The Senile Lung*
Comparison with Normal and Emphysematous Lungs

1. Structural Aspects


As part of a study of the structural-functional correlations of excised human lungs obtained at autopsy, the parenchyma and peripheral airways were examined by means of morphometric techniques. Among the 30 lungs characterized by the absence of fibrosis, ten differed from the normal and emphysematous lungs by a homogeneous dilatation of the airspaces, in excess of the dimensions predicted on the basis of age. Study of the standard deviations of the mean linear intercepts showed that the airspace dilatation was more regular than in emphysematous lungs; in addition, there was no clear-cut destruction, as estimated from the number of alveolar attachments. These lungs were characterized in addition by an increased thickening of alveolar septa, without inflammation or fibrosis, normal size of the diameter, and reduced density of the membranous bronchioles. Since these lungs were from people older than 60 years, it is assumed that they represent cases of exaggerated airspace enlargement of the aging lung, differing from emphysema by the absence of destruction of alveolar walls. The term “senile lung” is proposed for this condition.

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A recent report of the National Heart, Lung, and Blood Institute defines emphysema as a condition of the lung characterized by abnormal, permanent enlargement of airspaces, accompanied by the destruction of their walls and without obvious fibrosis. Destruction may be recognized by the disorder of the respiratory airspaces. “Single airspace enlargement,” on the other hand, is described as an increase in airspace size, distal to the terminal bronchioles, as compared with the airspaces of normal lungs. There is no evidence of destruction. The process may be acquired, as in the uniform respiratory airspace enlargement of the aging lung.

In a study of the functional-morphologic correlates of emphysema, we examined a number of lungs obtained at autopsy. Some of these lungs were normal; others were clearly emphysematous. A third group of lungs, however, demonstrated an enlargement of airspaces, markedly larger than that expected on the basis of aging alone. Originally, our hypothesis was that these lungs demonstrated panacinar emphysema. However, the absence of any disorganization by low-power magnification and of inflammation at the level of the airspaces and of the peripheral airways at the microscopic level prompted us to reconsider our opinion. We wondered if we were not dealing with instances of exaggerated respiratory airspace enlargement rather than with emphysema. To substantiate this impression, we performed a systematic morphometric study of airspaces and membranous bronchioles in an attempt to distinguish on an objective basis these lungs from normal and truly emphysematous lungs.

MATERIAL AND METHODS

Studies were performed on 17 right and 12 left human lungs and one isolated left lower lobe (V50), obtained at autopsy. Lungs were selected on the basis of absence of marked pleural adhesions and leaks, gross parenchymal consolidations, and/or generalized fibrosis. Most lungs were from patients who died of cardiovascular disease or of malignant neoplasms. The examined lungs represent a sample that can be considered unselected at least from the population of patients for whom an autopsy was being asked in our general hospital. An exception was made for three lungs (V50, V51, V52) that were selected because of clinical severe chronic obstructive lung disease and/or the presumption of advanced emphysema.

Following the functional measurements (see companion article), the lungs were perfused intrabronchially for at least 72 h with a 10 percent formalin solution, at a pressure of 2.5 to 3.0 kPa. Whole lung sections were prepared from 26 lungs following the technique of Gough and Wentworth. The lung was cut into 1.5-cm-thick sagittal slices and a 0.4-mm-thick whole lung section was prepared from the midsagittal slice. The remaining lung tissue of that section was also examined under the dissection microscope. The degree of airspace enlargement was assessed on the whole lung section by means of a plastic Ryder grid. This grid divides the lung in ten equal radiating segments. To each segment an “emphysema score” from 0 (no enlargement) to 3 (severe enlargement) is given, the maximal score thus being 30. Finally, tissue blocks were selected according to the following protocol. Twelve to 15 random tissue blocks were chosen from each lobe separately: the blocks were cut from both upper and lower lobes parallel to and about 1 cm from

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AA = alveolar attachments; CLE = centrilobular emphysema; CV = coefficient of variation; d = mean diameter; Lm = mean linear intercept; Lma = Lm air; Lmw = Lm wall mean transection length per airspace; n/sq cm = density; NI = number of intercepts; SDn = standard deviation of NI.
the pleural surface. Incompletely expanded lung regions were carefully avoided. Paraffin sections, 4 μm thick, were prepared in a standard way, and stained with Masson’s trichrome. Since the shrinkage from fixed lung to histologic slide is fairly constant even in different pathologic conditions, a constant shrinkage factor of 0.61 was used. The stained slices were examined by light microscopy with a ×10 eyepiece and a ×10 plano-objective (magnification ×100).

