Quantitative Study of Parenchyma and Small Conductive Airways in Chronic Nonspecific Lung Disease

Use of Histologic Stereology and Bronchial Casts

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Simultaneous morphometric studies of parenchymal loss and of internal diameters of membranous bronchioles were carried out at autopsy in 42 cases of chronic nonspecific lung disease. In a few cases, a bronchial cast of the right lung was made according to the slightly modified Tompsett's method with the use of resin. The quantitative data were assessed in four anatomic groups: panlobular emphysema, centrilobular emphysema, minimal emphysema, miscellaneous emphysema and were correlated to the right ventricular weight. Inflammatory bronchiolar stenoses were observed in most cases with centrilobular emphysema and with minimal emphysema as shown by the percentage of small airways less than 350μm in diameter. The degree of right ventricular hypertrophy appeared to correlate more with bronchiolar stenosis than with parenchymal loss. In panlobular emphysema without bronchitis or bronchiolitis or both and without right ventricular hypertrophy, bronchiolar diameters were in normal ranges. The bronchial casts of two patients with moderate emphysema and minimal respiratory failure showed disseminated small airways stenoses of which the site, the shape and the number have been assessed.

For the last ten years, stereologic methods as applied to the quantitative study of pulmonary pathology have provided a good deal of information about emphysema and chronic bronchitis and have led to more precise clinicopathologic correlations. Thus, Dunnill, when studying some selected cases of pure forms of centrilobular and panlobular emphysema, was able to describe new pathophysiologic concepts for these diseases. In the same way, Horsfield and co-workers contributed to the study of altered physiology in emphysema by morphologic studies of the respiratory airways using bronchial casts. All these studies have been concerned only with parenchymal destruction, and have neglected to localize and quantify airways obstruction, although many workers had previously shown narrowing or inflammation or both of small membranous airways in emphysema and bronchiitis. It was only in 1968 that obstruction at the level of small airways less than 2 mm in diameter was quantitatively demonstrated simultaneously by two different teams. Hogg and associates, by partitioning the measurement of resistance to air flow in the distal and proximal airways demonstrated a major increase in the distal airways, in emphysema, chronic bronchitis and bronchiectasis. Two of us with others were able, by direct histologic measurements, to assess the importance of the narrowing of membranous bronchioles in severe emphysema and in minimal emphysema. However, the method of quantitation of the calibers of the bronchioles based on stereologic and statistical principles, could not locate with accuracy the site, the length, the shape and the number of bronchiolar stenoses. For this reason, we undertook a study of bronchial casts. This paper gives the results of microscopic measurements of lung parenchyma as well as the number and dimensions of small airways in obstructive lung diseases and discusses the respective role of these lesions in the
production of clinical disability and right ventricular hypertrophy. In addition, preliminary results obtained by making bronchial casts in a few cases are reported.

**Material and Methods**

The lungs from 42 consecutive patients with chronic non-specific lung disease have been examined at autopsy. These 42 patients had been admitted in the department of respiratory disease (Laennec Hospital) with a history of chronic cough and sputum attributed to chronic bronchitis (38 of 42 cases) and for chronic respiratory failure with acute exacerbation (28/42 cases) or for both. Blood gases were abnormal in all cases. The functional tests carried out in 22 cases showed a reduced FEV... and FEV/VC ratio (clinical and functional data are included in Tables 1, 2, 3 and 4). The types of pathologic lesions have been specified in four groups on the basis of gross morphologic and quantitative anatomy: 1) pure or predominant severe panlobular emphysema (PLE) (eight cases); 2) pure or predominant centrilobular emphysema (CLE) of more than 10 percent (nine cases); 3) minimal emphysema (min E), whatever the type, less than 10 percent (nine cases); 4) miscellaneous emphysema (misc E) either “mixed,” panlobular and centrilobular, paraseptal, irregular or unclassified (16 cases). Bronchiectasis was not present in any case.

