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29

Bronchial Asthma

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Any discussion of bronchial asthma must begin with the recognition that no fully satisfactory definition of this disease has ever been formulated. The main difficulty in definition stems from the variety of disciplines involved to evaluate a distinct group of patients: clinicians review symptoms, physiologists deal with functional impairments, immunologists look at mechanisms, and pathologists rely on morphologic findings. Moreover, even within one field, no findings can be identified that are uniformly present in all asthmatics. Most available criteria must be quantified and dividing lines drawn between asthmatics and nonasthmatics. This differentiation is arbitrary to a large extent, and it is not always clear which types of patients should be excluded by a definition.

Obstruction to airflow is clearly an aspect of asthma. It usually occurs in episodes, with a capacity for reversal that can be spontaneous or take place in response to therapy and be either complete or partial. Bronchodilator agents are so effective that they can bring about near total reversal of airflow obstruction.

In 1991, a statement on asthma was issued from the National Heart, Lung, and Blood Institute (NHLBI).[1] This report deals with several aspects of asthma, including definition, classification, pathogenesis, pathophysiology, and therapy. I am in agreement with the concepts presented in the NHLBI report, and as a result this discussion will include not only the long-accepted morphology but a much broader and less specific set of lesions.

DEFINITION

Asthma is a lung disease with the following characteristics: airway obstruction that is reversible, either spontaneously or with treatment, but not completely so in some patients; airway inflammation; and increased airway responsiveness to a variety of stimuli.[1]

The broadened definition and classification of asthma proposed by the NHLBI will necessarily lead to a widened range of morphologic lesions that must be recognized as being causally related to the reversible airway obstructive phenomena. The description of the pathology of asthma will be simpler and more comprehensible to the reader if the mechanics of airway behavior are first clarified. Consideration will be given first to the behavior of the airways in normal lungs and later to the variety of intrapulmonary lesions that can alter such behavior.

CLASSIFICATION

- **I.** Atopic Asthma
  - A. Extrinsic
- **II.** Nonatopic Asthma
  - A. Intrinsic
  - B. Viral induced
  - C. Occupational

AIRWAY MECHANICS IN NORMAL LUNGS

Pathologists must be aware of the various terms used by physiologists to account for the phenomena observed in laboratory tests of ventilatory function. These include the effort-dependent and effort-independent portions of the forced expiratory flow-volume loop; the elastic recoil pressure; the equal pressure point; the driving pressure from alveoli to the equal pressure point; the upstream segment and the downstream segment of the airway, which meet at the equal pressure point; and the regulation of maximum flows by compression of the downstream segment.

During forced exhalation, the muscular effort raises the pleural pressure, but alveolar pressure and upstream airway pressure are higher than the pleural pressure because of elastic recoil pressure. The pressure at the outer wall of the airway can be visualized as equal to pleural pressure, and so the upstream segment is believed to be kept open by the greater pressure in the lumen, and flow is regulated by compression of the downstream segment. The driving pressure is the elastic recoil pressure. The greater the effort applied, the more the downstream airway is compressed, and therefore flow cannot be increased.[2]

These concepts would readily explain the effort-independent

segment of the flow-volume loop and the decreasing maximum flows as volume decreases because the elastic recoil pressure drops as lung volume decreases, the elastic recoil pressure being the driving pressure. However, they cannot be correct, because all airways throughout the lung are intimately surrounded by alveoli and thus are necessarily exposed to alveolar pressure, not pleural pressure. During exhalation, pressure in the lumen of all airways, even the smallest bronchioles, is lower than that in alveoli. If this were not true, air would not flow into the airways.

An alternative mechanism is necessary to explain maintenance of their open lumens against this compressive force. The alternative mechanism was proposed in theory many years ago[3] but has been impossible to demonstrate with *in vivo* studies. The theory was that elastic tension in the alveolar septa attached to airways would pull outward and provide mechanical distending force to counterbalance the hydraulic compressive effect of alveolar pressure.

