Occasional reviews

Structural and inflammatory changes in COPD: a comparison with asthma

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Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. In Europe COPD and asthma, together with pneumonia, are the third most common cause of death. In North America COPD is the fourth leading cause of death, and mortality rates and prevalence are increasing. The incidence and morbidity from COPD are rising. The main risk factors are cigarette smoking and occupational exposure. Part of the reason for the slow advance in our understanding has been the difficulty of distinguishing, with certainty, the difference between subjects with COPD who may show a degree of airways reversibility and those older subjects with asthma whose reversible airflow obstruction has become more "fixed". There may also be mixtures of COPD and asthma which co-exist in any one patient (fig 1).

For the purpose of the present synopsis the definitions of COPD and asthma are those included in the recently published ERS and ATS guidelines;¹⁻³ there is, however, much debate and the clinical definitions are still imprecise. The difficulties of definition are compounded by the recognition that both COPD and asthma are not disease entities but, rather, each is probably a complex of conditions which contribute to airflow limitation (*syn* obstruction). In asthma, airflow limitation is usually variable over short periods of time and reversible, although an underlying irreversible component may develop when inflammation persists in association with repeated allergen or occupational exposure; extrinsic

(allergic) and intrinsic (late onset) and occupational forms are recognised. In COPD the limitation, particularly to expiratory airflow, is usually, but not always, persistent and typically shows a more rapid progressive deterioration with age than is normal. Accordingly, the most recent and generally accepted definition in Europe is: "Chronic obstructive pulmonary disease (COPD) is a disorder characterised by reduced maximum expiratory flow and slow forced emptying of the lungs; features which do not change markedly over several months".¹ Three conditions may contribute to airflow limitation to varying degrees in each patient:

(1) Chronic bronchitis (mucus hypersecretion) which is defined as the presence of chronic cough and recurrent increases in bronchial secretions sufficient to cause expectoration. The secretions are present on most days for a minimum of three months a year, for at least two successive years, and cannot be attributed to other pulmonary or cardiac causes.⁴⁻⁶ Chronic bronchitis can occur in the absence of airflow limitation.

(2) Adult chronic bronchiolitis (small or peripheral airways disease) which is difficult to define clinically but may be recognised by sophisticated tests of function of the small airway – that is, airways of 2 mm diameter or less.^{7,8}

(3) Emphysema which is defined anatomically by permanent, destructive enlargement of airspaces distal to terminal bronchioli without obvious fibrosis.⁹ However, the presence or absence of an ongoing fibrotic process is still debated (see below).

The airways in chronic bronchitis and COPD are also markedly inflamed; however, in contrast to asthma the predominant type of inflammatory cell and the main anatomical site of the lesion appear to differ.¹⁰

The following synopsis focuses on the structural changes and the inflammation of conducting airways and lung in COPD and briefly makes comparisons with what is known in asthma. For further details of the effects of smoking and comparisons of COPD with asthma the reader is referred elsewhere.¹¹⁻¹⁴

Figure 1 Airflow limitation: simplified interrelationships between COPD and asthma.

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Pathology

PROXIMAL BRONCHI (CHRONIC BRONCHITIS)

Cough and sputum production are the symptoms most frequently experienced by smokers;

Figure 2 Scanning electron micrograph of the surface of human bronchial mucosa showing a field of cilia with flakes of mucus at their tips.

both mechanisms are effective in clearing large proximal airways (down to about the sixth generation of branching). Sputum and respiratory tract secretions are a mixture of constituents including glycoproteins, glycosaminoglycans, lipids and transudate. Respiratory tract secretions normally amount to less than 100 ml/day¹⁵ and are thought to consist primarily of glycosaminoglycans.^{16,17} Chronic irritation by pollutants causes alterations in the biochemistry and flow of mucus and in the number and activity of secretory cells – that is, there is an enlargement of the mass of sub-mucosal gland (by an increase in both the number and size of its cells) and an increase in the number of mucous cells (goblet cells) in the surface epithelium. Mucous gland enlargement and hyperplasia of goblet cells are the historical hallmarks of chronic bronchitis.¹⁸ The changes to secretory cells are also reported in asthma. However, in contrast to chronic bronchitis, the airways in fatal asthma are occluded by tenacious plugs of exudate and mucus, there is patchy loss of surface epithelium, relatively uniform thickening and hyaline appearance of its reticular basement membrane, marked enlargement of the mass of bronchial smooth muscle and bronchial vessel dilatation, congestion, and oedema.^{11,19}