The methods used for macroscopic and microscopic measurements have been described in detail elsewhere.15-17 Lungs were inflated at a transpulmonary pressure of 25 cm of formalin. The volumetric proportion of emphysema was assessed in all cases by the point counting method performed on all slices of the lung.18 Parenchymal stereologic microscopic measurements were carried out by the mean of the grid method19 on sections 5 μ thick obtained from 20 stratified random blocs of tissue for each lung. The shrinkage factor was evaluated in each case.17 The quantitative data thus obtained served to calculate the alveolar surface density expressed in square centimeters per cubic centimeters corrected to the predicted lung volume (SVA c) according to the formula:

\[
SVA_c = \frac{4N_i}{L(\frac{VL_{pred}}{VF})^{1/3}}
\]

where \(N_i\) is the number of intersections with alveolar walls per unit of length of test lines; VF, the anatomic lung volume and VL pred, the predicted lung volume according to Cotes20 and the internal avascular surface area corrected to an arbitrary lung volume of five liters (ISAa) expressed in square meters. Both data were also expressed as a percentage of reduction of the predicted, according to the regression equations obtained by the study of 11 lungs with normal parenchyma.21

Morphometry of membranous bronchioles (nonrespiratory and noncartilaginous) was carried out on the same sections according to a method already published.16 For measurement of internal diameters a special test system has been used which allowed the transverse or oblique-sectioned bronchioles to be counted directly in nine groups of internal fixed diameters, ranging from group 0, less than 100 μ; group 1, 101 to 200 μ; group 2, 201 to 300 μ; group 3, 351 to 500 μ; group 4, 501 to 700 μ; group 5, 701 to 900 μ; group 6, 901 to 1200 μ; group 7, 1201 to 1700 μ; group 8, over 1700 μ. The measurement permitted histograms of internal diameters to be obtained in each case, which showed that in five normal adult lungs the percentage of bronchioles less than 350 μ in diameter was from 5 percent to 15.5 percent (mean: 13.3 percent).17 On the graphs and tables of the paper, the degree of narrowing of bronchiolar lumen in patients with obstructive lung disease (most of whom died after acute respiratory failure) has been expressed by this percentage matched with the mean obtained in normal cases. The number of bronchioles per square centimeter of fixed lung was calculated by counting on the same sections all bronchiolar transsections, whether transversal, oblique or longitudinal. Bronchiolar transsections intercepted by the right and upper border lines were dismissed. The number of bronchioles per square centimeter of fixed lung was corrected to the predicted lung volume (N Br/cm2 C) as previously described.17

These parenchymal and bronchiolar measurements were carried out in both lungs, except in three cases where only the left lung was available; the right one, fixed in the same way, had been used to make a bronchial cast. ISAa was calculated from the fixed volume of both lungs measured in all cases by water displacement.

In cases No 26, 41, and 42, a bronchial cast of the right lung was made in the manner described by Tompsett22 and modified by Horsfield and co-workers23 and by one of us24 using a plastic formed by the interaction of a polyester resin, a catalyst and an accelerator. Details concerning the modifications of the method will be given here only. Lungs were fixed through a plastic tube tied into the main bronchus by bronchial instillations of a solution of 10 percent formalin and 5 percent sodium acetate with a transpulmonary pressure of 20 to 25 cm H2O according to a previously described method.16 Before resin injection, the lung was filled with water at room temperature. Then, the resin was allowed to run in from a height of about 50 centimeters. Six days were allowed for the cast to harden. After hardening, the bronchial cast was obtained by corroding away lung tissue with 50 percent sodium hypochlorite, a process which took about two days. The resin generally reached the third order of respiratory bronchioles. The shrinkage coefficient of the resin after hardening was 8.2 percent for the volume. The bronchiolar diameter size given here has not been corrected for shrinkage.

