Mechanisms in COPD*

Differences From Asthma

Peter J. Barnes, MA, DM, DSc

Although considerable progress has been made in understanding the cellular and molecular mechanisms of asthma, much less attention has been paid to COPD. The inflammatory process in COPD is very different from that in asthma, with different inflammatory cells, mediators, inflammatory effects, and response to therapy. Airway inflammation in asthma, characterized by an eosinophilic inflammation affecting all the airways but not lung parenchyma, is linked to airway hyperresponsiveness. In COPD, there is a predominantly neutrophilic inflammation in the airways. Parenchymal destruction is an important irreversible feature and leads to airflow obstruction through dynamic compression. The eosinophilic inflammation in asthma is markedly suppressed by corticosteroids, but they have no appreciable effect on the inflammation in COPD, consistent with a failure of long-term corticosteroids to alter the progression of COPD.

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Key words: antiprotease; corticosteroids; eosinophil; macrophage; matrix metalloprotinase; neutrophil; neutrophil elastase; protease

Abbreviations: AHR = airway hyperresponsiveness; IL = interleukin; LTB_4 = leukotriene-B_4; MMP = matrix metalloproteinase

Considerable progress has been made in understanding the cellular and molecular mechanisms of asthma as an inflammatory disease, but despite its importance, COPD has been relatively neglected. COPD is often managed in clinical practice as poorly responsive asthma, but these diseases are very different in terms of cellular mechanisms, inflammatory mediators, inflammatory effects, and response to therapy. However, some patients with COPD (~10%) also have asthma, and these patients have some of the characteristics of asthma, which has confused the picture (Fig 1). Both diseases are characterized by airflow obstruction and a chronic persistent inflammatory process, but the nature of the inflammation differs markedly between these diseases (Table 1).

Inflammatory Cells and Pathology

Airway inflammation in asthma is characterized by an eosinophilic inflammation, with an increase in activated and degranulating eosinophils in bronchial biopsies, BAL, and in induced sputum.[1,2] There is also an increase in $CD4^+$ T lymphocytes (T-helper type 2 cells) that appear to orchestrate the eosinophilic inflammation and degranulated mast cells that underlie the rapid and episodic bronchoconstrictor responses that are so characteristic of asthma. Epithelial shedding is a common feature of biopsies from asthmatic airways and may be a consequence of eosinophilic inflammation. Inflammation affects all of the airways in asthma and does not involve the lung parenchyma. Fibrosis is remarkable by its absence, and although much has been made of the subepithelial fibrosis, this is trivial in amount and is seen even in patients with very mild asthma of short duration. Airway hyperresponsiveness (AHR) is the characteristic physiologic abnormality in asthma, and although its mechanism is uncertain, it is linked to eosinophilic inflammation.

The pathology of COPD differs markedly from that of asthma.[2–4] In larger airways, there is evidence of neutrophil rather than an eosinophilic inflammation, as judged by increased numbers of neutrophils in BAL.[5] Induced sputum shows a characteristic increase in the proportion of neutrophils that is much greater in patients with COPD than in smokers without obstruction (Fig 2).[6] Granulocyte markers of neutrophil inflammation, namely myeloperoxidase and human neutrophil lectin, are actively degranulating.[7] Unexpectedly, there is also an increase in eosinophil basic proteins (eosinophil cationic proteins and eosinophil peroxidase) in induced

*From the Department of Thoracic Medicine, National Heart and Lung Institute, London, UK.
Correspondence to: Peter J. Barnes MA, DM, DSc, Department of Thoracic Medicine, National Heart and Lung Institute, Dovehouse St, London SW3 6LY, UK; email: p.j.barnes @ic.ac.uk

