Cryptogenic obliterative bronchiolitis in adults

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ABSTRACT Patients referred for assessment of severe chronic airflow obstruction over a three-year period were reviewed, and when all smokers and ex-smokers, those with asthma, chronic bronchitis, emphysema, and other specific pulmonary diagnoses were excluded 10 patients remained. Their clinical, lung function, and bronchographic features were consistent with obliterative bronchiolitis. Nine were women, five had rheumatoid arthritis, and five had survived for more than 10 years after first symptoms. Obliterative bronchiolitis has not previously been considered as a cause of chronic airflow obstruction but the distinctive features suggest that it is a true disease entity.

There are several well-recognised causes of chronic airflow obstruction, notably cigarette smoking, asthma, chronic bronchitis, and emphysema. However, some patients do not fit into any of these categories and the nature of their disorder remains mysterious. We set out to define such patients (by exclusion of all other recognised causes of chronic airflow obstruction) to see if they had common characteristics. Ten such patients were identified among those referred for assessment of chronic airflow obstruction over a period of three years. These 10 patients have similarities of clinical history, radiology, and lung function tests which lead us to conclude that they have obliterative bronchiolitis. Recently Geddes et al described a rapidly progressive form of obliterative bronchiolitis occurring in six patients with collagen vascular disorders, and eight similar cases have since been described. However this condition has not previously been considered as a cause of chronic airflow obstruction in adults, although it is recognised to occur after infection in children and in adults after exposure to toxic fumes and in association with chronic bronchitis and emphysema. reviewed, a total of 2094. All those who had recognised causes of chronic airflow obstruction were excluded as follows.

Asthma Patients were excluded if there was a history of chest symptoms in childhood, attacks of wheezy breathlessness, allergic rhinitis, eczema, or a positive family history. All patients were given a trial of salbutamol inhalation and were excluded if FEV1 or FVC increased by more than 15%. Peak expiratory flow (PEF) rates were recorded four times daily for at least one week using a Wright peak flow meter. Patients with PEF variability of more than 50 l/min were considered to have asthma. All patients had a therapeutic trial of prednisolone, 30 mg daily or more for at least two weeks, and improvement in PEF of more than 50 l/min or 20% (whichever was least) after prednisolone was considered to be evidence of asthma.

Chronic bronchitis All current and ex-smokers were excluded since cigarette smoking has been reported to be associated with chronic airflow obstruction in the absence of mucus hypersecretion. Patients who satisfied the Medical Research Council criteria for chronic bronchitis were also excluded.

Emphysema Emphysema is defined in pathological terms and so cannot be excluded definitely in life, but patients were excluded if the chest radiograph showed low flat diaphragms and attenuation of peripheral

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vascular markings in four of six zones,16 or if lung function tests showed both hyperinflation (total lung capacity, TLC, by plethysmograph greater than 115% predicted) and reduced gas transfer coefficient (Kco less than 85% predicted).

Other causes
Patients with chronic airflow obstruction associated with bronchiectasis, extrinsic airway compression, sarcoidosis, cryptogenic fibrosing alveolitis, eosinophilic granuloma, pulmonary haemosiderosis, relapsing polychondritis, tracheobronchial amyloidosis, or any specific pulmonary diagnosis were also excluded.

This rigorous process of exclusion left a group of 10 patients who showed certain clinical, radiological, and lung function similarities which will be described below. We believe these features are compatible with a diagnosis of obliterative bronchiolitis.

CLINICAL FEATURES
Clinical details of the 10 patients are shown in the table. There were nine women and one man, aged from 27 to 67 years at presentation. All were breathless on exertion and had at least moderate limitation of exercise tolerance. Eight patients complained of cough but none expectorated sputum regularly. Four gave a history of wheeze but this was not paroxysmal or episodic and was not associated with changes of peak expiratory flow rate. The duration of symptoms varied from three months to 15 years. One patient died (necropsy not carried out), the others being followed for up to four years. Five patients had suffered from rheumatoid arthritis for between two and 11 years before chest symptoms developed. All these had been treated with non-steroid anti-inflammatory drugs and three had also received penicillamine. The five patients without clinical rheumatoid arthritis had negative rheumatoid factors and anti-nuclear antibodies. Three patients had histories of respiratory infection immediately before the onset of their breathlessness.

