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Chronic Bronchitis

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The term "chronic bronchitis" has been used since the last century to describe a clinical picture of chronic cough and infection. With the advent of antibiotic therapy in the late forties, there was reason to believe that conditions such as tuberculosis, childhood infections, and various types of bacterial pneumonia would cease to exist as major causes of morbidity and mortality; such has been the case for the most part, except perhaps for the rise of tuberculosis and other infections in patients with AIDS. Yet an important contingent of patients with chronic airway obstruction, increased sputum production, and super-added infections has defied control; it is clear now that chronic bronchitis is the cause of such symptoms in these patients.[1–3]

As characteristically seen in cigarette smokers, chronic bronchitis is usually defined as excessive mucus production. Detailed epidemiologic surveys have made clear that this clinical sign can be present for many years before the patient seeks professional help. When the latter happens, serious airway obstruction and reduction in respiratory reserve may already exist. Epidemiologists are responsible for a definition of chronic bronchitis: "chronic sputum production for at least three months of the year, for more than two years."[4] This definition encompasses the mildest form of the disease as well as those complicated by recurrent infections, severe respiratory insufficiency, and, ultimately, heart failure. Two clinical types of chronic bronchitis are frequently recognized: simple chronic bronchitis, in which the sputum is mucoid, and purulent chronic bronchitis, in which pus cells and bacteria are present in the sputum. It is essential to realize that the normal airways are sterile, but with continuing irritation and mucus hypersecretion they may become colonized with bacteria. From extensive epidemiologic, clinical, and experimental studies, it has become quite clear that infection with the development of purulent sputum is not the original triggering event of chronic bronchitis; significantly, when infection is present, it is not necessarily associated with such basic signs as leukocytosis and a rise in temperature.

During exacerbations, the sputum often becomes purulent, or if it is already purulent, the degree of purulence increases. It was common in the past to call this condition "acute and chronic bronchitis." Such incidents are often associated with worsening atmospheric pollution, but a new infection, typically viral, can also trigger the exacerbation. In some patients, the retention of purulent secretions sets the stage for the development of bronchiectasis (see Chap. 28).

Irritation and infection play a major role in chronic bronchitis because each contributes to the inflammatory response. This involves the amplification of injury by mediators that are secreted as a result of direct tissue injury or as an attempt to restore homeostasis. Injury can be equated to irritation and infection, both leading to inflammation in the wall of the airway with the presence of fixed as well as migrating cells. Mucus hypersecretion is a response that develops early[5] and can occur with an acute challenge, even when the submucosal glands are of normal size. Also, hypertrophy of submucosal bronchial glands develops quickly, with an increase in the number of goblet cells in the surface epithelium.[6–8] Mucus hypersecretion ultimately favors colonization by bacteria, leading to further inflammation.

Animal studies show that mucus hypersecretion with gland hypertrophy and goblet cell hyperplasia can be induced in a variety of ways (Display 27-1). Exposure to tobacco smoke increases goblet cell density within a matter of days. Bhaskar and colleagues[9–11] and others[12] showed a slower development of goblet cell hyperplasia in dogs exposed to SO_2. Biochemical changes in the airway secretions also become apparent before the actual increase in volume of bronchial glands.

PATHOLOGY OF CHRONIC BRONCHITIS

Lesions of Major Airways

Estimates of the volume of the mucous glands and goblet cells in the adult human airway indicate about 4 ml of secreting tissue.[3] Under normal circumstances, the bronchial epithelium includes

DISPLAY 27-1. SOME EXPERIMENTAL MODELS OF MUCUS HYPERSECRETION OR CHRONIC BRONCHITIS

Inhalation of Irritant

Sulfur dioxide
Nitrogen dioxide
Chlorine
Tobacco smoke

Intranasal Instillation and Infection

Mycoplasma hyorhinis
Pseudomonas aeruginosa
Bronchial ligation and spontaneous infection

Systemic Drugs

Isoproterenol
Pilocarpine
Methacholine
Estradiol

Intratracheal Instillation of Enzymes

Elastase

Endogenous

Sex hormones

From Reid L, Jones R. Experimental chronic bronchitis. Int Rev Exp Pathol 1983;24:335.

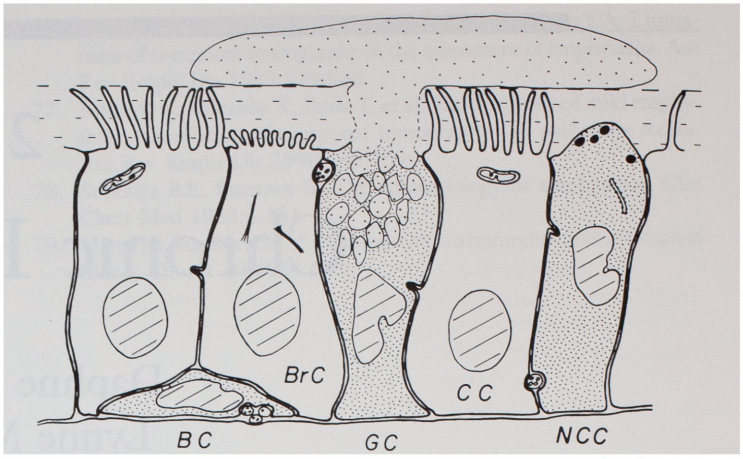

FIGURE 27-1. Cell types in the pseudostratified ciliated columnar epithelium that lines larger airways. A nerve ending is present. Note the periciliary liquid layer near the surface and the glob of secretion on the surface that is being secreted by a goblet cell. (BC, basal cell; BrC, brush cell; CC, ciliated cell; GC, goblet or serous cell; NCC, nonciliated cell.)