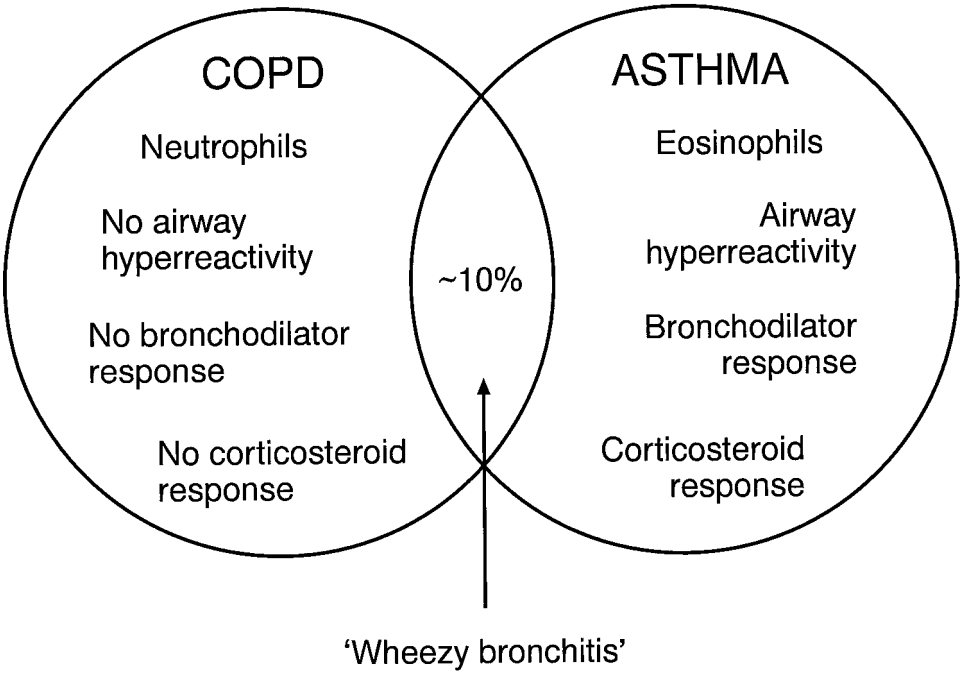

FIGURE 1. Overlap between COPD and asthma. Approximately 10% of patients with COPD also have asthma and therefore share pathologic features ('wheezy bronchitis').

sputum of COPD patients, although no increase in the number of eosinophils. This may indicate that any eosinophils have degranulated and therefore cannot be recognized. This may be because of the effects of neutrophil elastase.[8] Bronchial biopsies have demonstrated an infiltration with mononuclear cells, $CD4^+$ and particularly $CD8^+$ T lymphocytes, rather than neutrophils, suggesting that neutrophils may transit rapidly from the circulation into the airway lumen.[2,3] Biopsies of ex-smokers show a similar inflammatory process, suggesting that inflammation may persist in the airway once established.[9] Similar cellular changes are found in the lung parenchyma with a predominance of macrophages and $CD8^+$ T cells at sites of parenchymal destruction.[4,10] In contrast with asthma, most of the pathologic changes are found in peripheral airways, where there is also fibrosis, resulting in an obliterative bronchiolitis. There is no epithelial shedding in COPD, and, in fact, squamous metaplasia is more likely. AHR is not a feature of COPD, although there may be an increased responsiveness to constrictors such as cholinergic agonists and histamine. In COPD, this can be explained entirely by the geometric effect of fixed airway narrowing, whereas in asthma the hyperresponsiveness is unrelated to baseline airway caliber. Furthermore, in COPD, unlike asthma, patients do not constrict with indirect bronchial challenges, such as exercise and bradykinin. Mucus hypersecretion is a prominent feature of COPD, with metaplasia of submucosal glands and goblet cells, whereas this is a less prominent feature of asthma.

Cigarette smoking and other inhaled irritants may initiate an inflammatory response in the peripheral airways and lung parenchyma. It is likely that neutrophil chemotactic factors are released from activated macrophages and possibly from epithelial cells and $CD8^+$ T lymphocytes (Fig 3). Macrophages may

Table 1—*Differences Between COPD and Asthma

Inflammation	Asthma	COPD
Inflammatory cells	Mast cells	
	Eosinophils	Neutrophils
	$CD4^+$ cells (Th2)	$CD8^+$ cells (Tc)
	Macrophages+	Macrophages++
Inflammatory mediators	LTB_4, histamine	LTB_4
	IL-4, IL-5, IL-13	TNF-α
	Eotaxin, RANTES	IL-8, GRO-α
	Oxidative stress+	Oxidative stress+++
Inflammatory effects	All airways	Peripheral airways
	AHR+++	AHR±
	Epithelial shedding	Epithelial metaplasia
	Fibrosis+	Fibrosis++
	No parenchymal involvement	Parenchymal destruction
	Mucus secretion+++	Mucus secretion+++
Response to corticosteroids	±	

*Th2 = T-helper type 2.

