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NORMAL ANATOMY

The normal human bronchogram (Fig. 6.1) shows that the length of pathways from the trachea to the terminal airways differs depending on the pathway followed and it can take as few as 8 or as many as 24 divisions of airway branching to reach the gas-exchanging surface [1]. The small bronchi and bronchioles 2 mm in diameter are spread out from the fourth to the fourteenth generation of airway branching [2]. The total airway cross-sectional area expands rapidly beyond the 2 mm airways to provide for rapid diffusion of gas between the distal conducting airways and the gas-exchanging surface. The central conducting airways larger than 2 mm internal diameter are the major site of resistance to airflow in the normal lung because of their much smaller total cross-sectional area [3, 4].

The conducting airways are lined by epithelium and surrounded by an adventitial layer [5]. The submucosa between the epithelium and outer edge of the muscle layer is often referred to as the “lamina propria,” but this term is technically incorrect because many airways are not completely surrounded by muscle [6]. Bronchi are defined by the presence of a layer of fibrocartilage external to the smooth muscle and tubuloalveolar glands, which communicate with the airway lumen via ducts [7]. Bronchioles lack both cartilage and glands and become respiratory bronchi-oles when alveoli open directly into their lumen [7]. The lining of the trachea and major bronchi consists of pseudostratified, ciliated columnar epithelium which gradually becomes more cuboidal.

FIG. 6.1 Postmortem bronchogram from an otherwise normal 19-year-old man who died suddenly for reasons unrelated to the lung. Note the difference in airway length depending upon the pathway that is followed.
with fewer ciliated cells as the alveolar surface is approached [6–8]. Light microscopy reveals that the basal aspect of airway epithelial cells is attached to a thin basement membrane (80–90 nm width) that contains primarily type IV collagen and elastin [9]. Transmission electron microscopy shows that a true basement membrane or basal lamina can be readily distinguished from the connective tissue observed with the light microscope [6, 7]. Quantitative studies [10–12] have shown that the trachea and mainstem bronchi of normal subjects consist of by volume:

- 30% cartilage;
- 15% mucous glands;
- 5% smooth muscle; and
- 50% connective tissue matrix containing the bronchial arterial, venous, and lymphatic vessels.

With progression toward the periphery of the bronchial tree, the amount of cartilage and glands decrease, and the percentage of smooth muscle increases to account for approximately 20% of the total wall thickness in the bronchioles.

The degree to which the smooth muscle surrounds the airway lumen varies according to site. In the trachea and mainstem bronchii, the airway smooth muscle is located within the posterior membranous sheath, whereas, in the bronchioles, it surrounds the entire lumen of the airway [7, 8, 13]. Consequently, the same degree of muscle shortening has a smaller effect on the caliber of the trachea and central airways than on the distal bronchi and bronchioles [14]. The adventitial layer consists of loose bundles of collagen admixed with blood vessels, lymphatics, and nerves. In the peripheral conducting airways, this layer interacts with the surrounding lung parenchyma through alveolar attachments that are distributed along the circumference of the adventitia. These alveolar attachments have the ability to limit the amount of airway narrowing produced by smooth muscle contraction, particularly at higher lung volumes [14].

The systemic arterial supply to the bronchial tree originates from the ventral side of the upper thoracic aorta in the left hemithorax, while on the right the origin of the bronchial vessels is more variable. They may originate from the first to the third intercostal artery, from the right internal mammary artery, or from the right subclavian artery [8, 15]. Miller’s classic anatomical account [8] showed that two to three arterial branches accompany each of the larger bronchi and that anastomoses between these branches form an arterial plexus in the outer wall of the airway. Small branches of this plexus penetrate the smooth muscle layer to form a capillary network below the epithelium. Short connecting branches extend from this plexus through the muscle layer to form a secondplexus of venules along the outer surface of the airway smooth muscle (Fig. 6.2). In some species, this outer plexus contains large venous sinuses that can extend into the submucosal layer of the major bronchi, where there is no smooth muscle between the cartilage and epithelium [16].

The venous blood from the first two or three subdivisions of the bronchial tree drains into the azygous and hemiazygous venous systems that empty into the vena cava. The remainder of the bronchial venous flow drains directly into the pulmonary circulation, although there is debate as to how much enters at the precapillary, capillary, and postcapillary levels [8, 15]. Airway disease increases the anastomotic flow between the pulmonary and the bronchial vascular systems; and in diseases such as bronchiectasis, injection of the bronchial arteries can result in rapid filling of the entire pulmonary vascular tree right back to the pulmonic valve [15].