The mean linear intercept, Lm, was measured following the technique of Dunnill. Briefly, crossed hair lines with known length are projected on the parenchyma, and the intersections between lines and alveolar septa are counted. The length of the line divided by the number of intercepts (NI) yields Lm. To partition Lm into its two components, namely the mean transaction length, which reflects the thickness of the septal wall (Lm wall:Lmw) and the internal diameter of the airspaces (Lm air:Lma), Dunnill’s technique was slightly modified by adding a point counting method. The hair line was divided in 100 equally distant points, with a point spacing of the lattice (Zeiss Kp—W10×18) of 0.00955 mm at a magnification of 100 times. The sum of the points falling over the parenchyma equals the total transaction length of the parenchyma. Dividing the latter by NI yields the mean transaction length per airspace (Lmw). Two hundred points were counted for each of the 120 microscopic fields investigated per lung, thus ensuring a statistically representative sample.

Since Lm is known to be a function of age in normal lungs, Lm is expressed in percent predicted, using the regression of Thurbeck: Lm = 0.0011 age + 0.2174. In agreement with the data of Thurbeck, airspace enlargement was considered to be exaggerated when Lm exceeded 120 percent of its predicted value.

To evaluate objectively the uniformity of airspace enlargement, we determined the standard deviation of NI. The latter (SDNI) is a function of (1) the inhomogeneity of the alveolar sizes, and (2) the average alveolar size, the larger the alveoli, the less the number of intercepts (provided the optical magnification remains constant), and thus the smaller SDNI. Accordingly, to estimate the uniformity of airspace enlargement, we used the coefficient of variation of NI: SDNI divided by the mean value of NI. With the exception of three lungs, both NI and SDNI were also determined separately for upper and lower lobes.

As an index for destruction, we counted the number of alveolar attachments on membranous bronchioles (the nonalveolated peripheral airways without cartilage or mucus glands in their walls) per millimeter of perimeter (AA/mm). For each lung we measured the internal diameter and the corresponding AA from seven membranous bronchioles both in the upper and lower lobes. These 14 airways, chosen at random, had to meet the following criteria: their walls had not been sectioned because they were adjacent to the edge of the block, the portion bordered by accompanying blood vessels did not exceed 25 percent of the total perimeter, and the section was (almost) completely transversal.

The internal diameter of at least 23 membranous bronchioles per lobe, with an internal diameter of 2 mm or less, was measured following the technique of Matsuba and Thurbeck. Airway density (n/sq cm) was defined as the number of membranous bronchiolar airways per square centimeter of lung tissue; n/sq cm was measured by a Leitz image analysis system.

RESULTS

The lungs were divided into three groups on the basis of the global aspect of the parenchyma on the whole lung sections (examined by eye and under the dissection microscope) and of the value of Lm. Lungs of group A had a normal aspect, the value of Lm did not exceed 120 percent of expected. In the lungs of groups B and C, the value of Lm was higher than 120 percent. The enlargement of the respiratory airspaces was homogeneous in group B, irregular in C. Morphologically the lungs of group C were typical for centrilobular emphysema (CLE). According to the clinical history, group A consisted of five nonsmokers, four current smokers, and one exsmoker. None had a history of chronic bronchitis. In group B, three subjects were smokers, two were exsmokers, and one was a nonsmoker. The smoking habits were not documented in three subjects. Two subjects had a history of chronic productive cough. Group C consisted of six current smokers, three exsmokers, one nonsmoker, and one unknown. Eight subjects of group C had a