None had been exposed to smoke or fumes. The abnormal physical signs noted were auscultation of inspiratory crackles in five patients and a mid-inspiratory squeak in four. Wheeze was not a prominent feature and there were no signs of cardiac failure. One patient (case 7) was atopic. Alpha-1-antitrypsin levels were normal in all.

IMAGING
The plain chest radiographs were reviewed by a specialist in chest radiology. Three patients showed transient local fine linear infiltrations, and three patients had some diffuse attenuation of peripheral vascular shadows, although this was not associated with hyperinflation. Otherwise the films were judged to show no significant abnormalities.

Ventilation-perfusion lung scans (using Krypton 81 and Xenon 133) were performed in five patients. One was normal, while four showed several matched non-segmental defects of both ventilation and perfusion.

Three patients (numbers 3, 5, and 8) underwent bronchography. These were technically satisfactory. In each case they showed obstruction of peripheral airways, reduced branching and no normal alveolar filling pattern. An example is shown in fig 1.

LUNG FUNCTION TESTS
Dynamic lung volumes (FEV1 and FVC) and maximal expiratory and inspiratory flow-volume loops were recorded using an Ohio spirometer. Total lung capacity and inspiratory airways resistance, Raw, were measured in a body plethysmograph (Fenyves and Gut, Basle, Switzerland). Lung volume accessible to a single inhalation of helium (VA) and the diffusing capacity for carbon monoxide (DL) were determined using a Respirameter (PK Morgan, Chatham) and the carbon monoxide coefficient derived.17 Predicted values were calculated from sex, age, and height.18 Dynamic lung compliance was measured18 in five patients (numbers 1, 3, 8, 9, and 10).

Table  Clinical features

<table>
<thead>
<tr>
<th>Case number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tr>
<td>Age at presentation (yr)</td>
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<td>41</td>
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<td>40</td>
<td>27</td>
<td>27</td>
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<tr>
<td>Duration of symptoms at time of presentation (yr)</td>
<td>0-6</td>
<td>0-5</td>
<td>1-5</td>
<td>2-0</td>
<td>13-0</td>
<td>8-0</td>
<td>0-3</td>
<td>10-0</td>
<td>10-0</td>
<td>15</td>
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<tr>
<td>Duration of follow-up (yr)</td>
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<td>2</td>
<td>11</td>
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<td>-</td>
<td>-</td>
<td>3</td>
<td>10</td>
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<tr>
<td>Associated rheumatoid arthritis (duration in years)</td>
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<td>4-0</td>
<td>0-8</td>
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<td>1-0</td>
<td>0-5</td>
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<td>Preceding chest infection</td>
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<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>History of cough</td>
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<td>-</td>
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<td>-</td>
<td>+</td>
<td>-</td>
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<td></td>
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<tr>
<td>History of wheeze</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<td>+</td>
<td>-</td>
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<tr>
<td>Inspiratory squeak auscultated</td>
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<td>+</td>
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<td>+</td>
<td>-</td>
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<tr>
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*Indicates death.
Figure 2 shows the results of lung function tests. FEV₁ was reduced considerably while FVC was decreased to a lesser degree, and all patients had low FEV₁/FVC%. TLC varied from 70 to 123% predicted but lung volumes by single breath helium dilution were appreciably smaller. Residual volume (RV) was high in all subjects which is reflected by the increased RV/TLC%.

Figure 3 shows the difference between TLC and VA which has been used as a measure of gas trapping¹⁷ and reflects impaired gas mixing in the lungs. In normal subjects this difference is less than 0·5 litres, but all of the patients with obliterative bronchiolitis had increased trapped gas volumes. Raw was increased in all subjects.