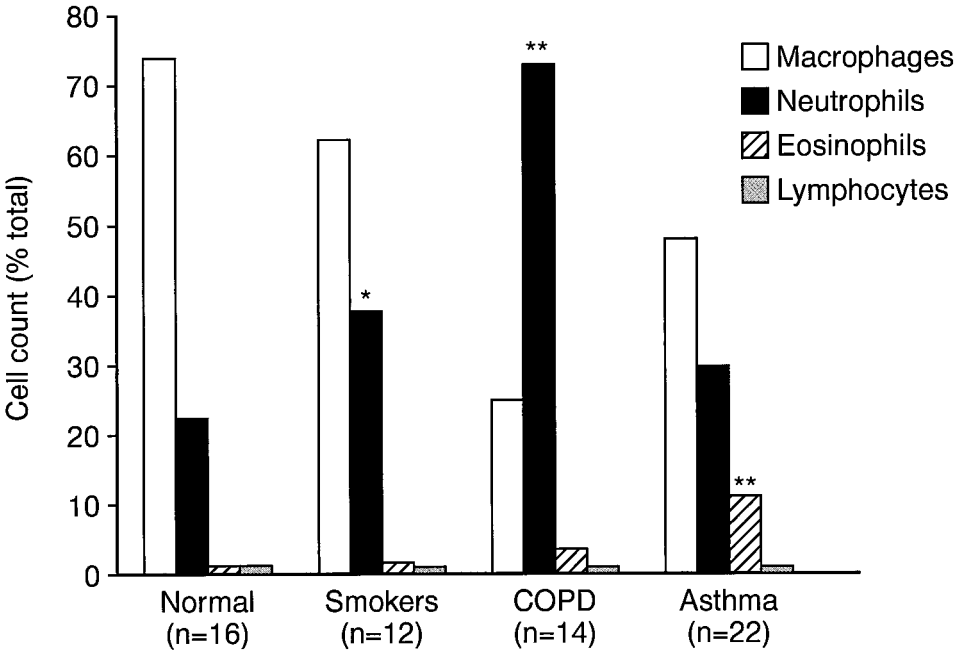

FIGURE 2. Inflammatory cells in induced sputum. Shown is a profile of inflammatory cells in induced sputum in normal subjects, cigarette smokers, and patients with COPD and asthma. There is a significant increase in neutrophils in smokers and COPD patients, but significantly higher in COPD, whereas there is a significant increase in eosinophils in asthma. Mean values are shown; * $p = 0.05$; ** $p < 0.01$. Adapted with permission from Keatings et al.[6]

play an important role in driving the inflammatory process in COPD and may release neutrophil chemotactic factors as well as proteolytic enzymes. Macrophages may be activated by cigarette smoke and other inhaled irritants. Macrophage numbers are increased by five- to ten-fold in BAL of patients with COPD and are concentrated in the centriacinar zones where emphysema is most marked. Furthermore, the numbers of macrophages and T lymphocytes, but not the numbers of neutrophils, in the alveolar wall correlate with the amount of parenchymal destruction.[10] Macrophages may be responsible for the continued proteolytic activity in the lungs of patients with emphysema.

Inflammatory Mediators

More than 50 inflammatory mediators have been implicated in asthma.[11] Cysteinyl-leukotrienes are prominent bronchoconstrictors in asthma and are derived from mast cells and eosinophils. Histamine, prostaglandins, and kinins may also contribute to bronchoconstriction in asthma. Cholinergic reflexes may be activated by these inflammatory mediators, particularly kinins. β_2-Agonists are by far the most effective bronchodilators in asthma, as they act as functional antagonists and counteract the bronchoconstrictor action of multiple mediators. In contrast, there are likely to be few bronchoconstrictor mediators released in COPD airways, and cholinergic tone is likely to be the only reversible component. This explains why anticholinergic drugs are relatively more effective in COPD and may be even more effective than β_2-agonists. Leukotriene-B_4 (LTB_4) is more likely to be important in COPD than in asthma, as it is a potent neutrophil chemoattractant. Elevated levels of LTB_4 have been found in induced sputum of patients with COPD.[12]