The existence of the postulated mechanical tension force was demonstrated with the use of excised autopsy lungs in my laboratory some years ago. Two different techniques were used,[4,5] and both showed that the outward force applied by alveolar tension (*i.e.*, radial traction) is greater than alveolar pressure during passive deflation at all stages of the deflation cycle, except at residual volume where tension actually reaches zero and the bronchioles, indeed, close.[6] There is still, in fact, air under positive pressure in the alveoli, but the lung cannot deflate because of the closed bronchioles.

Because the papers describing these experiments may not be readily available, one of them is presented here (Fig. 29-1). The procedure involved the wedging of a small, square pressure transducer (4 × 4 × 1 mm) in an intrapulmonary artery. The transducer responded to alveolar pressure changes by linear deflections of the recorder pen above or below the baseline of atmospheric pressure. Tension in alveolar septa surrounding the vessel pulled the vessel wall away from the flat sides of the transducer and caused pressure on its edge. This force caused deflection of the recorder pen in the opposite direction from the pressure signal.

In Figure 29-1*A*, the lung is fully inflated by reduction of pressure in the box to -14 cm H_2O. The trachea is open and atmospheric pressure is present throughout the airways and alveoli. The intravascular transducer indicates the presence of tractional force equivalent to -17 cm H_2O.

In Figure 29-1*B*, the box is open and is at atmospheric pressure. The lung is inflated to the same volume as in Figure 29-1*A* by positive intrabronchial pressure of 14 cm H_2O. All airways and alveoli are at this pressure, yet the intravascular transducer indicates a net outward force of -3 cm H_2O. Total traction force, therefore, is still equivalent to -17 cm H_2O.

Morphology dictates that all airways are constantly exposed to alveolar pressure. Air can move from alveoli to airways only if pressure is lower in the airways. The walls of non–cartilage-containing airways are flexible and must necessarily be kept open by an opposing force. The data presented above show that it is outward mechanical tension in attached alveolar septa that maintains the airway lumens open against the hydraulic compression by alveolar pressure. During forced exhalation maneuvers, extremely high alveolar pressures can be attained. As the lung deflates, the available outward mechanical traction support on airways diminishes but still contributes to keep them open.

As the lung deflation continues, traction support progressively diminishes, and larger airway compression and airway resistance must increase.[5] Thus, maximum forced flow decreases because traction force decreases. This sequence of events is the true explanation for the effort-independent segment of the forced expiratory flow-volume loop. Eventually, the traction force reaches zero; the flexible airways do, indeed, close; and the lung becomes airtight. This point determines residual volume in both normal and abnormal lungs. The lung still contains air, whether or not it has been removed from the chest, and, in an excised lung, the air is at a pressure above atmospheric pressure.[7] This supports the concept that it cannot be true that elastic recoil pressure keeps small airways open.

One may be tempted to ask why the lung is designed in this way. This may not be a proper question, but it is pertinent to outline the benefits of these mechanisms for lung function or integrity. The first benefit is that an excess of traction force over achievable transmural airway pressure means that, at lung volumes above about 50% of total lung capacity, it is possible to increase

