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Parenchymal, bronchiolar, and bronchial measurements in centrilobular emphysema

Relation to weight of right ventricle

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Measurements of lung parenchyma, membranous bronchioles, and bronchial mucous gland hyperplasia were made on lungs from eight cases of pure centrilobular emphysema (CLE) and on five normal lungs. The lungs were fixed in formalin and inflated under partial vacuum at a standard transpulmonary pressure of +30 cm. H_2O. The results obtained from the upper halves and the lower halves of the lungs were compared. The circulatory effects of the disease were measured by weighing the heart ventricles, by studying the small pulmonary arteries in microscopical sections, and by post-mortem arteriography. Whereas the parenchymal and internal surface areas destroyed by the emphysematous spaces were relatively moderate and localized, right ventricular hypertrophy was noted in most of the cases. In these cases bronchiolar stenoses were found scattered throughout the whole lung and there was a reduction in the number of these bronchioles, mainly in the upper halves of the lungs. In CLE ventilatory disturbances were caused not only by the centriacinar dilated spaces delaying gas diffusion, but also by scattered bronchiolar stenoses situated at the termination of the conducting air passages. The stenoses seemed the more important cause. It was shown statistically that chronic arterial pulmonary hypertension and right ventricular hypertrophy were mainly the result of functional disturbances, especially hypoxia and abnormalities of $\dot{V}A/\dot{Q}$ produced by the two structural changes situated at the end of the small airways.

In centrilobular emphysema, parenchymal destruction is situated at the level of the respiratory bronchioles, producing initially enlarged centriacinar air spaces but leaving more or less intact alveoli distal to these spaces (Reid, 1967). The centriacinar holes may join to form larger centrilobular spaces (Leopold and Gough, 1957). This type of emphysema is usually associated with chronic bronchitis and is thought to result from respiratory bronchiolitis. During its course, and often at an early stage, it usually results in severe respiratory failure with right ventricular hypertrophy (Leopold and Gough, 1957; Dunnill, 1965; Hicken, Heath, and Brewer, 1966b; Wyatt and Ishikawa, 1968; Bignon, Khoury, Even, Andre, and Brouet, 1969).

The ventilatory disturbances produced by centrilobular emphysema have been shown by the use of a model to be almost exclusively caused by an increased diffusion time of gas molecules through distended centriacinar or centrilobular spaces before they reach the respiratory exchange area of the lung (Staub, 1965; Gomez, 1965; Cumming, Horsfield, Jones, and Muir, 1968). However, such a model hardly accounts for the severity of most of the changes observed in cases of centrilobular emphysema. Usually only the upper zones of the lung and less than 40% of the parenchymal volume show centriacinar spaces (Snider, Brody, and Doctor, 1962; Thurlbeck, 1963), and it is uncertain whether, in addition to the centriacinar spaces, some other obstacle to alveolar ventilation may be present throughout the lung. Such an obstacle might be caused by bronchiolar narrowings which were described by McLean (1958). Previously we have shown, using a quantitative method, that widespread bronchiolar stenoses were present in chronic obstructive bronchopulmonary disease with or without emphysema (Bignon, Khoury, Even, Andre, and Brouet, 1968, 1969). Recently it has been emphasized that in chronic obstructive pulmonary disease the obstruction to airflow is situated in small bronchi of less than 2 mm. diameter (Hogg, Macklem, and Thurlbeck, 1968).

The present study, employing morphometric methods, was designed to investigate the quantitative relationship between the alveolar (lung parenchymal) and bronchiolar damage in centrilobular emphysema, and the severity of the resulting chronic pulmonary hypertension and right ventricular hypertrophy. The importance of permanent structural changes in the pulmonary arteries as a cause of the pulmonary hypertension was also investigated.

MATERIAL AND METHODS

Eight cases of pure centrilobular emphysema (CLE) were studied. Post-mortem examinations were carried out according to a method described previously (Bignon *et al.*, 1968). The lungs were fixed by endobronchial formalin infusion and expanded by a partial vacuum of -30 cm. H_2O for 72 hours. The lung volume was measured after fixation by weighing the volume of water it displaced. The lungs were then sliced into five or six sagittal macrosections with a thickness of 1 cm., and the appearances of CLE were similar to those described by Leopold and Gough (Fig. 1). The proportion of the total lung parenchyma made up by the centrilobular spaces was evaluated by submerging the slices of lung in water and using a stereomicroscope combined with the point-counting method (Dunnill, 1962). The proportion of the lung tissue volume due to CLE was calculated for the upper half, the lower half, and the whole lung separately.

Twenty standardized blocks of lung tissue (10 from the upper half and 10 from the lower half of one lung), and taken from each lung, were sampled by a stratified randomized technique. These blocks, measuring about 20×30 mm., were then processed in the usual way and embedded in paraffin under vacuum. Sections, 5 μ thick, were stained with haematoxylin and eosin and by Weigert/van Gieson for elastic fibres. The mean linear shrinkage (p) for processing was determined in each case by measuring the length (L) and breadth (l) of fixed blocks (1) and processed slides (2) on the 20 randomized samples calculated from the formula (Weibel, 1963)

$$p = \sqrt{\frac{L_1 \times l_1}{L_2 \times l_2}} \qquad (1)$$

Alveolar internal surface area (ISA) was determined by the mean linear intercept method of Campbell and Tomkeieff (1952) using Weibel's multipurpose test system (Weibel, Kistler, and Scherle, 1966) inserted into the head of a Leitz microscope (magnification $\times 50$). The number of intercepts in each field were card-punched and the variance was calculated for the upper half, the lower half, and the whole lung as follows:

$$\mathrm{Var}\ (\bar{\bar{Y}}) = \frac{\frac{1}{n}\Sigma \bar{y}i^2 - \bar{\bar{y}}^2}{(n-1)} \qquad (2)$$

where Var $(\bar{\bar{Y}})$ = variance of the mean obtained by two-stage sampling (sections and fields), n = number of sections, $\bar{y}i$ = mean for sections and $\bar{\bar{y}}$ = mean for all microscopical fields. Then, σ and relative error in per cent $\left(100 \times \frac{\sigma}{\bar{\bar{y}}}\right)$ were calculated.