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Duncan’s Test</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>49.1 ± 20.3</td>
<td>69.9 ± 4.8</td>
<td>61.3 ± 16.5</td>
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<td>Body length, cm</td>
<td>166 ± 11</td>
<td>166 ± 9</td>
<td>166 ± 7</td>
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<tr>
<td>Emphysema score</td>
<td>1.2 ± 1.6</td>
<td>9.1 ± 4.6</td>
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<td>Lm, mm</td>
<td>0.289 ± 0.039</td>
<td>0.492 ± 0.094</td>
<td>0.584 ± 0.140</td>
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<td>Lm % pred†</td>
<td>105.6 ± 9.5</td>
<td>168.6 ± 31.6</td>
<td>203.0 ± 47.2</td>
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<td>NI</td>
<td>5.49 ± 0.72</td>
<td>3.26 ± 0.55</td>
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<td>SDNI</td>
<td>3.22 ± 0.28</td>
<td>2.06 ± 0.24</td>
<td>2.42 ± 0.39</td>
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<td>SDNI/NI × 100%</td>
<td>59.3 ± 4.2</td>
<td>64.0 ± 7.4</td>
<td>87.5 ± 11.0</td>
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<td>Lma, mm</td>
<td>0.265 ± 0.035</td>
<td>0.453 ± 0.084</td>
<td>0.530 ± 0.123</td>
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<td>Lma % pred‡</td>
<td>100.0 ± 8.5</td>
<td>156.0 ± 28.8</td>
<td>189.1 ± 42.5</td>
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<td>Lmw, mm</td>
<td>0.024 ± 0.005</td>
<td>0.039 ± 0.011</td>
<td>0.054 ± 0.017</td>
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<td>Lmw % pred‡</td>
<td>98.2 ± 7.7</td>
<td>150.4 ± 50.9</td>
<td>205.8 ± 67.4</td>
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<td>d, mm</td>
<td>0.50 ± 0.09</td>
<td>0.85 ± 0.14</td>
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<td>n/sq cm</td>
<td>0.85 ± 0.11</td>
<td>0.70 ± 0.15</td>
<td>0.64 ± 0.11</td>
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<tr>
<td>AA/mm</td>
<td>6.72 ± 0.57</td>
<td>6.75 ± 0.91</td>
<td>5.76 ± 0.72</td>
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*Duncan’s multiple range test: the dashes indicate a significant (p<0.05) difference between groups A, B, or C. Lm = mean linear intercept; NI = number of interceptions per line; SDNI = standard deviation of NI; Lma = internal diameter of airspaces; Lmw = alveolar wall thickness; d, n/sq cm = mean internal diameter and density of membranous bronchioles; AA/mm = number of attachments per millimeter of perimeter.

†Prediction values according to Thurbeck.

‡Prediction equations calculated from 19 normal lungs (see text).
history of chronic productive cough. The mean values (± 1 SD) of the biometric and morphometric data of the three groups of lungs are listed in Table 1.

Respiratory Airspaces

Lm: In agreement with Thurlbeck, Lm was found to depend on age: a similar age dependence was observed in the group of ten normal lungs (Lm = 0.0014 age + 0.2202, p<0.02). The relationship was not improved by taking, in addition, height or lung weight into account. Lm, when corrected for age (Lm %pred), is significantly larger in group B than in normal lungs, and in group C than in B (Table 1). In all lungs of B and C, except for one lung of group C (V16), the absolute values of Lm exceeded 0.38 mm.

The distinction between group B and emphysematous lungs, achieved by examination of whole lung sections, was reevaluated by a quantitative method based on the relationship between SDni and NI for the whole lung. For a given value of NI, SDni and, accordingly, the coefficient of variation (CV = SD/NI × 100 percent) will be larger in the presence of a larger inhomogeneity of airspaces. The CV turned out to be quite similar in lungs of groups A and B, but significantly larger in group C (Table 1). A value of CV larger than 70 percent was met only in one lung of group B (79 percent, in a lung with an emphysema score of 20, the highest of this group), a value less than 70 percent in one lung of group C (67 percent, in a lung with an emphysema score of 6). A systematic quantitative difference between upper and lower lobes was found in group C: both NI and SDni were significantly lower (p<0.05) in the upper than in the lower lobe.