The normal presence of a gel-like mucus is essential to mucociliary clearance – in normal healthy subjects the mucus is present as discrete flakes (fig 2) but in subjects with smokers' bronchitis it is thought to be present as a continuous sheet or "blanket" (fig 3). Whilst bronchial goblet cell hyperplasia may be a feature of both chronic bronchitis and asthma, the appearance and increase of goblet cells in the small airways – that is, small bronchi and bronchioli of less than 2 mm diameter – where goblet cells are normally absent or sparse (a change referred to as mucous metaplasia) is a key alteration that contributes to small airways disease and the development of COPD.^{20,21} In the large airways disproportionate reduction of serous acini of the submucosal glands which contain lysozyme, lactoferrin, and a small

Figure 3 Scanning electron micrograph of bronchial surface showing the experimental effects of subacute exposure to cigarette smoke: there is a near complete sheet of mucus.

molecular weight antiprotease tends to favour bacterial colonisation. This is reported not to occur in asthma.²² Other epithelial changes in chronic bronchitis may include atrophy,²³ focal squamous metaplasia,²⁴ ciliary abnormalities,²⁵ and decreases in both ciliated cell number and mean ciliary length.^{26–28} Loss of mucociliary clearance due to alterations in the flow/adhesive properties of mucus or to ciliary damage results in pooling of secretions. These pooled secretions support the growth of bacteria (fig 4) which release products known to damage both cilia and the underlying epithelial cells. Once damaged, the epithelial cells are sloughed and only then may bacteria be found directly adherent to them (fig 5).

SMALL AIRWAYS (CHRONIC BRONCHIOLITIS)

Measurement of sputum only reflects secretions obtained by cough from about the first six generations of airway branching. Mucus produced at this proximal site probably serves to protect the more distal and respiratory portions of the lung. However, mucus produced inappropriately in bronchioli by the process of mucous metaplasia has a number of detrimental effects including a reduction of bronchiolar antiproteases leading to proteolytic digestion and the development of centrilobular emphysema.

As the cross sectional area of the bronchiolar zone of the lung is normally large in relation to the bronchial divisions,²⁹ breathlessness and airflow limitation due to small airway disease are detectable only late in the course of the condition. This means that, once detected,

Figure 4 Scanning electron micrograph of human airway surface but not the underlying airway epithelial cells showing colonisation of airway mucus by bacteria (*Pneumococcus* sp).

Figure 5 Scanning electron micrograph of surface mucosa illustrating the effects of bacterial (*Haemophilus* sp) toxins on the epithelium; ciliated and non-ciliated cells are damaged and sloughing and now bacteria have attached to their cell membranes.

Figure 6 Bronchial cast of human small airways illustrating the marked focal constriction of one airway branch in COPD (courtesy of Professor J Bignon).

relatively severe progressive changes are already well established. However, inflammation in small airways occurs relatively early and may be detected physiologically well before the age of 30 years.^{7,30} The small airway defect is characterised by persistent airflow limitation which may show progressive deterioration in the absence of emphysema. Whilst the site of the lesion and diagnosis is, as yet, difficult to pinpoint by lung function, experimental physiologists have indicated that the dominant site lies in small bronchi and bronchioli of less than 3 mm diameter.^{31,32}

