

*ABC of chronic obstructive pulmonary disease*

This is the second in a series of 12 articles

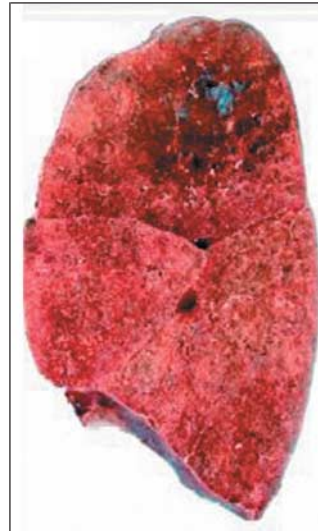
**Pathology, pathogenesis, and pathophysiology**

William MacNee

**Pathology**

Chronic obstructive pulmonary disease (COPD) is characterised by poorly reversible airflow obstruction and an abnormal inflammatory response in the lungs. The latter represents the innate and adaptive immune responses to long term exposure to noxious particles and gases, particularly cigarette smoke. All cigarette smokers have some inflammation in their lungs, but those who develop COPD have an enhanced or abnormal response to inhaling toxic agents. This amplified response may result in mucous hypersecretion (chronic bronchitis), tissue destruction (emphysema), and disruption of normal repair and defence mechanisms causing small airway inflammation and fibrosis (bronchiolitis).

These pathological changes result in increased resistance to airflow in the small conducting airways, increased compliance of the lungs, air trapping, and progressive airflow obstruction—all characteristic features of COPD. We have good understanding of the cellular and molecular mechanisms underlying the pathological changes found in COPD.



Sagittal slice of lung removed from a patient who received a lung transplant for COPD. Centrilobular lesions have coalesced to produce severe lung destruction in the upper lobe

**Pathological changes found in COPD****Proximal cartilaginous airways (>2 mm in diameter)**

- Increased numbers of macrophages and CD8 T lymphocytes
- Few neutrophils and eosinophils (neutrophils increase with progressive disease)
- Submucosal bronchial gland enlargement and goblet cell metaplasia (results in excessive mucous production or chronic bronchitis)
- Cellular infiltrates (neutrophils and lymphocytes) of bronchial glands
- Airway epithelial squamous metaplasia, ciliary dysfunction, hypertrophy of smooth muscle and connective tissue

**Peripheral airways (non-cartilaginous airways <2 mm diameter)**

- Increased numbers of macrophages and T lymphocytes (CD8 > CD4)
- Increased numbers of B lymphocytes, lymphoid follicles, and fibroblasts
- Few neutrophils or eosinophils
- Bronchiolitis at an early stage
- Luminal and inflammatory exudates
- Pathological extension of goblet cells and squamous metaplasia into peripheral airways
- Peribronchial fibrosis and airway narrowing with progressive disease

**Lung parenchyma (respiratory bronchioles and alveoli)**

- Increased numbers of macrophages and CD8 T lymphocytes
- Alveolar wall destruction from loss of epithelial and endothelial cells
- Development of emphysema (abnormal enlargement of airspaces distal to terminal bronchioles)
- Microscopic emphysematous changes:
  - Centrilobular—dilatation and destruction of respiratory bronchioles (commonly found in smokers and predominantly in upper zones)
  - Panacinar—destruction of the whole acinus (commonly found in  $\alpha_1$  antitrypsin deficiency and more common in lower zones)
- Macroscopic emphysematous changes:
  - Microscopic changes progress to bulla formation (defined as an emphysematous airspace > 1 cm in diameter)

**Pulmonary vasculature**

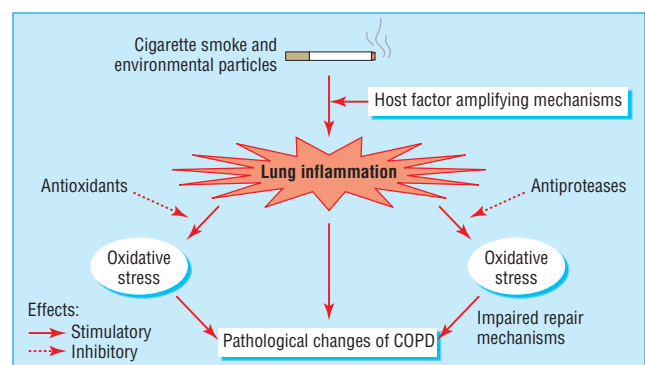
- Increased numbers of macrophages and T lymphocytes
- Early changes—Intimal thickening, endothelial dysfunction
- Late changes—Hypertrophy of vascular smooth muscle, collagen deposition, destruction of capillary bed, development of pulmonary hypertension and cor pulmonale

