Pathophysiology of airflow limitation in chronic obstructive pulmonary disease

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Summary

The airflow limitation that defines chronic obstructive pulmonary disease (COPD) is the result of a prolonged time constant for lung emptying, caused by increased resistance of the small conducting airways and increased compliance of the lung as a result of emphysematous destruction. These lesions are associated with a chronic innate and adaptive inflammatory immune response of the host to a lifetime exposure to inhaled toxic gases and particles. Processes contributing to obstruction in the small conducting airways include disruption of the epithelial barrier, interference with mucociliary clearance apparatus that results in accumulation of inflammatory mucous exudates in the small airway lumen, infiltration of the airway walls by inflammatory cells, and deposition of connective tissue in the airway wall. This remodelling and repair thickens the airway walls, reduces lumen calibre, and restricts the normal increase in calibre produced by lung inflation. Emphysematous lung destruction is associated with an infiltration of the same type of inflammatory cells found in the airways. The centrilobular pattern of emphysematous destruction is most closely associated with cigarette smoking, and although it is initially focused on respiratory bronchioles, separate lesions coalesce to destroy large volumes of lung tissue. The panacinar pattern of emphysema is characterised by a more even involvement of the acinus and is associated with α1 antitrypsin deficiency. The technology needed to diagnose and quantitate the individual small airway and emphysema phenotypes present in people with COPD is being developed, and should prove helpful in the assessment of therapeutic interventions designed to modify the progress of either phenotype.

This is the second Seminar in a series about COPD

Introduction

The defining feature of chronic obstructive pulmonary disease (COPD) is irreversible airflow limitation measured during forced expiration,[1,2] caused by either an increase in the resistance of the small conducting airways,[3,4,5] an increase in lung compliance due to emphysematous lung destruction,[6] or both. The units for airway resistance are cm H_2O/L per s and for compliance are L/cm H_2O, and their product (time), provides the time constant for lung emptying.[7] This constant is reflected in measurements of the volume of air that can be expired in one second (FEV_1) and its ratio to forced vital capacity (FEV_1/FVC), which are reliable screening tools because they are affected by both airway obstruction and emphysema.

Figure 1 reproduces classic data from Fletcher and colleagues[8] showing the different rates of decline in FEV_1 with age for non-smokers and smokers who either do or do not develop COPD. The horizontal lines have been added to show the boundaries of COPD severity recommended by a global initiative on obstructive lung disease (GOLD).[1,2] Fletcher and colleagues[8] showed that the rate of decline in FEV_1 of most people who smoke is similar to that for non-smokers, in that they remain in the GOLD 0 and 1 category with greater than 80% predicted FEV_1. These investigators also showed that in a susceptible minority of tobacco smokers (estimated at 15–20% of the total), lung function declines rapidly to levels consistent with moderate (GOLD 2), severe (GOLD 3), and very severe (GOLD 4) COPD. Their data also showed that stopping smoking had a beneficial effect at any age. Findings based on post mortem examination,[9,10] resected lung specimens,[11,12] biopsies,[13] induced sputum,[13,14] and bronchoalveolar lavage,[13,15] all indicate that the lung inflammation is present in everyone with a tobacco smoking habit. The reason why only a minority of smokers experiences an excessive decline in FEV_1 is unknown, but preliminary evidence suggests that the lung inflammatory response is amplified in the susceptible group.[12,16] The purpose of this review is to discuss the nature of the lesions associated with airflow limitation in terms of the host defence of the lung.

Host defence of the lung

The cause of COPD is attributed to the total burden of toxic gases and particles that individuals inhale during their lifetime.[1,2] Although atmospheric pollution contributes to this burden, the smoking of tobacco products is the major risk factor.[1,2,17] The host defence system against this type of insult is provided by the

Figure 1: **Rate of decline in FEV_1 with age**
Adapted from references 2 and 8.