The cytokines of asthma differ from those involved in COPD. In asthma, interleukin (IL)-4 and IL-13 are likely to be important, as they are necessary for IgE formation, whereas IL-5 is critical for eosinophilic inflammation.[13] Eosinophil chemotactic cytokines (CC chemokines), such as eotaxin and RANTES, are also important in asthmatic inflammation and selectively recruit primed eosinophils from the circulation into the airways. In COPD, IL-8 is prominent and is a selective attractant of neutrophils.[6] IL-8 levels in induced sputum are correlated with the extent of neutrophilic inflammation and with disease severity (% predicted FEV_1).[6,14] Other CXC chemokines, such as GRO-α, may also be involved in neutrophil recruitment in COPD. Tumor necrosis factor-α, also present in high concentration in the sputum of COPD patients, may activate the transcription of nuclear factor-κB, which switches on

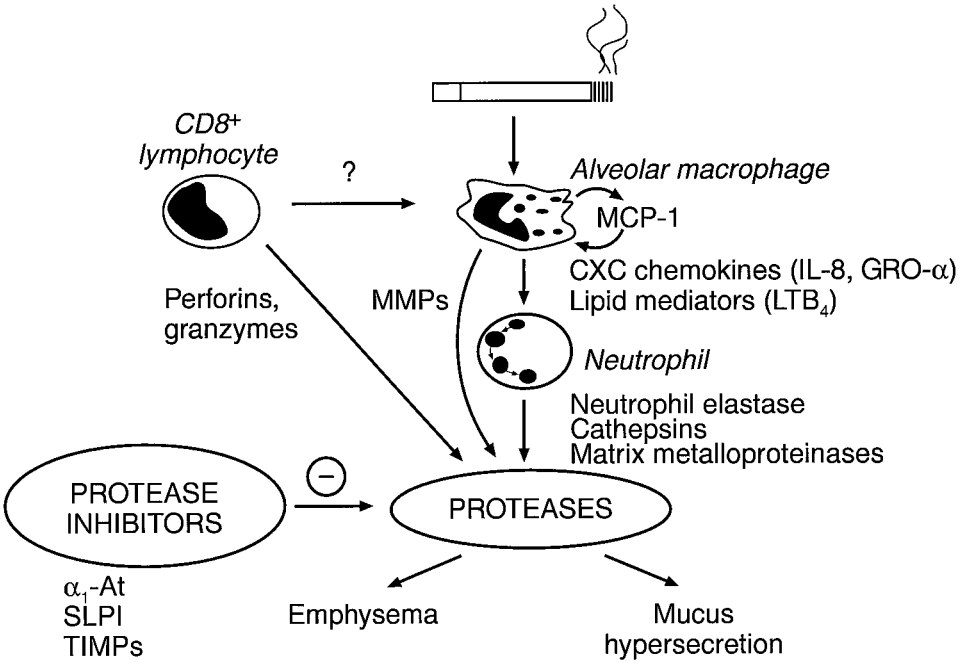

FIGURE 3. Inflammatory mechanisms in COPD. Cigarette smoke (and other irritants) activate macrophages in the respiratory tract that release neutrophil chemotactic factors, including IL-8 and LTB_4. These cells then release proteases that break down connective tissue in the lung parenchyma, resulting in emphysema, and also stimulate mucus hypersecretion. These enzymes are normally counteracted by protease inhibitors, including α_1-antitrypsin (α_1-At), secretory leukoprotease inhibitor (SLPI), and tissue inhibitor of MMPs (TIMPs). Cytotoxic T cells ($CD8^+$) may also be involved in the inflammatory cascade.

the transcription of the IL-8 gene.[15] LTB_4 is increased in the sputum of patients with COPD.