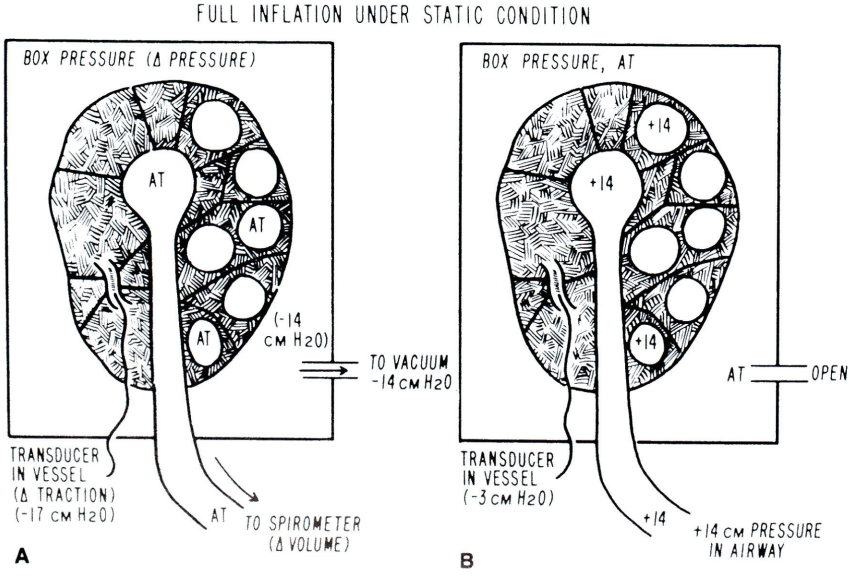

FIGURE 29-1. Experimental demonstration of alveolar elastic tension (radial traction) on airways during expiration. An excised lung is enclosed in a respirator box representing the thorax. The lung is connected to the outside through a main airway (trachea) seen exiting at the base of the box. The inside of the box (pleural space) is connected to the outside through a lateral tube for regulation of pressure. A transducer placed within a pulmonary vessel, seen exiting at the base of the box, allows measurements of alveolar tissue pressure. (**A**) Lung inflation). (**B**) Lung deflation (expiration).

alveolar pressure without any corresponding change in either small or large airway diameter so that flow rate increases. Thus, the total ventilation of the lung can be increased with little added effort. This is the standard response to exercise.

At the point in a forced exhalation where small airway traction support becomes less than transmural pressure and narrowing begins to occur, constriction of larger airways is necessary to keep the lumen of the smaller ones open. The mechanism, of course, is that narrowing of larger airways causes an increase in resistance to airflow and raises the pressure in the lumen. As effort increases above this level, larger airways become more narrowed but flow remains constant because the small airway size and the driving pressure from alveoli to bronchioli is necessarily fixed.[5] The result of this is to increase progressively the velocity of air through the larger airways. This is a second benefit, because high velocity increases the effectiveness of entrainment and expulsion of any secretions present in the lumen of larger airways.

The practical mechanism that uses the increased velocity of air through the larger airways is the cough. A cough begins with closure of the glottis and contraction of the chest and abdominal muscles, which creates positive pressures of up to 100 cm H_2O from the alveoli throughout all the airways. Sudden opening of the glottis creates a transmural pressure drop that rapidly ascends the airway but creates maximum compression of the largest intrathoracic airways (*i.e.*, trachea and lobar bronchi) as the first effect. Repeated closing and opening of the glottis during a staccato cough applies diminishing transmural pressures, which create the maximum compressive response on progressively narrower cartilaginous airways. Therefore, the site of maximum velocity at the start of a cough is in the largest airways but later shifts into the smaller ones.

At first thought, the sequence of a cough might seem less than ideal, because if there are no secretions in larger airways, the effort of creating maximum velocity of air movement would be wasted. This would be true if only a single staccato cough were to occur. However, coughing is usually repeated. If one effort displaces secretions from a smaller airway into a lobar or a main bronchus, then after a new inhalation the next cough would expel them from these larger airways.

DYNAMIC AIRWAY BEHAVIOR IN PATHOLOGICAL LUNGS

The aforementioned physiologic considerations provide several new insights into factors that can come into play in reversible small airway obstruction. In essence, the situation is determined by a balance between the traction force and several factors (*e.g.*, steady, smooth muscle tone; active contraction); by the transmural air-pressure difference; by wall thickness (*i.e.*, inflammation); and by secretions in the lumen. All factors that can increase any of these can contribute to reduction in achievable flows and a rise in the lung volume at which flow regulation begins. The obvious mechanisms are those that cause active airway constriction (*e.g.*, smooth muscle contraction, secretions in the lumen, edema or inflammatory cell infiltration in the submucosa or wall, fibrosis of the wall).