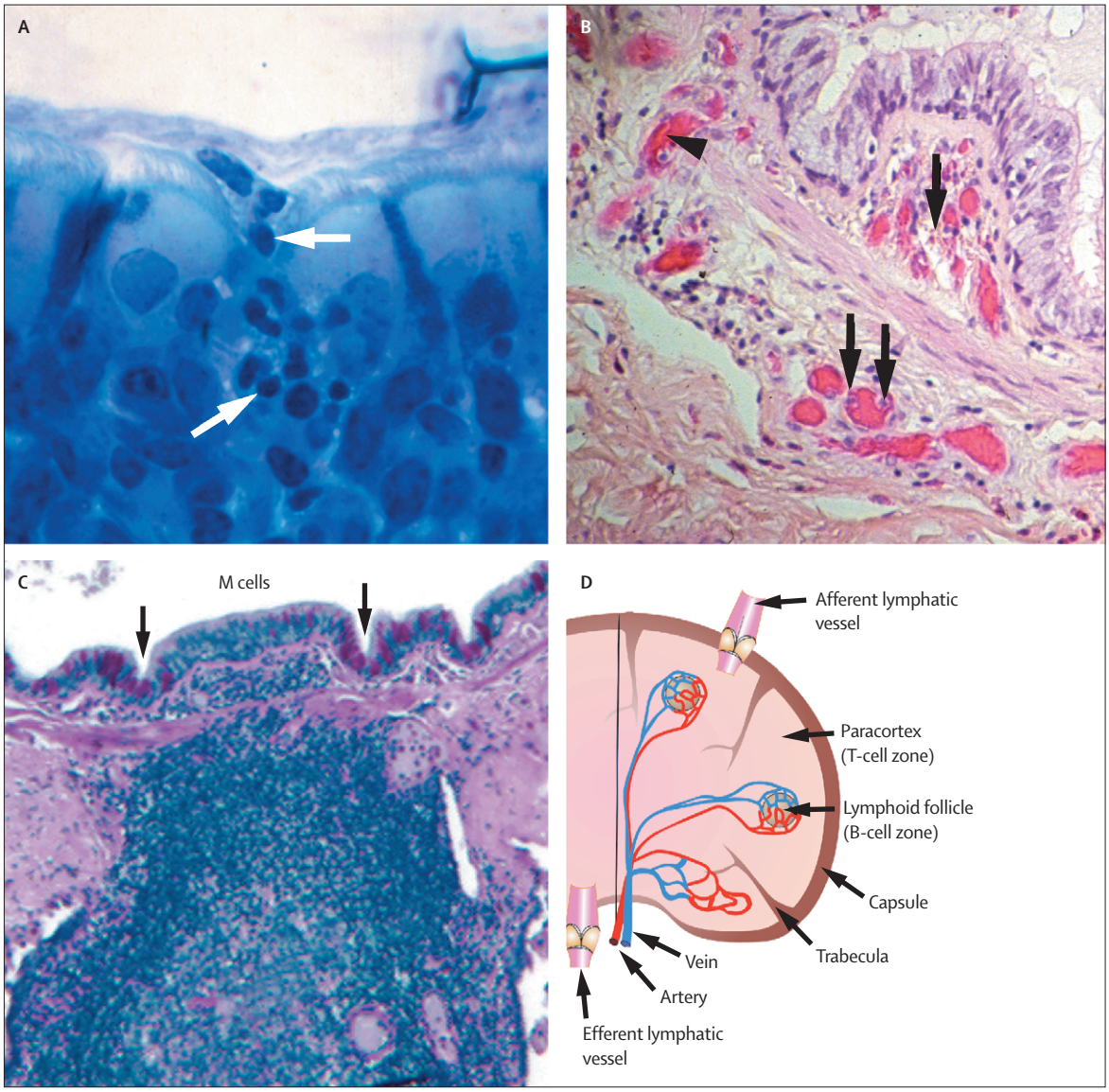

Figure 2: **Anatomical features of the innate and adaptive inflammatory immune responses**
(A) Migration of inflammatory cells in the epithelial layer (white arrows) and entry into the surface mucous layer of a guineapig after exposure to cigarette smoke. (B) Histology of bronchial microvasculature. One capillary bed lies between the epithelium and muscle (single arrow) and a second lies in the adventitial compartment below outside the muscle (double arrow). These two capillary beds are joined by connecting vessels (arrow head) that pass between the muscle bundles. (C) Lymphoid follicle in BALT with a germinal centre (GC). The follicle is covered by a specialised epithelium containing M cells (between the arrows), which transport antigens from the lumen into the subepithelial tissue. (D) Diagram of a regional lymph node, which differs from BALT in that it has afferent lymphatic vessels that penetrate a capsule surrounding the node and an efferent lymphatic vessel that leaves at the hilum. The blood supply to the follicle forms a network around the outer edge of the follicles in both lymph nodes and BALT. The vessels that form this network around the follicles located in BALT arise from the outer vascular plexus shown in (B).

innate and adaptive inflammatory and immune response.

Innate response

The innate defence system includes mucociliary clearance of the airways, which works cooperatively with the monocyte/macrophage system to move deposited particles up the mucociliary escalator.[18,19] Additionally, tight junctions connecting lung epithelial cells provide a physical barrier between the tissue and airspace. This protective barrier is broken down by chronic exposure to cigarette smoke,[20–22] and this epithelial disruption initiates an acute inflammatory response. The inflammatory cells that migrate into the epithelium (figure 2A) are delivered in subepithelial microvessels, and those found in the outer wall of the airways are delivered in a second microvascular bed located in the adventitia of the airway wall (figure 2B). Proteins delivered to the site of exudation[23,24] and produced locally[25–27] assist the migrating phagocytes in taking up and destroying foreign particles.

The cells that participate in the innate response include polymorphonuclear cells (PMNs), eosinophils, macrophages, natural killer cells, and mast cells. Uncommitted B cells and CD4 and CD8 lymphocytes can also be mobilised during an innate response, but antigen presentation and lymphocyte interaction are needed to initiate the cellular and humoral components of the adaptive immune response.[28]

Airways below the larynx are normally sterile but the nasal passages and oropharynx are permanently colonised by microbes.[29] Aspiration from the upper airway into the lower respiratory tract is common in healthy people, especially during sleep, and brings large numbers of microorganisms into the lung. The normal host response is sufficient to remove these micro-organisms and maintain sterility,[29] but suppression of this response by chronic cigarette smoke exposure allows some of these microbes to invade the natural tissue barriers and overcome the local host defence system to produce infection.[30]

Adaptive response

The innate system can recognise antigens deposited on the lung surface and react to them but it has a limited memory of previous exposure.[31] By contrast, the cellular and humoral immune components of the adaptive response have exquisite memory for both soluble and particulate antigens that are aspirated or inhaled into the lung.[32–36] Antigens deposited on the epithelial surface of the airways may either be transported across the intact epithelium in specialised epithelial M cells located in the surface epithelium covering bronchial associated lymphatic tissue (BALT; figure 2C), or penetrate the epithelium at the site of injury. Dendritic cells arranged in a network at the base of the epithelium and in the lamina propria beneath the basement membrane[34–36] pick up these antigens and transport them to the BALT (figure 2C) or to regional lymph nodes (figure 2D). BALT differs from regional lymph nodes in that it does not have a capsule or afferent lymphatics, and receives antigen transported from the epithelial surface.

Antigen presentation links innate and adaptive responses

The lymphoid follicles in the BALT and regional lymph nodes (figure 2C and D) greatly enhance the opportunities for antigen presentation, which is the critical link between the innate and adaptive response. Lymphocytes migrate out of the blood at the venous end of the microvasculature that supplies the follicle (figure 2D) by attaching to specialised high endothelial cells that line the venules.[37] The B cells leaving the blood accumulate near the edge of the follicles and the T cells accumulate in the parafollicular areas (figure 2D). This accumulation allows the antigen-presenting cells percolating through the regional lymph nodes and BALT to present antigen to separate concentrations of T and B lymphocytes.[38,39] The T cells activated by an antigen migrate out of the parafollicular areas to the edge of the follicle, where their chance of meeting B cells that have recognised the same antigen is improved several times compared with the likelihood of doing so in peripheral blood, where only one in 10^5 or 10^6 lymphocytes recognises the same antigen. The signals delivered from the CD4 T-helper lymphocytes to B cells that have been activated by the same antigen initiate B-cell proliferation at the edge of the follicle and migration into the germinal centre where they begin to produce antibody.[38,39] B cells that produce high affinity antibody capable of binding antigen presented by a separate set of follicular dendritic cells survive to become either memory cells or antibody-producing B cells. These cells re-enter the circulating blood as the lymph drains into the central venous system and home back to the site of injury. The IgM and IgG antibodies manufactured by the plasma cells can neutralise extracellular microbial toxins and initiate a much more efficient process of opsonisation and phagocytic killing than can be mounted by the innate response. Th-2 subpopulations of CD4 T-helper cells stimulate B-cells to manufacture greater amounts of IgE by secreting interleukin 4, whereas transforming growth factor (TGF) β and interleukin 5 stimulate another population of B-cells to produce IgA.[40–43]