several types of cells producing baseline secretion and providing the liquid component for the mucociliary escalator (*i.e.*, the cilia beat in a periciliary fluid layer; Fig. 27-1).[13,14] It is now known that in the normal airway the glycoconjugate present is a proteoglycan rather than a typical epithelial glycoprotein.[15] In chronic bronchitic patients or cystic fibrosis patients with excessive mucus production there is an added mucus blanket; however, for the normal person this is certainly not so, because the bronchial surface is a shining, moist surface, similar to the inside of the mouth.

In tobacco smoker's chronic bronchitis, the mucus hypersecretion corresponds to an increase in the number of goblet cells on the surface epithelium as well as to hypertrophy of the submucosal glands. The increase in size of the bronchial glands can conveniently be measured by relating the depth of the gland to the thickness of the wall inside the cartilage and expressing this as gland-to-wall ratio (Fig. 27-2). This ratio can be applied to lungs of all sizes, of any age, and of either gender. The easy way to recall the normal size is that the gland-to-wall ratio is less than one third. In all patients in whom there is chronic hypersecretion of mucus, an increase in the gland-to-wall ratio is found.

Hypertrophy of submucosal glands is associated with not only an increase in their depth but also hypertrophy of the individual acini, particularly the mucous acini (Fig. 27-3). The serous acini probably change little in size. In the normal gland, both neutral and acid glycoproteins are produced, but with hypertrophy there is a shift in the ratio and an increase in acid over neutral glycoprotein production.[16–18] Vascularity of the gland is also increased. In the simple bronchitic, there is no striking cellular infiltration to suggest that infection is important, but the development of vasodilatation suggests the operation of cytokines and mediators.

In the surface epithelium there is also hypertrophy, which is apparent by the increase in the height of this layer and also an increase in the number (*i.e.*, density) of both the goblet and ciliated cells (see Fig. 27-3*C, D*).[19–22] The normal number of goblet cells is difficult to ascertain. In the peripheral small airways,

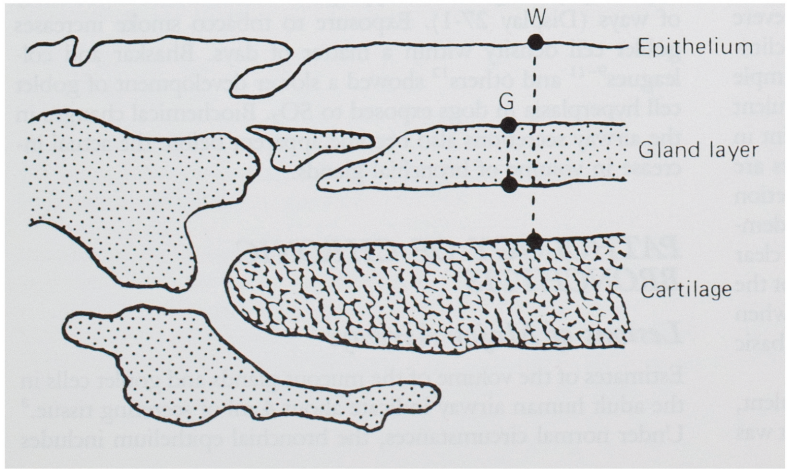

FIGURE 27-2. The gland-to-wall (G/W) ratio. In a bronchus, at a site where epithelium and cartilage are parallel, gland thickness (G) and wall thickness (W) are measured and expressed as a ratio (see Fig. 27-3.) (From Reid LM. Chronic obstructive pulmonary diseases. In: Fishman AP, ed. Pulmonary diseases and disorders. New York: McGraw-Hill, 1988:1247.)