In cases 26 and 42, the cast was only used for morphologic studies. A quantitative study of the cast of case 41 was carried out as follows: the diameter of all the branches down to the eighth order (principal bronchus equals first order) for the upper lobe and to the tenth order for the lower lobe was measured and indicated no narrowing of the calibre of the airways. Further down, ten stratified samples were taken off for each lobe and then all the branches of each sample were quantitatively investigated; the diameter of each structure was measured at the middle of its length, in both major and minor axes when needed, under a binocular dissecting microscope with the use of an eyepiece micrometer; the stenoses were localized on a schema showing their position counting down from the principal bronchus (designated first order), and their smallest diameter measured. The stops of filling with irregular or spiked cone-shaped endings were counted as stenosis due to complete organic obliteration of the lumen. Thus 2501 micrometric measurements have been carried out and only preliminary results will be given here.

The heart was studied quantitatively according to the method described by Fulton and co-workers.25 The degree of...
of right ventricular hypertrophy (RVH) was arbitrarily graded as follows: grade 0 (no RVH) when the right ventricular weight (RVW) was lower than 70 gm; grade 1: mild RVH when the RVW was from 71 to 90 gm; grade 2: moderate RVH when the RVW was from 91 to 130 gm; grade 3: severe RVH when the RVW was higher than 130 gm. The Fulton ratio was calculated but not retained for evaluating the degree of RVH because of biventricular hypertrophy (BVH) in a few cases.

Some clinical and physiologic data when available have been assessed and are given in Tables 1, 2, 3 and 4. Nevertheless, the extent of the anatomic right ventricular hypertrophy (RVH) was only regarded as an indication of the severity of the disease.

RESULTS

Histologic Measurements

1) Quantitative data about lung parenchyma and bronchiolar diameters (Fig 1)

a) In eight cases of severe panlobular emphysema (Table 1) we found a mean of 83 percent of parenchyma was involved. The measurement of alveolar surface density (SVA c) and of internal surface area five liters (ISAs) gave a more accurate assessment of parenchymal loss by showing a reduction of internal alveolar surface area of approximately 50 percent and even more when counting only the intercepts with the walls of alveoli less than 1 mm diameter21 (Table 1). On the other hand, the estimation of bronchiolar diameters showed variable results: in cases 2 and 8, the percentage of bronchioles with internal diameter lower than 350μm was below normal and in cases 5 and 6 a little above normal (13.3 percent of bronchioles with internal diameter lower than 350μm as a mean value in five control cases). In the other cases, the percentage was increased and microscopic study showed that bronchiolar narrowing was due either to inflammatory sclerosis sometimes correlating with clinical chronic bronchitis, or to

Table 1—Panlobular Emphysema (PLE)

| Case | Age (Yrs) | Sex | FEV1  | FEV1% | PLE | SVA cm⁻¹ | SVA | ISAs | ISAs% | Nbr | RF | RVW (g) | Fulton Ratio | Causes of Death
<table>
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<td>1</td>
<td>60</td>
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<td>48(34)</td>
<td>37(26)</td>
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<td>61(71)</td>
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<td>78*</td>
<td>69</td>
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</tr>
<tr>
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<td>M</td>
<td>37</td>
<td>51</td>
<td>68</td>
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<td>68(49)</td>
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<td>39(55)</td>
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<td>6</td>
<td>45</td>
<td>3.11</td>
<td>0: Cardiac arrest</td>
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<td>55</td>
<td>65</td>
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<td>65(53)</td>
<td>38(20)</td>
<td>30(44)</td>
<td>0.83</td>
<td>34</td>
<td>79</td>
<td>2.70</td>
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<td>4</td>
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<td>82</td>
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<td>F</td>
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<td>92</td>
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<td>33(13)</td>
<td>40(77)</td>
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<td>2: Major PTE</td>
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<td>61</td>
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<td>42(37)</td>
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<td>53(60)</td>
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<td>0: Major PTE</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>M</td>
<td>19</td>
<td>23</td>
<td>51</td>
<td>45(55)</td>
<td>42(24)</td>
<td>33(19)</td>
<td>21(12)</td>
<td>63(76)</td>
<td>0.65</td>
<td>40</td>
<td>1.70</td>
<td>2: Stom hemor</td>
</tr>
<tr>
<td>8</td>
<td>77</td>
<td>M</td>
<td>26</td>
<td>26</td>
<td>70</td>
<td>35(85)</td>
<td>57(46)</td>
<td>61(49)</td>
<td>29(23)</td>
<td>41(52)</td>
<td>0.47</td>
<td>5</td>
<td>55    2.54</td>
<td>0: Pneumonia</td>
</tr>
</tbody>
</table>
Mean: 65 | 22 | 24 | 54 | 45 | 85 | 57(38) | 51(24) | 27(10) | 48(64) | 0.55 | 26 | 73 | 2.06 |

