A Pathologist Looks at Respiratory Failure Due to Obstructive Lung Disease

William M. Thurlbeck, M.D.*

An unusual case of chronic respiratory failure will be used to illustrate some of the problems that face the pathologist at necropsy. Several reviews of the pathology of the various causes of obstructive lung disease are available so that there is little purpose in providing a comprehensive review. Instead, less understood and controversial areas arising from this single case will be stressed and a reasonably comprehensive list of important references will be provided.

CASE REPORT

A 57-year-old woman had five admissions for respiratory failure to a nearby community hospital, dying on her last admission in November, 1969. She had been hypertensive (200/100) for many years. Her first admission was in 1967 for wheezing and marked respiratory distress following a "cold" a few weeks previously. Prior to this she had never had cough or produced sputum and had never smoked. A chest roentgenogram showed overinflation with no peripheral pulmonary arterial deficiency suggestive of emphysema. The forced vital capacity was 1.9 liters and the FEx1 was 0.7 liters. Other pulmonary function tests are shown in Table 1. A diagnosis of asthma was made and she was treated appropriately, but without benefit. She was admitted on four further occasions with complaints of dyspnea and wheezing, with progressively worsening respiratory failure and evidence of cor pulmonale. Blood gases were always abnormal with Pco2 values of between 45 and 60 mm Hg and P02 of between 49 and 60 mm Hg. She generally had mild respiratory acidosis with compensation. On her last admission she was admitted with marked hyperoxia and hypercapnia and a pH of 7.16. She died despite active treatment including assisted ventilation.

The autopsy was performed elsewhere, but one lung was inflated post mortem. Inflated slices of this lung were referred for study. Careful examination with a dissecting microscope of a barium sulphate impregnated slice of inflated lung floated under water showed no emphysema and a paper-mounted whole lung section (Fig 1) was scored as 0 emphysema using carefully selected standards. The mean linear intercept (average interalveolar distance) was 0.250 mm (normal). The Reid index of bronchial mucous gland hypertrophy was 0.43 and the Donnill point count of mucous gland size was 10.1 percent, within normal limits for this laboratory. The major airways showed an increased proportion of bronchial muscle (5.99 percent) and there appeared to be some hypertrophy of the muscle of the smaller airways. There was no basement membrane thickening or eosinophilic infiltrate. Consistent abnormalities were found in conducting airways 0.5 to 1.5 mm in diameter. Some were completely occluded by loose tissue (Fig 2 and 3), and others were partly narrowed. Yet others contained mucus plugs and there was some peribronchial fibrosis. There was moderate intra-alveolar edema. Three organizing pulmonary emboli were seen in conducting pulmonary arteries 500 to 750 µ in diameter. The right ventricle was described as dilated and slightly hypertrophied. The left ventricle was increased in thickness.

This case illustrates numerous interesting points: chronic bronchitis and emphysema are not the only causes of chronic airways obstruction. The tremendous amount of research in these two diseases in the last two decades has led to their emphasis, often to the exclusion of other diseases. Bronchiectasis is still a significant cause of obstructive lung disease and is a common finding in emphysematous lungs. Chronic bronchiolitis is an uncommon condition in adults and not adequately recognized, although Gough has stressed its importance.

Since emphysema and chronic bronchiectasis are the two common causes of obstructive lung disease, it follows that these two conditions should be carefully assessed at necropsy in any patient with chronic respiratory failure. Despite the fact that the present knowledge of the anatomic pathology of both emphysema and bronchiectasis is more than ten years old and despite the fact that these conditions

*Professor of Pathology, McGill University, Montreal, Quebec, Canada.
are a significant cause of mortality and morbidity in any general hospital, it is still a relatively uncommon procedure for lungs to be adequately examined at necropsy. Mucous gland hyperplasia in major bronchi can be quantitated rapidly and accurately by a variety of means, but these airways are seldom examined at autopsy. Examination of lungs for emphysema without prior inflation has been shown to be a valueless procedure and yet routine examination of lungs in this way is still common. The proper examination of lungs at necropsy is adequately described in the literature.