The cell-mediated component of the adaptive host response assists in the destruction of microbes taken up and processed by alveolar macrophages during the innate response. A Th-1 subpopulation of CD 4 T-helper lymphocytes recognises an antigen complex displayed on the surface of these macrophages and secretes interferon γ to activate the macrophages and destroy the particles inside.[28] A subpopulation of CD8 lymphocytes that also recognises antigen expressed on macrophages assists in this process by secreting additional interferon γ. A second component of the cell-mediated response provides a different population of CD8-positive cytotoxic lymphocytes, which recognise all nucleated cells infected by intracellular pathogens and destroy them. This destruction occurs in stages, including: a recognition step, in which the cytotoxic CD8 lymphocyte uses its T cell receptor to bind to antigen displayed on the target cell surface; a second step, in which the molecule perforin creates holes that connect the cytotoxic T-cell to the target cell, and delivers granzyme into the cytoplasm; and a third step, in which target cell caspases are activated by granzyme to initiate the intracellular signals that result in apoptosis of the target cell.[28]

Cytokine control of host response

Two important cytokines (tumour necrosis factor (TNFα and interleukin 1β) initiate and orchestrate the innate response and have a broad stimulating effect on the B and T cells needed to develop an adaptive response.[23,28,44] Experiments designed to overexpress these two cytokines individually have shown that both induce a substantial

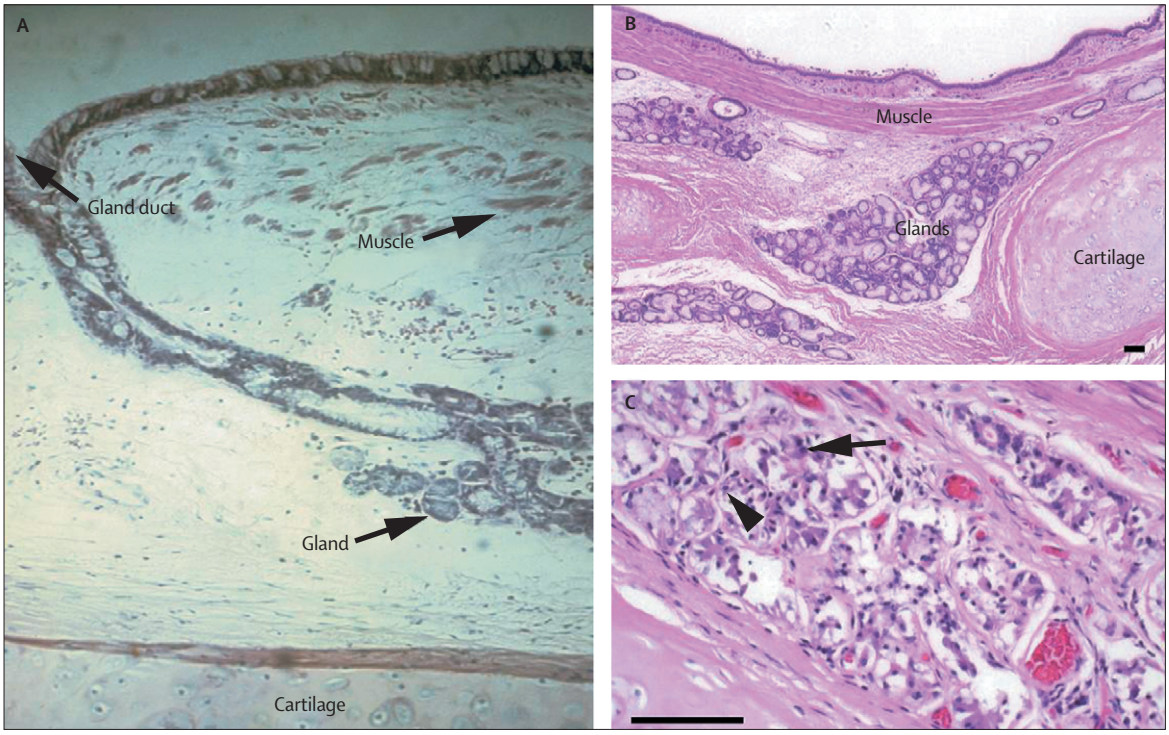

Figure 3: **Key lesions in chronic bronchitis**
(A) Histology of bronchus with epithelial lining that extends from lumen into gland duct and gland. (B) Enlarged glands from a patient with chronic bronchitis. (C) One of these gland at higher magnification showing inflammatory cells (arrow and arrowhead). Reproduced from reference 2 with permission.

local inflammatory reaction that disappears when cytokine expression stops. But only interleukin 1β overexpression stimulates the collagen deposition associated with the repair process.[45,46] Cytokines such as TGFβ, which have multiple roles—including antibody isotype switching, immunosuppression, and the initiation of connective tissue matrix production—are important in the transition from the inflammatory immune response to the repair process.[47,48]

The surface epithelial cells and migrating inflammatory cells attracted to the site of injury are a major source of the cytokines that initiate and control the host response.[49–55] When exposed to atmospheric particles in vitro, macrophages increase their production of TNFα, interleukin 1β, macrophage inflammatory protein 1α, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 6, and interleukin 8;[49,50] and bronchial epithelial cells increase their production of interleukin 1β and leukaemia inhibitory factor.[51–53] Stimulation of bronchial epithelial cells with conditioned media from macrophages also indicates that interactions between these two cell types enhance the production of GM-CSF, interleukin 6, and possibly interleukin 8.[54] Endothelial cells seem to regulate the degranulation of PMN.[55]

Some of the cytokines generated at the site of injury in the lung have an endocrine function that stimulates the hypothalamus to induce fever (TNFα, interleukin 1β), the liver to increase synthesis of acute-phase proteins (TNFα, interleukin 1β) and the bone marrow to increase production and release of leucocytes and platelets (TNFα, GM-CSF, interleukin 6).[23,24] The production of interleukin 8 and macrophage inflammatory protein 1α is important to the recruitment of both PMN and monocytes into sites of injured lung. GM-CSF, a haemopoietic growth factor, has been identified as an important degranulation factor that enhances tissue damage induced by granulocytes. The endocrine function generated during an acute response is relevant to human disease in that heavy exposure to toxic dust and fumes stimulates a rise in body temperature[56] and chronic cigarette smoking increases the production of acute phase proteins in the liver and stimulates the bone marrow to increase the production and release of circulating leucocytes.[57,58]

Pathology of COPD

The lungs of people that smoke 1–2 packages of cigarettes per day receive a cyclic exposure to toxic gases and particles that is repeated 20 to 40 times every day. Those with a 50 pack-year smoking history receive this type of daily stimulus for 25–50 years. The cough and sputum production that are the defining features of chronic bronchitis are a manifestation of the innate response to the toxic particles and gases in cigarette

smoke. But the airflow limitation that defines COPD is associated with lesions that obstruct the small conducting airways,[3–5] produce emphysematous destruction of the lung's elastic recoil force,[6] or both.