The processed mean linear intercept (Lm′) was determined according to

$$\frac{LT}{Ni} \qquad (3)$$

where LT = total length of the test system lines for all fields studied, and Ni = total number of times that the lines intersect alveolar walls. The result was expressed in microns. The fixed mean linear intercept (Lm) was obtained by:

$$Lm = Lm' \times p \qquad (4)$$

Lm was corrected to the radiographic lung volume (VL_{Rx}) or to the predicted lung volume (VL pred) according to the formula (Thurlbeck, 1967b)

$$Lmc = Lm \times \left(\frac{VI_{R_x} \text{ or pred}}{VF}\right) 1/3 \qquad (5)$$

The internal surface area at a transpulmonary pressure of 30 cm. of formalin was obtained in square metres using the formula:

$$ISA = \frac{4 \times V_F \times \lambda}{Lm} \qquad (6)$$

where V_F = fixed lung volume and λ = fraction of lung volume occupied by parenchyma. The ISA has been expressed at a standard lung volume of 5 litres (ISA_5), according to Thurlbeck (1967a, b), and at the predicted lung volume (ISAc pred.), or at the measured total radiographic lung volume ($ISAc_{Rx}$) as previously described by Bignon *et al.* (1969).

Morphometry of membranous bronchioles (non-respiratory and non-cartilaginous) was carried out using the method described by Bignon *et al.* (1969). Instead of micrometric measurement of bronchiolar internal diameters (ID), the bronchioles were counted in nine groups. The internal diameters of the bronchioles were chosen according to data obtained by Horsfield and Cumming in a normal bronchiolar tree (Horsfield and Cumming, 1968) and ranged from group 0, less than 100 μ; group 1, 101 μ to 200 μ; group 2, 201 to 350 μ; group 3, 351 to 500 μ; group 4, 501 to 700 μ; group 5, 701 to 900 μ; group 6, 901 to 1,200 μ; group 7, 1,201 to 1,700 μ; to group 8, over 1,700 μ. The scale used was inserted into a $\times$ 12·5 projector head and was made up of eight concentric circles, the distance between the circles representing the ranges of diameters described above. Using a $\times 4$ objective, the linear fixed dimensions were measured directly, the diameter of each circle being corrected by an arbitrary shrinkage coefficient (f = 0·77). An internal diameter of 350 μ was chosen as the lower limit for internal diameters of normal membranous

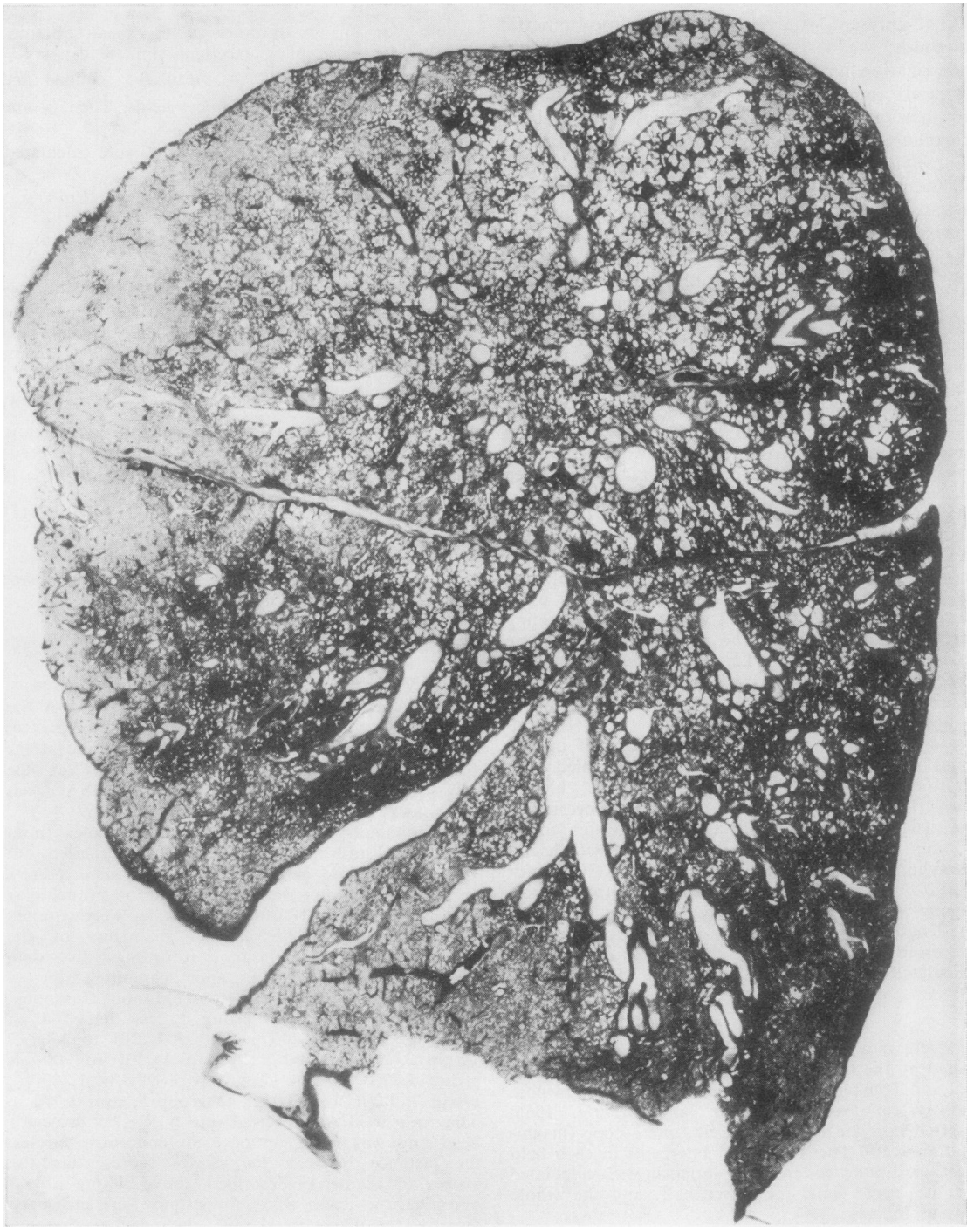

FIG. 1. *Whole-lung paper-mounted section in a pure CLE case, involving* 38% *of parenchyma* (*upper half* 44%, *lower half* 11%).