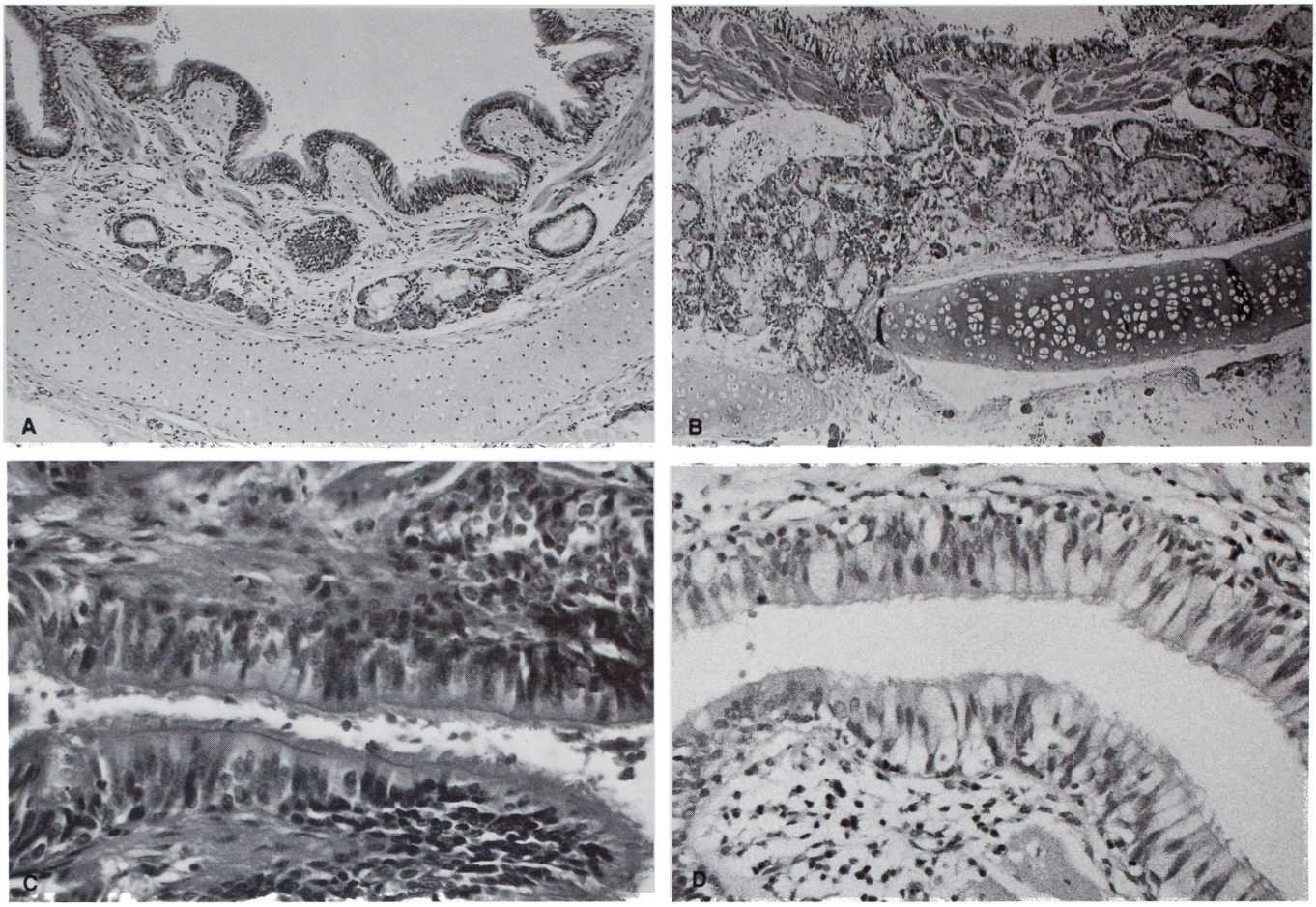

FIGURE 27-3. Airway changes in chronic bronchitis. (**A**) Normal bronchial wall has a gland-to-wall ratio of 1 : 3. (**B**) In chronic bronchitis, the gland-to-wall ratio is 1 : 2. (H & E stain; panoramic views.) (**C**) A normal bronchiolus with a few mucus-producing cells is seen in the largely ciliated epithelium. (**D**) In chronic bronchitis, the epithelium is thickened and mucus cells are numerous (*i.e.*, goblet cell hyperplasia). (H & E stain; intermediate magnifications.)

goblet cells are extremely rare; in the normal large airway there often are small islands of 6 to 12 cells in any random histologic section. Certainly, if the entire circumference of the airway shows numerous distended mucus-secreting cells, it is abnormal. It must be emphasized that the increase in goblet cells is not necessarily associated with an obvious increase in inflammatory cells. The level of atmospheric pollution probably influences goblet cell density. For example, pathogen-free rats have hardly any goblet cells; however, under ordinary laboratory conditions, the number of goblet cells increases, and in our experience, crowded conditions produce increased goblet cell counts.

Any infection, bacterial or viral, causes acute inflammation and necrosis with erosion of epithelium. In their studies of the effect of tobacco smoking, Auerbach and colleagues emphasized the development of the squamous epithelium as a stage in healing, but also as a metaplastic change.[23] The airways of the bronchitic do show both squamous metaplasia and goblet cell increase. Experimental studies show that the hypersecretory changes can reverse or be prevented (Fig. 27-4*A–C*), but slowly. In a pathologic-epidemiologic study it has been shown that the gland-to-wall ratio of ex-smokers falls midway between those of the nonsmoker and the smoker.[24]

If a chronic bronchitic patient stops smoking, mucus production sometimes falls below the threshold level, so mucus hypersecretion is no longer apparent. This does not necessarily mean that the gland-to-wall ratio has reverted to normal. Often in such patients a cold or other infection, or certainly a return to smoking, will rapidly bring the patient's mucus production back above the sputum threshold.