Chronic bronchitis

The inflammation associated with chronic bronchitis is located in the epithelium of the central airways (larger than 4 mm in internal diameter) where it extends along the gland ducts into the mucus-producing glands.[59,60] This inflammatory process is associated with increased production of mucus, defective mucociliary clearance, and disruption of the epithelial barrier provided by the innate host defence system.[20–22] Inflammatory cells from both the innate and adaptive host response participate in this process.[60–62] Reid[63] noticed that the bronchial mucous glands were enlarged in chronic bronchitis (figure 3) and used the ratio of gland to bronchial wall thickness (now referred to as the Reid index) as a diagnostic yardstick for the pathological diagnosis of chronic bronchitis. Thurlbeck and Angus[64] reported that the Reid index was normally distributed with no clear break between patients with and without bronchitis, but most studies have shown a fairly small overlap with higher values in patients with chronic bronchitis.[65,66] Chronic bronchitis is also associated with thickening of the bronchial walls that is mainly related to an increase in connective tissue deposition.[65] Growth factors such as TGFβ have been shown to be present in the central airways,[67] but the complexity of their role in this remodelling is beyond the scope of this review.

The recognition that the normal bacterial sterility in the lower airways is lost in the presence of chronic bronchitis[68] led to the hypothesis that there was a natural progression from the simple mucus hypersecretion associated with cigarette smoking to purulent hypersecretion and obstructive bronchitis.[69]

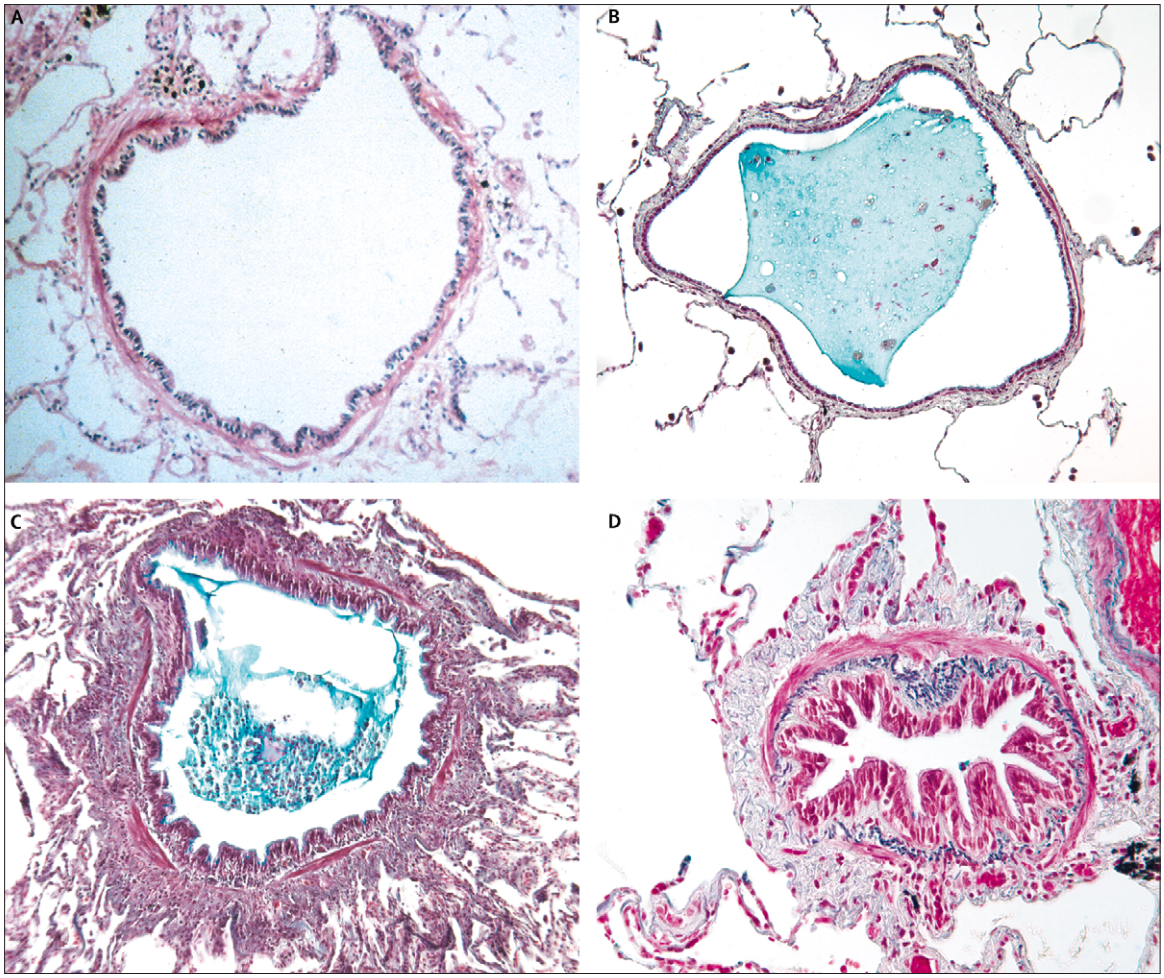

Figure 4: **Small airway obstruction**
(A) Normal small airway. (B) Small airway containing plug of mucus with relatively few cells, which could have been produced in the glands of the larger airways and aspirated into the smaller airways. (C) Acutely inflamed airway with thickened wall in which the lumen is partly filled with an inflammatory exudate of mucus and cells, which has probably been produced in the small airway. (D) Airway surrounded by connective tissue, which appears as if it might restrict normal enlargement of the lumen and unfolding of the epithelial lining that occurs with lung inflation.

But the longitudinal studies undertaken by Peto and colleagues,[70] and the Copenhagen group[71] have shown that the symptoms of chronic bronchitis do not predict the subsequent rapid decline in FEV_1 that leads to COPD (figure 1). However, acute lower respiratory tract infections in current smokers who already have COPD might result in a more rapid fall in FEV_1.[72]

Small airway obstruction

Although the terms chronic bronchitis and airway obstruction are often used interchangeably, the major site of obstruction is actually found in the smaller conducting airways (less than 2 mm in diameter).[3–5] These airways are spread out between the fourth and 14th generation of airway branching, since the human bronchial tree branches in a non-dichotomous fashion.[73] The increase in the numbers of airways with progressive branching rapidly expands their total cross sectional area and lowers their resistance. In the healthy lung, about 75% of total lower-airway resistance is located in the central conducting airways larger than 2 mm in internal diameter, compared with 25% in the smaller bronchi and bronchioles.[3,5] Furthermore, because the airways below the larynx account for only 50% of total resistance measured at the mouth, the airways smaller than 2 mm in internal diameter only account for 10–15% of total airway resistance. For this reason, Mead[74] referred to the peripheral conducting airways as the lungs' silent zone, where disease might accumulate for many years with very little effect.

