The Pathology of Chronic Obstructive Pulmonary Disease
Progress in the 20th and 21st Centuries

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Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the developed world, and thus it constitutes a major focus of medical investigation. The pathologic study of COPD includes gross, microscopic, and molecular modalities. Although the aim of pathologic analyses was once to distinguish COPD from asthma, bronchiectasis, and the interstitial lung diseases, the focus shifted toward providing clinical and physiologic correlations. The focus then progressed again toward understanding the mechanisms involved in the genesis of the alteration of tissue components, and it has culminated in analyses of gene regulation.

The practicing pathologist needs to be able to recognize the gross and histologic changes of COPD. This will allow pathologists to not only provide diagnostic information to correlate with the patient’s symptomatology and physiologic findings, but also to provide information to correlate with genetic and molecular biologic analyses. This article is not meant to be an all-inclusive review, but rather to provide a reprise of these developments and indicate areas in which there is a need for further research.

DEFINITION

Chronic obstructive pulmonary disease is one of a group of conditions defined by airflow limitation and thus must be distinguished from asthma, bronchiectasis, and airway obliteration. It is defined in the most recent update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as “a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.” This definition is quite different from those of the American Thoracic Society (1995) and the European Respiratory Society (1995), which respectively defined COPD as “a disease state characterized by the presence of airflow limitation due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyper-reactivity, and may be partially reversible” and “reduced maximum expiratory flow and slow forced emptying of the lungs, which is slowly progressive and mostly irreversible to present medical treatment.” The newer GOLD definition highlights the usually preventable nature of the disease, as well as the contribution of the patient’s inflammatory response, and variability between individuals. These clinical definitions, however, are not particularly helpful to the pathologist in making a clinical-pathologic correlation.

PATHOLOGY

The histology of pathologic descriptions of the lung disease that is now known as COPD is really the history of the description of emphysema and its differentiation from tuberculosis, which developed during the 20th century (see Snider3 for discussion). This not only includes gross pathologic descriptions but also microscopic descriptions, and early speculations on pathophysiology.

In 1952, Gough5 used paper-mounted sections to describe what he termed “fundamentally different” types of emphysema, types that we now know as centriacinar (centrilobular) and panacinar (panlobular) emphysema. He also first described how to pathologically differentiate emphysema from status asthmaticus and pneumoconiosis. This was followed by work involving microscopic 3-dimensional reconstruction, demonstrating that centrilobular emphysematous spaces were based on architectural alterations, inflammation, and destruction of the respiratory bronchi-
oles. Then, in 1958, McLean described vascular alterations in emphysema. This work brought us to the modern triad of pathologic alterations in COPD, namely, emphysema, smokers' bronchiolitis, and vascular alterations (summarized in the Table).

The 21st century has not yet seen any major changes to the pathologic description of COPD, but it has seen increasing recognition of the coexistence of COPD with interstitial lung disease, an area that is still being explored (see last subsection, Combination of COPD and Interstitial Lung Disease).

**Emphysema**

Emphysema is defined as "a condition of the lung characterized by permanent, abnormal enlargement of the respiratory airspaces, accompanied by destruction of their walls without obvious fibrosis." It is important to note here that the fibrosis refers to gross fibrosis, not microscopic fibrosis, and thus differentiates emphysematous destruction of airspaces from the airspace remodeling seen in interstitial lung diseases. The inclusion of "destruction" in the definition serves to differentiate emphysema from the simple airspace enlargements seen in aging, compensatory emphysema and congenital lobar hyperinflation.

There are 4 main types of emphysema: proximal acinar emphysema (including the centriacinar emphysema seen characteristically in cigarette smokers and the focal centriacinar emphysema seen in pneumococci); panacinar emphysema, characteristically found in α1-antitrypsin (protease) deficiencies; distal acinar (paraseptal) emphysema, characteristically seen in young adults with spontaneous pneumothorax, or in association with centrilobular emphysema; and finally airspace enlargement with fibrosis (also termed scar, irregular, or paracuticular emphysema).

The synonymous use of "lobular" and "acinar" makes sense when one considers the anatomy of the lung. A lobule is a gross and microscopic term defined as the amount of lung parenchyma that is encompassed by pleura and/or venous septa on its borders. It is usually approximately 2 to 3 cm on a side and so can be seen grossly on a lung slice (Figure 1). Each lobule itself contains 3 to 6 acini. To understand the acinus, one needs to recall the 3-dimensional anatomy of the lung, but beginning at the level of the terminal membranous bronchiole. The terminal membranous bronchiole is the final conducting airway with a complete fibromuscular wall. The terminal membranous bronchiole gives rise to 3 generations of respiratory bronchioles (airways with alveoli forming a component of their walls). An acinus is then defined as the amount of lung tissue that subtends from a single terminal membranous bronchiole. Thus, the acinus cannot be identified on a normal gross specimen but would require a 3-dimensional process to visualize the conelike arrangement of 3 generations of respiratory bronchioles with their branches of alveolar ducts, alveolar sacs, and alveoli.