The bronchial circulation accounts for about 1% of cardiac output and an average cardiac output of 5 l/min delivers approximately 721 of blood to the conducting airways over 24 h. Each liter of blood contains between 4 and $11 \times 10^9$ white blood cells, made up of approximately 60% neutrophils, 30% lymphocytes, 5% monocytes, 3% eosinophils, and 2% basophils. The neutrophils do not divide after they leave the marrow have a relatively short half life within the circulation and remain within the vascular space unless an inflammatory response is present. Although much less is known about eosinophils and basophil kinetics they are predominantly a tissue cell, indicating that their transit times through the tissue compartment is much longer than that for migrating neutrophils. Monocytes on the other hand leave the vascular space even in the absence of an inflammatory stimulus and divide in the tissue to form the alveolar macrophages
that are removed via the airways with very little if any re-entry into the tissue. On the other hand lymphocytes leave the circulation regularly with the assistance of specialized high endothelial cells and re-entering the circulating blood with the lymph as it drains into the venous system.

A study of lung tissue obtained from patients at all five Global Initiative for Chronic Obstructive Lung Disease (GOLD) categories of chronic obstructive pulmonary disease (COPD) severity has shown an association between the decrease in FEV\textsubscript{1} with both the extent of the accumulation of these cells (i.e. the percentage of airways containing cells) and severity of this accumulation (i.e. the total accumulated volume of cells) within small airway tissue [17]. The accumulating lymphocytes form follicles with germinal centers in both the small conducting airways [17] and the parenchyma [18] of the peripheral lung in both COPD [17, 18] and asthma [19]. These accumulations of lymphocytes (Fig. 6.3) are part of the bronchial associated lymphoid system or bronchial-alveolar lymphoid tissue (BALT) and differ from the regional lymph nodes in that they have no capsule and no afferent lymphatics. They are similar in structure to the tonsils and adenoids, the Peyers patches in the small bowel, and the appendix of the cecum which are also part of the mucosal immune system. They are organized in the same way as other lymph follicles (Fig. 6.3) in that the B-cells are found in the germinal center of the follicle and the CD4 and CD8 T-cells are located around the edges of the germinal center. Thus dendritic cells migrating from the epithelium and subepithelium circulate through the T- and B-cell rich regions of the follicle and can present antigen to uncommitted T and B lymphocytes moving through these regions in the lymph (Fig. 6.3). Moreover the recirculation of lymphocytes through the follicle and back into the circulation enhances the opportunity for T Helper cells and B-cells that have recognized the same antigen to interact with each other and initiate an adaptive immune response. The appearance of lymphoid follicles with germinal centers in the tissue provides histological evidence that an adaptive immune response has been mounted within the peripheral lung. Some investigators have begun to study this response in detail [18].

**THE PATHOLOGY OF ASTHMA**

**Postmortem studies**

At postmortem, the lungs of patients who have died in status asthmaticus remain markedly hyperinflated after the thorax is opened. This hyperinflation is due to air trapping
caused by widespread plugging of the segmental, subsegmental, and the smaller conducting airways by mucus and cellular debris [20]. Although this luminal content may extend to the respiratory bronchioles, it usually stops short of these structures and does not fill the alveolar airspaces. Examination of the cut surface of the lung reveals the plugged airways, but – in contrast to parenchymal destruction seen in hyperinflated emphysematous lungs – the parenchyma of the asthmatic lung remains intact.

Huber and Koessler’s [21] classic 1922 paper on the pathology of asthma reviewed 15 published cases and provided new data on 6 more. They noted that the pathology consisted of common features that allowed asthma to be distinguished from other conditions. They emphasized the presence of intraluminal mucus secretion, airway epithelial desquamation, and repair (e.g. goblet cell metaplasia), and airway inflammatory infiltrates consisting of an admixture of mononuclear cells and eosinophils and the presence of a thickened, “hyalinized” subepithelial basement membrane. Later studies based on electron microscopy and immunohistochemistry showed that this feature of the basement membrane was due to deposition of collagen fibrils and extracellular matrix below the true basement membrane, rather than thickening of the basal lamina. Huber and Koessler’s report noted that the tenacious plugs that fill the airway lumen consist of an exude of plasma containing inflammatory cells, particularly eosinophils, mixed with epithelial cells that had sloughed from the airway surface. Using an eyepiece micrometer to measure the external airway diameters, they concluded that the walls of bronchi and bronchioles of more than 2 mm outside diameter were thickened compared with non-asthmatic persons, and that this difference was due to an increased thickness of all of the components of the airway wall.