Histologically one of the most consistently observed early effects of cigarette smoke is a marked increase in the number of macrophages and neutrophils in the airways of both man and experimental animals. The increase is seen also within the lung interstitium and alveolar space and can be detected in bronchoalveolar lavage (BAL) fluid.^{33,34} The associated early smoking-related structural changes have been described in studies comparing lungs of young smokers and controls of similar age in a group who had experienced sudden non-hospital deaths.^{20,33,35,36} In these and more severely affected patients the structural changes include mucous metaplasia, bronchiolar smooth muscle hypertrophy, mural oedema, peribronchiolar fibrosis, and an excess of airways less than 400 μ m in diameter.^{20,33,35,36} It is suggested that the primary lesion is persistent and progressive inflammation then leads to peribronchiolar fibrosis. The resultant narrowing of small bronchioli has been convincingly demonstrated by Bignon and colleagues (fig 6).³⁷ The peribronchiolar inflammation (fig 7) and fibrosis may predispose to the development of centrilobular emphysema and may be responsible for the subtle abnormalities detected by lung function. Associated loss of alveolar attachments to the airway perimeter (fig 8) contributes to loss of elastic recoil and favours increased tortuosity and early closure of bronchioli during expiration.³⁸⁻⁴⁰

In bronchioli, non-ciliated secretory and ciliated cells are the main cell types^{41,42} and, of them, the Clara cell is the major secretory cell type as well as the progenitor cell from which ciliated and mucous cells may develop. It has been suggested that the Clara cell normally produces both a hypophase component of bronchiolar surfactant⁴³ and a low molecular weight protease inhibitor (*syn* antileukoprotease or bronchial mucosal protease inhibitor⁴⁴). The latter is the main anti-elastase screen in sputum and normally prevents autolysis of airway tissues.⁴⁵ In smokers Clara cells are replaced by mucous cells²¹ and mucus appears in peripheral airways and its secretion is abnormally increased therein.⁴⁶ The increase in mucus at this distal site is difficult to clear by cough. In addition, its replacement of the normal surfactant lining leads to an abnormally high surface tension and small airway instability and also predisposes to early airway closure during expiration.⁴⁷ In addition, replacement of Clara cells and their anti-elastase secretion predisposes the small airway to proteolytic digestion; such changes in respiratory bronchioli

Figure 7 Histological section of alveolar region in a case of COPD in which there are enlarged alveolar spaces surrounding a small airway with marked peribronchiolitis. Stain: haematoxylin and eosin (courtesy of Professor B Corrin).

Figure 8 Section of emphysematous lung in which there is destruction of alveolar attachments to the bronchiolar wall, resulting in its tortuous appearance and early collapse during expiration. Stain: haematoxylin and eosin.

may underlie the development of centriacinar emphysema.

EMPHYSEMA

The early changes of emphysema have been thought to include subtle disruption to elastic fibres with accompanying loss of elastic recoil, bronchiolar and alveolar distortion (see fig 8), and the appearance of fenestrae which enlarge,^{48,49} an alteration which has been referred to as "microscopic" emphysema (fig 9). These biochemical and microscopic changes lead to loss, by destruction of the elastic framework, of the interalveolar septa and the macroscopic appearance of spaces of more than 1 mm in diameter. Recent data have shown that this destructive process is accompanied by a net increase in the mass of collagen which suggests that, contrary to the current internationally accepted definition (see above), there is active alveolar wall fibrosis in the tissue which remains even in otherwise emphysematous lungs.⁵⁰

Two main morphological forms of emphysema have been described. They are distinguished anatomically by the region of the acinus which is destroyed. Centriacinar (or centrilobular) emphysema is characterised by focal destruction restricted to respiratory bronchioli and the central portions of the acinus, each focus surrounded by areas of grossly normal lung parenchyma. This form of emphysema is usually more severe in the upper lobes of the lung (fig 10). Panacinar (or panlobular) emphysema involves destruction of the walls, in a fairly uniform manner, of all the air spaces beyond the terminal bronchiolus. The panacinar form is characteristic of patients who develop smoking-related emphysema relatively early in life and, in contrast to the centriacinar form, has a tendency to involve the lower lobes more than the upper. In the familial form of panacinar emphysema it is usually associated with deficiency of α_1 -antitrypsin⁵¹ which normally protects the respiratory region by forming a highly effective anti-elastase screen. These distinct morphological forms are thought to have distinct functional properties.⁵²