Centriacinar emphysema affects respiratory bronchioles, with relative sparing of the distal alveoli. Because respiratory bronchioles are generally clustered in the center of the secondary lobule, their destruction (proximal acinar destruction) is seen as a hole in the center of the lobule, and hence the synonym centrilobular emphysema (Figure 2). In panacinar (panlobular) emphysema, the enlarged acini are uniformly distributed from the respiratory bronchioles to the terminal alveoli (Figure 3). In paraseptal emphysema, almost the entire proximal part of the acinus is normal, whereas distal alveolar ducts and sacs are abnormal (Figure 4). Irregular emphysema can be found in any area of the lobule because it is associated with scars from prior inflammatory processes, such as tuberculous complexes.

High-resolution computerized tomography scans can now essentially replace paper-mounted sections to characterize and grade emphysema phenotypes. Thus, it is not necessary for the pathologist to prepare paper-mounted sections, obviating the need for sledge microtomes and specialized technical processes. Instead, to make the appropriate correlations with clinical or radiologic features, the pathologist can inflate the lungs (or lobes) with an appropriate fixative, slice them thinly using a standardized knife board, and examine the cut surfaces. Such an examination can be aided by immersing the lung tissue in a water bath and then lifting the tissue out and evaluating how the tissue "drops away" or remains stable.

**Alteration of the Airways**

The pathologic changes of the airways are important for the practicing pathologist to be familiar with, because these changes are central to the clinical symptoms of COPD. Increased airflow resistance in COPD is associated with the alteration, remodeling, and obliteration of the small bronchioles (less than 2 mm internal diameter). The initial pathologic descriptions of these airway alterations in emphysema highlighted the importance of two features: inflammation as a mechanism, and respiratory bronchioles as the primary site of involvement. Smokers' bronchiolitis, or respiratory bronchiolitis, is recognized pathologically as an increase of macrophages, which contain a finely granular golden brown pigment, present within the lumen of the respiratory bronchiole and subverting alveolar spaces (Figure 5). Other inflammatory cell types, such as neutrophils and eosinophils, may be numerically increased, but such increases are generally subtle. Lymphoid follicles or aggregates can also often be identified within the adventitia of the airway. A mild degree of alveolar wall fibrosis is often associated with respiratory bronchiolitis and should not be interpreted as evidence of respiratory bronchiolitis–interstitial lung disease, which remains a diagnosis that should be considered only in conjunction with clinical information.

Detailed morphometric analysis has extensively expanded our knowledge of airway alterations in both membranous and respiratory bronchioles, and it has documented airway narrowing with inflammation and fibrosis, and loss of the peribronchial alveolar attachments. These alterations, as least theoretically, correlated with the early physiologic studies that demonstrated that airflow resistance in COPD was determined by the peripheral rather than the central airway compartment. With the development of more sophisticated physiologic tests of airway dysfunction, studies also showed that inflammation and fibrosis were the most important pathologic alterations in the bronchioles. Unlike evaluation of emphysema in the parenchyma, computed tomography analysis of the airways is, at present, restricted to airways greater than 2 mm in diameter. More recently, however, the combination use of micro–computed tomography and detailed morphometry has demonstrated narrowing and reduction in numbers of the terminal membranous bronchioles, which actually precedes emphysematous lung destruction. These data again emphasize that the 3 tissue compartments in lung are affected with...
### Histopathologic Features of Chronic Obstructive Pulmonary Disease

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<tr>
<th>Emphysema</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td>Panacinar emphysema</td>
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<td>• Destruction of respiratory bronchioles through to terminal alveoli</td>
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<tr>
<th>Alteration of the airways</th>
<th>Respiratory (smoker’s) bronchiolitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation and fibrosis of terminal and respiratory bronchioles</td>
<td></td>
</tr>
<tr>
<td>Reduction in terminal bronchioles</td>
<td></td>
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<tr>
<td>Goblet cell metaplasia</td>
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<td>Squamous metaplasia</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Alteration of the vasculature</th>
<th>Intimal thickening with smooth muscle proliferation and elastin/collagen deposition</th>
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<tr>
<td>Smooth muscle hyperplasia of the media</td>
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Changes in the airway epithelium can also be found, with the most marked changes in the larger conducting airways. The most obvious of these is goblet cell metaplasia of the usual pseudostratified epithelium (larger airways), or ciliated columnar epithelium (smaller airways), although squamous metaplasia can also often be identified in the larger airways. The practicing pathologist can certainly comment on the extent and severity of the above-described airway remodeling. As a caution, however, although goblet cell metaplasia is a feature of asthma, its presence should not cause the pathologist to suggest that airway hyperresponsiveness may be present in COPD; indeed, there is sufficient overlap between the airway pathology of asthma and that of COPD that a definitive separation based solely on evaluation of the conducting airways is quite difficult.