Over the next several decades, other reports confirmed and extended these findings [22–29]. Comparing Florey’s [30] basic studies of the inflammatory process with these pathological findings show that the structural changes associated with asthma are consistent with an inflammatory process involving a mucus-secreting surface. However, this knowledge had relatively little impact on the allergists, pulmonary physicians, and physiologists until the 1970s [31], because they were preoccupied with the concept that asthma was due to IgE sensitized mast cells releasing mediators that caused excessive contraction of airway smooth muscle following specific antigen challenge.

**Bronchoscopic studies**

The nature of the airway pathology in persons with asthma was further revealed by studies of tissue obtained through the rigid and flexible bronchoscope. These techniques allowed investigators to obtain cells from living asthmatic patients by both bronchoalveolar lavage and bronchial biopsies [31–34]. This brought physiologists and clinicians into closer agreement with the pathologist’s view that the inflammatory process was important to the pathogenesis of both bronchial hyperresponsiveness and reversible airflow obstruction.

A very important conceptual development based on the discovery that murine CD4+ T-cell clones showed that these cells can be divided according to the cytokine messenger RNA (mRNA) and proteins that they produce [35]. These experiments established that one type of T-cell clone (Th-1) produced IL-2 and interferon-γ but no IL-4 or IL-5; whereas the second (Th-2) produced IL-4 and IL-5, but no IL-2 or interferon-γ. Both clones produced IL-3 and GMCSF, and interactions between Th-1 and Th-2 subtypes allowed one type of clone to inhibit the other. For example, IL-4 is a mast cell growth factor that also stimulates IgE production, and IL-5 promotes the differentiation and survival of eosinophils. Robinson and associates [36] put forward the hypothesis that asthma was the result of a “Th-2 response” based on bronchoalveolar lavage and bronchial biopsy findings. And subsequent studies of surgically resected lung specimens from asthmatic patients established that a similar inflammatory process was present in the smaller airways [37].

It has now become clear that the structural features of the airways from asthmatic patients result from an inflammatory process involving tissue with a mucus-secreting surface. This response appears to be driven by a subset of CD4+ T lymphocytes producing cytokines that result in an excess of eosinophils and an overproduction of IgE. The end result is abnormal airway function, characterized by excessive airway narrowing in response to external stimuli, reversible airways obstruction, and gas trapping. Although the majority of the symptoms produced by the process can be rapidly reversed with appropriate treatment, the process can be life threatening and result in sudden death.

### The relationship between airway structure and function

The concept that the same degree of smooth muscle shortening will cause greater reduction in airway caliber when the wall is thickened by disease has been suggested by several authors [38, 39]. Moreno and associates [39] calculated that the thickening of the airway wall observed in asthma would have only a minor effect on the caliber of the lumen of a fully dilated airway. However, when the smooth muscle in the airway shortens, the increased tissue between the muscle and lumen causes an excess reduction in airway caliber. Subsequent studies by James et al. [40] showed that the increase in wall thickness observed in the small airways of asthmatics was sufficient to close the lumen of these airways, even when smooth muscle shortening remained within the accepted normal range. This suggests that normal smooth muscle shortening may act in series with an abnormally thickened airway wall to narrow the airway lumen and it follows that the reduction in airway caliber produced by this mechanism would be rapidly reversed when the smooth muscle relaxed. This showed that an important feature of the pathology of asthma was the change in the structure of the airway wall produced by the remodeling of the tissue that occurs in relation to the inflammatory process. The important point is that these structural changes could result in excess airway narrowing with normal smooth muscle contraction and that excessive smooth muscle shortening will enhance the effect of these structural changes on the airway lumen.
Wiggs et al. [41, 42] extended this concept using a computer model to test the effect of these structural changes on airway function. Their analysis (Fig. 6.4) showed that maximum stimulation of the smooth muscle caused airway resistance to increase and reach a plateau in the normal lung. This finding was consistent with previous observations by Woolcock et al. [43], who reported that the changes in the maximum volume of air that can be expired from the lung in 1 s (FEV₁) reached a plateau in normal subjects when maximally stimulated by inhaled bronchoconstrictors. However, when the data on airway structure were changed from normal values to those found in asthmatic lungs, a similar degree of airway smooth shortening produced widespread airway closure. The concept that the peripheral airways are the major site of obstruction in asthma has now been confirmed by direct measurements in living asthmatic patients reported by Yanai et al. [44].