Another factor that tends to result in narrowed small airways is diminished traction force, which occurs in emphysema caused by interruption of the radial alveolar attachments to the airway.[5,7] When this force is diminished, normal smooth muscle tone can narrow the small airways, and the effect of normal contraction would be exaggerated. Therefore, an individual with early emphysematous destruction might seem to have developed episodic, reversible airflow obstruction, even though the intrinsic airway behavior has not changed. Recognition of this phenomenon in an individual patient would require independent determination of the presence or absence of emphysema. This can be accomplished by conventional chest radiography[8] or by computed tomography.[9] Such cases presumably should be separated from those with straightforward asthma. To my knowledge, no attempt to do so has been made.

PATHOLOGY OF ASTHMA

Because of the broadened definition of asthma presented previously, it is necessary to describe the pathologic lesions relevant to each of the types that are encompassed by the term. The morphology of classical asthma, now classified as extrinsic or atopic asthma, is described and illustrated. Brief explanations of the similarities and differences between atopic asthma and the nonatopic types (*i.e.*, intrinsic, viral, and occupational) are also presented.

Atopic or Extrinsic Asthma

Atopic or extrinsic asthma refers to the classic combination of sensitivity to an inhaled antigen leading to an episode of shortness of breath, and wheezing followed by spontaneous recovery. It usually occurs in individuals with a past history or family history of hay fever or eczema. Most can be shown to have an IgE-related, or reaginic, acute response to one or more allergens (*e.g.*, pollens, house dust). In some of these cases, attacks can also be induced by ingestion of antiinflammatory drugs such as aspirin.[10] Extensive reviews of accumulating evidence concerning cellular and molecular mechanisms of asthma are readily available.[1,11]

Lung tissue from asthma patients most often becomes available as a result of death in a patient with status asthmaticus who has failed to respond to all available therapeutic efforts. Such cases do indeed occur and may even be more frequent now than in the past.[1] It has been suggested that this may be the result of overuse of inhaled bronchodilator agents (*i.e.*, β_2-agonists), but the matter is still controversial.

The lungs from a patient who has died in status asthmaticus are large and may completely fill the chest cavity. The pleura is smooth and tense, and occasional lobules may be collapsed. Following removal from the chest, the lungs usually are of normal weight, but they remain large because the air in alveoli cannot exit because of small airways occluded by mucoid secretions (Color Fig. 29-1).[11]

The patient whose lung tissue is illustrated in Figures 29-2 through 29-7 also died from status asthmaticus, at 48 years of age, having had a history of severe hay fever in childhood and having first experienced wheezing and dyspnea at 43 years of age. There was also a strong family history of asthma affecting her parents and other forebears, her siblings, and her children. Her symptoms had recurred frequently despite treatment with bronchodilators, inhaled and systemic steroids, desensitization, antibiotics, and numerous emergency room visits and hospital admissions.

On the last admission, response to these agents and mechanical ventilation was minimal, and the patient became exhausted.