Abbreviations: FEV1: forced expiratory volume in 1 sec; VC: vital capacity; O2: arterial pressure of oxygen (mm Hg); CO2: arterial pressure of carbon dioxide (mm Hg); PLE: point count percentage of panlobular emphysema; SVA: alveolar surface density in cm²/cm³ of lung parenchyma and in percent to the predicted normal values; ISAs: internal surface area corrected to an arbitrary lung volume of 5 liters, expressed in square meters and in percentage of reduction to the predicted normal values. For SVA and ISAs the first result is obtained when counting all intercepts; the second, in bracket, when counting only intercepts with alveolar spaces less than 1 mm in diameter; Nbr: number of bronchioles per square centimeters of fixed lung corrected to the predicted lung volume; RF<350μm%: percentage of bronchioles with internal diameter less than 350μm; RVW: right ventricular weight; Fulton ratio: ratio of left ventricle plus septum to right ventricle; RVH: right ventricular hypertrophy; CHF: congestive heart failure.
loss of attachment to surrounding alveoli and in case 1 to probable reversible contraction.

b) It is interesting to compare these findings in panlobular emphysema with those observed in centrilobular emphysema and in minimal emphysema (Tables 2 and 3).

In nine cases of centrilobular emphysema, we were able to confirm that emphysematous spaces, usually located predominantly in the upper half of the lung, were associated with bronchiolar stenosis due to inflammation and sclerosis.17

In nine cases of minimal emphysema, it appeared that the principal lesion responsible for obstructive disease and respiratory failure was located at the level of small peripheral airways, as assessed by the percentage of small airways less than 350 μ in diameter contrasting with the almost normal alveolar surface area.

c) In miscellaneous emphysema, the results were quite variable from case to case. Nevertheless the mean suggests both bronchiolar narrowing and parenchymal loss.

d) Comparison of results between normal and other groups and the relation to right ventricular hypertrophy.

The upper bar graph shown in Figure 1 indicates in each group the mean results of the positive percentage of small airways less than 350 μ and the negative percentage of reduction of internal alveolar surface area as compared with the predicted, and the lower bar graph the mean ventricular weight. We can see that the lowest right ventricular weight was seen in PLE cases, where bronchiolar stenosis is less frequent contrasting with the severest loss of parenchyma. By contrast, the highest right ventricular hypertrophy was observed in the centrilobular emphysema group where bronchiolar stenosis was the most pronounced. In minimal emphysema, the moderate mean right ventricular weight is in accord with the moderate amount of bronchiolar stenosis and parenchymal destruction. When cases have been grouped in four grades of RVH, we could observe that the mean for both bronchiolar stenosis and parenchymal loss was highest in cases with grades 2 or 3 as opposed to grades 1 or 0 (Fig 2).

2) Number of bronchioles

The mean number of bronchiolar sections per square centimeter of fixed lung is shown in the bar chart in Figure 3 for the different anatomic groups, as matched against the mean data from five control cases. In cases with minimal emphysema, the mean number was 0.87 Br/cm² C, a little more than in normal cases (0.73). By contrast, the mean number was reduced in the three other groups with emphysema, and paradoxically more in CLE than in PLE cases; however, when assessing all cases, the number of bronchioles per square centimeter of fixed