TABLE I

PARENCHYMAL, BRONCHIOLAR, AND BRONCHIAL QUANTITATIVE DATA AND RIGHT VENTRICULAR WEIGHTS (8 PATIENTS WITH CLE AND 5 NORMAL ADULTS)

Case	Sex	Age (yrs)	Body Height (cm.)	VL_F (ml.)	VL_{Rx} or VL pred. (ml.)	CLE (%)			Lmc			ISAc ($m.^2$)	ISA_5 ($m.^2$)	Relative error (%)	Br $<350\ \mu$ (%)			Nb/cm2 C			Reid Index	Percentage of Bronchial Mucous Glands	RVW (g.)	Fulton Ratio	Complications and Associated Diseases
						UH	LH	W	UH	LH	W				UH	LH	W	UH	LH	W					
1	M	53	172	4,300	6,880 (Rx)	12	8	10	400	400	400	62	50	±3	13	16	15	0·44	0·46	0·45	0·28	8·4	70	2·70	PTE, pneumonectomy for bronchial cancer
2	M	59	166	3,250	7,000 (Rx)	50	28	35	588	449	509	50	40	±7	37	50	46	0·22	0·34	0·28	0·49	13·4	165	1·00	Chronic PTE
3	M	39	170	6,245	6,500 (Rx)	27	8	18	470	376	423	55	46	±4	38	45	42	0·39	0·53	0·47	0·54	18·2	135	1·23	Pneumonia
4	M	71	167	8,000	6,500 (pre)	49	11	30	537	427	477	49	41	±6	38	30	33	0·43	0·57	0·50	0·46	22·3	75	1·81	Pneumonia
5	F	63	161	5,510	5,200 (pre)	39	6	23	528	415	468	40	39	±4	38	47	42	0·43	0·66	0·53	0·58	23·1	110	1·22	—
6	M	55	180	7,300	7,960 (pre)	56	44	50	765	618	688	42	31	±7	59	73	66	0·34	0·46	0·41	0·45	15·2	220	0·84	Chronic PTE
7	M	62	165	5,400	6,600 (pre)	44	11	38	740	445	560	43	35	±6	25	44	36	0·38	0·66	0·52	0·60	18·2	104	2·38 (BVH)	—
8	M	67	180	7,400	9,000 (pre)	30	6	18	523	454	486	67	45	±5	43	46	45	0·53	0·59	0·55	0·55	21·9	90	1·43	PTE, bronchial cancer
COL	M	63	175	7,920	7,900 (pre)	0	0	0	352	340	346	82	60	±4	22	9·5	14	0·73	0·83	0·79	0·33	10·9	75	2·60	Obesity
VAD	M	56	158	5,035	5,920 (pre)	0	0	0	332	299	314	67	60	±4	18·5	18·5	18·5	0·86	1·04	0·95	0·39	14·7	43	3·14	—
LOU	F	47	160	3,300	5,200 (pre)	0	0	0	261	247	254	73	71	±3	14	7·5	10	0·71	0·54	0·63	0·21	8·8	57	2·54	—
MOU	F	42	146	3,600	4,230 (pre)	0	0	0	360	308	332	50	55	±4	15	0	8	0·73	0·47	0·61	0·22	4·0	37	2·48	
BRO	F	66	157	3,660	4,800 (pre)	0	0	0	325	327	326	53	54	±2	10	22	16	0·68	0·67	0·68	0·27	6·0	60	—	—

Key: VL_F, fixed lung volume; VL_{Rx}, radiographic lung volume; VL pred., predicted total lung volume; CLE %, volume proportion of centrilobular spaces; UH, upper half; LH, lower half; W, whole lung; Lmc, mean linear intercept corrected to the radiographic or predicted lung volume; ISAc, internal surface area for the fixed lung, corrected to measured radiographic lung or to predicted total lung volume; ISA_5, ISA corrected to an arbitrary lung volume of 5 litres; Br $<350\ \mu$ %, bronchioles with internal diameter less than $350\ \mu$ %; Nb/cm2 C, number of bronchioles per square centimetre of fixed lung corrected to the radiographic or predicted lung volume; RVW, right ventricular weight, Fulton ratio: (LV+S)/RVW; PTE, pulmonary thrombo-embolism; BVH, biventricular hypertrophy.

bronchioles. In five normal adult subjects the percentage of bronchioles less than 350 μ diameter was from 8 to 18·5% (mean 13·3%).

The bronchiolar density per square centimetre of fixed lung was calculated by counting all bronchiolar transections, either circular, oblique or longitudinal. Counting was carried out on the whole area of the microscopical sections. Bronchiolar transections intercepted by the right and upper border lines were dismissed. The number of bronchioles was calculated per square centimetre of fixed lung (Thurlbeck, 1969), the surface of each block having been determined by accurate measurement of length and breadth under water. The number of bronchioles per square centimetre of fixed lung (Nb/cm2 F) was corrected to the radiographic or predicted lung volumes, using the formula:

$$\text{Nb/cm2 c} = \text{Nb/cm2 F} \times \left(\frac{\text{VF}}{\text{VL}_{\text{Rx}} \text{ or Pred.}}\right) 2/3 \quad (7)$$

These measurements (ID and Nb/cm2) were carried out separately for the upper half and the lower half of each lung.