Epidemiological studies have demonstrated a significant relationship between cigarette smoking and severity of emphysema⁵³ but the mechanism(s) by which cigarette smoke causes such damage is still the subject of much speculation. The working hypothesis has been that emphysema is the result of an imbalance between proteolytic enzymes and protease inhibitors in the lung, favouring an excess of enzyme and, in particular, elastases. In addition, the imbalance between oxidants and antioxidants also contributes by allowing an excessive oxidant burden to degrade the normal protease inhibitor screen.^{54,55} The proposed mechanism involves interactions between cigarette smoke, alveolar macrophages, chemoattractants, neutrophils, elastases, endogenous and exogenous oxidants, protease inhibitors, antioxidants, and lung connective tissue, primarily elastin, which undergoes repeated destruction, synthesis, and degradation.⁵⁶

Whilst the major pathological changes of COPD are thought to occur in the airways and lung parenchyma in patients with advanced COPD, changes also occur to the pulmonary circulation, the right heart, and respiratory muscles.⁵⁷ With alveolar hypoxia the medial vascular smooth muscle of pulmonary arterioles extends distally to vessels that normally lack muscle and there is intimal thickening. In addition, loss of the vascular bed occurs as a consequence of emphysema. Right ventricular enlargement due to dilatation and/or hypertrophy is not uncommon and atrophy of the diaphragm occurs in some cases of COPD. Whilst emphysema and right ventricular hypertrophy are common in COPD, both are uncommon findings in asthma.

Cellular infiltrate

Niewoehner and co-workers³³ and Cosio and colleagues²⁰ were among the first to describe the inflammation of the respiratory region in smokers dying suddenly: inflammation in bron-

Figure 9 Scanning electron micrograph of a human lung in which there is "microscopic" emphysema; the alveolar walls are peppered by fenestrae too small to be seen by the naked eye. Such early lesions probably result in loss of lung elastic recoil.

Figure 10 Gross appearance of the cut surface of a lung in which the centriacinar emphysema is restricted to the upper aspects of each lobe (courtesy of Professor B Heard).

chioles and a respiratory bronchiolitis and alveolitis consisting of pigmented macrophages.⁵⁸ These inflammatory changes to small airways appear to be related to clinical airflow obstruction in patients with COPD.^{31 59 60} The destruction of the respiratory zone in emphysema is also considered to be the result of an inflammatory reaction, much of this centred on respiratory bronchioli and the alveolar wall and largely initiated by products of inhaled tobacco smoke which recruit neutrophils to the lung.^{12 55 61} The average diameter of circulating neutrophils is 7.0 μm which necessitates their deformation as they squeeze through capillary segments of 5 μm diameter. Neutrophil traffic through the capillaries of the lung is normally slower – that is, there is a higher transit time – than that of red blood cells as

they are 700 times less deformable than red blood corpuscles.⁶¹ Recent studies with radioactively labelled neutrophils have shown that the normal delay in neutrophil transit is further exaggerated, transiently, even in healthy subjects during smoking.⁶² Exposure of neutrophils to cigarette smoke in vitro and in vivo results in decreased deformability associated with polymerisation of actin microfilaments.^{61 63} This is the probable mechanism of the observed cigarette smoke induced increase in neutrophil transit time in the periphery of the lung. More recently lymphocytes have been found to form a significant component of the alveolar wall inflammatory infiltrate in patients with COPD.⁶⁴

Inflammatory cells also infiltrate the bronchial mucosa of smokers and these relatively large airways have been the focus of recent biopsy studies conducted in volunteers using the flexible fiberoptic bronchoscope. The biopsy studies of the airways of smokers are of particular interest as they allow comparison with the biopsy changes reported in asthma. It is already known that in patients with atopic and non-atopic asthma there is an inflammatory infiltrate which comprises activated (CD25+), T helper (CD4+) lymphocytes and activated (EG2+) eosinophils associated with gene expression and secretion of interleukins (IL)-4 and IL-5, IL-10, and the pro-inflammatory cytokines GM-CSF and TNF- α .^{65–71} The production of IL-4 and IL-5 but not IL-2 and interferon γ is referred to as the T helper type 2 (Th2) phenotype.