### Table 2—Centrilobular Emphysema

<table>
<thead>
<tr>
<th>Case No</th>
<th>Sex</th>
<th>Age</th>
<th>Type</th>
<th>FEV₁</th>
<th>FEV₁ %</th>
<th>VC</th>
<th>CO</th>
<th>E</th>
<th>E %</th>
<th>SVA</th>
<th>SVA %</th>
<th>ISA₁</th>
<th>ISA₁ %</th>
<th>Br&lt;350μ</th>
<th>RVW</th>
<th>Ratio</th>
<th>RVH</th>
<th>Causes of Death Associated Diseases</th>
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<tr>
<td>0</td>
<td>M</td>
<td>67</td>
<td>B+D</td>
<td>27</td>
<td>32</td>
<td>45</td>
<td>11</td>
<td>163</td>
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<td>50</td>
<td>8</td>
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<td>15</td>
<td>84</td>
<td>1.65</td>
<td>1</td>
<td>PTE</td>
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</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
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<td>59</td>
<td>43</td>
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<td>26</td>
<td>0.44</td>
<td>43</td>
<td>119</td>
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<td>PTE</td>
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</tr>
<tr>
<td>±SD</td>
<td></td>
<td></td>
<td></td>
<td>±9</td>
<td>±22</td>
<td>±12</td>
<td>±12</td>
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*Most of the data of cases 1 to 8 have been previously published (Bignon and associates, Thorax, 25:556, 1970)*

Abbreviations: see Table 1.

### Table 3—Minimal Emphysema

<table>
<thead>
<tr>
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<th>Type</th>
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<th>FEV₁ %</th>
<th>VC</th>
<th>CO</th>
<th>E</th>
<th>E %</th>
<th>SVA</th>
<th>SVA %</th>
<th>ISA₁</th>
<th>ISA₁ %</th>
<th>Br&lt;350μ</th>
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<td>±45</td>
<td>±0.71</td>
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</table>

*Not available because of tracheal carcinoma.*

Abbreviations: E, Emphysema type; C, centrilobular emphysema; U, unclassified emphysema; P, panlobular emphysema. Other abbreviations are explained in Table 1.
Figure 2. Subdivision of cases in four RVH grades. Upper half: mean percentage of small airways with internal diameter less than 350μ; lower half: percentage of reduction of internal surface area (ISA,) to the predicted values. RVW = right ventricular weight.

Figure 3. Left: Variation in number of airways per sq cm from group to group, matched against normal results; right: correlation between the number of bronchioles and the percentage of emphysema (point count).
lung did not correlate closely with the percentage of emphysema.

**Bronchial Casts**

In case 42 (Fig 4), the bronchial cast of the right lung showed that the major and medium airways were irregularly annulated along their entire length and the small airways were narrowed or terminated by sharp or irregular stops of filling. Alveolated lung structures were normally injected only in a few zones in the upper and lower lobes. When excised from the thorax, both lungs appeared emphysematous with large bullae. The macroscopic study of the left lung showed mostly panlobular and bullous emphysema associated with parenchymal infectious consolidation in the upper lobe (Fig 4). In spite of the important reduction of internal alveolar surface area and of airways damage, blood gases were near normal and the right ventricular weight was below normal. The death of this 76-year-old woman was due to cardiac arrhythmia (Table 4).

In case 26 (Fig 5) the bronchial cast of the right lung showed numerous airways stenoses, approximately more than 100. These stenoses were widespread on branches of different order and size, from 3 to 0.4 mm in diameter and elsewhere morphologically normal. The narrowings were 1 to 10 mm in length and often eccentric; the diameter of the smallest approximated 0.05 mm. In the upper lobe and the apical part of the lower lobe of the cast, some centriacinar emphysematous spaces were also found where the tributary terminal bronchiole sometimes showed an obvious stenosis (Fig 6). The morphometric study of the left lung (Table 3 and Fig 5) demonstrated the almost total absence of emphysema and a normal alveolar internal surface area. The percentage of small conductive airways less than 350μ was 25 percent on microscopic sections. There was no right ventricular hypertrophy in this patient who died very early from tracheal carcinoma (Table 3).