The changes that are produced in the airway tissue also reduce the function of the conducting airways. Lambert [45] was the first to systematically study the normal folding pattern of the bronchial mucosa, and showed that in asthma the multiple mucosal folds that occur when normal airways narrow were replaced with fewer and larger folds that reduced airway caliber. Both Lambert and Wiggs et al. [46] suggested that the mucosal folding pattern was controlled by the stiffness of the subepithelial layer relative to that of the surrounding airway tissue. This analysis suggested that changes in the subepithelial connective tissue might play a key role in determining the pattern of mucosal folding. Lambert and Wiggs et al. argued that the formation of a large number of folds in the normal airway placed a load on the airway smooth muscle that tended to prevent airway closure at low lung volumes. It followed that a change in the mucosal folding pattern in asthma may be one way in which this disease causes peripheral airway dysfunction.

The caliber of the airway lumen is also influenced by airway surface tension that is normally low in the small airways because they are lined with surfactant [47]. Exudation of plasma and the secretion of mucus on to the small airway lumen surface should increase surface tension and cause the airways to narrow. The analysis of induced sputum has confirmed that plasma proteins, mucus, and inflammatory cells are present in the airway lumen even in mild asthma, suggesting that some of the abnormalities in airway function of asthmatics might result from the presence of this material in the lumen. Kuyper and colleagues [48] recently reassessed the importance of the occlusion of the airway lumen by inflammatory exudates in deaths attributed to asthma. By examining the airway wall and luminal content of 275 airways from 93 patients with fatal asthma aged 10–49 years. Compared with control airways obtained from persons that died of causes unrelated to the lungs, the asthmatic airways showed much more extensive lumenal occlusion, by mucus and cells. They concluded that widespread airway occlusion

**FIG. 6.4** Data from Wiggs et al. (Refs. [38, 39]) showing results from a computer model of the airways. The structural data from normal lungs were used to obtain the control measurements. These show that airway resistance increases from about 1 cmH₂O per liter per second to reach a plateau of 12 cmH₂O per liter per second, with maximum contraction of the airways smooth muscle. (A) When the structural features of asthmatic airways were used in the same computer model, the airway resistance continued to increase and did not reach a plateau at any physiologically meaningful value. (B) Data obtained from the model when the structural changes caused by asthma were limited to the central airway (i.e. those >2 mm diameter). Note that asthmatic changes in the central airways increased total resistance and resulted in a plateau slightly greater than the control lungs. (C) However, when the asthmatic changes were placed in the peripheral airway, the resistance increased without reaching a plateau. These data suggest that asthmatic changes in the peripheral airways have a much greater effect on overall airway function than changes that occur in the central airways. Reproduced from Ref. [38] with permission.
was the major cause of death from asthma and death due to closure of empty airways by excessive bronchoconstriction must be a rare event. Moreover the extensive nature of the airway occlusion observed at autopsy in these cases suggests that bronchoconstriction superimposed on airways that have become partially occluded is the most probable cause of sudden death.

THE PATHOLOGY OF COPD

The inflammatory process contributes to the pathogenesis of chronic cough and sputum production [49], peripheral airways obstruction [3, 17, 50], and emphysematous destruction of the lung surface [51] that define COPD. As tobacco smoking produces lung inflammation in everyone, and only 15–20% of heavy smokers develop COPD, clinical disease from cigarette smoke-induced airway inflammation must develop in this minority of people because it amplified by either genetic or environmental risk factors [52].

Chronic bronchitis

Cough and sputum production are the features of airways disease that define chronic bronchitis [53] and these symptoms can be present either with or without airways obstruction [49]. Figure 6.5 shows the histology of a normal bronchus at low power where with the connection between the epithelial lining of the bronchial lumen to the mucus duct and gland is clearly seen. Reid [54] used the relative size of the mucus glands to the airway wall as a yardstick for measuring chronic bronchitis and downplayed the influence of inflammation in driving mucus production. However, a reevaluation of this problem some years later showed that chronic bronchitis was associated with inflammation of the airway mucosal surface, the submucosal glands, and gland ducts, particularly in the smaller bronchi between 2 and 4 mm in diameter [49]. The nature of the inflammatory process present in these airways is now quite well established with several studies reporting that CD8⁺ lymphocytes are present in excess numbers in smokers with chronic bronchitis [55, 56].