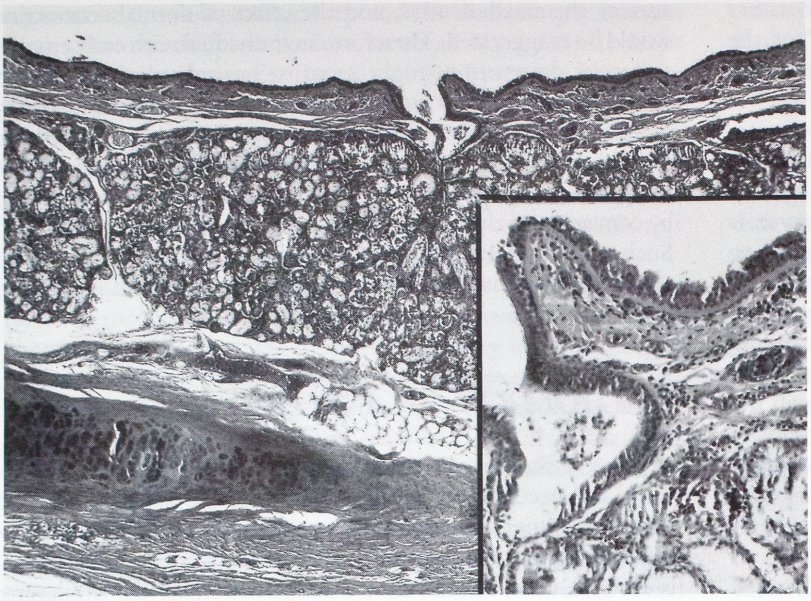

FIGURE 29-2. The tracheal wall in a 48-year-old woman who died in status asthmaticus. Figures 29-2 through 29-7 are from the same patient. There is marked hyperplasia of the mucous gland layer with dilatation of the duct. Inflammatory infiltration is mild. Detail of the area adjacent to the mucous gland duct is shown (*inset*). Ciliated epithelium is intact; basement membrane is normal; and rare eosinophils are present in the mucosa and subepithelial stroma. (H & E stain; low magnification; inset at intermediate magnification.)

There was no fever or purulent sputum, and chest films showed only overdistention with clear lung fields. At autopsy, the lungs were found to be distended with air and were of normal weight (*i.e.*, 250 g, left; 300 g, right).

This case illustrates well the histologic variability in various sites within the bronchial tree. The most severe lesions in this patient were in the smallest of the cartilage-containing bronchi, with lesser involvement in the larger airways and in the membranous and respiratory bronchioles. The terminal total airflow obstruction probably resulted from mucus in the lumens of the smallest bronchi. In other cases, the site of major involvement may be in bronchioles.[12] In autopsy material, there is often concern that infection may have obscured the original lesions; however, biopsy studies reveal lesions similar to those shown here.[13]

Nonatopic Asthma

As noted previously, the definition of asthma requires the consideration of numerous conditions, many of which have not fulfilled earlier definitions. These include intrinsic asthma, which has been long recognized and contrasted with extrinsic asthma, and the newer types, viral-induced asthma and occupational asthma.[1]

INTRINSIC ASTHMA

Intrinsic asthma occurs in patients who have chronic inflammatory changes in airways associated with chronic contact with irritants (*e.g.*, recurring infections, chronic aspiration, especially with gastric reflux[14]) or in patients who are excessively susceptible to general air pollution. The lesion generally consists of chronic

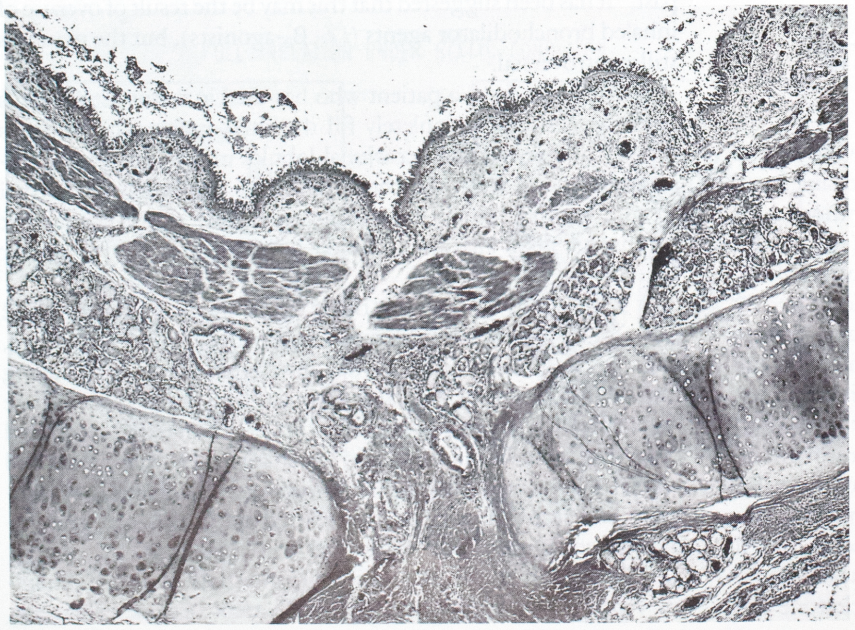

FIGURE 29-3. The surface epithelium of the main bronchus is somewhat fragmented, perhaps artifactually, but similar appearance has been demonstrated in tissue obtained by bronchial biopsy. Basement membrane is normal; smooth muscle bundles are hypertrophied; glands are hyperplastic; and inflammatory infiltrate is slightly more prominent than in the trachea. (H & E stain; low magnification.)