Oxidative stress is a feature of both asthma and COPD, but is more prominent in COPD.[16] This is likely to be because of the large increase in activated macrophages and neutrophils in COPD, and the effects of cigarettes, which provide a very large oxidative stress. Markers of oxidative stress are increased in COPD.[17]

ENZYMES

Several inflammatory enzymes are involved in asthma.[11] Mast cell tryptase may play an important role in AHR and in some aspects of airway remodeling in asthma. In COPD, there is excessive activity of proteases, and an imbalance between proteases and endogenous antiproteases. Several proteases are likely to be involved in lung parenchymal destruction. Neutrophil elastase, a neutral serine protease, is a major constituent of lung elastolytic activity and also potently stimulates mucus secretion. Although neutrophil elastase is likely to be the major mechanism mediating elastolysis in the patient's α_1-antitrypsin deficiency, it may well not be the major elastolytic enzyme in smoking-related COPD; it is important to consider other enzymes as targets for inhibition, including cathepsins and matrix metalloproteinases (MMPs). MMPs are produced by several inflammatory cells, including macrophages and neutrophils.[18] Increased levels of collagenase (MMP-1) and gelatinase B (MMP-9) have been detected in BAL fluid of patients with emphysema.[19] There is a marked increase in the expression and activity of MMP-2 and MMP-9 in the parenchyma of patients with emphysema compared with normal lung.[20] Lavaged macrophages from patients with emphysema express more MMP-9 and MMP-1 than cells from control subjects, suggesting that these cells, rather than neutrophils, may be the major cellular source.[21] Alveolar macrophages also express a unique MMP, macrophage metalloelastase (MMP-12).[22] MMP-12 knock-out mice do not develop emphysema and do not show the expected increases in lung macrophages after long-term exposure to cigarette smoke.[23] In contrast, the levels of MMPs are lower in patients with asthma and may be derived predominantly from eosinophils[24]; this is not surprising since parenchymal destruction is not a feature of asthma.

$CD8^+$ (cytotoxic or Tc cells) may also contribute to parenchymal destruction through the release of proteolytic perforins and granzymes.

Response to Anti-inflammatory Treatment

The response to treatment differs markedly between asthma and COPD. The eosinophilic inflammation in asthma is markedly suppressed by corticosteroids, which inhibit almost every aspect of the inflammatory process.[25] There is a disappearance of eosinophils from the airways and sputum, with a reduction in AHR. In contrast, corticosteroids do not appear to have any effect on the inflammation in COPD, with no changes in neutrophilic inflammation, reduction in inflammatory mediators, or proteases.[26,27] There is a contrasting effect of corticosteroids on granulocytes, with a reduction in eosinophil survival but a prolongation of neutrophil survival.[28] This is consistent with a failure of long-term corticosteroids to alter the progression of COPD, and indicates that new types of anti-inflammatory treatment need to be developed in the future.[29,30]

