Part I

Asthma and COPD

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Pathology of asthma and COPD : inflammation and structure

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Introduction

It is widely recognized that neither asthma nor COPD are disease entities but rather each is a complex of inflammatory conditions that have in common airflow limitation (syn. obstruction) whose reversibility varies (Fig. 1.1). The characteristics and distinctions between mild stable asthma and COPD have been reviewed[1,2]. However, these differences become less clear when the conditions become severe or there are exacerbations due to infection or other cause. An understanding of whether or not there are fundamental differences of inflammation and airway/lung structure between these two conditions is relevant to clinical decisions regarding both initiation and long-term treatment and to patient management during exacerbations. In the longer term it is of value to the design of specific therapy for asthma and COPD and to their prevention. Whilst the definitions of asthma and COPD highlight the differing degrees of airflow variability and reversibility[3,4], there is a prevailing clinical impression that, with age, there is often overlap and a progression from the reversible airflow obstruction of the young asthmatic to the more irreversible or 'fixed' obstruction of the older patient with COPD. The Dutch hypothesis encompasses the idea that both conditions are extreme ends of a single condition[5]. In the author's opinion it may, in the future, be less relevant to be concerned with the clinical labels of 'asthma' or 'COPD' and more important to ascertain and target treatment to the predominant pattern of inflammation and structural change that prevails in each patient.

Asthma may be divided into extrinsic (also called allergic or atopic), intrinsic (late onset or non-atopic) and occupational forms. At this time the pathologist cannot distinguish between these distinct clinical forms of asthma: there are alterations that appear to be common to all forms. COPD is associated, usually, with the smoking habit as the relationship between cigarette smoking and COPD is a strong one statistically. Three conditions can contribute, the degree varying in each patient, to the clinical expression of COPD: chronic bronchitis (syn. mucus hypersecretion), chronic bronchiolitis (syn. small airways disease) and emphysema, inflammatory conditions broadly affecting bronchi (airways with cartilage in their wall), bronchioli (membranous or non-cartilaginous airways) and lung parenchyma respectively. In both asthma and COPD, the persistence of distinct inflammatory cells initiated by allergen or cigarette smoke, respectively, is probably responsible for most of the structural change and usually referred to as 'remodelling': interactions with the effects of acute and chronic infection and genetic predisposition are clearly important also.

The chapter focuses on the patterns of infiltrating inflammatory cells in asthma and COPD and the associated remodelling of the airway wall. First, airway wall thickening is considered, particularly in asthma, remodelling is defined and the relationship between inflammation and remodelling discussed briefly. Lumenal secretions obtained as sputum or lavage and asphyxic plugging of the airways with mixtures of mucus and inflammatory exudate are discussed briefly. The chapter then divides into two
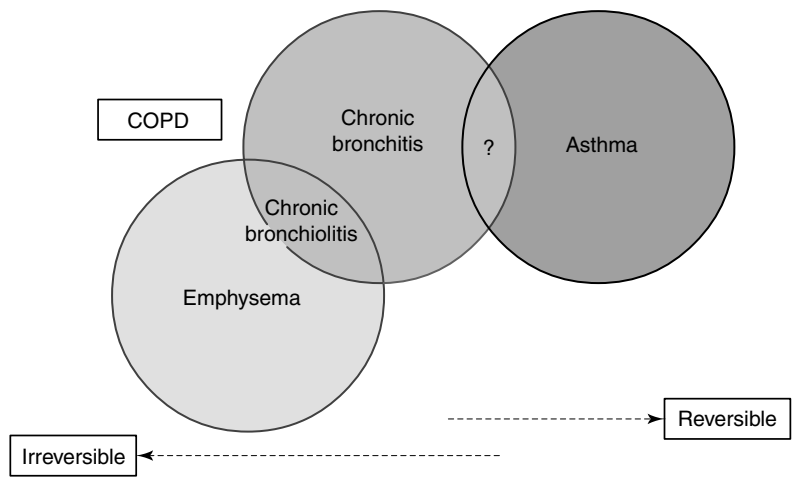
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Fig. 1.1 Venn diagram illustrating the overlap between asthma and COPD.

major sections considering first inflammation and then remodelling in asthma and COPD. The results of examination of the conducting airways by flexible fibre-optic bronchoscopy are included as this technique has provided the means by which the early inflammatory and structural alterations of asthma and COPD have been compared, free from the complications of end stage disease[6].