The bronchial cast of the right lung of case 41 also showed disseminated airways stenoses of which an extensive quantitative analysis is at present in progress. As preliminary results, we can report that 7.50 percent of the measured bronchioles of the upper lobe and 5.25 percent of the lower lobe were stenotic. These stenoses were quite different from those observed in case 26, being shorter, more symmetric, regular and concentric (Fig 7). The branches involved were from 0.2 to 0.9 mm in diameter and the narrowed diameters were from

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21551/)

**Figure 4.** On the left: bronchial cast of the right lung, showing deformities of major bronchi, narrowing of small airways and only a few alveoli fully injected. On the right: paper mounted section of the left lung showing panlobular, bullous and irregular emphysema with consolidation of the posterior part of the upper lobe.
QUANTITATIVE STUDY OF PARENCHYMA AND SMALL CONDUCTIVE AIRWAYS

Table 4—Miscellaneous Emphysema

<table>
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<th>FEV%</th>
<th>E</th>
<th>SVA</th>
<th>SVA</th>
<th>ISA%</th>
<th>ISA%</th>
<th>Br&lt;350</th>
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Mean ± SD | 61 ± 11 | 34 ± 10 | 61 ± 12 | 42 ± 11 | 78 ± 13 | 64 ± 12 | 39 ± 14 | 31 ± 14 | 0.56 ± 14 | 21 ± 10 | 104 ± 14 | 1.68 ± 1.03

*Not available because of biventricular hypertrophy (Fulton ratio: 4.40).

Abbreviations: E, emphysematous type; P, panlobular emphysema; C, centrilobular emphysema; M, mixed emphysema; L, linear emphysema; I, irregular emphysema. For other abbreviations, see Table 1.

0.025 to 0.5 mm. The length of stenoses was from 1 mm to 3 mm. Elsewhere, scarce emphysematous spaces, either centriacinar or panlobular were found on the cast. The stereologic study of the contralateral left lung indicated little alveolar damage. The histograms of bronchiolar diameters measured either microscopically or on bronchial cast appeared nearly similar, with about 30 percent of small airways less than 350 μm in diameter. A study on serial histologic sections showed that stenoses were due to inflammatory infiltration of the bronchiolar walls. In spite of these multiple bronchiolar stenoses, it is noteworthy to stress that this 72-year-old patient died from stomach carcinoma and Waldenström disease and that three months before his death he had nearly normal blood gases when breathing one liter of oxygen through a nasal catheter (Table 4). However, a few weeks before this patient died, two arterial blood samples showed a low resting PaO2 (77 mm Hg) associated with a low PacO2 (34 mm Hg), indicating a shunt effect. We are now computing the functional consequences of these small airways stenoses.

DISCUSSION

These results show that narrowing of the small conductive airways less than 2 mm in diameter appears to be a common denominator in most obstructive lung diseases. For many years, bronchiolitis has been described in emphysematous lungs and Anderson and Foraker as early as 1962, were able to show a reduction of small airways stenoses.
airways calibers in emphysema. Moreover, it appears now that such narrowing of small airways can exist independently of emphysema.\(^{15,16}\) Hence, the bronchiolar stenoses shown by bronchial casts and serial histologic sections in case 41 of this study appear quite similar to those described by Esterly and Heard\(^{36}\) in their case 2 where emphysema was minimal.

The nature of this small airways disease now appears clearer: it was obvious in the cases studied here that obstruction of small airways was due on one side to mucous plugs and even more on the other to mild chronic inflammation and sclerosis of the wall with stenosis and even obliteration of the lumen. Thus, this kind of inflammatory process could be responsible for the destruction of some bronchioles. Nevertheless, this has not been clearly demonstrated here by the histologic numeration of bronchiolar transections in cases with minimal emphysema as compared with normal lungs (Fig 3). Rather, emphysema, especially centrilobular, seemed more often associated with a significant