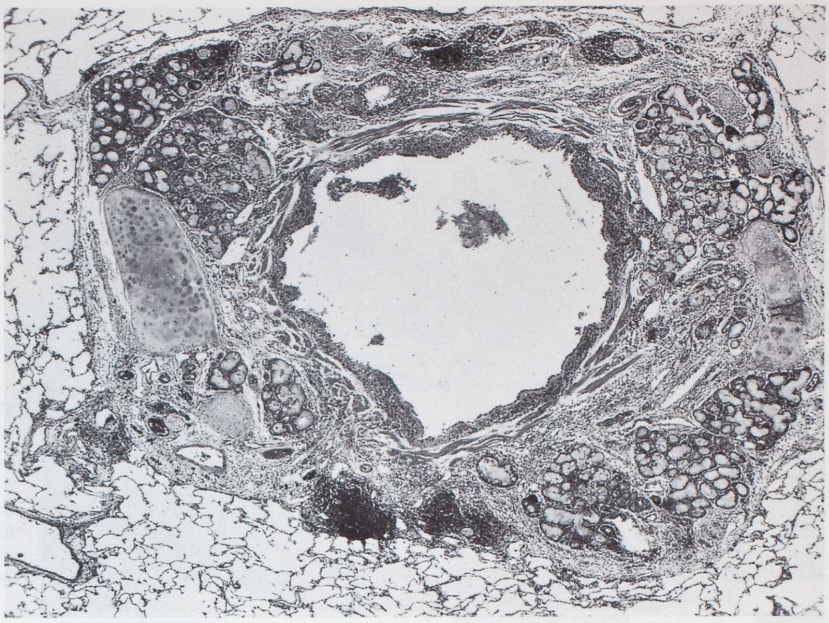

FIGURE 29-4. A branch bronchus of approximately the 10th order; note the presence of cartilages. The surface epithelium is partially eroded; smooth muscle is slightly increased; mucus glands are hyperplastic; there is prominent diffuse inflammatory infiltration; two lymphoid foci are present (*bottom*); and alveolar septa is attached at the outer margin. (H & E stain; low magnification.)

inflammatory infiltration of the submucosa and wall of the airways and an increased capacity to secrete mucus into the lumen. The inflammatory infiltrate may be associated with edema and mucus in the lumen and producing thickening of the wall and narrowing of the lumen.

When these changes occur mainly in larger airways (*i.e.,* bronchi), they are associated more with cough and sputum production than with airflow obstruction. The relatively slight narrowing does not reduce the lumen enough to affect flow. If bronchioles are involved, wheezing and flow impairment can result; the mechanism is the same as that described previously (see Dynamic Airway Behavior of Normal Lungs). Symptoms occur only when the majority of bronchioles are affected. If both large and small airways are involved, the patient will have both excessive cough and airflow obstruction.

The increased capacity for mucus production in bronchi results mainly from hyperplasia and hyperactivity of the submucosal glands, similar to that illustrated in Figures 29-2 through 29-5, but these changes usually occur with only chronic inflammatory infiltration and no eosinophils. In bronchioles, there are no submucosal glands; the excess mucus is produced by goblet cell metaplasia of the surface epithelium.

VIRAL-INDUCED ASTHMA

Viral-induced asthma was included in the NHLBI statement referred to previously.[1] It is true that most of the viral infections that involve the respiratory tract tend to damage the respiratory epithelium. Damage ranges from temporary loss of cilia, to nuclear or cytoplasmic inclusion bodies, to desquamation or necrosis (Fig. 29-8), usually followed by regeneration of the epithelium unless secondary infection supervenes.[15–17] Similar epithelial damage can