### Alteration of the Vasculature

As noted above, McLean9 as early as 1958 described intimal thickening with reduplication of the internal elastic fiber network and patchy “destruction” of the media in the arteries adjacent to the bronchioles. He interpreted these changes as secondary to inflammation of the bronchi and hypothesized that they were due to inflammation-induced thrombosis of the vessel. McLean also made the prescient suggestion that these changes would not only narrow and obliterate the small arteries, but would result in decreased distensibility, one of the basic premises behind endothelial dysfunction in COPD (see below).

Pulmonary hypertension (PHT) is now considered an important complication of COPD because it has been shown to be a significant predictor of mortality and is a major cause of morbidity in patients with COPD19 in which PHT is the strongest prognostic factor, independent of the severity of airflow limitation. The importance of PHT in COPD is apparent when one considers that, as a lower estimate, approximately 8% of people older than 40 years will develop COPD.20 If PHT develops in approximately 6% of these individuals,21 and is present in approximately 40% of patients with a forced expiratory volume in 1 second of less than 1 L, then 16.8 million people worldwide will experience significant morbidity and mortality related to PHT.

The increased thickness of the intima in the arterial vasculature in COPD has been shown to be caused by smooth muscle proliferation, with increased deposition of both elastin and collagen (see Wright et al,25 Peinado et al,26 and Budhiraja et al27 for review). In the very small arteries and large arterioles, the longitudinal smooth muscle remodeling results in the formation of a definite muscularis media (Figure 6).

The mechanisms by which such remodeling occurs, and their physiologic consequences, are postulated by the “endothelial dysfunction” paradigm. Endothelial dysfunction is defined as a physiologic alteration of the normal biochemical processes carried out by the endothelium.24 The characteristic feature of dysfunction is the inability of the arteries to dilate fully in response to exercise, acetylcholine, or increases in flow. This dysfunction in COPD could be explained by several contributing factors, including an increased production of vasoconstrictors, and a chronic insufficiency in the production of vasodilators, thus allowing constriction to be either progressive or maintained. Other factors relate to the action of vasoactive mediators, particularly endothelin and nitric oxide synthetases (eNOS and iNOS), which regulate cell growth and vascular contraction. Long-term smoking appears to be associated with a decreased nitric oxide response,25 and impaired endothelium-dependent relaxation of the main pulmonary artery is found in patients with COPD.26,27 In addition, reduced immunohistochemical expression of nitric oxide synthase has been found in the vessels of patients who had pulmonary hypertension due to a variety of etiologies.28 Thus, the stage is set for proliferation of the vascular muscle cells and fibroblasts, culminating in thick-walled vessels with narrowed lumens, and impaired ability to vasodilate. The endothelial-targeted treatment aspects of this hypothesis have been tested in both humans and in animal models of COPD, with variable results. This is an area of ongoing research that will be needed to provide any therapeutic interventions for this aspect of COPD.

The practicing pathologist should be aware of the above vascular changes, if only to exclude idiopathic pulmonary hypertension.

### Combination of COPD and Interstitial Lung Disease

People who smoke cigarettes not only can develop respiratory bronchiolitis–interstitial lung disease, but they also have a higher incidence of developing usual interstitial pneumonia/idiopathic interstitial fibrosis. Mixtures of these diseases with emphysema are not uncommon.29–31 The practicing pathologist must be aware of this coexistence; we have recently reviewed this topic with a focus on the pathologic differential diagnosis.30 Computed tomography scans generally show findings typical of COPD, with centrilobular or mixed centrilobular and paraseptal emphysema in the upper lobes, and also findings typical of usual interstitial pneumonia, with increased reticular markings, traction bronchiectasis, and honeycomb remodeling in the
Figure 1. Paper-mounted section illustrating a lung lobule.

Figure 2. A, Gross photograph of a lung lobule with centrilobular destruction. B, High-resolution computerized tomography image showing the radiologic correlate with “holes” in the center of the lung lobules.