Airway wall thickening

The airway walls in asthma are thickened by the remodelling process by between 50 and 300% of normal and there is lumenal narrowing, which is further compromised by excessive mucus admixed with an inflammatory exudate (Fig. 1.2, see colour plate section). In cases of fatal asthma, the longer the duration of asthma, the thicker becomes the airway wall[7]. However, it has been suggested that airway wall thickness *per se* is not a requirement for asphyxic fatality as a group of relatively young asthmatics (i.e. with a relatively short history of asthma) had an airway wall thickness not significantly different from that of non-asthma controls. Lumenal secretions and plugging are likely the greater contribution to asthmatic death in these young cases of

fatal asthma[7]. All tissue structural components, as well as inflammatory cell infiltration and edema, can contribute to the observed thickening; however, in the last mentioned study it is thickening of the (outer) adventitial layers that was most pronounced in the older group with the longest duration of disease. The airway walls are also thickened in COPD. One systematic study has described changes in large airway dimensions in relation to the lung function of patients with COPD and found wall area internal to the muscle to be significantly thickened over the entire range of cartilaginous airways measured[8]. The relative contributions of the airway wall components contributing to the thickening, however, vary with airway generation.

Inflammation and remodelling

Acute inflammation is the response of vascularized tissue to injury: the inflammatory reaction is designed to protect the host and to restore tissue and its function to normal. One generally accepted proposal is that the accelerated decline in forced expiratory flow over time in COPD, and that which occurs also in an important subset of asthmatics, is the direct result of a switch from acute, episodic, to chronic inflammation and to consequent airway and parenchymal remodelling[1]. The proposal is

attractive but, as yet, there is no convincing evidence that the remodelling process is dependent upon the prior development of chronic inflammation. It is equally plausible that the processes responsible for the development of chronic inflammation are distinct to those responsible for remodelling. The last consideration has important implications for the design of disease modifying therapy: thus those agents that are effective antiinflamatory compounds will not necessarily prevent or attenuate the process of remodelling for which new classes of drugs will be required.

Definition

The concept of 'remodelling' implies that a process of 'modelling' must have preceded it. The lung, in utero, undergoes extensive modelling and remodelling yet these processes are entirely appropriate to the normal process of lung development. Many of the cytokines and growth factors thought to be pro-inflammatory in asthma and in COPD are also expressed normally without detriment to the developing lung; these include: members of the fibroblast growth factor family, the transforming growth factor family, epithelial-derived growth factor, granulocyte–macrophage colony stimulating factor, platelet-derived growth factor, vascular endothelial growth factor and hepatocyte growth factor[1,9]. Accordingly the working definition of remodelling proposed herein recognizes that the process of remodelling *per se* is not of necessity abnormal. It is: an alteration in size, mass or number of tissue structural components that occurs during growth or in response to injury and/or inflammation. It may be appropriate, as in normal lung development or that which occurs during acute reaction to injury, or 'inappropriate' when it is chronic and associated with abnormally altered tissue structure and function as, for example, in asthma or COPD.