Sputum production represents the clearance of a mucoid inflammatory exudate from the lumen of the bronchi. This exudate contains plasma proteins, inflammatory cells, and small amounts of mucus added from goblet cells on the surface epithelium and the epithelial glands. Although the size of the bronchial mucous glands tends to increase [49] in chronic bronchitis, Thurlbeck and Angus [57] showed that the Reid index was normally distributed with no clear separation between patients with chronic bronchitis and controls. Chronic bronchitis also results in an increase in airway smooth muscle, a generalized increase in the connective tissue in the airway wall, degenerative changes in the airway cartilage, and a shift in epithelial cell type that increases the number of goblet and squamous cells [58–62].

The site of airways obstruction

The site of airways obstruction in COPD is in the smaller conducting airways that include bronchi and bronchioles of less than 2 mm diameter [3]. Direct measurements of airways resistance in dogs [4] and in similar measurements in postmortem human lungs [3] established, in the normal lung, that the small peripheral airways offer very little resistance to air flow. Although van Brabant et al. [63] subsequently argued that these peripheral airways account for a larger proportion of the total airways resistance in the normal lung, there is general agreement that the peripheral airways are the major site of obstruction in COPD [3, 44, 63].

The causes of the reduced forced expiratory flow that define COPD include destruction of alveolar support of the peripheral airways [64], the loss of elastic recoil in the parenchyma supporting the airways [65], a decrease in the elastic force available to drive flow out of the lung [66], and structural narrowing of the airway lumen by a remodeling process [3, 17, 67]. Comparison of the histological appearance of peripheral airways at different degrees of severity of COPD shows a progressive increase in the magnitude of the inflammatory process with thickening of the airway walls accompanied by occlusion of the airway lumen by inflammatory mucous exudates [17]. However, multivariate analysis of
these data indicated that thickening of the airway walls and the occlusion of the lumen by inflammatory exudates containing mucus explained more of the variance in the decline in FEV\(_1\) than the infiltration of the airway tissue by any of the inflammatory cell types examined [17]. Interestingly the severity of the occlusion of the airways lumen by inflammatory exudates containing mucus (Fig. 6.6) has also associated with premature death in persons with severe (GOLD-3) and very severe (GOLD-4) disease [68].

The lung inflammatory changes that are associated with cigarette smoking have been documented in autopsy studies [69–73], resected lung specimens [49–51, 74] lung biopsies [75], and indirectly by examining bronchoalveolar lavage fluid [76–78]. Collectively these data support the concept that cigarette smoke-induced lung inflammation is present in all smokers, including those with normal lung function and that it persists long after people have stopped smoking [17]. The reasons for both the amplification of the smoking-related inflammatory process in individual that develop COPD, the persistence of this response after the smoking has stopped and the precise relationship between the inflammatory response and the remodeling process needs further clarification.

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**Emphysema**

Emphysema has been defined as “abnormal permanent enlargement of airspaces distal to terminal bronchioles, accompanied by destruction of their walls without obvious fibrosis” [79]. This definition emphasizes the destruction of the alveolar surface with a minimal reparative response in the lung matrix and the ability of this destructive process to reduce the gas-exchanging surface of the lung. The centrilobular form of emphysema (Fig. 6.7) resulting from dilatation and destruction of the respiratory bronchioles in the center of secondary lobule of Miller has been most closely associated with smoking [80, 82]. The panacinar form of emphysema, on the other hand, results from a uniform destruction of all of the acini in the entire secondary lobule and is characteristic of the lesions found in the lungs in \(\alpha_1\)-antitrypsin deficiency [83]. The terms “distal acinar,” “mantle,” or “perisepal” emphysema are used to describe lesions that occur in the periphery of the lobule and along the lobular septae particularly in the subpleural region. These lesions have been associated with spontaneous pneumothorax in young adults and bullous lung disease in older individuals [84]. In far-advanced parenchymal destruction such as that frequently observed in end-stage...
COPD, these descriptive terms are less helpful because centrilobular disease eventually destroys the entire lung lobule and destroyed lobules can coalesce to form much larger lesions.