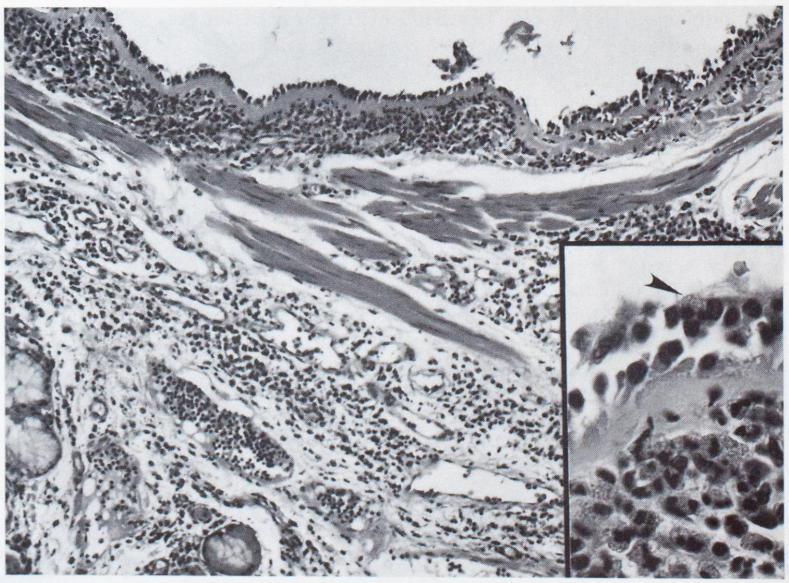

FIGURE 29-5. Detail of the area at about the 4-o'clock position in Figure 29-4. Only the basal cell layer of epithelium remains (*inset*). The basement membrane is considerably thickened; smooth muscle is slightly hypertrophied; and there is dense, diffuse inflammatory infiltrate in the submucosa and wall. (H & E stain; low magnification; inset at intermediate magnification.)

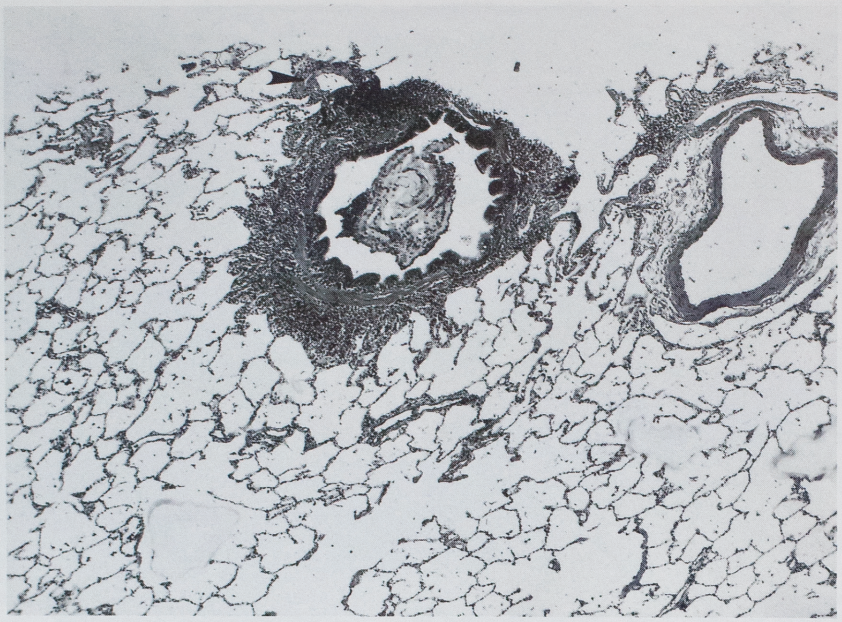

FIGURE 29-6. Mucus in the lumen of this bronchiole shrank during fixation but clearly filled it completely; note the fitting contours, especially in the left lower quadrant. The epithelium is intact, and there is intense eosinophilic infiltrate throughout the wall. An attached alveolar septa provides mechanical support, and a pulmonary artery (right) and a bronchial artery (*arrow*) can be seen. (H & E stain; low magnification.)