   In wound healing (in the skin) the components of an appropriate response include: clot formation, swelling/edema, rapid restitution of the denuded areas by epithelial dedifferentiation, proliferation and migration from the margins of the wound. This is normally associated with an inflammatory reaction, i.e. early infiltration of the injured tissue by neutrophils and later by lymphocytes and macrophages. Reticulin is deposited within days and this may mature to form interstitial collagen, a scar, within 2–3 weeks. In addition, healing may involve contraction of the surrounding tissue (in the case of an open wound), by myofibroblasts that may proliferate transiently in relatively large numbers[10]. Vasodilatation, congestion and mucosal oedema are also cardinal signs of acute inflammation and the angiogenesis of the granulation tissue is an integral part of the reparative response. Thus, normal tissue architecture and function is restored consequent to an entirely appropriate inflammatory reaction with which there has been an associated remodelling process. Each of these stages in normal wound healing and many of the inflammatory cell types and cytokines involved appear also in asthma and in COPD, but in these last two conditions both the inflammation and remodelling persist and result in exaggerated remodelling inappropriate to the maintenance of normal (airway) function. The reasons for the persistence of the inflammation are unknown but may be the result of repeated inhalation of allergen or exposure to high concentrations of allergen, irritation (e.g. by tobacco smoke) or persistent infection or a genetically influenced abnormal host inflammatory response or a defective repair process.

Lumenal secretions

Sputum and bronchoalveolar lavage

The examination of spontaneously produced or saline-induced sputum has become a much used and relatively non-invasive method for determining the extent of inflammation in the asthmatic airway[11,12] (Fig. 1.3(*a*), 1.2(*b*), see colour plate section). Corkscrew-shaped twists of condensed mucus (Curshmann's spirals), clusters of surface airway epithelial cells (referred to as Creola bodies and named after the first patient in whom they were described)[13], and the presence of Charcot–Leyden

crystals, composed of eosinophil cell and granule membrane lysophospholipase (Fig. 1.3(a), (b), see colour plate section[14]), together with eosinophils and metachromatic cells, are characteristic features of sputa obtained from asthmatic, but not bronchitic patients[15]. Sputum eosinophilia has, however, also been reported in non-asthmatics in the absence of the airways hyper-responsiveness (AHR) characteristic of asthma[16]. In contrast, sputa from bronchitic patients may be mucoid or, during infective exacerbations, purulent when neutrophils may be present in large numbers. BAL in mild (allergic) asthma demonstrates the presence of sloughed epithelial cells, the numbers of which show an association with AHR,[17] and of eosinophils and their highly charged secreted products (such as eosinophil cationic protein (ECP) and major basic protein (MBP))[18]. In contrast, in smoker's bronchitis, macrophages are the most usually reported cell type and neutrophils are numerous as are their secreted products.

Airway plugging

Examination, postmortem, of cases of fatal asthma has shown that the lungs are hyperinflated and remain so on opening the pleural cavities due to the widespread presence of markedly tenacious airway 'plugs' in both large (segmental) and small bronchi (Fig. 1.4(a)), see colour plate section. Even intrabronchial inflation with fixative to a 1.5-metre head of pressure hardly moves these sticky lumenal plugs[19]. Histologically the airway plugs in asthma are composed predominantly of inflammatory exudate together with mucus in which lie: eosinophils, lymphocytes and desquamated surface epithelial cells. The arrangement of the eosinophilic elements of the plug is often as concentric, multiple lamellae suggesting that several episodes of inflammation have led to their formation rather than a single terminal event (Fig. 1.4(b), see colour section). The nonmucinous, proteinaceous contribution is the result of increased vascular permeability and includes a fibrin. Electrostatic interaction of positively charged (cationic) eosinophil products and serum constituents and negatively charged (due to carboxyl and sulfate groups) mucin likely contributes to the particular stickiness of the airway plug. There are, however, reports of sudden death in asthmatics in which intraluminal plugs are absent[20] but these are rare. In the absence of a history of smoking, emphysema in fatal asthma and right ventricular hypertrophy is uncommon. However, areas of atelectasis and petechial hemorrhages may be present in asthma due to bronchial obstruction, reabsorption collapse and repeated forced inspiratory efforts. The asthmatic who has smoked will likely have features which overlap between asthma and COPD and, in these cases, there may be focal evidence of centriacinar (i.e.bronchocentric) alveolar destruction (see Fig. 1.4(a), colour plate section).