**Figure 6.** Two examples of stenosis of the terminal bronchioles leading to emphysematous centri-acinar spaces.

**Figure 7 (left).** Example of one stenosis of small airways from the bronchial cast of case 41.
decrease in the number of bronchioles. However, to date, the method of counting bronchioles in histologic sections has been insufficiently accurate, as shown by the wide range of results given here and in other studies.27,28

Simultaneous quantitative studies of alveolar internal surface area and of small airways calibers seem to contribute greatly to a better understanding of the pathophysiology in the different clinicopathologic types of obstructive lung disease. Hence, when comparing the different cases, one can find quite different features in the degree of respiratory failure, functional disturbance and right ventricular hypertrophy, not only from case to case but also from group to group and particularly between the panlobular emphysema group on one hand and the centrilobular and minimal emphysema groups on the other. It has been demonstrated already that, among structural damages, the loss of alveolated gas exchanging portion of the lung is not alone sufficient to account for the degree of clinical disability, blood gas abnormalities or right ventricular hypertrophy or both. Indeed, most of the patients with panlobular emphysema (cases 1-3, 6, 8) and one case (No 42) with miscellaneous emphysema, though with a dramatically reduced internal alveolar surface area, could live long, almost asymptomatic and, at autopsy, right ventricular hypertrophy was minimal or absent. The anatomic quantitative data obtained here seem to indicate that in lungs with severe panlobular emphysema corresponding to the type A patients,29 ventilation could be effective in zones where patent small airways led to still preserved alveoli, although there was no ventilation and no perfusion in the most severe emphysematous zones where alveoli and vessels were simultaneously destroyed, which accounted for an absent or mild shunt effect and probably for the almost normal right ventricular weight. By contrast, when panlobular emphysema was associated with chronic bronchitis (type B patients) and with inflammatory bronchiolar stenoses, respiratory failure and right ventricular hypertrophy were usually noted, as if small airways disorder was needed to impair the function.30

Previous workers have explained the usual clinical severity of centrilobular emphysema by referring only to the strategic site of emphysematous spaces, which delays the gas diffusion towards the air-blood barrier.5,8 Nevertheless, it appeared to us that centrilobular lesions were not alone sufficient to account for respiratory failure and severe right ventricular hypertrophy, usually observed in CLE cases. The cases reported here, as previously published,17 tend to prove that, besides emphysema, widespread bronchiolar narrowings caused by bronchiolitis play an important part leading to low ventilation/perfusion ratios and cor pulmonale. Moreover, bronchial casts enabled us to show narrowing of the terminal bronchiole leading to some of the centriacinar holes.

Many authors have previously focused on patients who died of chronic respiratory failure and whose lungs when examined at autopsy were described as having no or minimal emphysema.26-28,31-34 The anatomic quantitative study in such cases provides a better understanding of the background of airways obstruction associated with chronic bronchitis. In a few cases reported here and elsewhere,10 bronchiolar narrowing was the principal lesion able to impair ventilation without impairing perfusion. The bronchial casts obtained in cases 26 and 41 demonstrate that these small airways narrowings may be numerous and disseminated throughout the whole lung even with little abnormal function tests or blood gases or both. From that point of view, an advance has been made in the study of chronic bronchitis by Anthonisen and associates.30 When they were investigating some cases of chronic bronchitis without clinical disability, radiographic evidence of emphysema and with near normal tests of pulmonary function, they found by the xenon technique significantly low ventilation/perfusion ratios in the lung periphery, most commonly in the lower lobes. It seems that such interference with ventilation must be due to disordered small airways since in normal subjects these contribute such little resistance to air flow.14 In such cases, blood gases may be found nearly normal if an arteriolar compensatory vasoconstriction intervenes at the level of poorly ventilated zones. In the future, the search must be for structure-function correlation between quantitative data obtained on one hand by morphologists when measuring airways diameters from microscopic sections or bronchial casts and on the other hand by physiologists when measuring small airways resistance to air flow, regional ventilation/perfusion ratios, and shunt effect. This seems to be a positive way to progress in understanding the pathophysiology and in diagnosing the earliest stages of obstructive lung diseases.

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