Airspace Size (Lma) and Septal Wall Thickness (Lnw): In normal lungs, Lma corresponds on the average to 92 percent of Lm. Lma is also linked to age: to correct for this influence, we used the following relationship: Lma = 0.0012 age + 0.2031, calculated from 19 normal lungs (adding nine normal lungs not included in the present study). On the other hand, Lnw was significantly related not only to age, but also to height (negatively) and lung weight (positively), the addition of the latter two factors resulting in a significant improvement of the regression (r²: 0.27 for age, 0.49 for age and height, and 0.78 for age, height and lung weight). (Correlations were maintained and significance levels improved when the data from nine

Figure 1. Normal lung (V10). Overview of the parenchyma (magnification ×6) (Masson's trichrome stain). Lm = 0.279 mm or 105 percent of the predicted value.  

Figure 2. Example of a lung of group B (V19) (magnification ×6) (Masson's trichrome stain). Lm = 0.532 mm or 184 percent of the predicted value.
additional normal lungs were included in the multiple regression.) Both \( LmA \) and \( LNw \) are significantly different among the three groups of subjects, also when they are corrected for age (\( LmA \)), or for age, height, and lung weight (\( LNw \)) (Table 1). A tight correlation was found between \( LmA \) and \( LNw \) for the three groups of lungs considered together (\( r = 0.95, p < 0.0001 \)). The correlation was statistically significant in group C (\( r = 0.94, p < 0.0001 \)) and in B (\( r = 0.92, p < 0.008 \)).

**Emphysema Score vs \( Lm \):** The emphysema scores are significantly larger in group B than in normal lungs, and in group C than in B (Table 1). A satisfactory correlation is found between emphysema score and \( Lm \) (\( r = 0.95 \); \( p < 0.0001 \)). The correlation is also observed within the three groups separately and is especially good in the CLE group.

**Histologic Examination:** Simple histologic examination of the lungs of group B revealed a rather homogeneous airspace enlargement throughout. Any disorganization of the alveolar parenchyma or bronchioles was not seen. Except for the most affected lungs, one had the impression when looking at lungs of group B, to examine a normal lung, but at a higher magnification. The alveolar walls were diffusely thickened, the exact nature of which was not detected by light microscopy. Fibrosis or inflammation was not a feature of the lungs of group B. Figures 1 and 2 present examples, respectively, of a normal lung and a lung of group B at the same magnification.

The emphysematous destruction was distributed irregularly throughout the lungs in group C. In addition to the thickened septal walls surrounding enlarged air alveoli, as seen in group B, the parenchyma was characterized by mild focal fibrosis, at times accompanied by a mononuclear inflammatory infiltrate and varying amounts of fibrosis, especially around the respiratory bronchioles.

**Membranous Bronchioles**

**Mean Diameter (\( \bar{d} \)) and Density (\( n/\text{sq cm} \):** The mean values of \( \bar{d} \) and \( n/\text{sq cm} \) of peripheral airways of the three groups of lungs are shown in Table 1. In lungs of group A and B, the values of \( \bar{d} \) are similar, on the average slightly larger in group B, whereas \( \bar{d} \) is markedly smaller in CLE. This difference is statistically significant. The distribution of diameters of membranous bronchioles in the three groups of lungs is shown in Figure 3: with respect to the other two groups, group C is characterized by a relative increase in airways with an internal diameter of less than 0.6 mm and a reduction of larger airways, the distribution of diameters \( \bar{d} \) of normal lungs being intermediate between groups B and C. The density, \( n/\text{sq cm} \), is reduced in groups B and C (Table 1). Both \( \bar{d} \) and \( n/\text{sq cm} \) are similar in upper and lower lobes in groups A and B. In group C, \( \bar{d} \) is significantly smaller in the lower lobes (mean: 0.47 vs 0.56 mm; paired \( t \) test: 3.31; \( p < 0.01 \)), \( n/\text{sq cm} \) being similar in upper and lower lobes.