Electron microscopic and immunohistochemical techniques are only just beginning to be applied to examine the nature of the inflammatory infiltrate in COPD. In bronchial biopsy specimens taken from subjects with stable COPD and exacerbations of bronchitis there is evidence of inflammation (fig 11).^{72–76} Similar to the periphery of the lung, bronchial mononuclear cells also appear to form a predominant cell type with scanty neutrophils (in the absence of an exacerbation of infection) and, in contrast to asthma, there are relatively few eosinophils; the mononuclear component comprises lymphocytes, plasma cells, and macrophages. Significant increases are reported in the numbers of CD45 (total leucocytes), CD3 (T lymphocytes), CD25 activated and VLA-1 (late activation) positive cells and of macrophages.⁷⁴ There is an increased number of tissue eosinophils compared with that found in normal healthy controls and it has been suggested that, in contrast to asthma, the tissue eosinophils found in COPD do not degranulate.⁷² However, Saetta and co-workers found that the numbers of tissue eosinophils were only increased when there was an exacerbation of bronchitis.^{76 77} The same group of workers, together with another, report increases in the cell surface adhesion molecules associated with such inflammation.^{75 76} Our own recent study found few neutrophils and eosinophils in bronchial biopsy specimens from stable bronchitic smokers with or without COPD; as airflow limitation progressively worsened T lymphocytes and neutrophils in-

Figure 11 Histological section of a mucosal biopsy specimen taken by flexible fiberoptic bronchoscopy from a patient with an exacerbation of bronchitis. There are large numbers of CD45 + leucocytes infiltrating the subepithelial zone and fewer within the squamoid surface epithelium. (Immunostained by Dr Li using the APAAP technique and new fuchsin to stain the CD45 + cells red; biopsy specimen kindly obtained by Dr Saetta.)

Table 1 Fold increases (compared with healthy controls) in subjects with chronic bronchitis alone (CB) or with airflow limitation (CB + COPD) and atopic asthma

	CB	CB + COPD	Asthma
CD45 +	2.2	2.3	2
CD3 +	2.3	4.0	2
CD4 +	±	2.8	2.5
CD8 +	3	8.4	2
CD4:CD8 +	1:4	1:2	3:1
Neutrophil	±	2.2	−1.5
Eosinophil	1.7	3.5	93
Macrophage	4.5	8.6	±

creased in the surface epithelium as did T lymphocytes and macrophages in the subepithelium. We found that it is the CD8+ lymphocyte subset which increases in number and proportion in COPD and the increase of CD8+ cells shows a significant association with decline in lung function.¹⁰ This contrasts with the predominance and activation of the CD4+ T cell subset which is the characteristic change of mild atopic asthma. Interestingly, the high numbers of neutrophils found in lavage fluid from subjects with COPD⁷⁸ is not reflected in their numbers in the bronchial mucosa, at least in the subepithelial zone (often referred to as the lamina propria) which is the zone usually quantified in bronchial biopsies.^{10 79}

The relative changes in each cell immunophenotype in chronic bronchitis or COPD, compared with their respective values in asthma and in normal healthy subjects, are summarised in table 1. Comparative studies of the distinct patterns of interleukin and cytokine gene expression in COPD and asthma are now urgently needed.

Concluding comments

Table 2 summarises the main distinctions between COPD and asthma. There is evidence of inflammation in both conditions but there are considerable differences in terms of the predominant phenotype and the site and functional consequences of such inflammation. At this stage in our knowledge the distinctions do not appear to be absolute. However, the author believes that by rigorous recordings of clinical data, careful application of the histological, cytological, immunological and molecular techniques now available, it will be possible for biopsy specimens of conducting airways to provide for differential diagnosis and the monitoring of either disease progression or responsiveness to treatment in both COPD and asthma.

Understanding the functional consequences of persistent inflammation and the ensuing structural damage/remodelling of airway and lung structure is important, difficult, and beyond the scope of this mini-review; for a succinct summary the reader is referred to an excellent article on the subject¹³ and another which outlines the functional distinctions between the centrilobular and panlobular forms of emphysema.⁵²

The hypersecretion of mucus which characterises chronic bronchitis has traditionally been considered to be irrelevant to the accelerated rate of decline in forced expiratory volume in one second (FEV₁) and to the disability of COPD.^{80 81} However, even the role of this apparently innocuous feature of chronic bronchitis has recently been questioned as two relatively recent studies have reported that sputum volume is associated with an accelerated decline in FEV₁, increased hospital admission, and increased mortality.^{82 83} This is in addition to the undoubted detrimental effects of mucus on the stability of small airways in COPD.⁴⁷