When bronchoscopy was common in chronic bronchitis, localized forms of inflammation with focal areas of mucosal reddening and swelling were described. The patchy distribution of inflammation needs to be stressed, because its presence is important when examining biopsy material. Under baseline conditions in organ culture, human bronchial submucosal glands secrete a proteoglycan.[25–27] When the glands are stimulated with a cholinergic agent, the typical epithelial glycoprotein is discharged.[28] It is also known from experimental studies that the first change in the composition of the airway mucus is in the lipids.[10] Normally, the lipids are neutral, but after irritation, phospholipids are also produced.

In vivo study of the control of airway secretion is difficult. Most of the available information comes from *in vitro* investigations in which the bronchial wall or the isolated bronchial gland can be studied. In this way the secretagogue effect of a variety of agents can be investigated. The latter is demonstrated by a wide range of agents, which include neurotransmitters as well as a variety of inflammatory mediators.[29]

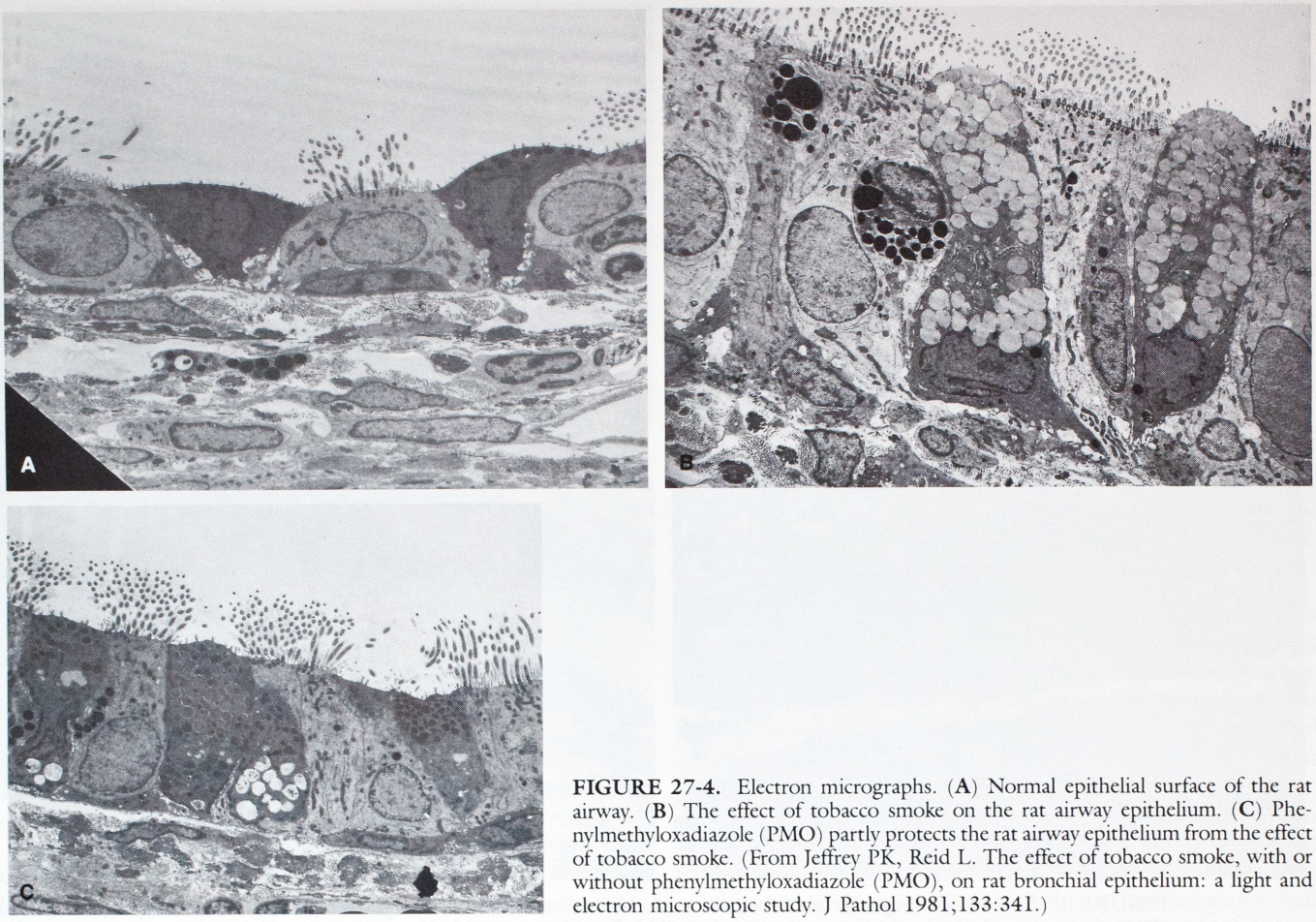

FIGURE 27-4. Electron micrographs. (**A**) Normal epithelial surface of the rat airway. (**B**) The effect of tobacco smoke on the rat airway epithelium. (**C**) Phenylmethyloxadiazole (PMO) partly protects the rat airway epithelium from the effect of tobacco smoke. (From Jeffrey PK, Reid L. The effect of tobacco smoke, with or without phenylmethyloxadiazole (PMO), on rat bronchial epithelium: a light and electron microscopic study. J Pathol 1981;133:341.)