Inflammation

To the physiologist, inflammation is characterized by cardinal signs: redness, heat, swelling, pain and loss of normal function. To the pathologist, inflammation is recognized in tissue sections as congestion of vessels together with the recruitment (i.e. margination within and emigration from vessels) of a variety of morphologically and immuno-phenotypically distinct inflammatory cells. It is now recognized that both asthma[21,22] and COPD are inflammatory conditions albeit the relative magnitude and site of the inflammatory infiltrate and the predominant inflammatory cell phenotype differs.

Asthma

Studies of biopsies obtained by fibreoptic bronchoscopy or at open lung biopsy in asthma demonstrate the presence of an inflammatory cell infiltrate even in patients with newly diagnosed asthma[23]. The infiltrate comprises CD3 immuno-positive (T) lymphocytes of the CD4 (i.e. T-helper) subset and eosinophils[17,24–26]. An increase in leukocytes, including lymphocytes and eosinophils, occurs in relatively mild atopic, occupational and intrinsic asthma and it is associated with an increase of 'activation' markers for both lymphocytes (CD25 + cells)

and eosinophils (EG2 + cells)[21,24,26–28]. In symptomatic atopic asthmatics, in electron microscopic studies, irregularly shaped lymphomononuclear cells appear and these may represent ultrastructural forms of the CD25 + (activated) lymphocyte. EG2 is a marker for the cleaved ('secreted') form of eosinophil cationic protein that can be found both within eosinophils and diffusely in the wall, often in association with the epithelial reticular basement membrane. Eosinophil-derived products such as major basic protein[29] together with toxic oxygen radicals and proteases probably all contribute to the epithelial fragility described in asthma (see below). Eosinophil cytolysis or disintegration and release of granules[30,31] and of cytokines may also stimulate nearby fibroblasts to produce additional reticulin and so induce thickening of the reticular basement membrane.

In fatal asthma there is a marked infiltrate throughout the airway wall, in sputum and also in the occluding plug. Compare Fig. 1.5(*a*) and (*b*), see colour plate section, see Figs. 1.3(*a*) and 1.4(*b*), see colour plate section: lymphocytes are abundant[22,32,33] and (EG2+)eosinophils are characteristic (Fig. 1.6, see colour plate section)[22,34,35]. Neutrophils are sparse in mild asthma[21] albeit they are present in relatively large numbers in sputa during infective exacerbations[36], in biopsies of severe asthmatics refractory to high dose treatment with corticosteroids[37] and in status asthmaticus when death is sudden (i.e. within 24 hours of the attack)[38]. It has been suggested based on examination of biopsy tissue that two forms of asthma may be usefully distinguished: those with a relatively high eosinophil count and those with predominant neutrophilia[39]. The inflammation of the airway wall may involve the adjacent pulmonary artery[33] and, in small (distal) airways, may spread to surrounding alveolar septae[40]. Alveolar walls may thus show evidence of eosinophilic infiltration[40] and alveolar spaces may contain a fibrillar-rich component, most likely fibrin (author's unpublished observations). However, destruction of the parenchyma (i.e. emphysema) is not a feature of asthma. Thus, both small and large airways may be inflamed in asthma:

transbronchial biopsy studies of relatively severe asthma and studies of resection tissue in asthmatics have demonstrated infiltration of bronchioli by eosinophils and lymphocytes[40,41]. There are also recent data in severe asthma that demonstrate the inner wall to be infiltrated by neutrophils in numbers considerably greater than in larger airways[42]. Thus the pattern of inflammation in severe asthma appears to be different from that in mild and, in order to be effective, treatment needs to be tailored accordingly. The association of tissue eosinophilia and asthma is a strong one. However, the extent of tissue eosinophilia varies greatly with each case and with the duration of the terminal episode[22,38,43]. The variation may be due, in part, to eosinophil degranulation, which makes cell identification difficult. In comparison with mild asthma, fatal asthma is reported to be associated with a higher concentration of eosinophils in the large airways and a reduction of lymphocytes in the peripheral (smaller) airways[35].