Table 2 Simplified comparison of COPD and asthma

	COPD	Asthma
Airflow obstruction	Progressive deterioration of lung function (? reversible component)	Variable (± irreversible component)
Post mortem	Excessive mucus (mucoid/purulent), small airway disease, emphysema	Hyperinflation, airway plugs (exudate + mucus), no or little emphysema
Sputum	Macrophage, neutrophil (infective exacerbation)	Eosinophilia, metachromatic cells, Creola bodies
Surface epithelium	Fragility undetermined	Fragility/loss
Bronchiolar mucous cells	Metaplasia/hyperplasia	Mucous metaplasia is debated
Reticular basement membrane	Variable or normal	Homogeneously thickened and hyaline
Congestion/oedema	Variable/fibrotic	Present
Bronchial smooth muscle	Enlarged mass (small airways)	Enlarged mass (large airways)
Bronchial glands	Enlarged mass (increased acidic glycoprotein)	Enlarged mass (no change in mucin histochemistry)
Cellular infiltrate	Predominantly CD3, CD8, CD68, CD25, VLA-1 and HLA-DR + ve, mild eosinophilia (not degranulated?), mast cell increase	Predominantly CD3, CD4, CD25 (IL-2R) + ve, marked eosinophilia (ED2 + ve) (degranulated), mast cell increase (decrease in severe/fatal)
Cytokines (ISH)	GM-CSF protein ± IL-4 but not IL-5	IL-4 + IL-5 gene expression (Th2 profile)

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Inflammation appears to be present throughout the bronchial tree and respiratory portion of the lung in COPD. Similarly, there is widespread inflammation in asthma and tissue eosinophilia has recently been reported even in the alveolar walls.⁸⁴ The involvement of activated lymphocytes seems to be a common theme in both conditions yet the profound tissue eosinophilia of asthma does not appear in COPD. The predominant lymphocyte subsets in COPD and asthma appear to be distinct – that is, CD8+ and CD4+ cells, respectively (see table 1). Whilst there is consequent tissue destruction and remodelling in the periphery in COPD, there seems to be a contrasting trend towards involvement of relatively large proximal airways in asthma, particularly in respect of thickening of the reticular basement membrane and enlargement of the mass of bronchial smooth muscle – changes which do not occur in the large airways in COPD. The airflow limitation of COPD has two major recognised components: (1) increased resistance to airflow due mainly to the inflammatory and structural changes described in small airways and (2) loss of lung elastic recoil due to inflammation and alveolar wall destruction. It has been suggested that, when emphysema is mild to moderate, small airway lesions assume overriding importance, but if emphysema is “severe” it then dominates the contribution to decreased lung function.⁵⁹ Interestingly, a report by Hogg and co-workers found little relationship between macroscopic emphysema, severity score and FEV₁ and concluded that microscopic emphysema and small airway lesions were probably most responsible⁸⁵ for the deficit in lung function; this conclusion has received lively debate.⁸⁶

As many life long smokers do not succumb to emphysema, constitutional factors are also likely to be important. Genetic deficiency of α_1 -antitrypsin is well documented and smoking in this group clearly advances the onset of emphysema and accelerates its subsequent progression. Other genetic factors such as variation in cellular response to cytotoxicity, phagocytosis, and enzyme release may be important determinants of susceptibility to cigarette smoke.⁸⁷ More recently O’Shaughnessy and colleagues¹⁰ have suggested that airway (and lung) susceptibility to the effects of cigarette smoke is likely to be greater in those individuals who already have a genetically determined low CD4/CD8+ cell ratio in their peripheral blood.⁸⁸ This is a novel explanation as to why only about 20% of smokers might succumb to its deleterious effects; however, the hypothesis requires testing and epidemiological proof.

Long term studies (soon to be reported) of the use of inhaled corticosteroids in COPD are currently in progress to test the hypothesis that airways inflammation bears a relationship with the rate of decline in FEV₁; if the relationship is a direct one then there should be a slowing of the rate of decline following attenuation of the inflammatory reaction. We await these results with interest.

The author wishes to thank Miss Leone Oscar for her help in the preparation of the manuscript.

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