There is a significant inverse relationship between \( \bar{d} \) and \( n/\text{sq cm} \) in groups A and B. This relationship is not observed in C (Fig 4). In addition, an inverse relationship between small airway diameter, \( \bar{d} \), and density, \( n/\text{sq cm} \), is observed in A and B. No correlation is observed in group C.
relationship is found in emphysematous lungs between \( d \) and Lma (r: 0.68; p<0.03) or Lmw (r: 0.63; p<0.04).

Similar relationships were found in both upper and lower lobes, considered separately.

**Alveolar Attachments (AA):** The number of AA is related to the diameter of the corresponding airways. Accordingly, AA was expressed per millimeter of bronchiolar perimeter (AA/mm). AA/mm was similar in groups A and B, significantly lower in group C (Table 1). Though the lowest values are met in group C only, there is a large overlapping between individual lungs. There is a negative correlation between AA/mm and Lma in group A (r: \(-0.73\), p<0.02). The latter correlation, not observed in group B, is at the limit of statistical significance in group C (r = \(-0.57\), p = 0.06). AA/mm is similar in both upper and lower lobes, also in C (in the latter group: 5.76 ± 1.38 in upper lobes vs 5.77 ± 0.72 in lower lobes).

**Histologic Examination:** In contrast to normal and group B lungs, where most airways are histologically normal, the walls of the membranous bronchioles in group C are characterized by the presence of inflammation and some fibrosis, extending into the walls of respiratory bronchioles.

**Discussion**

The use of morphometric techniques allowed us to delineate an anatomic entity of lungs characterized by an exaggerated but homogeneous enlargement of airspaces without destruction (group B), distinct on the one hand from normal (group A), and on the other hand from emphysematous lungs (group C).

The estimation of the enlargement of the airspaces was achieved on the basis of the mean linear intercept, Lm, the uniformity of the airspaces by comparing Lm in upper and lower lobes and by computing the coefficient of variation of NL, the number of intercepts counted to measure Lm. The amount of destruction was evaluated by determining the number of AA on membranous bronchioles (AA/mm).

It is known that Lm increases with aging also in normal lungs.\(^6,9,10\) To appreciate the effect of age on Lm, we used the regression equation of Thurlbeck,\(^6\) which is very close to that calculated by Greaves and Colebatch\(^4\) and to the regression we computed in our group of normal lungs. According to Thurlbeck,\(^11\) the dispersion of normal values around Lm corrected for age is ±20 percent. A value of Lm exceeding 120 percent of predicted may thus be considered as abnormal. This limit was used to separate the lungs of groups B and C, from those of group A, and in this respect appeared a better criterion than an absolute upper limit for Lm.\(^15\) For instance, taking 0.38 mm as an upper limit for nonemphysematous lungs\(^16\) would result in accepting the Lm value (0.32 mm) of one lung of group C as normal which is unlikely considering the age of the subject (23 years). In comparison, the scores attributed on whole lung sections, by means of a Ryder grid,\(^3\) appeared to correlate satisfactorily with Lm. This is in agreement with the findings of others in emphysematous lungs.\(^8,17-20\) In the present study, a correlation was found also in group B, because the score was based on airspace enlargement, whether regular or not.

A characteristic of airspace enlargement in emphysema as compared with that in aging lungs is its irregular distribution.\(^9\) The airspace enlargement in the lungs of group B was remarkably homogeneous in upper and lower lobes. In contrast, in group C, besides the presence of bullae, also the enlargement of smaller airspaces was irregular and differed topographically: Lm was systematically larger in the upper (0.607 ± 0.123 mm) than in the lower lobes (0.545 ± 0.157 mm). This is in agreement with the findings of Bignon et al\(^21\) and was not observed in the lungs of groups A and B. Within the acinus, the airspaces varied also more in size in group C than in B. As an estimate for this variability, we determined the CV of the number of intercepts counted in the determination of Lm. The latter CV was indeed significantly larger in group C, and almost identical in groups A and B (Table 1).