Many studies have shown that there are structural abnormalities in the small airways of smokers who might or might not have COPD.[75–90] Some investigators suggest that accumulation of mucus obstructs the small airways of patients with COPD, but this "mucus plugging" has also been attributed to a postmortem artefact related to the events leading to death. However, a recent study based entirely on surgically resected lung tissue from patients at all stages of the GOLD classification of COPD showed a relation between the accumulation of inflammatory exudates containing mucus in the airway lumen and severity of COPD.[90] Although some of this mucus might be produced by the glands in the more central bronchi and aspirated into the peripheral airways, most seems to be added to inflammatory exudates that form in the lumens of the small airways (figure 4).

The cells that migrate through the epithelium of the small airway lumen are delivered by the subepithelial vessels, but the lymphoid follicles associated with the BALT are centred on the vessels in the adventitial layer (figure 2). Any increase in tissue between the airway smooth muscle and the lumen surface will encroach on lumen calibre and raise resistance. Furthermore, this effect may be amplified by smooth-muscle contraction to account for the airway hyper-responsiveness noted in COPD.[91] Matsuba and Thurlbeck[10] showed preferential deposition of connective tissue in the adventitial compartment of the airway wall in advanced emphysema. Our more recent findings[90] have confirmed this observation and suggested that this peribronchiolar fibrosis might contribute to fixed airway obstruction by restricting the enlargement of airway calibre that occurs with lung inflation (figure 4D). The inflammatory process in the adventitial compartment of the small airways might also destroy the support the small airways receive from the alveoli attached to their outer walls. Although a decrease in the number and strength of these attachments has been implicated in small airway obstruction[92,93] and correlates with the decline in FEV_1,[94] direct measurements of peripheral airway resistance indicate that this loss of alveolar support is a less important cause of obstruction than the pathology in the airway wall and lumen.[3]

Previous reports have also shown that B cells and CD4 and CD8 lymphocytes are present in the airway tissue of patients with COPD, and that increases in CD8 lymphocytes[95–97] and B cells[98] are associated with a decline in FEV_1. This increase in lymphocytes is also associated with an increase in BALT which is rarely found in healthy non-smokers, is more frequent in cigarette smokers,[99] and shows a further sharp increase in patients with severe (GOLD 3) and very severe (GOLD 4) COPD.[90] This increase in lymphocyte subtypes and the appearance of BALT at this stage of COPD suggest the development of an adaptive immune response that might be driven by microbial colonisation and infection.[30]

Emphysema

Emphysematous lung destruction reduces maximum expiratory flow by decreasing the elastic recoil force available to drive air out of the lung.[6] The lesions produced by emphysema were first described by Laennec[100] and are defined by dilatation and destruction of lung tissue beyond the terminal bronchiole.[101,102] The practice of examining the postmortem lung in the inflated state led to the modern descriptions of the various forms of emphysematous lung destruction.[103–110] The unit of lung anatomy on which these descriptions are based is defined by its surrounding connective tissue septa (figure 5A) and is commonly referred to as the secondary lobule of Miller. This unit is visible on the surface of the lung to the naked eye and contains several acini, defined as the unit of lung supplied by a single terminal bronchiole (figure 5B). The centrilobular or centriacinar form of emphysema results from dilatation and destruction of the respiratory bronchioles (figure 5C and D). This type of emphysema is most closely associated with tobacco smoking[109] and is most often found in the upper lobes of the lung, where separate lesions may coalesce to produce larger cavities (figure 6A). The panacinar form of emphysema is usually associated with α1 anti-trypsin deficiency,[106,107,110]

and is more common in the lower lobes (figure 6B) where it causes a more even dilation and destruction over the entire acinus. Kim and colleagues[110] have presented data suggesting that one or the other of these types of emphysema usually dominates in advanced disease, and that dominance of the centriacinar form is associated with more severe small-airway obstruction. Paraseptal emphysema is defined by destruction of the outer part of the lobule near the septa and irregular emphysema that occurs in relation to scars are discussed elsewhere.[109]

The relation between cigarette smoking and the presence of emphysema (figure 7A) shows a rough dose-response curve between pack-years of smoking and the presence of emphysema, but only about 40% of heavy smokers develop substantial lung destruction, even at the very highest levels of smoking.[111] This observation should not be confused with the fact that only 15% of people develop COPD,[8] because emphysema is sometimes found in people who maintain normal lung function.[111] This type of observation has become more common since the introduction of the CT scan, but the hypothesis that this early form of emphysema predicts a rapid decline in function and subsequent development of COPD has not been tested. The fact that about 40% of heavy smokers develop emphysema and only 15% develop airflow limitation reflects the long subclinical course of COPD.

Figure 7B shows data from a study[12] in which smokers who developed severe emphysema had an increase of about tenfold in neutrophils, macrophages, T lymphocytes, and eosinophils present in their lungs, compared