**Pathogenesis**

Inflammation is present in the lungs, particularly the small airways, of all people who smoke. This normal protective response to the inhaled toxins is amplified in COPD, leading to tissue destruction, impairment of the defence mechanisms that limit such destruction, and disruption of the repair mechanisms. In general, the inflammatory and structural changes in the airways increase with disease severity and persist even after smoking cessation. Besides inflammation, two other processes are involved in the pathogenesis of COPD—an imbalance between proteases and antiproteases and an imbalance between oxidants and antioxidants (oxidative stress) in the lungs.

**Inflammatory cells**

COPD is characterised by increased numbers of neutrophils, macrophages, and T lymphocytes (CD8 more than CD4) in the



The pathogenesis of COPD; dashed bars represent inhibitory effects

lungs. In general, the extent of the inflammation is related to the degree of the airflow obstruction. These inflammatory cells release a variety of cytokines and mediators that participate in the disease process. This inflammatory pattern is markedly different from that seen in patients with asthma.

### Inflammatory mediators

Many inflammatory mediators are increased in COPD, including

- Leucotriene B<sub>4</sub>, a neutrophil and T cell chemoattractant which is produced by macrophages, neutrophils, and epithelial cells
- Chemotactic factors such as the CXC chemokines interleukin 8 and growth related oncogene  $\alpha$ , which are produced by macrophages and epithelial cells. These attract cells from the circulation and amplify pro-inflammatory responses
- Pro-inflammatory cytokines such as tumour necrosis factor  $\alpha$  and interleukins 1 $\beta$  and 6
- Growth factors such as transforming growth factor  $\beta$ , which may cause fibrosis in the airways either directly or through release of another cytokine, connective tissue growth factor.

### Protease and antiprotease imbalance

Increased production (or activity) of proteases and inactivation (or reduced production) of antiproteases results in imbalance. Cigarette smoke, and inflammation itself, produce oxidative stress, which primes several inflammatory cells to release a combination of proteases and inactivates several antiproteases by oxidation. The main proteases involved are those produced by neutrophils (including the serine proteases elastase, cathepsin G, and protease 3) and macrophages (cysteine proteases and cathepsins E, A, L, and S), and various matrix metalloproteases (MMP-8, MMP-9, and MMP-12). The main antiproteases involved in the pathogenesis of emphysema include  $\alpha_1$  antitrypsin, secretory leucoprotease inhibitor, and tissue inhibitors of metalloproteases.

### Oxidative stress

The oxidative burden is increased in COPD. Sources of oxidants include cigarette smoke and reactive oxygen and nitrogen species released from inflammatory cells. This creates an imbalance in oxidants and antioxidants of oxidative stress. Many markers of oxidative stress are increased in stable COPD and are further increased in exacerbations. Oxidative stress can lead to inactivation of antiproteases or stimulation of mucous production. It can also amplify inflammation by enhancing transcription factor activation (such as nuclear factor  $\kappa$ B) and hence gene expression of pro-inflammatory mediators.

## Pathophysiology

The above pathogenic mechanisms result in the pathological changes found in COPD. These in turn result in physiological abnormalities—mucous hypersecretion and ciliary dysfunction, airflow obstruction and hyperinflation, gas exchange abnormalities, pulmonary hypertension, and systemic effects.

### Mucous hypersecretion and ciliary dysfunction

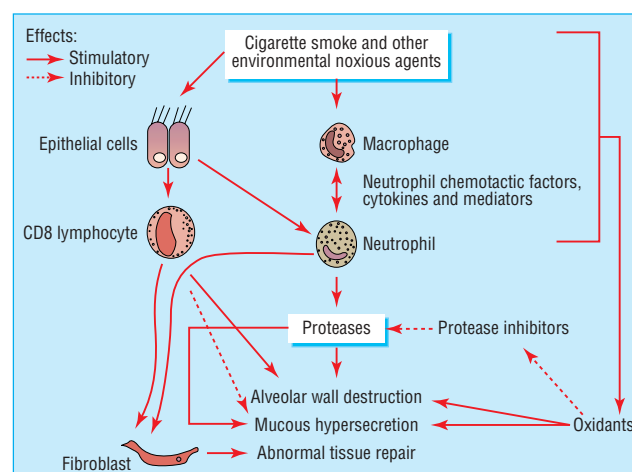
Mucous hypersecretion results in a chronic productive cough. This is characteristic of chronic bronchitis but not necessarily associated with airflow obstruction, and not all patients with COPD have symptomatic mucous hypersecretion. The hypersecretion is due to squamous metaplasia, increased numbers of goblet cells, and increased size of bronchial submucosal glands in response to chronic irritation by noxious particles and gases. Ciliary dysfunction is due to squamous metaplasia of epithelial cells and results in an abnormal mucociliary escalator and difficulty in expectorating.