The bronchi were studied grossly and microscopically. Mucous gland hyperplasia was estimated by two methods: (1) measurement of the Reid index (Reid, 1960, 1967) (ratio of bronchial gland thickness to wall thickness) and (2) measurement of the volume of the mucous glands situated inside the bronchial wall to the total volume of the bronchial wall using the point-counting procedure (Hale, Olsen, and Mickey, 1968; Dunnill, Massarella, and Anderson, 1969), using Weibel's test-system with 42 points (Weibel *et al.*, 1966). The result was expressed as a percentage. This measurement was carried out at a magnification of $\times 50$ using an automatic stage on a section of the whole bronchial wall extending from the peribronchial connective tissue to the lumen. Both measurements were carried out on five bronchial transverse sections 5 μ thick (1 principal bronchus, 2 upper and lower lobar bronchi, and 2 segmental bronchi). The results were the mean data obtained on five bronchi.

Elastic and muscular pulmonary arteries as well as pulmonary arterioles were studied qualitatively both in microscopical sections and by postmortem arteriography. Arteriograms were carried out by a method described previously by Schlesinger (1957).

The left and right ventricles were carefully dissected free from fat and weighed separately according to the method described by Fulton, Hutchinson, and Jones (1952). A right ventricular weight less than 65 g. and a Fulton's ratio higher than 2·2 were regarded as normal. The extent of the right ventricular hypertrophy (RVH) was regarded as an indication of the severity of the chronic pulmonary arterial hypertension (PAH) (Hicken, Heath, Brewer, and Whitaker, 1965).

Statistical analysis was carried out by the paired 't' test and by the relationship coefficient.

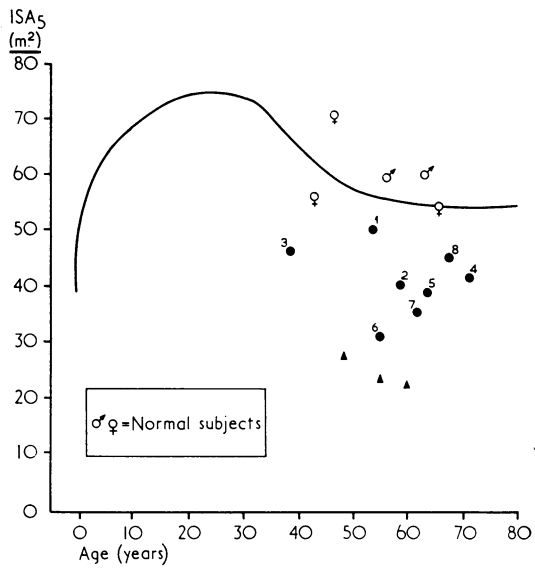

FIG. 2. *Internal surface area corrected to a standard volume of 5 litres (ISA_5) has been plotted on a diagram from 8 patients with CLE, 5 normal subjects, and 3 patients with PLE grade III involving more than 60 per cent of parenchyma, with no or moderate right ventricular hypertrophy. The smooth curve represents mean normal values from cases reported elsewhere (Weibel, 1963; Dunnill, 1962; Duguid et al., 1964; Hicken et al., 1966a; Thurlbeck, 1967b).* ● *CLE;* ▲ *PLE>60%*

RESULTS

Table I shows the quantitative anatomical findings for lung parenchyma, membranous bronchioles, bronchi, and right ventricular weights.

LUNG PARENCHYMA Macroscopic and microscopic studies showed that emphysematous destruction occurred predominantly in the upper half of the lung. Thus, the volumetric proportion of CLE evaluated in macrosections was, in every case, significantly ($P<0.001$) greater in the upper half (mean=38·7%) than in the lower half (mean=16%) of the lung. Likewise, the mean linear intercept (Lm and Lmc) was significantly ($P<0.001$) larger in the upper half (mean=569 μ) than in the lower half (mean=448 μ). Such parenchymal destruction was, however, relatively limited. Thus in seven out of the eight cases the internal surface area, expressed at a 5 litres standard lung volume (ISA_5), was moderately decreased compared with the theoretical values in cases without emphysema. It was not, however, reduced as much as in cases of severe panlobular emphysema (Fig. 2). Further-

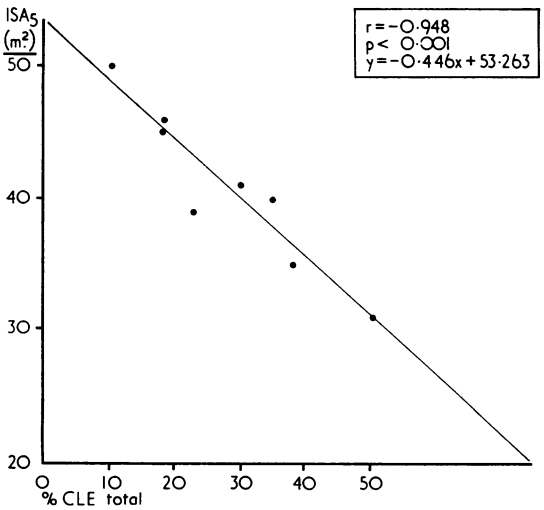

FIG. 3. *Diagram showing a high degree of correlation between macroscopic volumetric proportion of CLE and ISA_5 measured microscopically on randomized sections.*

TABLE II

COMPUTED CORRELATION COEFFICIENTS FOR SOME VARIABLES

Relationship	8 CLE Cases		13 (CLE+Control) Cases	
	r	P	r	P
% CLE and Lmc (UH)	0·796	<0·02	0·917	<0·001
% CLE and Lmc (LH)	0·870	<0·01	0·877	<0·001
% CLE and Lmc (W)	0·930	<0·001	0·961	<0·001
% CLE and ISA_5	−0·948	<0·001		
% CLE and Nb F (UH)	−0·800	<0·02		
% CLE and Nb F (LH)	−0·576	>0·05		
% CLE and Nb F (W)	−0·569	>0·05		
% CLE and Nb C (UH)	−0·540	>0·05		
% CLE and Nb C (LH)	−0·610	>0·05		
% CLE and Nb C (W)	−0·358	>0·05		
Lm and Nb F (UH)	−0·556	>0·05	−0·830	<0·001
Lm and Nb F (LH)	−0·411	>0·05	−0·488	>0·05
Lm and Nb F (W)	−0·456	>0·05	−0·744	<0·01
Lmc and Nb C (UH)	−0·410	>0·05	−0·793	<0·01
Lmc and Nb C (LH)	−0·244	>0·05	−0·398	>0·05
Lmc and Nb C (W)	−0·212	>0·05	−0·653	<0·02
% bronchial mucous glands and Reid index			0·891	<0·001
% CLE and RVW	0·758	<0·05		
% CLE and Fulton ratio*	−0·690	>0·05		
ISA_5 and RVW	−0·654	>0·05		
ISA_5 and Fulton ratio*	−0·740	>0·05		
% br <350 μ and RVW	0·857	P<0·01		
% br <350 μ and Fulton ratio*	−0·925	P<0·01		
% CLE+% br <350 μ and VD	0·859	P<0·01		
% CLE+% br <350 μ and Fulton ratio*	−0·859	P<0·02		
% CLE and % br <350 μ (UH)	0·665	P>0·05		
% CLE and % br <350 μ (LH)	0·717	P<0·05		
% CLE and % br <350 μ (W)	0·714	P<0·05		
% CLE and RVW (% br <350 μ being constant)	0·408	P>0·05		
% br <350 μ and RVW (% CLE being constant)	0·692	P>0·05		