The role of the activated T-helper (Th) lymphocyte in controlling and perpetuating the chronic inflammatory reaction in asthma has received much attention[24,44]. The T-lymphocyte is thought to control allergic inflammation via the selective release of the proinflammatory cytokines (interleukins) IL-4 and IL-5, which characterize the T-helper (type 2) phenotype[45]. IL-5 gene expression has been shown to be increased in bronchial biopsies from symptomatic atopic asthmatic subjects[46] (Fig. 1.10), and this is supported by studies of cells obtained at bronchoalveolar lavage[47,48] and peripheral blood[49]. IL5 appears to be a key cytokine required to induce terminal differentiation of eosinophils and, together with IL4, enhances their vascular retention and longevity in tissues. It is also a key cytokine in the late phase reaction to allergen challenge[48]. IL4 is also increased in atopic asthma[50,51] and may be important in both the initiation and persistence of allergic inflammation. IL4 encourages the selective recruitment of eosinophils by up-regulating adhesion molecules (V-CAM) on bronchial endothelium whose ligand on the eosinophil cell surface is VLA-4. The last is absent from the surface of neutrophils

and helps to explain the eosinophil predominance in mild asthma. There is currently debate as to the involvement of IL4 in asthma of the intrinsic (i.e. non-atopic) form[52]. IL4 and IL5 are not, however, unique to asthma and may occur in other inflammatory conditions such as fibrosing alveolitis[53]. Whilst IL5 may be important in promoting eosinophil terminal differentiation, and the release of eosinophils into the blood from bone marrow, other molecules such as eotaxin and RANTES (regulated on activation normal T-cell expressed and secreted) are involved as selective chemokines inducing eosinophil emigration from blood vessels and their migration through the mucosa to the airway lumen from whence they are cleared[54–56]. The same or distinct molecules may be involved in eosinophil activation, a process about which little is as yet known. Symptomatic asthma is associated with the production of additional cytokines including $TNF\alpha$, GM–CSF, $IL1\beta$, IL2 and IL6[45,57]. GM–CSF has also been reported to increase during the late phase reaction to allergen[58]. In addition to their production of toxins and lipid-derived mediators, eosinophils themselves may also produce proinflammatory cytokines and growth factors as evidenced by their gene expression for $TNF\alpha$, IL6 and $GM-CSF\beta$[45,59,60]. Macrophages have been reported to increase in number in more severe asthma of the intrinsic form[28].

Mast cells have long been thought to play a key role in the immediate (type I sensitivity) reaction in asthma through their release of a variety of mediators including those which bronchoconstrict i.e. histamine, prostaglandin D_2 and leukotriene D4. Mast cells are now thought to act as an important source of IL4 and other proinflammatory cytokines whose secretion may act as a trigger to the induction of subsequent persistent production of IL4 and IL5 by lymphocytes[61,62.] There are reports of decreases, increases and no change of mast cell numbers. Early biopsy studies demonstrated an apparent reduction in bronchial mast cell numbers in asthma due to their degranulation[63]. Studies of bronchoalveolar lavage report increased intralumenal mast cell numbers together with increased numbers of T-

helper cells and eosinophils and evidence of histamine release and of eosinophil degranulation[18,64,65].

Although considered to be important in allergic conditions, little is known of the role of basophils in these conditions albeit there is evidence for increased recruitment of basophils and their precursors to sites of allergic reaction in atopic patients[66]. Asthma is also characterized by infiltration of the bronchial surface epithelium by dendritic cells (i.e. Langerhans' cell equivalent)[67]. These non-phagocytic histiocytes are rich in surface receptors and their functions are thought to include the presentation of antigenic information to T lymphocytes; very few Langerhans' cells are found in the normal lung although there is a rich network of their probable precursor dendritic cells[68]. Thus lymphocytes of the T-helper (CD4+) subset appear to be key to the controller cell and eosinophils the prime effector cell in mild asthma. However, with increasing severity of asthma and in infective exacerbations there is an increasing involvement of neutrophils and perhaps also of macrophages and these changes appear to be more refractory to conventional treatment with inhaled or even oral corticosteroids. Alternative approaches would seem to be required to treat more severe than mild asthma and the reasons for this may in part be explained by the altered pattern of inflammation.