Lesions of Peripheral Airways

In the peripheral airways (*i.e.*, bronchioles distal to the last piece of cartilage), no submucosal glands are present. In the normal human airway at this level, goblet cells are extremely sparse, and increased secretory activity is reflected by an increase in the number of goblet cells. Serous and Clara cells also convert to the typical goblet or chalice-shaped cell filled with large granules of glycoprotein. In these small airways, just as in the large, colonization of the surface epithelium by bacteria occurs. The presence of purulent sputum is still compatible with an intact epithelial lining. Polymorphonuclear leukocytes are commonly seen migrating through an intact epithelium. As mentioned, the airways may be sterile for many years and the sputum mucoid. But once sputum is purulent, bacteria are commonly recovered. This stage of lung involvement is of special significance because colonization by bacteria produces secondary inflammation.[30] For treatment, it is now recommended that both antiinflammatory agents and antibiotics be given in chronic bronchitis.

The continuing injury of inflammation, and especially infection, produces narrowing of the lumen of small airways, ulceration of the wall with loss of surface epithelium and deeper wall structures, and the development of fibrosis. Such an endobronchiolar abscess can lead to serious bronchiolitis obliterans and bronchiolectasis (Fig. 27-5).

Obstruction of small airways favors alveolar airlessness or collapse. The effective operation of collateral ventilation usually keeps the lung well aerated (Fig. 27-6), but regions of airlessness can be mixed with regions of hyperinflation. Whereas acute severe lung injury is often associated with massive collapse, the indolent and recurring injury of chronic bronchitis is usually found in an aerated lobe.

One type of lesion in the small airways is described as follicular bronchiolitis. Collections of lymphoid tissue are seen within the airway wall in association with some ulceration of the airway epithelium (see Chaps. 28 and 30). These follicular lesions are far to the periphery and are usually associated with a virtually intact bronchial tree. If a bronchogram is done, it usually shows abnormalities such as incomplete peripheral filling and some irregularity of the distal airways. A count of bronchial airway generations, however, shows that the changes causing the obstruction are well within the airways of the lobule.

Another type of bronchiolitis is seen with rheumatoid arthritis[31] and results in associated submucosal and sometimes peribronchiolar fibrosis. An additional type of small airway chronic inflammation, diffuse panbronchiolitis, is associated with airway obstruction and a special indolent form of suppuration within the small airways (see Chap. 30).

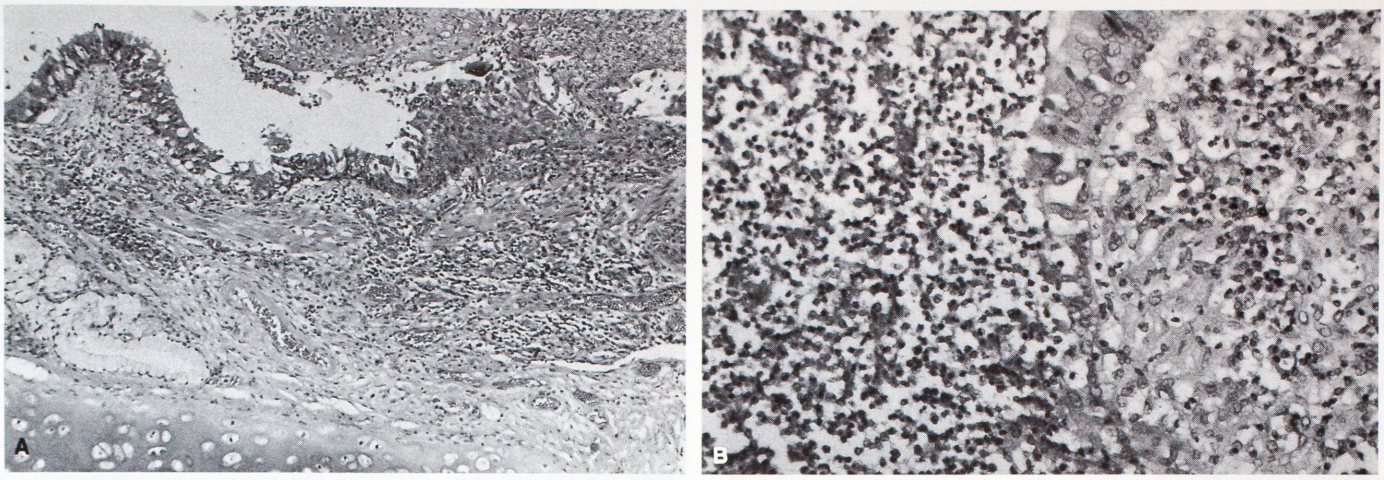

FIGURE 27-5. Airway changes produced by chronic bronchitis with infection. (**A**) In the bronchus, infection produces focal squamous metaplasia of the epithelium, erosion, and a transmural inflammatory cell infiltrate. (H & E stain; low magnification.) (**B**) In a bronchiole, infection produces ulceration of the wall; loss of surface epithelium and deeper layers leads to an endobronchiolar abscess. (H & E stain; intermediate magnification.)