The mean DL was reduced but Kco was not (fig 4). Flow-volume loops showed reduced flows at low lung volumes and severe volume-dependent airflow obstruction¹⁷ in all cases—fig 5 shows a characteristic example. Compliance was no greater than the mean predicted value in any of the five patients in which it was measured, and in two was near the lower limit of the normal range (0·103 1·cmH₂O⁻¹ (1·03 1 kPa⁻¹) in patient 9 and 0·115 1·cmH₂O⁻¹ (1·151 kPa⁻¹) in patient 1).

![Fig 1 Left-sided bronchogram from case 9. There is marked lack of side branches from subsegmental bronchi and generalized obliteration of airways smaller than 3 mm. The normal alveolar filling pattern is absent.](image)

![Fig 2 Lung function tests. Values of FEV₁, FVC, TLC, and VA are expressed as percentage of predicted values. FEV₁/FVC and RV/TLC are expressed as ratios percent. Bars represent the mean values and hatched areas the predicted normal range.](image)
Discussion

These 10 patients were identified by a rigorous process of exclusion. We did not attempt to analyse or to characterise in detail the diagnoses of the other patients since we were only concerned to exclude all patients with other possible causes of chronic airflow obstruction. Thus the cigarette smokers with chronic airflow obstruction may have been a heterogeneous group with different causes of airways obstruction, including perhaps some with obliterative bronchiolitis.

We believe the 10 patients described here have features compatible with a diagnosis of chronic obliterative bronchiolitis on the basis of their histories, lung function tests, and radiology. Open lung biopsy was not felt to be clinically justifiable in view of their chronic illness and breathlessness. This group of patients had very similar features clinically, on lung function, and radiographically,
to those described by Geddes et al. However the disease deteriorated rapidly in Geddes' series and thus at necropsy pathological evidence that the underlying defect was indeed obliterative bronchiolitis could be obtained. Our patients presented with breathlessness and some had an unproductive cough. An inspiratory squeak or crackles were auscultated in some but wheeze was not predominant. The chest radiographs were unremarkable. Lung function tests showed an obstructive ventilatory defect with little hyperinflation but considerable gas trapping, which was reflected by a low FVC and DL but normal Kco. The diagnosis was confirmed in some by bronchography which showed changes similar to those reported in obliterative bronchiolitis, and distinct from the abnormalities described in chronic bronchitis and emphysema.

The pattern of lung function abnormality is of interest, even though confident physiological localisation of airway damage can be difficult. The reduced FEV1/FVC% and high Raw show that there is an obstructive ventilatory defect, but such changes occur when larger airways are affected. However, the reduced FVC, VA, and DLCO, and increased trapped gas volume suggests either damage to lung parenchyma or occlusion of small airways. The normal Kco shows that gas transfer in the alveoli reached by ventilating gas is normal and the normal TLC and compliance are not consistent with generalised emphysema or fibrosis. Lung function therefore is consistent with small airway obstruction and occlusion, as well as some flow limitation in larger airways. Since FVC is low but TLC normal we conclude that the air spaces distal to obstructed airways are ventilated by collateral air drift.

The pattern of lung function abnormality differed from a group of smokers who developed a comparable degree of airflow obstruction (matched for Raw) without mucus hypersecretion or emphysema. The latter groups had smaller FVC, lower FEV1/FVC%, higher VA, lower trapped gas volumes, and lower Kco (unpublished observations). Such functional differences suggest that the pathology might also differ.

The marked reduction of FVC is compatible with the hypothesis that in this group vital capacity reflects the degree of medium and small airways closure. Such a mechanism might explain the reduced FVC found in chronic airflow obstruction resulting from other causes, and indeed it may be that in patients with airflow obstruction but normal Kco the FVC is a useful measure of the degree of impairment of smaller airways.