Even if lungs are inflated, the recognition, measurement and classification of emphysema at necropsy is difficult and several studies have shown the wide discrepancy in the recognition of the presence and measurement of severity of emphysema at autopsy even with careful methodology and assessment by experts. Most methods are subjective and meaningful comparisons between observers can only be made if tested grading systems are used. It seems that a recently developed, very simple grading system is as good as other described methods and may even be better than machine operated systems which utilize whole slices of lung. This grading system has been designed for use with paper mounted whole lung sections and a recent modification of the original Gough-Wentworth method makes this technique possible in any pathology laboratory. Measurement of average interalveolar distance and alveolar surface area are the only truly objective methods presently available and the former has certain advantages over the latter. These measurements, however, suffer from the defect that they are both time-consuming and relatively insensitive as presently performed.

It is interesting to speculate how this case would have been diagnosed if the lungs had not been examined properly. Some pathologists might have diagnosed it as a case of emphysema; others might have diagnosed chronic bronchitis because of the excess mucus in the airways. Certainly, the diagnosis of "no emphysema" would not have been acceptable and similarly, without the standard grading
panel and interalveolar distance measurements, this negative diagnosis would likely not be acceptable either.

Pulmonary hypertension in patients with obstructive lung disease is primarily due to hypoxemia and to a lesser extent to acidemia and hypercapnia. This patient illustrates that fact that cor pulmonale due to obstructive lung disease can occur in the absence of emphysema: restriction of the vascular bed is seldom the cause of cor pulmonale in emphysema.

There are a number of series of moderate size and one large series describing the findings in patients dying of respiratory failure due to chronic obstructive lung disease. We have reported that about one-third of patients with obstructive lung disease and respiratory failure had less than severe emphysema in their lungs at autopsy.\textsuperscript{11} Similar, but slightly lower proportions, are reported by other investigators. The emphasis on the patho-physiologic mechanism of pulmonary hypertension should not obscure the fact that the most common finding in patients with respiratory failure due to chronic obstructive lung disease, with or without cor pulmonale, is severe pulmonary emphysema.

Alveolar hypoventilation may be due entirely to abnormalities in the small conducting airways (bronchioles, or airways less than 2 mm in internal diameter). In this case, this is an easy concept—there was extensive airway obliteration and narrowing, thus ventilation beyond them must have been poor. Unless there is an as yet undescribed, localized homeostatic mechanism, blood flow to the areas of lung parenchyma which are supplied by this irregularly distributed, variable affection of the airways was normal with missed gross alveolar underventilation, and consequent hypoxemia, hypercapnia, and acidemia. Disease of the small airways is the common denominator in both the usual (emphysema and chronic bronchitis) and unusual (bronchiectasis and bronchiolitis) causes of chronic obstructive lung disease.\textsuperscript{25} It is of interest that functional obstruction of the small airways may theoretically occur. This is because the small airways behave as though they were lined by surface active material.\textsuperscript{26} Macklem and colleagues\textsuperscript{27} have pointed out that if mucus lines these airways, rather than surface active material, then they are likely to collapse more readily and open with greater difficulty.\textsuperscript{28} Karpick and co-authors\textsuperscript{29} have shown that the most common finding in patients with chronic respiratory failure is goblet cell metaplasia of the small airways, thus providing substantiating evidence for the above hypothesis.

**Table 1—Pulmonary Function Tests**

<table>
<thead>
<tr>
<th>Observed</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital capacity (liters)</td>
<td>2.00</td>
</tr>
<tr>
<td>Functional residual capacity (liters)</td>
<td>3.32</td>
</tr>
<tr>
<td>Residual volume (liters)</td>
<td>2.37</td>
</tr>
<tr>
<td>Total lung capacity (liters)</td>
<td>4.37</td>
</tr>
<tr>
<td>Airway resistance (cm H(_2)O/L·sec)</td>
<td>12.00</td>
</tr>
<tr>
<td>Peak expiratory flow rate (L/sec)</td>
<td>2.55</td>
</tr>
<tr>
<td>Maximum elastic recoil pressure (L·cm H(_2)O/L)</td>
<td>-30</td>
</tr>
<tr>
<td>Static compliance (L·cm H(_2)O/L)</td>
<td>100</td>
</tr>
<tr>
<td>Dynamic compliance (L·cm H(_2)O/L)</td>
<td>10</td>
</tr>
</tbody>
</table>

\*After bronchodilator.

\[f = 17, 075\]
\[f = 28, 047\]
\[f = 100, 030\]
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Emphysema is defined and classified in terms of the lung parenchyma—abnormal, permanent enlargement of the gas exchanging portion of the lung accompanied by destructive changes. It is not unnatural for the pathologist to consider the emphysema he observes as the primary cause of physiologic abnormalities both because of the definition and because it is the lesion that he recognizes readily. However, the site of increased airway resistance lies proximal to the emphysematous lesions and it is because of the lesions in the small airways that ventilation/perfusion abnormalities and respiratory failure ensue.