COPD

T-lymphocytes appear also to be key controller cells in COPD but in contrast to asthma it is the CD8+ cells that are the predominant cells in COPD[69]. It is currently presumed that the majority of these CD8+ cells are T-lymphocytes of the cytotoxic/suppressor subset, but this is as yet unproven and these may also include natural killer cells and even a dendritic cell sub-type. The altered CD8:CD4+ cell ratio appears, however, to be a fundamental distinction between the CD4+T-cell, allergen-driven process of allergic asthma in non-smokers and the CD8+T-cell, cigarette smoked-induced inflammation of COPD[70].

Smoking tobacco *per se* induces an inflammatory

response. Smoking shortens the transit time of neutrophils through the bone marrow, causes a leukocytosis and alters the immunoregulatory balance of T-cell subsets found in blood, bronchoalveolar lavage (BAL), and tissues of the conducting airways and lung[71–73]. Smoking initiates a peripheral blood leukocytosis and a reversible decrease in the normally high CD4 to CD8 cell ratio in blood of heavy smokers (i.e. > 50 pack–years). There is also a significant reduction of the CD4:CD8 + cell ratio in BAL fluid but not blood of a group of milder smokers (i.e. on average who have smoked 14 pack–years). The increase in the number of BAL and tissue CD8 + T-cells is positively associated with pack–years smoked[72,74,75].

Chronic bronchitis

Histological examination of airway tissues (taken at resection for tumour) from smokers demonstrates that inflammatory cells are present in and around the area of mucus-secreting submucosal glands and that scores of inflammation show a better association with the subjects who have symptoms of mucus hypersecretion than does gland size *per se*[76]. In bronchial biopsies of subjects with mild stable chronic bronchitis and COPD there is infiltration of the mucosa by inflammatory cells[75,77–79] (Fig. 1.7, see colour plate section): this is associated with up-regulation of cell surface adhesion molecules of relevance to the inflammatory process[80]. In the surface epithelium where, in contrast to the subepithelium, CD8 + cells normally predominate, Fournier and colleagues have demonstrated by comparison with non-smokers, an increase in all inflammatory cell types in smokers with chronic bronchitis and mild COPD[81]. In a subepithelial zone (also referred to as the lamina propria), bronchial lymphomononuclear cells appear to form the predominant cell type with scanty neutrophils (in the absence of an exacerbation): the lymphomononuclear component is composed of lymphocytes, plasma cells and macrophages. Significant increases are reported in the numbers of CD45 (total leukocytes), CD3 (T-lymphocytes), CD25 (i.e.activated) and VLA-1 (late activation) positive

cells, presumed to be T-lymphocytes and of macrophages. The endobronchial biopsy studies of O'Shaughnessy and co-workers have demonstrated that by comparison with normal non-smokers, T-lymphocytes and neutrophils increase in the surface epithelium whilst T-lymphocytes and macrophages increase in the subepithelium of smokers with COPD[79,82]. In contrast to asthma, in COPD it is the CD8 + cell and not the CD4 + T-cell subset, which increases in number and proportion to become the predominant T-cell subset. Furthermore, the increase of CD8 + cells shows a negative association with the forced expiratory volume in one second (FEV1 expressed as a percentage of predicted). This novel distinction between the relative proportions in T-cell subsets of smokers with mild stable COPD and non-smoking mild asthmatics has received the support of subsequent studies of both resected tissues and bronchial biopsies[74,83,84]. The increase of the CD8 + phe‴ notype and of the CD8/CD4 ratio seen in the mucosa also occurs deeper in the airway wall in association with submucosal mucus-secreting glands in bronchitic smokers[83]. In addition neutrophils increase in the surface epithelium and glands especially when the disease increases in severity (Fig. 1.8, see colour plate section).

