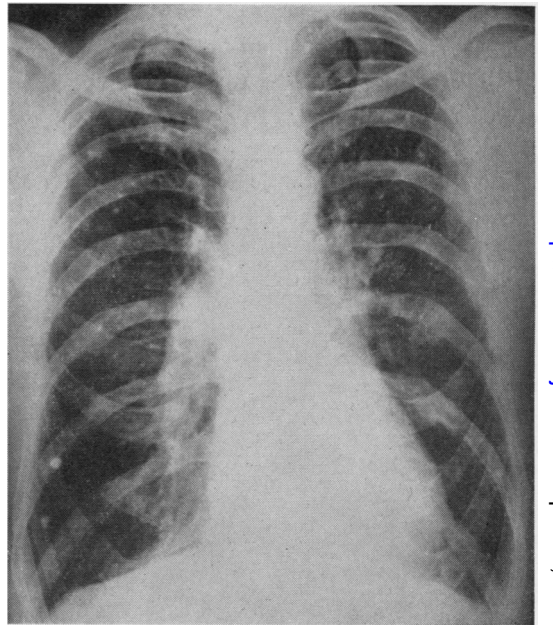


FIG. 13

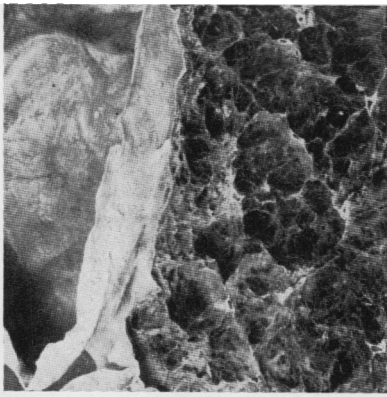


FIG. 11

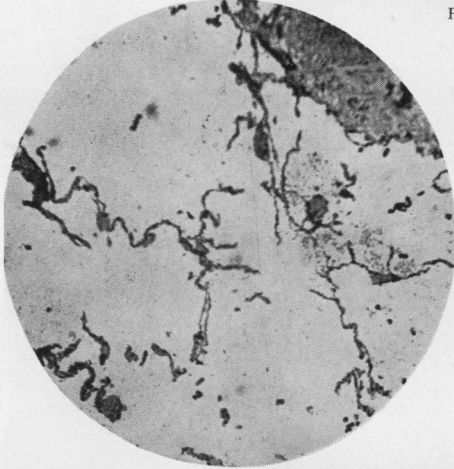


FIG. 12

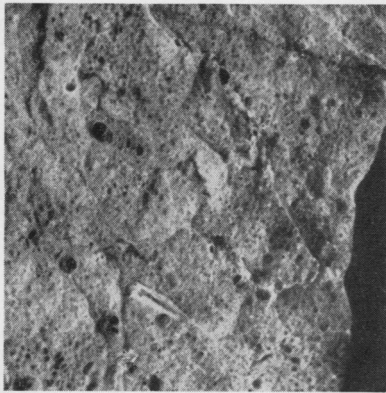


FIG. 14

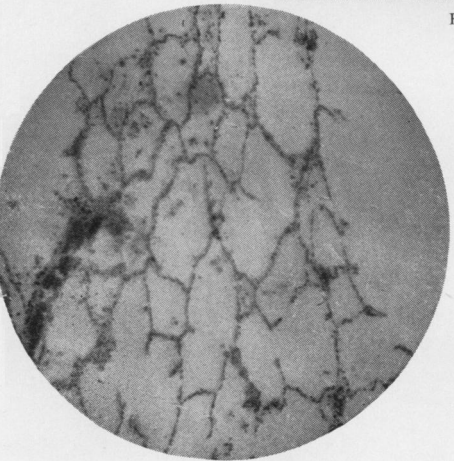


FIG. 15

at right base and no loss of peripheral markings on left (Fig. 10).

The resected specimen (Fig. 11) showed a large bulla in a grossly emphysematous right upper lobe, but at operation it was noted that the right middle lobe was much less affected and the right lower lobe scarcely affected. The left lung may well be normal.

Fig. 12 shows the gross alveolar destruction in the affected lobe.

The view expressed before operation was: "No gross general emphysema, no spasm, difficulties could all be accounted for by the presence of a bulla, even the failure to reduce the ventilation equivalent on exercise could be due to useless ventilation of the bulla." This is probably localized emphysema.

CASE 4.—P. S., aged 57. Old healed tuberculosis of lungs. Ten years' chronic bronchitis with much wheezing. Increasing exertional dyspnoea over same period. Clinical evidence of severe bronchospasm.

In May, 1959, after recovery from severe bronchial infection, blood pressure 120/75 mm. Hg, Hb 16.8 g.%, P.C.V. 55%, E.C.G. right ventricular hypertrophy and right bundle branch block. Radiograph showed

radiological emphysema and scattered calcification (Fig. 13).

Physiology	May, 1959	
	Rest	Exercise
F.E.V./I.C. (%)		42
F.R.C./T.L.C. (%)		71
Mixing efficiency (%)		15
Art. O ₂ saturation (%)	93	95
V.E. (l.)	3.7	2.8

Readmitted on March 17, 1960, in respiratory failure. Responded to oxygen and intramuscular nikethamide, but died suddenly the same evening. Necropsy showed old fibrous pleural adhesions. Scattered calcified nodules in lungs. Small bullae at apices. Lung parenchyma showed only mild centrilobular change with largely normal parenchyma (Figs. 14 and 15). Hypertrophy of right heart.

Clinical, radiographic findings, and ordinary physiological testing favoured true emphysema with severe spasm and right heart involvement, but there was no desaturation on exercise. The "necessary" combination was not present.