A similar situation exists both in chronic bronchitis and bronchiectasis. The former condition is defined in terms of chronic excessive mucus production, derived from the bronchi, and because of this and because of the term itself, it is tempting to regard the major bronchi as being the site of airways obstruction. Chronic bronchitis is recognized morphologically by enlargement of the mucous glands in the major airways giving additional credence to the view that they are the site of airways obstruction. There is now excellent evidence that the major serious effect of bronchitis is on the small airways with predictable effects on gas exchange. Recognition of the importance of peripheral obstruction by mucus introduces an important concept. The serious effect of bronchitis is the accumulation of intra-bronchial secretions rather than excess production and expectoration which is the usual definition. It is thus possible for a patient to have the functional consequences of chronic bronchitis with normal or reduced secretion (and presumably normal bronchial mucous gland size) if clearance is inadequate as in this patient. Parenthetically, it should be noted that narrowing of the major airways due to mucous gland hyperplasia and consequent impingement upon the bronchial lumen has been shown to be partly responsible for airways obstruction but cannot account for respiratory failure.

Bronchiectasis is defined and classified in terms of permanent dilatation of the major airways and thus it is easy to think of these as being the site of obstruction. However, it is clearly not possible for dilated airways to cause airway obstruction. Obiterated and obstructed airways distal to the bronchiectatic areas have been well documented anatomically and Hogg et al have been able to demonstrate this functionally. Much of the airway obstruction in bronchiectasis is due to mucus plugging due to repeated or continual infection of the bronchiectatic segments and impairment of the cough mechanism by downstream closure.

Asthma is a difficult problem for pathologists as well as clinicians. Classic "extrinsic" or "allergic" asthma presents little diagnostic problem, especially if death occurs in status asthmaticus. The diagnostic criteria are clear-cut and well known to pathologists. However, many patients, such as the one reported here, with chronic obstructive lung disease have wheezing and are, rightly or wrongly, diagnosed as having asthma or "asthmatic bronchitis." Until recently there have been no useful anatomic criteria for separating these patients from other patients with chronic obstructive lung disease. Quantitative measurements of bronchial muscle in the major airways has shown that there is increased muscle in patients with asthma while this is not true in the usual case of chronic bronchitis. This important observation suggests that the pathologist may be able to assess the element of bronchospasm that appears to occur in some patients with chronic bronchitis. In the patient presented here, bronchial muscle was increased and this suggests that bronchospasm was an important part of her illness.

Pathologists have recognized for many years that left ventricular hypertrophy sometimes accompanies cor pulmonale. Until recently, left ventricular failure, left atrial hypertension or pulmonary venous hypertension was thought never to complicate cor pulmonale. It is now clear that extravascular lung water increases in episodes of cor pulmonale as seen histologically in this case, and that this may be associated with the radiologic changes of pulmonary venous hypertension.

Presumably because of increased stiffness of the lung and pulmonary capillary congestion, total lung capacity, functional residual capacity and single breath diffusing capacity may return towards normal values in emphysematous patients. Following treatment, the values become more typical of emphysema. In these patients, the radiologic changes of emphysema may disappear only to reappear when the episode of cor pulmonale is successfully treated. The exact sequence of events and the pathogenesis is still uncertain. The increase in extravascular lung water may produce changes in the radiologic pulmonary venous pattern which mimic pulmonary venous hypertension and left atrial hypertension and thus left ventricular failure need not be implicated. The lesion may thus be related to increased capillary permeability. However, the well-documented occurrence of left ventricular hypertrophy in autopsy studies suggests that left ventricular failure may occur. Common explanations of this include gross hypoxia and polycythemia. An additional mechanism may be anatomic right to left shunts via enlarged and incompetent bronchial...
Patients with left ventricular hypertrophy and obstructive lung disease that we have seen have invariably had extremely severe cor pulmonale, anoxia and erythremia. They also had evidence of pulmonary edema, often only interstitial. One of our patients had secondary pulmonary hemosiderosis. Another explanation which is invoked is that patients have associated cardiovascular disease which may produce coincidental left ventricular failure and hypertension. This is quite well illustrated in our patient who had hypertension which was the likely cause for left ventricular hypertrophy.