Figure 3. A, Gross photograph of a lung lobule with panlobular destruction. B, High-resolution computed tomography image showing the radiologic correlate with the entire lobule destroyed.

Figure 4. A, Paper-mounted section illustrating paraseptal emphysema. B, High-resolution computed tomography correlate showing a large space in the subpleural position.

Figure 5. First-generation respiratory bronchiole with macrophages within the airway lumen and also within the adjacent alveolar airspaces (hematoxylin-eosin, original magnification ×4.5).

Figure 6. Muscularization of the normally poorly muscularized small arteries/arterioles adjacent to alveolar ducts (immunohistochemistry for smooth muscle actin, original magnification ×20).
lower lobes. Pathologically, there are defined areas of emphysema, both gross and microscopic, and areas of defined usual interstitial pneumonia, with interstitial fibrosis and fibroblast foci in the areas of active fibrosis.\textsuperscript{30} Correlation with computed tomography findings is essential because biopsy samples are usually directed toward the areas of usual interstitial pneumonia.

**PATHOGENESIS**

There are several mechanisms that appear to be pertinent to the genesis of emphysema, none of which are entirely mutually exclusive.\textsuperscript{32,33} Although the mechanisms are discussed below as distinct theories, there is considerable overlap between them, and it is likely that emphysema and airway remodeling are a consequence of the interplay of the inflammatory and immunologic systems, resulting in genetic alterations and abnormal maintenance and repair of the lung.

**Protease/Antiprotease Hypothesis**

The most longstanding theory is that emphysema results from an imbalance between inflammatory-induced proteolytic enzymes and the ability of the antiproteolytic activities of the lung to inhibit these proteases. There is a long list of proteases of importance, including serine and metalloproteases, and there is an equally long list of inflammatory cascades that may be involved in the induction of these proteases. Environmental oxidants have effects both in inflammatory protease activation and antiprotease inactivation.

**Disruption of Homeostatic Maintenance and Repair System**

This hypothesis suggests that there is an intrinsic balance between apoptosis and cell proliferation in the lung, and that vascular endothelial growth factor is central to the stability of this system as a survival signal. The hypothesis suggests that cigarette smoke activation of caspase, ceramide, and oxidative stress acts to induce apoptosis and will ultimately produce emphysema through induction of senescence. This results in cellular dropout and loss of alveolar wall integrity.

This theory also includes speculation as to the role of autoimmunity in induction of both centriacinar and panacinar emphysema. Certainly, there are data that imply that an adaptive immune response is involved in either or both of the genesis and perpetuation of emphysema. Exposure of recognition domains, membrane lipid alteration, and dendritic cell activation can all lead to activation of T cells targeted toward the lung endothelium and/or epithelium.

The lung microbiome appears to be important in the host immune response in COPD. Recently, Sze and colleagues\textsuperscript{24} have found not only that analysis of the microbiome can be used to discriminate between control and severe COPD lung tissue, but they also demonstrated that a decline in microbial diversity correlated with emphysematous lung destruction, airway remodeling, and CD4 T-cell lymphocyte accumulation within the lung.

Genetic changes in COPD can occur at several levels. There are germ line alterations, such as are found in Fabry disease, Ehlers-Danlos syndrome, and Marfan syndrome, which result in alteration of the lung matrix proteins. Genetic alterations may also explain some of the familial-related susceptibilities for emphysema and airway disease. In a general population of COPD patients, genome-wide study of emphysema has identified loci associated with emphysema-related phenotypes.\textsuperscript{25} One of the most interesting associations are variants near SERPINA10 that are not due to PI ZZ antitrypsin. Further, a rather diverse number of single-nucleotide polymorphisms have been found not only in severe but also in mild COPD, suggesting that clinical heterogeneity may be at least partially related to genetic heterogeneity;\textsuperscript{36} this is an area of ongoing research. Epigenetic modifications, through DNA methylations and histone modifications, may also have an important role in COPD progression or exacerbations.\textsuperscript{27}

**SUMMARY**

In the 20th and now in the 21st century there have been remarkable advances in our knowledge of the pathology and pathophysiology of COPD. Alterations of lung anatomy can be identified not only by the pathologist but also by the radiologist, and have shown that the 3 lung compartments of parenchyma, airways, and vasculature must be considered both separately and together. Genetic and epigenetic studies have placed us on the threshold of the ability to identify populations who are at risk of developing COPD and COPD exacerbations. It continues to be necessary for the practicing pathologist to be able to identify all components of COPD (Table: emphysema, smokers’ bronchiolitis, and pulmonary vascular alterations) at the autopsy or surgical pathology bench.

**References**