* Case 7 was excluded because of a left ventricular hypertrophy
Key: see Table I

more, it appeared that the mean linear intercept method carried out on a limited number of randomized microscopic samples gave as good an indication of parenchymal destruction as the macroscopic quantitative study. This was shown by the good correlation which existed between the macroscopic volumetric proportion of emphysema on one side and, on the other side, ISA_5 (Fig. 3), the mean linear intercept for an upper half, lower half, and total lung (Table II).

MEMBRANOUS BRONCHIOLES In seven cases, as shown by bronchiolar histograms, the percentage of membranous bronchioles with internal diameters less than 350 μ was increased (range 33 to 66% for the whole lung). In case 1, in whom the results were nearly normal, CLE and chronic bronchitis were mild and there was little airways obstruction (FEV_1=2,345 ml., i.e., 75% of theoretical values, and FEV_1/VC=58%), only slight right ventricular hypertrophy, and no respiratory failure.

In these seven cases, the stenoses in the membranous bronchioles were scattered throughout the lung with slightly more in the lower halves than in the upper halves (P<0·05) (mean percentage of membranous bronchioles with internal diameters less than 350 μ were 39·7% for the upper halves and 47·8% for the lower halves) (Fig. 4). The

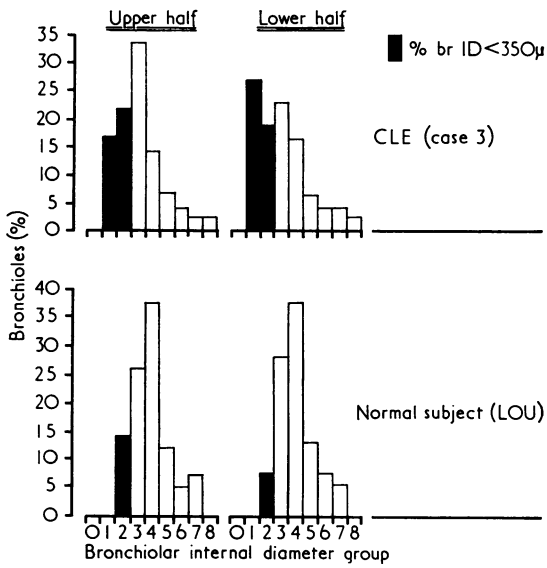

FIG. 4. *Bronchiolar histogram in a patient with CLE compared with a normal subject (ranges of internal diameter groups are given in the text).*

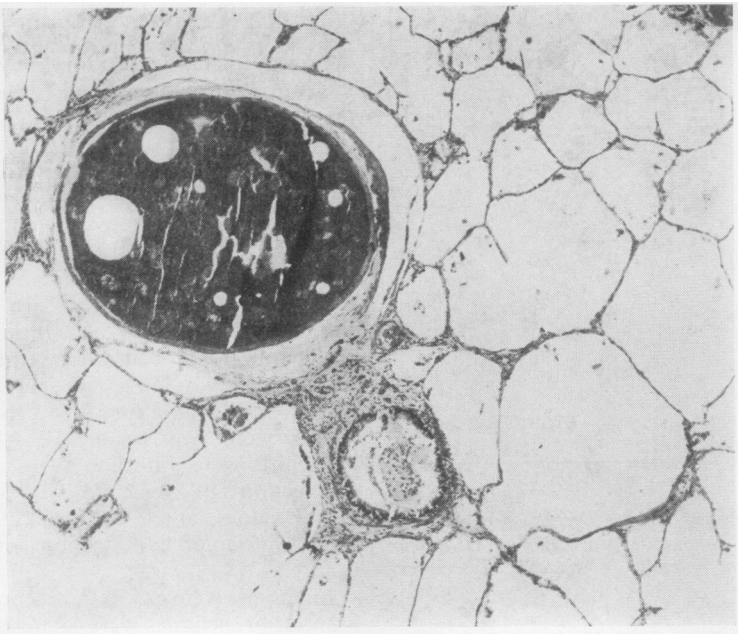

FIG. 5 (a)

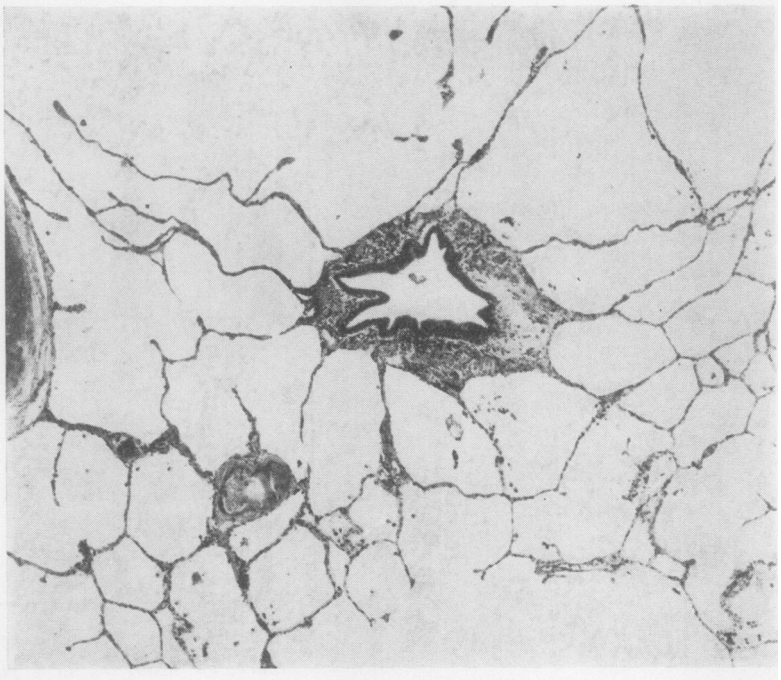

FIG. 5 (b)