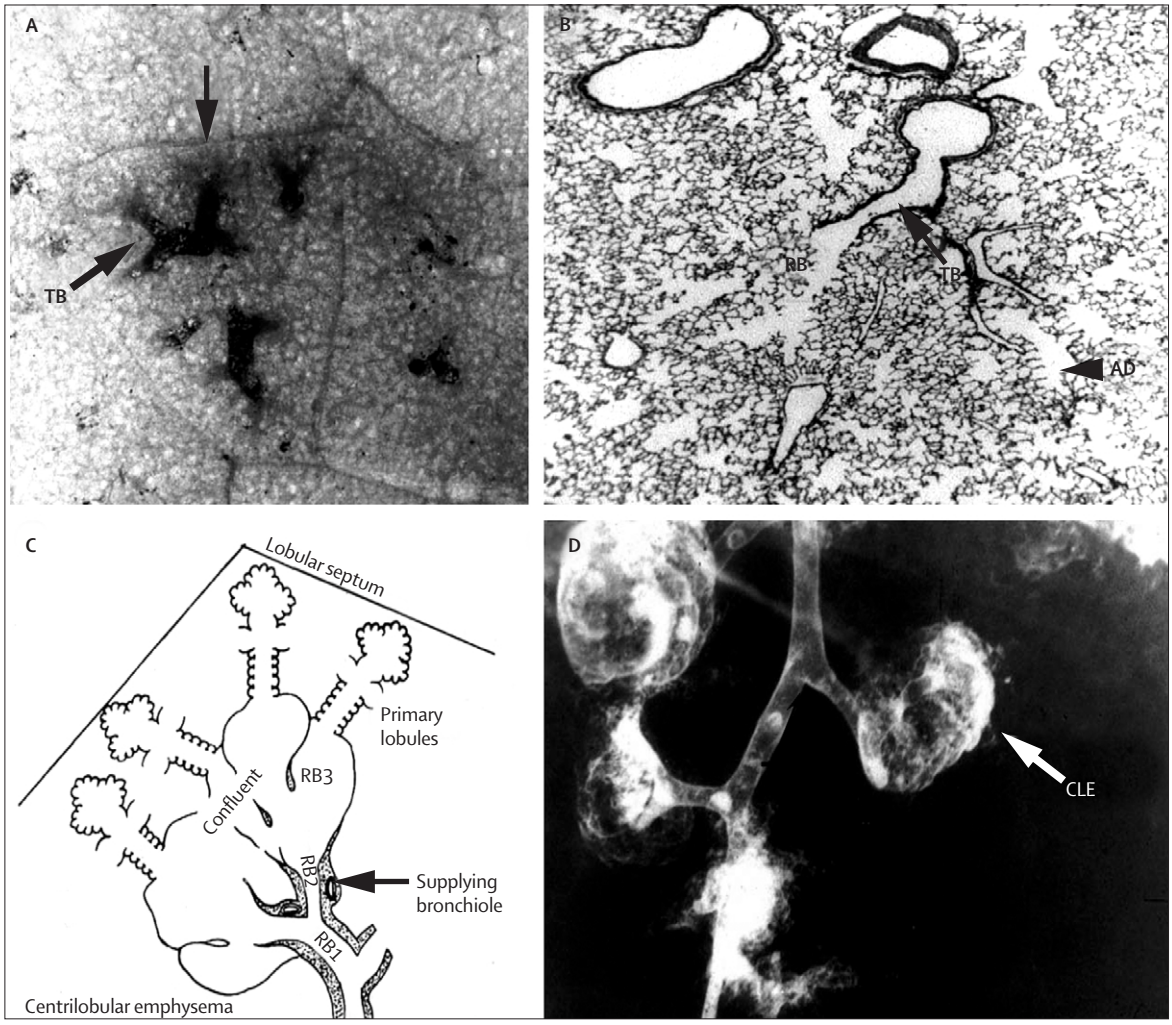

Figure 5: **Anatomy of centrilobular emphysema**
Adapted from reference 2. (A) Photograph of the pleural surface with peripheral airways filled with contrast material. The connective tissue border (single arrow) surrounds a secondary lobule of Miller, and every terminal bronchus (TB) supplies a unit termed an acinus. (B) Low-power photomicrograph with respiratory bronchioles (RB) and alveolar ducts (AD) branching off a terminal bronchiole. (C) Diagram adapted from reference 104 showing that centrilobular or centriacinar emphysema is the result of dilatation and destruction of the respiratory bronchioles. (D) Contrast media filling a centrilobular emphysematous lesion (CLE).

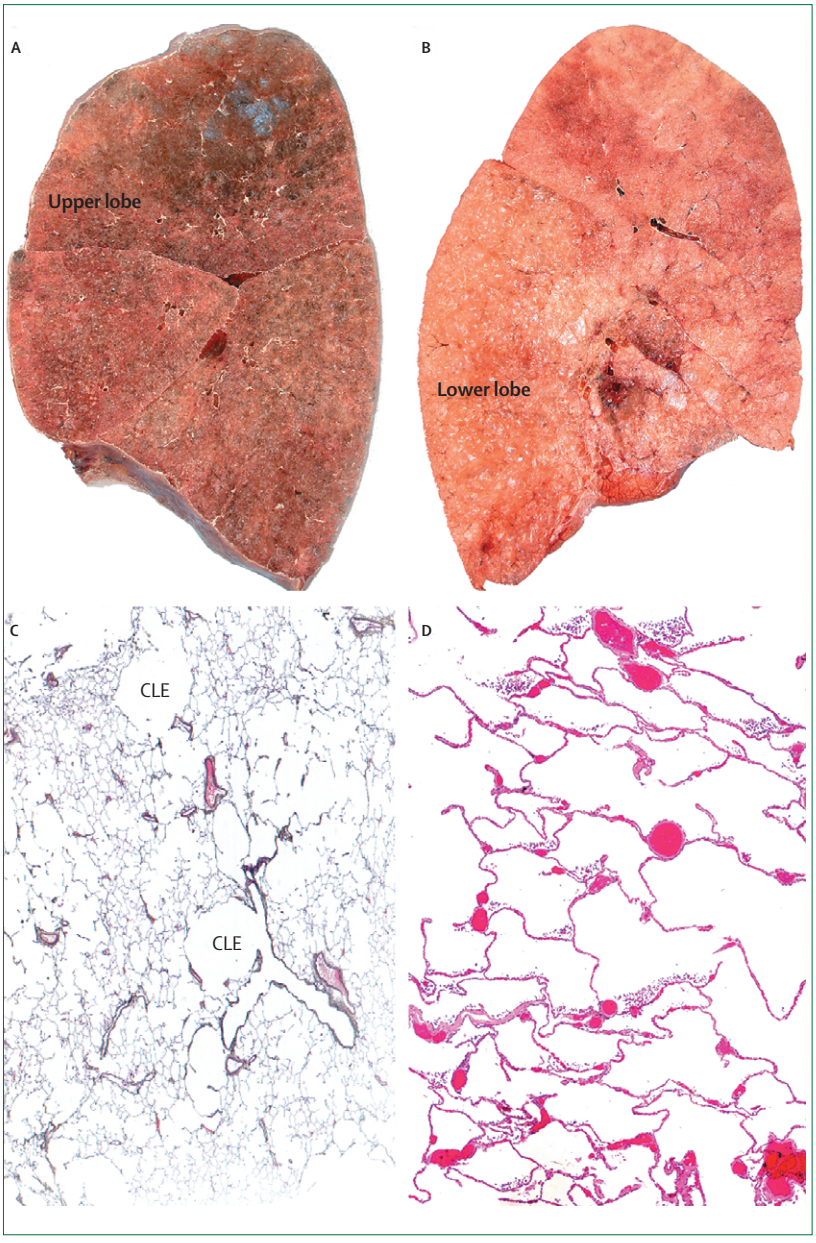

Figure 6: **Comparison of centrilobular and panacinar emphysema**
(A) Photograph of a mid-saggital slice of lung removed from a patient who received a lung transplant for COPD. Note that the centilobular lesions have coalesced to produce severe lung destruction in the upper lobe. (B) Similar specimen from a patient who received a lung transplant for α1 antitrypsin deficiency, in which there is less severe but more extensive involvement of the lower lobe by panacinar emphysema. (C) Low-power photomicrograph of the early lesions of centrilobular emphysema (CLE) that have destroyed central portions of several acini of a single secondary lobule. (D) Slightly higher-power photomicrograph than (C), showing the much more even destruction of the lobule in panacinar emphysema. (Specimens from Barnes Jewish hospital, Washington University, St Louis, courtesy of Joel Cooper, with permission).