Pulmonary thromboembolism appears to be more common in patients with obstructive lung disease than in comparable patients in the same hospital without obstructive lung disease. Thromboembolism is also rather more common in patients with obstructive lung disease and cor pulmonale, raising the possibility that in these patients thromboemboli cause pulmonary hypertension or that pulmonary thrombosis may complicate pulmonary hypertension. Since it has been shown that there is a quantitative relationship between the extent of thromboembolism and the degree of pulmonary hypertension, it is usually possible to assess the contribution to cor pulmonale by thromboemboli in patients with chronic obstructive lung disease. In the above case, for example, the emboli were occasional and incidental. In other patients with obstructive lung disease it may be possible to incriminate pulmonary emboli as being the cause of pulmonary hypertension. Clinically, emboli can be suspected when pulmonary hypertension occurs in patients with obstructive lung disease and normal Pao2 values.

Although chronic bronchitis and emphysema can, and often do, exist independently, they occur together more often than can be accounted for by chance. It is quite unusual for patients with severe emphysema not to have clinical chronic bronchitis. The association between bronchitis and emphysema has both theoretical and practical interest. From the practical point of view, their frequent co-existence often makes it impossible to attribute accurately their relative contributions to disability in any one given case, so much so that patients are treated similarly irrespective of the amounts of emphysema in their lungs. Even if it were possible to predict accurately the amount of emphysema in a patient’s lung this would not materially affect the management of the case. Another practical implication is shown in this case—severe emphysema is unlikely to be present in a patient with obstructive lung disease who does not have clinical bronchitis. The meaning of the association between bronchitis and emphysema is of considerable theoretical interest. One may cause the other or they may often have a common etiologic factor. In this patient, who was neither a clinical bronchitic nor had bronchial mucous gland hyperplasia, there was quite extensive mucus plugging in the small airways at necropsy. The implication is that the organic obstruction of her small airways may have impaired clearance of mucus from them. The likely explanation is impaired aerodynamic clearance of mucus and ineffectiveness of coughing. If the equal pressure point lies downstream to the obstructed airways, then coughing will be ineffective in clearing the airways of mucus. Mucus would then accumulate and the patient enter a vicious circle from which escape is difficult. This mechanism may also be operative in emphysema and account for the association between bronchitis and emphysema. Another explanation for the association between bronchitis and emphysema is the common etiologic agent of cigarette smoking—cigarette smoking is such an important etiologic factor that its absence should, as in this case, cast doubt on the presence of these two diseases.

SUMMARY
A rare case of chronic respiratory failure due to chronic bronchiolitis of uncertain etiology is described in a 57-year-old woman. Increased resistance to flow in the small airways, as in her case, is the common denominator in most cases of chronic obstructive lung disease. Obstruction in these airways produces alveolar hypoventilation which results in respiratory failure and is the major cause of pulmonary hypertension. Recognition of emphysema or bronchitis, or, in her case, recognition of their absence, requires special procedures at autopsy which, although simple, are not frequently performed. Although she did not have clinical or morphologic chronic bronchitis, excess mucus was present in the small airways, likely a defect in clearance of mucus consequent to bronchiolar narrowing and occlusion. The excessive mucus in turn compounded small airways obstruction and this mechanism may be involved in many patients with severe emphysema. Pulmonary thromboemboli, commonly seen in patients with obstructive lung disease, were found in the pulmonary vessels although they did not contribute to pulmonary hypertension. Left ventricular hypertrophy was present but not related to cor pulmonale, but it seems likely that pulmonary edema and left ventricular hypertrophy may complicate cor pulmonale. Although severe emphysema does not invariably cause re-
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spiratory failure and although restriction of the pulmonary vasculature is not an important cause of necropsy in patients with obstructive lung disease, respiratory failure and pulmonary hypertension is severe emphysema.

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Reprint requests: Dr. Thurlbeck, Department of Pathology, McGill University, Montreal 110, Quebec, Canada