Legend to Fig. 5 on facing page

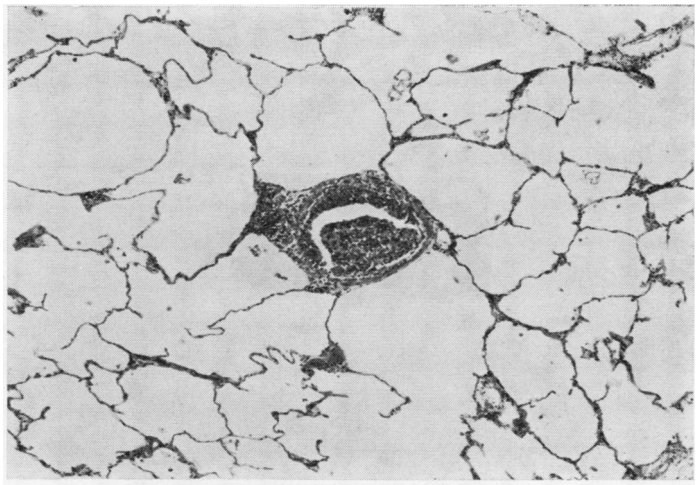

FIG. 5 (c)

FIG. 5. *Different histological patterns of narrowed membranous bronchioles in CLE: (a) bronchiolar stenosis with inflammatory changes in the wall; (b) narrowed bronchiole with an infolded mucosa; (c) mucopurulent plugs in bronchiolar lumen (H. and E.* ×45).

narrowings were due to bronchiolar wall lesions, often severe, and were accompanied by inflammatory cellular infiltration and fibrosis. Mucus or muco-purulent plugs obstructing the bronchiolar lumens were observed in some cases, and in case 6 bronchiolar contraction had caused infolding of the wall (Fig. 5). The bronchiolar density per square centimetre was much less in the upper halves (mean: Nb/cm2 C=0·39) than in the lower halves (mean: Nb/cm2 C=0·53) ($P<0·02$) of the lung. This difference was not observed in four normal lungs. In the present series of CLE cases, the bronchiolar density appeared to be reduced as the extent of the parenchymal destruction increased, as shown by the correlation existing in Table II. This was probably a consequence of destruction of some of the bronchioles situated in the zones of CLE.

BRONCHI The mucous gland hyperplasia was demonstrated by two different quantitative methods which gave similar results (Table II). Whereas clinical chronic bronchitis was found in all cases, mucous gland hyperplasia was found only in seven. No other important changes or localized bronchiectasis were detectable.

PULMONARY ARTERIES In cases 1, 3, 4, 5, and 7 no qualitative alteration of the muscular pulmonary arteries (with external diameters ranging from 1 to 0·1 mm.) or pulmonary arterioles (with external diameter less than 0·1 mm.) was detected. In cases 2 and 6, however, intimal fibrous thickening reduced the lumen of the pulmonary arteries. Many thrombi were noticed in branches of the pulmonary arteries, some of them having undergone organization. The heaviest right ventricles were found in these two cases. The appearance of the pulmonary arterioles in case 6 is shown in Fig. 6 and is compared with those observed in case 3 in which there was much less right ventricular hypertrophy. Cardiac catheterization showed that in case 3 the mean pulmonary artery pressure was 42 mm. Hg, and the calculated pulmonary arterial resistance was 450 dynes/sec./cm.$^{-5}$, whereas in case 6 the mean pulmonary artery pressure was 60 mm. Hg, and the calculated pulmonary arterial resistance was 1,140 dynes/sec./cm.$^{-5}$. Bronchopulmonary arterial anastomoses were not found in any of the cases.

RELATION BETWEEN STRUCTURAL AND QUANTITATIVE LUNG DATA AND WEIGHT OF RIGHT VENTRICLE A significant correlation was found between the macroscopic volumetric proportion of CLE and the right ventricular weight. Likewise, ISA_5 correlated with right ventricular weight. The right ventricular weight, or Fulton's ratio, correlated closely with the percentage of bronchioles of less than 350 μ in diameter. The addition of both percentages (i.e., percentage of emphysema and percentage of bronchioles of less than 350 μ diameter)