PATHOPHYSIOLOGY OF CHRONIC BRONCHITIS

Association With Emphysema

It is important to emphasize that chronic bronchitis and emphysema can occur together in the same lung, although frequently they present as solitary conditions. Even if solitary, each can be the cause of severe functional impairment and death.

It is also important to understand that the patient dying from airway obstruction caused by chronic bronchitis may have no anatomic emphysema at all, and, by contrast, a patient who has been disabled and crippled for years with severe emphysema can die without any structural stigmata of chronic bronchitis. This is particularly seen in panacinar emphysema caused by the absence of α_1-antitrypsin (Fig. 27-7). In this condition, there is typically no infection of the airways and no mucous gland hypertrophy. Dissection of the airways shows them to be patent to the periphery with no secretions in the lumen or stenosis. In such pure cases of emphysema, the airways obstruction is functional and secondary to loss of lung elasticity or recoil.

This loss in elasticity leads to an abnormally large lung because of increased distensibility and premature closure of the airways on expiration. Very little gas needs to be expired before there is functional closure (*i.e.*, expiration ends at very high lung volumes). Often, patients who have emphysema are smokers, so there are signs of chronic bronchitis in addition to the emphysema. Then the changes of chronic bronchitis are superimposed on those of emphysema, and both contribute to respiratory failure.

Airways Obstruction

The reason for airways obstruction in chronic bronchitis is not absolutely clear. Several factors are present, but their relative contribution varies from patient to patient. Although the volume of mucus hypersecretion reflects mainly changes in large airways, the disability, or the severity of airway obstruction, almost certainly reflects changes at the periphery.[32–35] Because small airways normally contribute about 10% of the measured resistance, severe small airway damage may not be detectable until late in the disease.

Other features of chronic bronchitis clearly cause airway obstruction. Retained secretions and edema of the airway wall, as well as excessive bronchial tone, or constriction, can mechanically

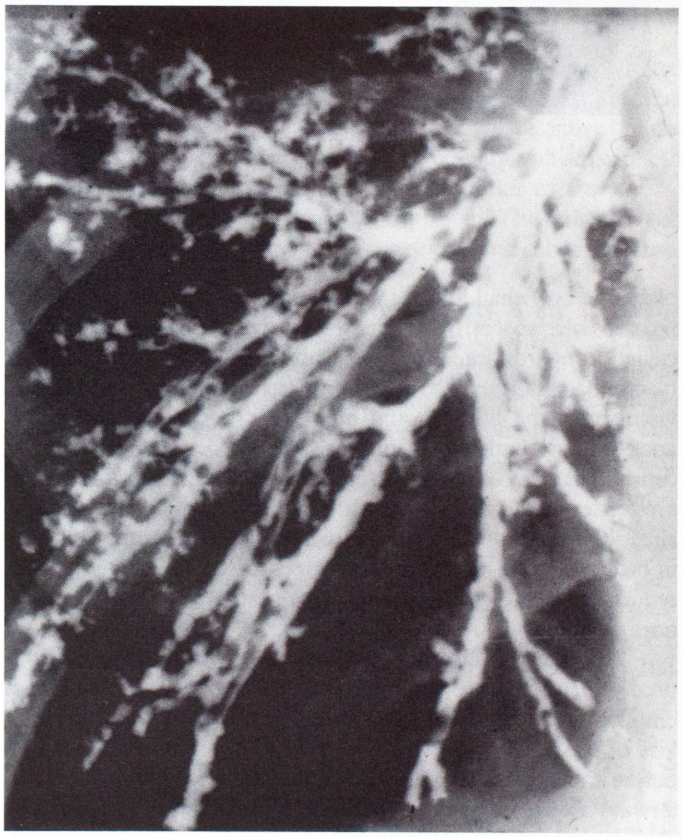

FIGURE 27-6. A bronchogram in chronic bronchitis shows absence of peripheral filling without reduction in volume in right lung base. There are multiple peripheral bronchial blocks, yet lung aeration is maintained by collateral drift.