### Inflammatory cells and mediators in COPD

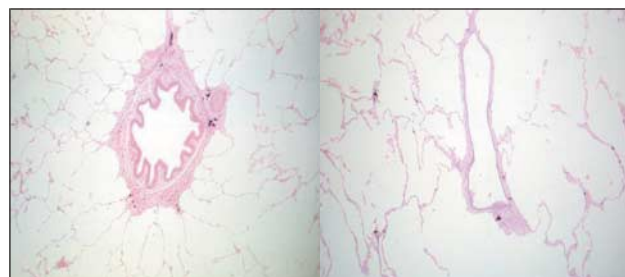
- Neutrophils, which release proteases, are increased in the sputum and distal airspaces of smokers; a further increase occurs in COPD and is related to disease severity
- Macrophages, which produce inflammatory mediators and proteases, are increased in number in airways, lung parenchyma, and in bronchoalveolar lavage fluid
- T lymphocytes (CD4 and CD8 cells) are increased in the airways and lung parenchyma, with an increase in CD8:CD4 ratio. Numbers of Th1 and Tc1 cells, which produce interferon  $\gamma$ , also increase. CD8 cells may be cytotoxic and cause alveolar wall destruction
- B lymphocytes are increased in the peripheral airways and within lymphoid follicles, possibly as a response to chronic infection of the airways.

### Proteases and antiproteases involved in COPD

Proteases	Antiproteases
Serine proteases	$\alpha_1$ antitrypsin
Neutrophil elastase	
Cathepsin G	Secretory leucoprotease inhibitor
Protease 3	Elafin
Cysteine proteases	
Cathepsins B, K, L, S	Cystatins
Matrix metalloproteases (MMP-8, MMP-9, MMP-12)	Tissue inhibitors of MMP (TIMP 1-4)



Inflammatory mechanisms in COPD. Cigarette smoke activates macrophages and epithelial cells to release chemotactic factors that recruit neutrophils and CD8 cells from the circulation. These cells release factors that activate fibroblasts, resulting in abnormal repair processes and bronchiolar fibrosis. An imbalance between proteases released from neutrophils and macrophages and antiproteases leads to alveolar wall destruction (emphysema). Proteases also cause the release of mucous. An increased oxidant burden, resulting from smoke inhalation or release of oxidants from inflammatory leucocytes, causes epithelial and other cells to release chemotactic factors, inactivate antiproteases, and directly injure alveolar walls and cause mucous secretion



Left: Normal small airway with alveolar attachments. Right: Emphysematous airway, with loss of alveolar walls, enlargement of alveolar spaces, and decreased alveolar wall attachment

### Airflow obstruction and hyperinflation or air trapping

The main site of airflow obstruction occurs in the small conducting airways that are < 2 mm in diameter. This is because of inflammation and narrowing (airway remodelling) and inflammatory exudates in the small airways. Other factors contributing to airflow obstruction include loss of the lung elastic recoil (due to destruction of alveolar walls) and destruction of alveolar support (from alveolar attachments).

The airway obstruction progressively traps air during expiration, resulting in hyperinflation at rest and dynamic hyperinflation during exercise. Hyperinflation reduces the inspiratory capacity and therefore the functional residual capacity during exercise. These features result in breathlessness and limited exercise capacity typical of COPD. The airflow obstruction in COPD is best measured by spirometry and is a prerequisite for its diagnosis.

### Gas exchange abnormalities

These occur in advanced disease and are characterised by arterial hypoxaemia with or without hypercapnia. An abnormal distribution of ventilation:perfusion ratios—due to the anatomical changes found in COPD—is the main mechanism for abnormal gas exchange. The extent of impairment of diffusing capacity for carbon monoxide per litre of alveolar volume correlates well with the severity of emphysema.