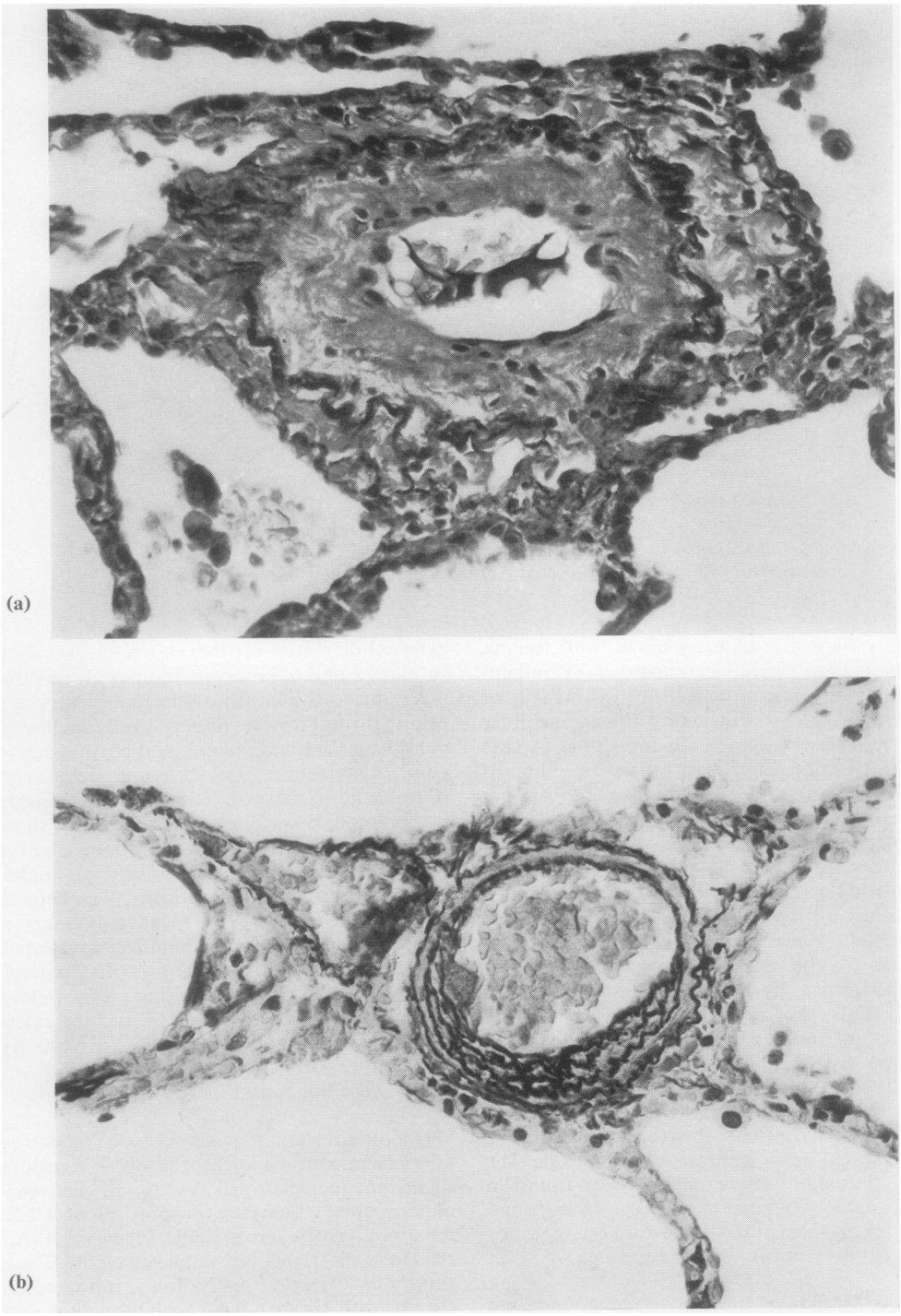

FIG. 6. *Small pulmonary arteries (filled with barium gelatine injection mass) with external diameters of about* 100 μ. (*a*) *Case* 6 (*RVW* = 220 *g.*). *Pulmonary arteriole with a single elastic lamina. Fibrous intimal thickening was noted in most arteries of this size, as shown here* (× 420). (*b*) *Case* 3 (*RVW* = 135 *g.*). *Small pulmonary artery showing a distinct coat of circular muscle and an elastic tissue hyperplasia* (× 420).

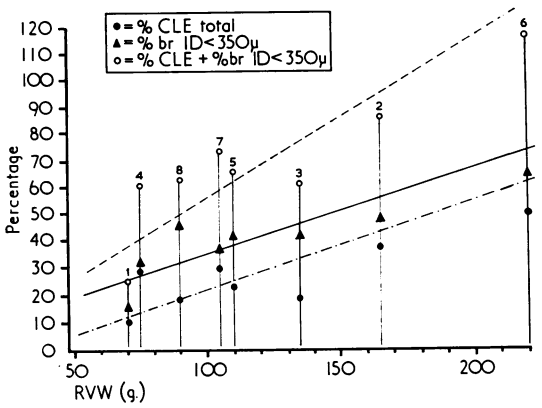

FIG. 7. *Correlations between right ventricular weights (x-axis) and percentages (y-axis) of centrilobular emphysema or of bronchioles with internal diameter less than 350 μ. Correlation with addition of both percentages with right ventricular weight is shown by the dotted upper line.*

correlated well with the right ventricular weight or Fulton's ratio (Fig. 7). As both these percentages showed a correlation, partial correlations were calculated with the right ventricular weight. The coefficient r was higher (0·692) between RVW and percentage of bronchioles of <350 μ (the percentage of CLE being constant) than between RVW and percentage of CLE (0·408) when the percentage of bronchioles of <350 μ was constant.

DISCUSSION

MECHANISM OF VENTILATORY DISTURBANCES IN CENTRILOBULAR EMPHYSEMA Ventilatory disturbances in CLE cannot be accounted for only by decrease of internal surface area. Indeed, in the majority of the cases studied the intact parenchyma accounted for 50 to 77% of the volume of the lungs and the internal alveolar surface area was only slightly reduced. These results, as previously stressed by Dunnill (1965), are the reverse of the findings in severe PLE cases in which there is frequently minimal respiratory failure and right ventricular hypertrophy, although emphysema may destroy as much as 80% of the lung parenchyma, thus seriously reducing the internal ventilatory surface area. Staub (1965) and Gomez (1965) emphasized that the ventilatory disturbances in CLE were mostly due to the enlarged centriacinar spaces, which were situated in a strategic position between the conductive zone and the respiratory exchange area, and slowed down gas diffusion. As a result, Dunnill (1965) pointed out that the number and the distribution of these abnormal air spaces were a more reliable guide than their size and the total lung volume involved. However, the predominant location of the centrilobular foci in the upper half of the lung, demonstrated here as well as by Snider *et al.* (1962) and Thurlbeck (1963), suggests that this theory cannot account for all the facts. Indeed, more than half of the lung parenchyma and particularly the lower halves of the lungs, which are the best perfused and ventilated (West, 1965), generally show much less centrilobular emphysema. This suggests that other mechanisms are responsible, especially increase of terminal airways resistance. Leopold and Gough (1957) noticed inflammatory narrowings in 12% of the respiratory bronchioles supplying CLE spaces, and narrowing of membranous bronchioles was not reported by them. The present morphometric study of the membranous bronchioles showed that bronchiolar narrowings were scattered randomly inside the lung, including zones without emphysema. Moreover, the degree of these bronchiolar narrowings seemed related to the severity of chronic respiratory failure. These inflammatory stenoses situated at the end of the conductive air passages could play an important part in ventilatory disturbances, as discussed in a previous paper (Bignon *et al.*, 1969), and were demonstrated in recent physiological studies by Hogg *et al.* (1968).