Obliterative bronchiolitis is known to occur as part of the pathological process in other conditions such as chronic bronchitis and asthma. Since these patients and those of Geddes et al. had no evidence of known causative processes, it seems reasonable to distinguish them as a separate disease entity of unknown aetiology. For this reason we suggest the term "cryptogenic" to describe such patients. Both bronchograms in our patients and histology and pathology in those of Geddes et al. have shown that the airways are obliterated hence "obliterative". This process seems similar to the obliterative bronchiolitis described in children in whom it usually follows adenovirus infection. Bronchi smaller than about 3 mm as well as bronchioles appear to be involved but the term obliterative bronchitis would be misleading, and broncho-bronchiolitis cumbersome, so "bronchiolitis" as suggested by Geddes et al. is used for convenience and also by analogy with the comparable disorder in children.

Cryptogenic obliterative bronchiolitis is thus another cause of the more general "small airways disease" coined by Hogg et al. to emphasise the involvement of peripheral airways in chronic bronchitis, emphysema, and bronchiectasis. The patients described by Macklem et al. as having chronic obstructive disease of the small airways subsequently turned out to have conditions such as bronchiectasis or emphysema, and so most would have fulfilled our criteria for cryptogenic obliterative bronchiolitis, even though the small airways were involved. In addition to small airway occlusion our cases had some associated irreversible larger airway narrowing. This may suggest that the disease is diffuse, with particular damage to the smaller airways.

The patients described here are similar to those reported by Geddes et al. but contrast in two important respects. Firstly, the patients in this series did not follow a fulminating course. Relatively mild cases occurred and five patients have now survived for up to 10 years. Thus the condition can cause chronic disability lasting many years. Although it cannot at present be cured, correct diagnosis may allow its natural history to be studied in more detail and perhaps therapies evolved. Secondly, the disease can occur in patients without clinical or serological evidence of rheumatoid arthritis or other collagen vascular disorders. Patients with cryptogenic obliterative bronchiolitis differ from those with bronchiolitis after infection in children or exposure to fumes in adults in having minimal radiographic changes and less active histopathology with concentric fibrous narrowing rather than cellular infiltration.

The airflow obstruction of cryptogenic obliterative bronchiolitis is essentially irreversible since, by the defining criteria used, reversibility was diagnosed as asthma. Slight responses to inhaled broncho-
dilators were recorded in some patients and were of a
similar order to those seen in patients with chronic
obstructive bronchitis or emphysema. Such responses
may be associated with a small degree of symp-
tomatic relief, particularly after intermittent viral
infections.

The aetiology of this disease is unknown. Some
patients gave a history of respiratory infection
immediately before the onset of their symptoms but
no particular organism was implicated. Various
infections can result in obliterative bronchiolitis in
children and perhaps in some adults epithelial
damage by viruses can progress to fibrosis, and
obliteration instead of the usual resolution.26 This
might be liable to occur particularly in subjects with
altered host defences, such as in rheumatoid arthritis.
Possibly some infectious agents can themselves alter
immune responses in predisposed individuals. Recent
reports6 5 6 have implicated penicillamine treatment but most of the patients in this series had
never been treated with this drug, suggesting that
other factors may be more important.

Obliterative bronchiolitis is not diagnosed often,
perhaps because of the frequent uncritical use of the
term “chronic obstructive airways/lung/pulmonary
disease”. All of these patients had less specific
diagnoses made previously by experienced chest
physicians. Although the condition appears to be
unusual it may be less rare than suggested by the
previous literature. Other cases may occur in those
with less severe airflow obstruction and among
smokers.

The diagnosis of obliterative bronchiolitis has been
based on the finding of chronic airflow obstruction in
non-smokers in the absence of evidence of asthma,
chronic bronchitis, or emphysema. The similarity of
the clinical features, the distinctive lung function
changes, and the characteristic abnormalities seen on
bronchography all suggest that obliterative bronchi-
olitis is a true disease entity and not a variant of
asthma or emphysema. The diagnosis should be
considered in adults when irreversible airflow
obstruction develops in the absence of another
cause.

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