Similarity between COPD and asthma

COPD and asthma would seem to differ at the tissue level in a number of respects; for example the marked tissue eosinophilia and thickening of the reticular basement membrane of asthma (see below) is not usually a feature of COPD[85]. However, compared to normal healthy control tissue, there are a number of studies that report a small but significant increase in the number of tissue eosinophils in subjects with chronic bronchitis or COPD[76,79,86]. Sputum eosinophilia is also reported in cases of 'eosinophilic bronchitis', i.e. patients without a history of asthma and without bronchial hyper-responsiveness[12,87]. Furthermore, in mild COPD, the numbers of tissue eosinophils are markedly and significantly increased when there is an exacerbation of bronchitis (defined as a need by the patient to seek

medical attention due to a sudden worsening of dyspnoea or an increase in sputum volume or purulence)[88,89]. In such mild cases of COPD the exacerbation is associated with an increase in eosinophil chemoattractants, especially RANTES[90]. The bronchial mucus-secreting glands of smokers may also show gene expression for both IL4 and IL5 and the numbers of these cells are significantly higher in smokers with chronic hypersecretion as compared with their asymptomatic controls[91]. Thus, IL4, IL5 and eosinophil chemoattractant gene expression is not restricted to asthma and, like the recent reports of fibrosing lung disease[92], these regulatory cytokines can be expressed also in chronic bronchitic smokers.

Chronic bronchiolitis

Histologically, the earliest observed effects of cigarette smoke in small airways and surrounding alveoli is a marked increase in the number of macrophages and neutrophils, both in human and experimentally in animal studies. The increase is seen within both the tissue and lumena and can be detected in bronchoalveolar lavage fluid (BAL)[93]. Examination of small airway tissue in lungs resected from smokers also shows that the same profile of CD8-predominant inflammation reported in bronchial biopsies of the larger airways occurs deeper in the lung in both the 'small' airways[74,84] and also the lung parenchyma[94,95]. As with the findings in the large conducting airways there are significant negative associations of the numbers of CD8 + cells and FEV1% of predicted in both the small (peripheral) conducting airways and lung parenchyma. However, at these sites the negative correlations are stronger than in the large airways. Thus the patterns of inflammation are similar at both proximal and distal sites. However, in contrast to the larger airways, the CD8 + T-cell predominance in the small airways and lung parenchyma is more closely associated with decreased lung function in these subjects with COPD.

The infiltration of the airway wall by lymphocytes is associated with loss of alveolar attachments to the outer wall of small airways, a characteristic of centri-acinar emphysema. The accompanying loss of radial traction and lung elastic recoil leads to early airway closure during expiration (Fig. 1.9(*a*), (*b*), see colour plate section). The loss of alveolar–bronchiolar attachments is thought to be due to the circumferential spread of small airway wall inflammation.

Emphysema

In the normal, the macrophage is the resident phagocyte of the alveolus: neutrophils are rarely present[96]. Neutrophils are recruited to the lung in smokers, albeit the extent of tissue neutrophilia is highly variable. On exposure to cigarette smoke, there is recruitment of macrophages and phagocytosis of cigarette smoke components. A macrophage alveolitis and respiratory bronchiolitis are the early changes in young cigarette smokers[97,98]. As in the large and small conducting airways in COPD, CD8 + cells also become the predominant inflammatory cell phenotype in the parenchyma and their numbers show a strong inverse correlation with FEV1% of predicted[95].

Inflammation and the pathogenesis of COPD

The neutrophil, the macrophage and the CD8 + cell may each be involved in the destruction of the lung parenchyma by distinct mechanisms.

The neutrophil

The alveolar microcirculation is composed of a network of short interconnecting tubules of average diameter 5 μm. The average diameter of circulating neutrophils is 7.0 μm, which necessitates their deformation as they squeeze through capillary segments. Neutrophil traffic through the capillaries of the lung is normally slower (i.e. there is a higher transit time) than that of red blood cells as they are 700 times less deformable than RBCs[99]. Studies with radioactively labelled neutrophils have demonstrated that the normal delay in neutrophil transit is