The destruction of the lung by centrilobular emphysema results in a loss of elastic recoil with subsequent hyperinflation and a change in the pressure–volume relationship of the emphysematous lung tissue compared to the surrounding normal lung such that at any volume recoil pressure is less [81]. This decrease in lung elastic recoil diminishes expiratory flow by reducing the pressure available to drive air out of the lung [66], and interferes with gas exchange by reducing lung surface area [85].

**Acute exacerbations of COPD**

In a hospital-based study of 1205 admissions to five hospitals for acute exacerbations of COPD, infections accounted for 520 (43%), heart failure for 260 (22%), and 122 (10%) cases were attributed to a variety of etiologies that included arrhythmia, pulmonary embolism, pneumothorax, postoperative complications, and lung cancer [86], with no cause being established in 303 (25%) of these 1205 admissions. Early studies by Stuart-Harris and associates [87, 88] showed that COPD patients with acute upper respiratory infections are more likely to have signs of infection in the lower airways than normal controls. Probably because acute viral upper respiratory tract infections increase the risk of aspiration of mucoid exudate containing large numbers of bacteria from the upper airways, but also because viral infection reduces both the mucociliary clearance and bacterial killing in the lower airways [89–91]. *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Hemophilus influenzae* are the most common bacteria infecting the lower airways during an acute viral infection [90, 91], and these infections account for the positive effect of antibiotics in some exacerbations of COPD [92]. Two important early studies established an association between acute illness and serologic laboratory evidence of viral infection in patients with COPD [93, 94]. The development of polymerized chain reaction (PCR)-based viral
diagnostic techniques have improved the sensitivity of the diagnosis of viral infection and the use of real time PCR to measure viral copy numbers will likely improve its specificity. Early reports of studies based on these techniques indicate the importance of rhinoviral infection in causing acute exacerbations in an outpatient setting with influenza A and the corona virus OC-43 being more prominent causes of exacerbations that require admission to hospital [95–97].

The pathological features of the lung during acute exacerbations of COPD are incompletely defined. Primarily because postmortem studies of patients that die during exacerbations are complicated by terminal events and biopsy studies of patients with severe (GOLD-3 and very severe GOLD-4 disease during an exacerbation cannot be carried out without excess risk to the patient. One exception is an important study by Saetta et al. [98] in less severely ill patients with GOLD class 2 disease and a mean FEV₁ of 62 ± 7% predicted implicated the eosinophil as a cell of interest. Clearly more studies especially those that can make use of non-invasive or less invasive techniques than biopsy are needed to help clarify this important area of COPD.

SUMMARY

Asthma

The pathology of asthma is dominated by widespread plugging of the segmental, subsegmental, and smaller conducting airways that leads to hyperinflation but not destruction of the parenchyma. These airway plugs are a manifestation of the inflammatory process located in the mucosa, gland ducts, and glands of intermediate-sized bronchi between 2 and 4 mm internal diameter. The airway obstruction in COPD is the result of a similar inflammatory response in the smaller bronchi and bronchioles under 2 mm internal diameter, where the repair process associated with chronic inflammation thickens the airway wall and narrows the lumen to cause fixed airway obstruction. Emphysematous destruction of the lung surface contributes to the decline in FEV₁ by reducing the elastic recoil force available to drive air out of the lung and is responsible for reduced gas exchange. The acute exacerbations of COPD that occur with increasing frequency as the disease progresses have several known causes including infection, right heart failure, and pulmonary embolism but it is discouraging that in up to 25% of cases admitted to hospital the cause is unknown.

COPD

The chronic bronchitis of COPD is defined by excess cough with sputum production and is associated with an inflammatory process located in the mucosa, gland ducts, and glands of intermediate-sized bronchi between 2 and 4 mm internal diameter. The airway obstruction in COPD is the result of a similar inflammatory response in the smaller bronchi and bronchioles under 2 mm internal diameter, where the repair process associated with chronic inflammation thickens the airway wall and narrows the lumen to cause fixed airway obstruction. Emphysematous destruction of the lung surface contributes to the decline in FEV₁ by reducing the elastic recoil force available to drive air out of the lung and is responsible for reduced gas exchange. The acute exacerbations of COPD that occur with increasing frequency as the disease progresses have several known causes including infection, right heart failure, and pulmonary embolism but it is discouraging that in up to 25% of cases admitted to hospital the cause is unknown.

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