with people who smoked similar amounts but maintained normal lung function.[12] Comparison of figure 7A and 7B strongly suggests that people who develop emphysema have an amplified response to cigarette smoke, but the mechanism of this amplification is unknown.

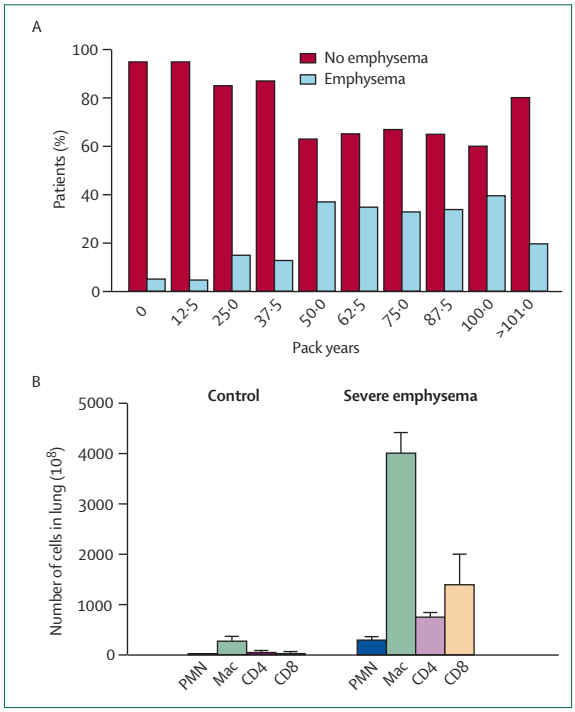

Figure 7: **Emphysema and cigarette smoking**
(A) Relation between cigarette smoking and presence of emphysema in a series of lungs resected for small peripheral lung tumours (author's data re-plotted from reference 111). (B) For similar smoking histories (50–70 pack years), control cases with normal lung function had many fewer inflammatory cells in their lungs than individuals with severe emphysema ($p<0·05$ for all types of cell shown; data from reference 12). Mac=macrophages.

Leucocyte kinetics in smokers

One possibility is that the effect of smoking on leucocyte kinetics increases the numbers of these cells in lung tissue. A cardiac output of 6 L/min distributes about 8640 L of blood to the lung in the pulmonary circulation every 24 h, and an additional 86 L (about 1% of the cardiac output) is delivered by the systemic bronchial vessels. Since each litre of blood contains about 10^9 leucocytes, about $8·7\times10^{12}$ leucocytes flow through the lung every day. Both direct observations of the pleural surface in animals and indirect measurements in human beings have shown that leucocytes are delayed with respect to erythrocytes as they pass through pulmonary microvessels.[112] Both leucocytes and erythrocytes are slowed down in lung microvessels because their maximum diameters are slightly larger than those of pulmonary capillaries. But the discoid shape of the erythrocyte allows it to fold and move through these restrictions much more quickly than the leucocytes. The arrangement of the alveolar wall capillary bed into short interconnecting segments provides a large number of parallel pathways for the faster-moving erythrocytes to stream around slower-moving leucocytes (figure 8A). This effect concentrates leucocytes with respect to erythrocytes, producing a large pool of marginated leucocytes in the lung

microvessels. These leucocytes can be rapidly mobilised back into the circulating pool by stress and exercise.[112]

Cigarette smoking is known to raise the circulating leucocyte count[58] and to increase the size of the marginated pool of leucocytes in lung capillaries by activating PMNs and slowing them down.[113,114] As flow limitation becomes more severe, the time constant for lung emptying eventually exceeds that for the chest wall, first during exercise and then at rest. This change produces dynamic hyperinflation, in which an increase in alveolar pressure over pleural pressure will result in capillary compression. Studies in patients who needed cardiac catheterisation for other reasons have shown that capillary compression during valsalva manoeuver increases the pool of marginated leucocytes.[115] Furthermore, the PMNs tend to be activated by their deformation as they pass through this type of restriction.[116] Chronic exposure to cigarette smoke also stimulates the bone marrow to release into the circulation more immature cells that are more readily delayed in the marginated pool in lung microvessels.[117] All these factors increase the population of leucocytes in lung capillaries.

Only a small proportion of the cells delivered to an acute inflammatory site migrate out of the vascular space into the lung tissue and airspaces.[118] This migratory process is controlled by a complicated series of molecular events that first prime and then trigger a graduated response in the circulating cells. This response begins by stiffening the cells to make them less deformable and slow them down, followed by mobilisation of their cytoskeleton to allow them to move purposefully along the migratory pathway, and the expression of adhesion proteins that allow them to adhere to the structural cells and develop the traction they need to move.[119,120] An important series of studies by