Finally, the amount of airspace enlargement was estimated by counting the number of AA on the membranous bronchioles. Since this figure depends on the size of the bronchioles in normal lungs,\(^12\) the number of attachments was expressed per millimeter of bronchiolar perimeter (AA/mm). The AA/mm was similar in normal lungs and lungs of group B and significantly smaller in C. The number of attachments decreases, indeed, with the amount of emphysema.\(^22-24\) There was no difference in the number of attachments between upper and lower lobes.

Summarizing, a number of lungs were characterized by an increase in airspace size out of proportion to the increase expected on the basis of age. This increase was probably not a consequence of emphysema. Indeed, the airspace enlargement was regular and there was no loss of AA. In addition, there was neither conspicuous chronic inflammation nor postinflammatory fibrosis. These lungs should thus be classified in the category of simple airspace enlargement. Because all subjects of this group were older than 60 years, we are probably dealing with an exaggerated form of aging lung, which we suggest to designate by the term "senile lung."

Senile lungs demonstrate two other characteristics, so far unexplained, which they share with CLE: a thickening of alveolar walls and a reduction of the number of peripheral airways.

A partitioning of Lm into its airspace (Lma) and wall components (Lmw) shows that alveolar walls are significantly thicker in groups B and C than in normal.
lungs. The latter increase in thickness, also described by Anderson et al., in emphysematous lungs is not easily observed by eye: it is only in advanced emphysema that a diffuse thickening of the walls surrounding large holes is noticed. Simple histologic examination does not reveal any differences between the increase in Lmow in groups B and C.

The density of membranous bronchioles is generally reduced in emphysematous lungs; this is in agreement with our findings in CLE. A similar reduction in density is observed in the lungs of group B. On the other hand, bronchiolar diameter is normal in group B and decreased in emphysema. The latter decrease accompanied by an excess of Airways with a diameter of 0.6 mm or less has been documented previously by others. Bronchiolar diameter and density are negatively correlated in both groups A and B. This relationship, observed by Matsuba and Thurlbeck in nonemphysematous lungs and by Nagai et al. in patients with airflow obstruction is not observed in emphysematous lungs (Fig 4). In the latter, we found in agreement with Mitchell et al. and Hale et al. a negative correlation between bronchial diameter and the severity of emphysema, expressed by the size of Lm.

The reduction of bronchiolar diameter is more pronounced in the lower than in the upper lobes in CLE. In contrast, Lm is larger in the upper lobes. This is in agreement with the data of Berend, who observed more bronchiolar infl ammation and narrowing in the lower lobes in CLE and suggested that different mechanisms may be responsible for small Airways narrowing and alveolar enlargement and/or destruction. On the other hand, we observed an inverse relationship in CLE between Lm and diameter in both upper and lower lobes, considered separately. This, in turn, supports the classic idea of a direct causal relationship between small Airways abnormality and the occurrence of emphysema.

In a study of 80 lungs from nonsmokers, Anderson et al. observed the presence of mild to moderate emphysema of the panacinar type in 20 elderly subjects (60 years or older). There was a diffuse dilatation of alveolar spaces, distributed more or less evenly throughout secondary lobules and lobes or lung. Alveolar walls were often thickened by subtle, diffuse interstitial infl ammation. There was rupture of alveolar structures with occasional simple dilatation. We submit that a number of these lungs might be categorized as senile lungs. The distinction between mild panacinar emphysema and senile lungs is often very difficult by visual inspection. It is important that quantitative techniques are developed further for separation of borderline cases ("equivocal" emphysematous areas of Thurlbeck). We suggest that the determination of the CV of the number of intercepts, counted to determine Lm, is useful for this purpose: a value of 70 percent appears to separate quite well emphysematous from normal and senile lungs.

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