MECHANISMS OF CHRONIC PULMONARY ARTERIAL HYPERTENSION AND RIGHT VENTRICULAR HYPERTROPHY IN CLE Right ventricular hypertrophy was noted in 55% of the 75 cases studied by Leopold and Gough, and the majority of authors have noticed the frequency of RVH in CLE (Dunnill, 1965; Hicken *et al.*, 1966b; Bignon *et al.*, 1968; Wyatt and Ishikawa, 1968) even in cases with moderate emphysema and sometimes at an early stage. Nevertheless, the cause of the PAH or RVH is often uncertain or controversial.

Permanent structural changes in the pulmonary arterial system are a matter of debate, and even if pulmonary arterial destruction occurs, it is of minor importance as a cause of chronic cor pulmonale in CLE, because in some cases RVH develops with only moderate parenchymal destruction (Hicken *et al.*, 1966b). Compression of the pulmonary arterioles by the centrilobular air-distended spaces, which was suggested by Dunnill (1961) as a cause of pulmonary hypertension, was not found in this study. Heath (1968) showed that the small pulmonary arterial vessels often presented characteristic histological features in

emphysema when there was associated right ventricular hypertrophy. These changes included development of longitudinal muscle in the intima of pulmonary arterioles, the development of medial circular muscle in the pulmonary arterioles, and a lack of hypertrophy of the medial muscle in the large muscular pulmonary arteries. This triad of structural changes might account for the increased pulmonary vascular resistances in CLE. Such vascular changes, however, are not only characteristic of emphysema but are found in all conditions of chronic hypoxia (Naeye, 1962). The potentially reversible nature of these arterial changes is probably related to the reversibility of pulmonary arterial hypertension following relief of chronic hypoxia (Peñaloza, Sime, Banchero, and Gamboa, 1962; Vogel, Cameron, and Jamieson, 1966; Abraham, Cole, and Bishop, 1968).

In six cases of the present series there were no major structural changes in the muscular pulmonary arteries and pulmonary arterioles. The pulmonary arterial vessels, however, were not subjected to quantitative studies, as proposed by Arias-Stella and Saldaña (1962), Naeye (1962) or Hicken *et al.* (1965). Thus detection of mural changes in distal precapillary arterioles, similar to those observed in healthy subjects living at a high altitude, in kyphoscoliosis (Naeye, 1961) or in the Pickwickian syndrome may have been missed. Only in two cases were permanent and irreversible vascular changes found to explain the extent of RVH, and these consisted of intimal fibrous thickening causing narrowing of the arterioles and, to a lesser extent, of the muscular arteries. These changes most probably resulted from organized scattered thrombo-emboli. Thus pulmonary thrombo-emboli, which are frequently found in chronic bronchopulmonary disease (Dunnill, 1961; Ryan, 1963; Bignon *et al.*, 1969), may help to increase the pulmonary hypertension in some cases.

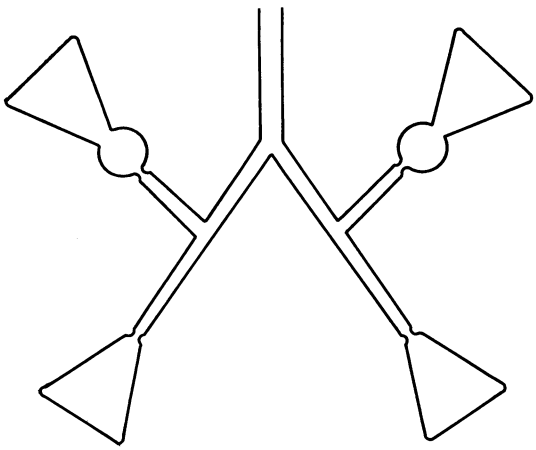

FIG. 8. *Structural model designed to show the site of ventilatory obstacles in CLE.*

In our cases, RVH and, in consequence, PAH appeared to be related to the quantitative structural damage to the lung parenchyma and bronchioles. Of these changes, bronchiolar stenoses played the more important part and its importance, even when minimal emphysema is present, has been stressed previously (Esterly and Heard, 1965; Bignon *et al.*, 1969). It is questionable, however, whether the high pressures generated beyond bronchiolar narrowings during coughing could disrupt respiratory bronchioles, as suggested by McLean (1958). This would not account for the localization of centriacinar holes in the lungs. Pulmonary hypertension appears to result from functional factors, especially hypoxia, caused by structural changes in the airways. Thus, a new structural model can be constructed to account for ventilatory obstacles in CLE (Fig. 8). In the upper half of both lungs there are two obstacles 'in series', first, bronchiolar narrowing in the conduction zone and, second, centriacinar dilated air spaces in the intermediate zone. In the lower halves of the lungs there is mainly bronchiolar narrowing before the zone of diffusion. Thus, these two obstacles interfere with the transfer of respiratory gases in a zone where good gas conduction and diffusion are most needed (Gomez, 1965). Because the centriacinar branches of the pulmonary artery generally remain intact, there is good vascular perfusion but little or no ventilation at the level of the peripheral alveolar exchange zone. Therefore, in CLE a significant ventilation/perfusion abnormality occurs throughout the lung, even though parenchymal destruction is moderate and localized to its upper portion. Pulmonary arterial hypertension and the resulting right ventricular hypertrophy are a sequel to muscularization of the pulmonary arterioles caused by hypoxia (Heath, 1968), but in some cases these changes in the pulmonary vessels are increased by widespread organized thrombotic emboli.

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