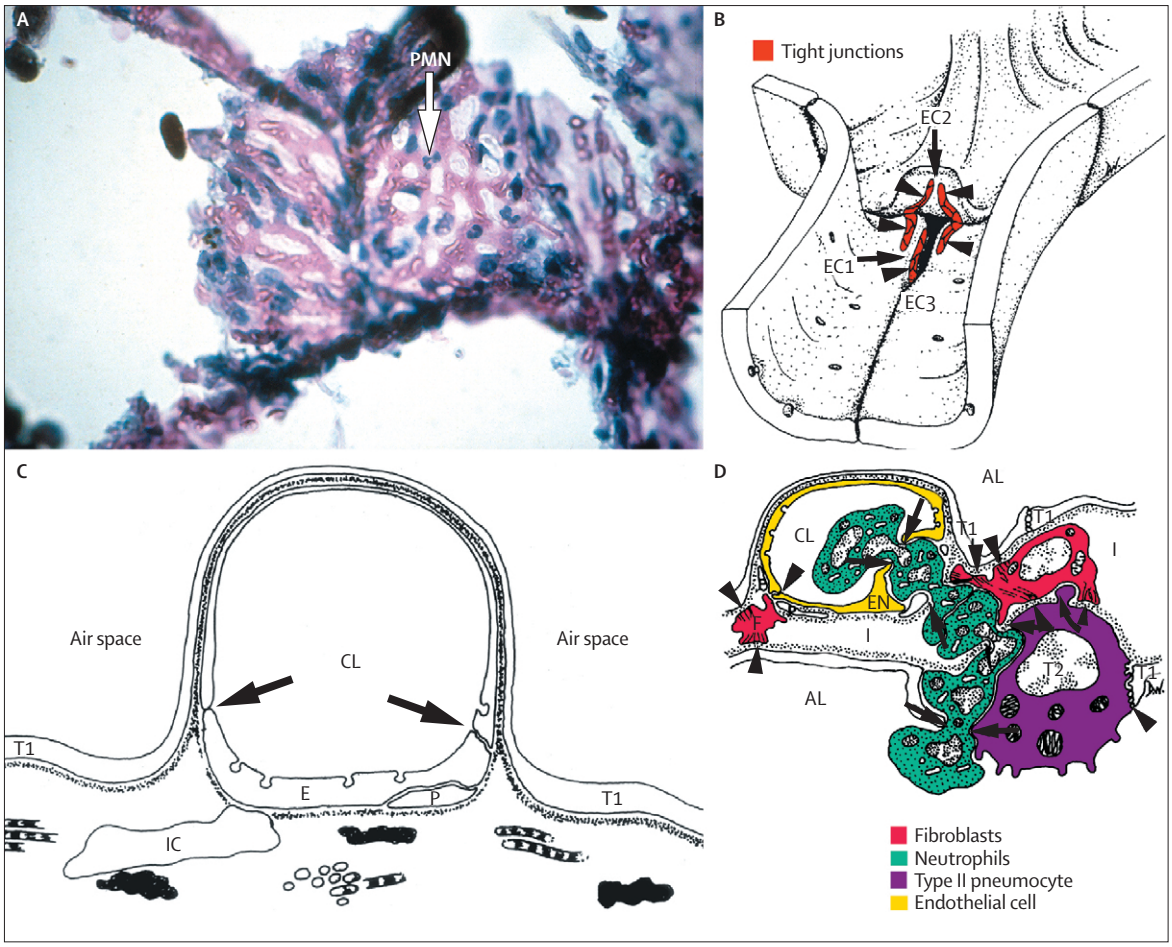

Figure 8: **Migratory pathways for inflammatory cells in alveolar tissue**
(A) Low-power view showing interconnected network of short capillary segments in alveolar wall with a PMN within one of the segments. (B) Diagram of a tight junction between endothelial cells lining capillaries. Two cells in the same plane (EC1 and EC3) are joined by the flap of a third cell (EC2) that is fastened to the other two, leaving an open pore that migrating cells use to penetrate the endothelial barrier. (C) Diagram of cross section of a single capillary segment showing that the capillary has a thin side that bulges into the alveolar lumen and a thick side that is in the plane of the alveolar wall. The pores shown in (B) are located near the thick side of the capillary. (D) Pathway of migrating PMN. AL=alveolar lumen. CL= capillary lumen. E= endothelial cell. I=interstitial space. IC=interstitial cell. T1=type 1 epithelial cell. T2 =type 2 epithelial cell. F=fibroblast. P=pericyte. Reproduced courtesy of David Walker from references 120, 121, and 122, with permission.

Walker and co-workers[120–122] has shown that inflammatory cells begin this migratory process by seeking out areas of endothelium where gaps form at corners where three endothelial cells meet (figure 8B). After they migrate through these gaps they come into contact with the endothelial basement membrane near the thick side of the capillary wall (figure 8C). Careful three-dimensional reconstructions of the alveolar wall based on serial electron micrographs have shown (figure 8D) that the PMN migrate through pre-formed holes in this basement membrane and come into contact with fibroblasts as they enter the interstitial space. They then use the surface of the fibroblast as a guide as they cross the interstitial space and make contact with the epithelial basement membrane.[121,122] The very close association between migrating inflammatory and interstitial cells suggests that the interstitial fibroblast may function as the "quarterback" directing the flow of inflammatory cells through the interstitial compartment of the airway wall. When the PMN arrives at the epithelial basement membrane it passes through existing pores, then migrates between alveolar type 1 and type 2 cells onto the alveolar surface of the airspace.

The concept that the pathogenesis of emphysema is caused by an imbalance between proteolytic enzymes was introduced by the discovery linking severe emphysema to α1-antitrypsin deficiency in humans and by animal experiments showing that the deposition of powerful enzymes produced emphysema-like lesions in the lung.[123] Although neutrophil elastase is the enzyme that has been most heavily implicated in this process, there is growing evidence that other cells and enzyme systems are involved. Quite recent findings have also suggested that emphysema can develop with little or no inflammation, by disturbing proteoglycan synthesis and by increasing apoptosis in the lung tissue.[123]

These important observations should be reconciled with the much larger body of evidence that lung inflammation provides the link between cigarette smoking and emphysema. A better understanding of the migratory behaviour of the inflammatory cells through the alveolar wall tissue, their interaction with structural cells, and their activation sequence as they encounter foreign material in tissue could provide clearer insight into the pathogenesis of the disappearance of tissue in emphysema.

Small-airway-obstructive and emphysema phenotypes of airflow limitation

Progress toward specific treatments for COPD might be accelerated by moving beyond measurements of airflow limitation to the precise diagnosis of the specific targets responsible for the airflow limitation. This step will require precise, safe, non-invasive quantitative methods of diagnosis that will allow both the airway-obstructive and emphysema phenotypes to serve as measurable endpoints in clinical trials. The introduction of CT scanning has provided an objective method for measuring the extent and severity of emphysema on a regional basis.[124–127] This approach has been used to measure the effect of replacement therapy on the progression of emphysema in α1-antitrypsin deficiency.[128,129] Reports from Japan also indicate that it may be possible to separate emphysematous from obstructive phenotypes of COPD with high resolution CT.[130] MRI imaging of inhaled hyperpolarised gas holds a similar promise for the diagnosis of emphysema, and has the distinct advantage that it eliminates exposure to ionising radiation.[131–135] Although these procedures offer limited value to practical clinical medicine in the short term, they could become extremely important for determining outcomes in clinical trials of any new treatment for either phenotype of COPD.

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