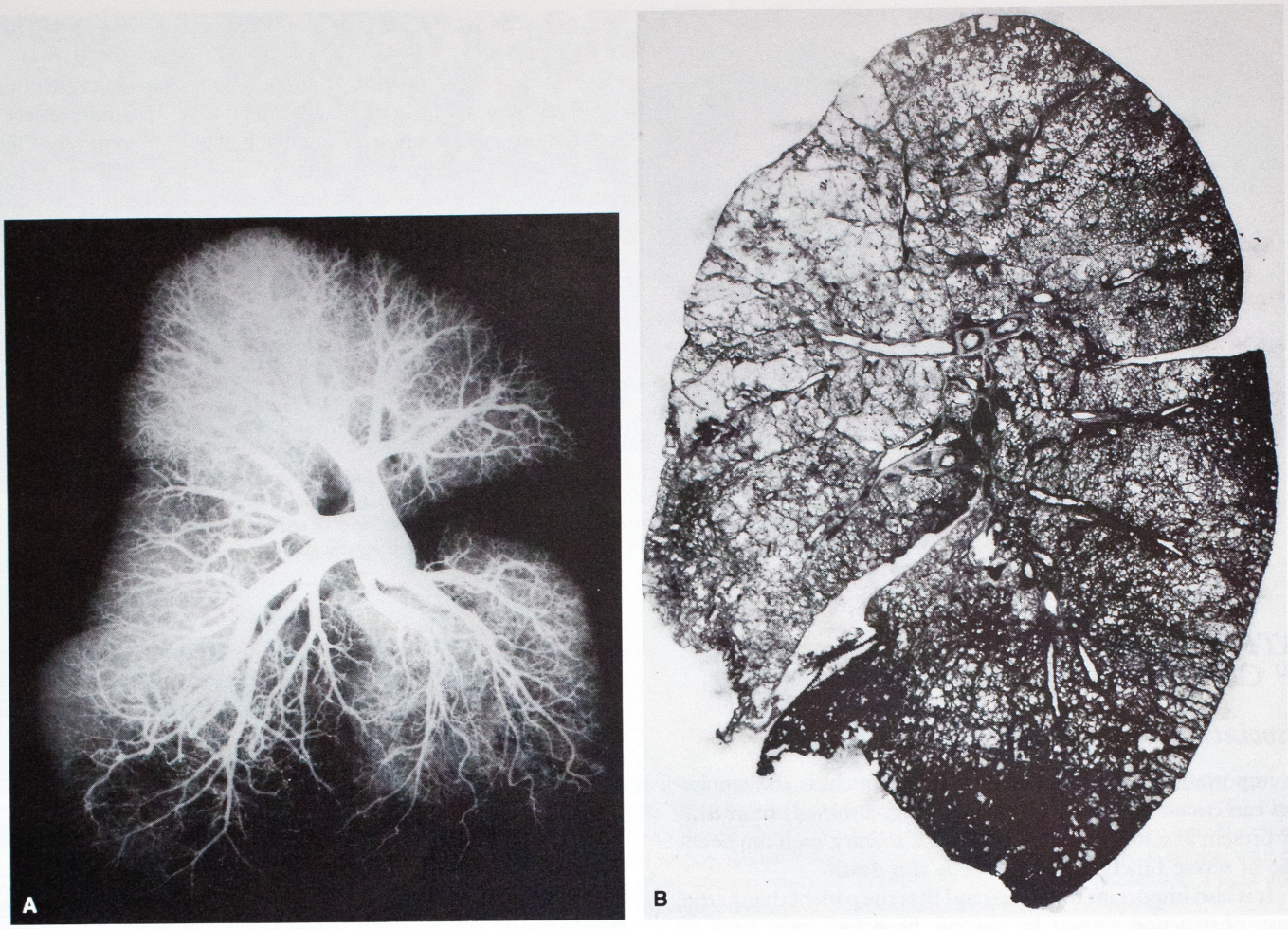

FIGURE 27-7. Severe panacinar emphysema in a patient with α_1-antiprotease deficiency. (**A**) A postmortem angiogram shows good peripheral filling. (**B**) A slice of perfusion-fixed lung shows some regions of grade III disease (*i.e.*, air spaces up to 5 mm) and some of more severe grade IV panacinar emphysema.

block the bronchial lumen. Secretion is also sometimes aspirated into alveolar spaces, where it is removed by macrophages.[36] Its chelation by iron leads to iron accumulation within intraalveolar macrophages. Other factors also tend to increase resistance: higher viscosity of the lining liquid phase of bronchi increases resistance.[37] Physiologists have proposed that a peribronchial cuff of consolidated alveoli increases resistance by altering the mechanical properties of the airway wall. It is also clear that if the lumen is already reduced by airway wall thickening, even a minor increase in bronchial tone or constriction causes a relatively larger percent reduction of the cross-sectional area of the airway than in the normal state.

Whereas the airways obstruction in chronic bronchitis is predominantly based on structure, the airways obstruction in emphysema is essentially functional. In emphysema, because of loss of elastic recoil, very little air leaves the lung on expiration before the airways mechanically collapse. Thus, in emphysema, airways obstruction can be associated with air trapping and failure of the lung to deflate, although the airways themselves are patent. The pathologist's view of this is particularly striking. If the lung is inflated with air and then allowed to deflate, the normal lung recoils and reduces to about one third or one half of its original volume. In severe emphysema, when the lung is inflated it will be bigger than normal, and yet when the pressure is released it fails to deflate because of air trapping.

In looking at a bronchitic, therefore, a pathologist is looking for evidence of epithelial layer and mucous gland hypertrophy thickening, mucosal swelling from either edema or cells, muscle layer hypertrophy, peribronchial cuffing by consolidated alveoli, and also, of course, obstruction and narrowing by secretions and fibrosis. As noted, another set of obstructive phenomena reflects changes affecting the patency of peripheral airways (*i.e.*, bronchioles; see Chap. 30).