### Pulmonary hypertension

This develops late in COPD, at the time of severe gas exchange abnormalities. Contributing factors include pulmonary arterial constriction (as a result of hypoxia), endothelial dysfunction, remodelling of the pulmonary arteries (smooth muscle hypertrophy and hyperplasia), and destruction of the pulmonary capillary bed. Structural changes in the pulmonary arterioles result in persistent pulmonary hypertension and right ventricular hypertrophy or enlargement and dysfunction (cor pulmonale).

### Systemic effects of COPD

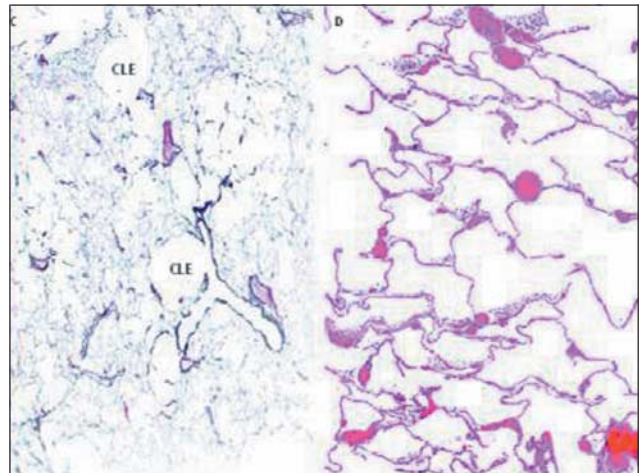
Systemic inflammation and skeletal muscle wasting contribute to limiting the exercise capacity of patients and worsen the prognosis irrespective of degree of airflow obstruction. Patients also have an increased risk of cardiovascular disease, which is associated with an increase in C reactive protein.

### Pathophysiology of exacerbations

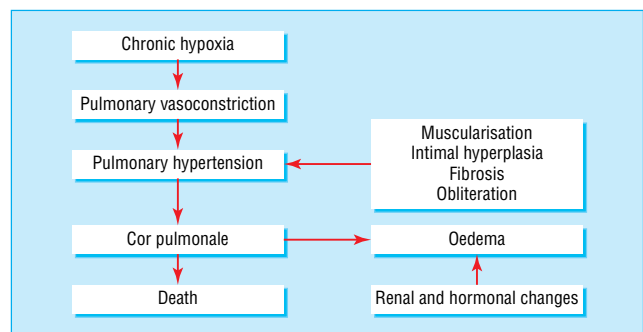
Exacerbations are often associated with increased neutrophilic inflammation and, in some mild exacerbations, increased numbers of eosinophils. Exacerbations can be caused by infection (bacterial or viral), air pollution, and changes in ambient temperature.

In mild exacerbations, airflow obstruction is unchanged or only slightly increased. Severe exacerbations are associated with worsening of pulmonary gas exchange due to increased inequality between ventilation and perfusion and subsequent respiratory muscle fatigue. The worsening ventilation-perfusion relation results from airway inflammation, oedema, mucous hypersecretion, and bronchoconstriction. These reduce ventilation and cause hypoxic vasoconstriction of pulmonary arterioles, which in turn impairs perfusion.

Respiratory muscle fatigue and alveolar hypoventilation can contribute to hypoxaemia, hypercapnia, and respiratory acidosis, and lead to severe respiratory failure and death. Hypoxia and respiratory acidosis can induce pulmonary vasoconstriction, which increases the load on the right ventricle and, together with renal and hormonal changes, results in peripheral oedema.



Left: Low power photomicrograph of the early changes of centrilobular emphysema (CLE) that have destroyed central portions of several acini of a single secondary lobule. Right: Slightly higher power photomicrograph showing the more even destruction of the lobule in panacinar emphysema



Development of pulmonary hypertension in COPD

### Systemic features of COPD

- Cachexia
- Skeletal muscle wasting and disuse atrophy
- Increased risk of cardiovascular disease (associated with increased concentrations of C reactive protein)
- Normochromic normocytic anaemia
- Secondary polycythaemia
- Osteoporosis
- Depression and anxiety

William MacNee is professor of respiratory and environmental medicine, ELEGI, Colt Research, MRC Centre for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh, Edinburgh.

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Competing interests: GPC has received funding for attending international conferences and honoraria for giving talks from pharmaceutical companies GlaxoSmithKline, Pfizer, and AstraZeneca. The pictures of a mid-sagittal slice of lung removed from a patient with COPD and of the early changes of centrilobular emphysema and of panacinar emphysema are reproduced with permission from Hogg JC. *Lancet* 2004;364: 709-21. The pictures of normal small airway and of emphysematous airway are reproduced with permission from W MacNee and D Lamb.