References

1 Barnes PJ. Pathophysiology of asthma. Br J Clin Pharmacol 1996; 42:3–10
2 Jeffery PK. Structural and inflammatory changes in COPD: a comparison with asthma. Thorax 1998; 53:129–136
3 Saetta M, Di Stefano A, Maestrelli P, et al. Activated T-lymphocytes and macrophages in bronchial mucosa of subjects with chronic bronchitis. Am Rev Respir Dis 1993; 147:301–306
4 Saetta M, Di Stefano A, Turato G, et al. CD8+ T-lymphocytes in peripheral airways of smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998; 157:822–826
5 Thompson PB, Daughton D, Robbins GA, et al. Intramural airway inflammation in chronic bronchitis: characterization and correlation with clinical parameters. Am Rev Respir Dis 1989; 140:1527–1537
6 Keatings VM, Collins PD, Scott DM, et al. Differences in interleukin-8 and tumor necrosis factor-α induced sputum from patients with chronic obstructive pulmonary disease or asthma. Am J Respir Crit Care Med 1996; 153:530–534
7 Keatings VM, Barnes PJ. Granulocyte activation markers in induced sputum: comparison between chronic obstructive pulmonary disease, asthma and normal subjects. Am J Respir Crit Care Med 1997; 155:449–453
8 Liu H, Lazarus SC, Caughey GH, et al. Neutrophil elastase and elastase-rich cystic fibrosis sputum degranulate human eosinophils in vitro. Am J Physiol 1999; 276:L28–L34
9 Turato G, Di Stefano A, Maestrelli P, et al. Effect of smoking cessation on airway inflammation in chronic bronchitis. Am J Respir Crit Care Med 1995; 152:1262–1267
10 Finkelstein R, Fraser RS, Ghezzo H, et al. Alveolar inflammation and its relation to emphysema in smokers. Am J Respir Crit Care Med 1995; 152:1666–1672
11 Barnes PJ, Chung KF, Page CP. Inflammatory mediators of asthma; an update. Pharmacol Rev 1998; 50:515–596
12 Zakrzewski JT, Barnes NC, Costello JF, et al. Lipid mediators in cystic fibrosis and chronic obstructive pulmonary disease. Am Rev Respir Dis 1987; 136:779–782
13 Chung KF, Barnes PJ. Cytokines in asthma. Thorax 1999; 54:825–857
14 Yamamoto C, Yoneda T, Yoshikawa M, et al. Airway inflammation in COPD assessed by sputum levels of interleukin-8. Chest 1997; 112:505–510
15 Barnes PJ, Karin M. Nuclear factor-κB: a pivotal transcription factor in chronic inflammatory diseases. N Engl J Med 1997; 336:1066–1071
16 Repine JE, Bast A, Lankhorst I. Oxidative stress in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997; 156:341–357
17 Pratico D, Basili, S, Vieri M, et al. Chronic obstructive pulmonary disease is associated with an increase in urinary levels of isoprostane F_{2a}-111, an index of oxidant stress. Am J Respir Crit Care Med 1998; 158:1709–1714
18 Shapiro SD. Elastolytic metalloproteinases produced by human mononuclear phagocytes: potential roles in destructive lung disease. Am J Respir Crit Care Med 1994; 150(Suppl): S160–S164
19 Finlay GA, Russell KJ, McMahon KJ, et al. Elevated levels of matrix metalloproteinases in bronchoalvoelar lavage fluid of emphysematous patients. Thorax 1997; 52:502–506
20 Ohnishi K, Takagi M, Kurokawa Y, et al. Matrix metalloproteinase mediated extracellular matrix protein degradation in human pulmonary emphysema. Lab Invest 1998; 78:1077–1087
21 Finlay GA, O'Driscoll LR, Russell KJ, et al. Matrix metalloproteinase expression and production by alveolar macrophages in emphysema. Am J Respir Crit Care Med 1997; 156:240–247
22 Shapiro SG, Kobayashi DK, Ley TJ. Cloning and characterization of a unique elastolytic metalloproteinase produced by human alveolar macrophages. J Biol Chem 1993; 268:23824–23829
23 Hautamaki RD, Kobayashi DK, Senior RM, et al. Requirement for macrophage metalloelastase for cigarette smoke-induced emphysema in mice. Science 1997; 277:2002–2004
24 Vignole AM, Riccobono L, Mirabella A, et al. Sputum metalloprotinase-9/tissue inhibitor of metalloprotinase-1 ratio correlates with airflow obstruction in asthma and chronic bronchitis. Am J Respir Crit Care Med 1998; 158:1945–1950
25 Barnes PJ. Mechanism of action of glucocorticoids in asthma. Am J Respir Crit Care Med 1996; 154(Suppl):S21–S27
26 Keatings VM, Jatakanon A, Worsdell YM, et al. Effects of inhaled and oral glucocorticoids on inflammatory indices in asthma and COPD. Am J Respir Crit Care Med 1997; 155:542–548
27 Culpitt SV, Nightingale JA, Barnes PJ. Effect of fluticasone propionate on induced sputum matrix metalloproteinases and tissue inhibitors of metalloproteinases in patients with COPD. Am J Respir Crit Care Med 1999; 160:1635–1639
28 Meagher LC, Cousin JM, Seckl JR, et al. Opposing effects of glucocorticoids on the rate of apoptosis in neutrophilic and eosinophilic granuloctyes. J Immunol 1996; 156:4422–4428
29 Barnes PJ. New therapies for chronic obstructive pulmonary disease. Thorax 1998; 53:137–147
30 Barnes PJ. Chronic obstructive pulmonary disease: new opportunities for drug development. Trends Pharmacol Sci 1998; 19:415–423