Association With Cor Pulmonale

The best definition of cor pulmonale is the presence of right ventricular hypertrophy (RVH) in the absence of a cardiac cause; this means that the RVH arises because of disease in the lung. RVH is more commonly seen and is more severe in patients with chronic bronchitis than in those with severe panacinar emphysema.[38]

The definition of cor pulmonale in terms of RVH is important because it represents a phase of adaptation of the heart without necessarily implying heart failure. RVH can be masked by dilatation, but in the normal individual the right ventricle should not be above 3 mm in thickness. A greater thickness justifies a

diagnosis of RVH, but if less than this, RVH cannot be excluded. Intuitively, the evidence of ventricular hypertrophy must be muscle mass, not simply wall thickness (Fig. 27-8). Dilatation can mask hypertrophy; the right ventricle may be more than double its normal weight, and yet, because of dilatation, the thickness can be within normal limits. This is a problem for the pathologist, because at autopsy the heart is often in the stage of dilatation due to heart failure.

A relatively quick way of establishing precisely the degree of ventricular hypertrophy is the method proposed by Fulton and colleagues.[39] The ratio of the weight of the left ventricle plus septum to the weight of the right ventricle is the measure of RVH. The heart is best fixed before dissection and weighing is carried out. Fat and coronary arteries are removed from the external ventricular walls. Because the septum behaves as part of the left ventricle, they are included together. The crescent-shaped, free, right ventricular wall is removed from the left ventricle and septum, and the chordae are shaved from the interventricular septum and weighed with the right ventricle. In the human, the ratio of left ventricle plus septum weight to right ventricle weight (LV + S:RV) is 2.3:1 to 3.3:1.

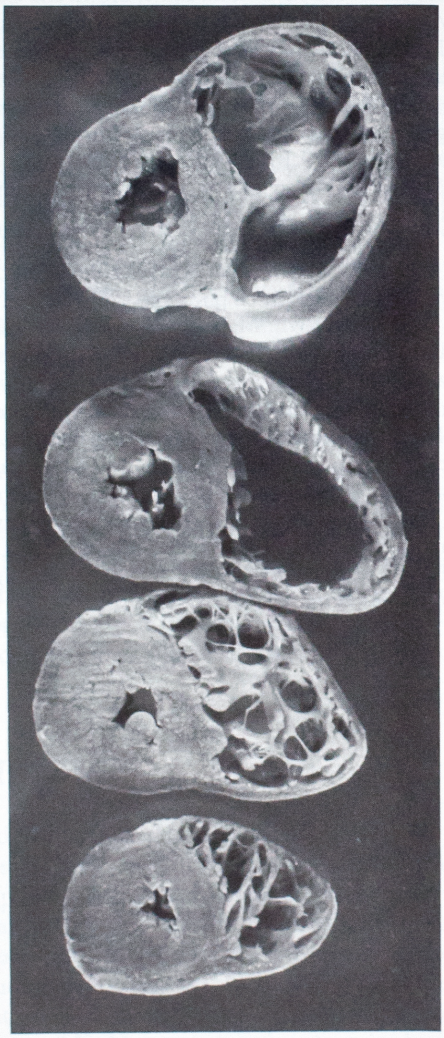

FIGURE 27-8. Cross sections of the human heart reveal that the thick-walled left ventricle and septum are like a tube, and that the thin-walled right ventricle forms a crescent of muscle. The septum participates in left ventricular hypertrophy.

The common wisdom is that RVH reflects the loss of pulmonary vascular bed, but this is not so. It needs qualification in that many patients with severe panacinar emphysema or severe pulmonary fibrosis have no RVH at all. Therefore, RVH must reflect the restriction of the pulmonary vascular bed in a different way. One of the reasons the loss of the vascular bed may not be functionally significant in these conditions could be the opening up of pulmonary artery arcades, typically within the pleura, in cases of panacinar emphysema. In congenital heart disease, they often occur deeper in the lung. Such vessels provide some sort of sluice. The destruction of small muscular resistance arteries could also be another factor.

Almost certainly, alveolar hypoxia is the single most important factor in the development of RVH.[33] Hypoxia produces pulmonary hypertension by the following mechanisms:

- a vasoconstrictive response of small muscular arteries and arterioles that occurs acutely and is immediately reversible by oxygen administration
- arterial structural remodeling of the normally nonmuscular precapillary segment, resulting in muscularization and lengthening of the resistance segment
- polycythemia, which increases the blood viscosity and, therefore, the resistance against which the right ventricle has to work. In one study, if the hematocrit was above 58%, severe RVH was always present.[38]

OCCUPATIONAL BRONCHITIS

Intuitively, it is easy to believe that working in a dusty and polluted atmosphere cannot be good for the lungs. Yet, it is surprising that in a number of conditions a large amount of dust is stored in the lung with few functional effects. For example, plumbism can lead to a strikingly red lung because of the amount of stored lead particles, yet no functional disability is present. The same can also be said for the storage of certain types of coal and other industrial dusts (see Chap. 34).

Byssinosis, which occurs in cotton carders, is also a puzzling example of an occupational bronchitis (see Chaps. 17 and 29). Certain types of asthma have been identified that are chemically induced (see Chap. 17). Such conditions call for vigilance on the part of the pathologist, because he or she is often the one who receives clues regarding a possible causative factor.

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