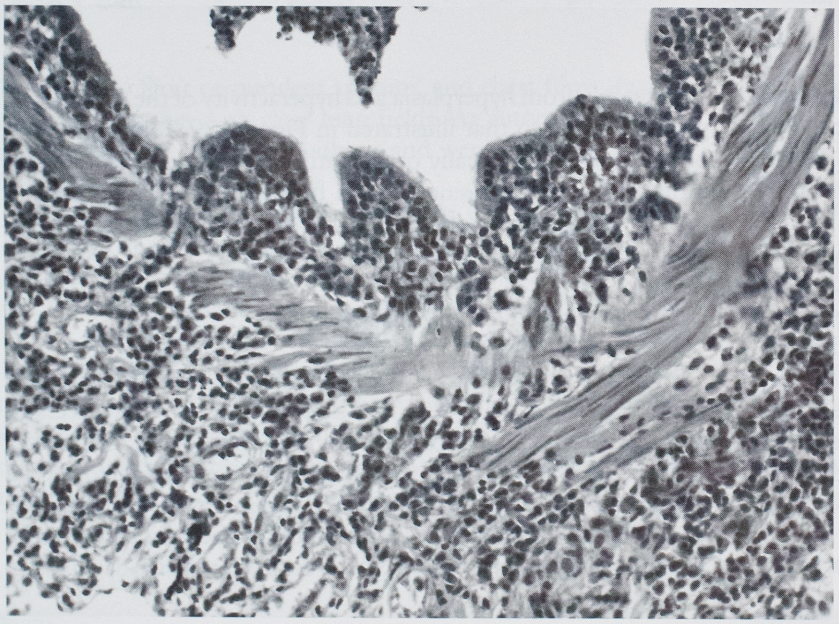

FIGURE 29-7. Detail of the area at about the 8-o'clock position in Figure 29-6. Ciliated epithelium is present; basement membrane is not visible; smooth muscle is hypertrophied; there is intense diffuse eosinophilic cell infiltration in the submucosa and wall; and there are few lymphocytes. (H & E stain; intermediate magnification.)

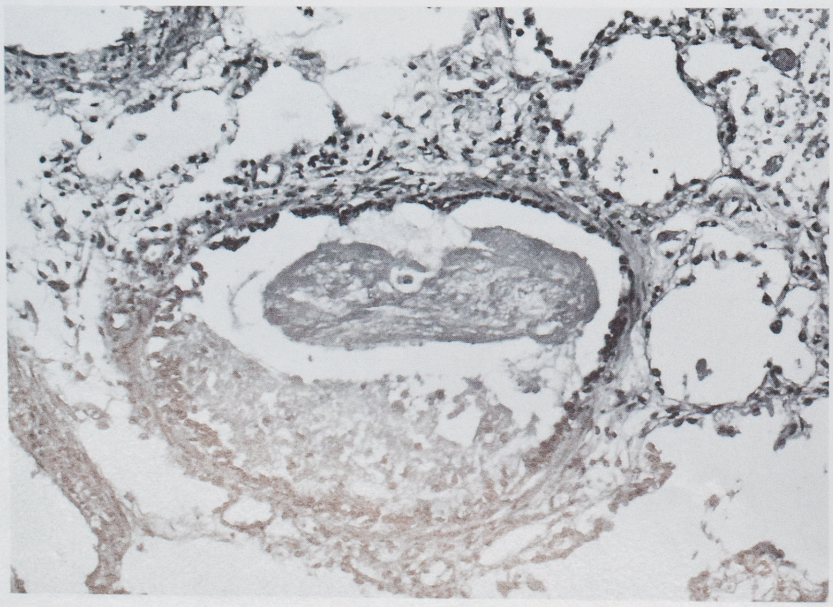

FIGURE 29-8. Bronchiole from autopsy of a patient with known (*i.e.*, cultured) influenza viral infection 8 days in duration. Partial erosion of the surface epithelium has taken place; with only basal cells remaining (top). Goblet cell metaplasia is present (bottom); there is mucus in the lumen (bottom) and fibrin is seen (*top*); interstitial edema is present in adjacent alveolar septa; and there is prominent cuboidal epithelium lining alveoli in the right upper quadrant (*i.e.*, type II cells). (H & E stain; intermediate magnification.)

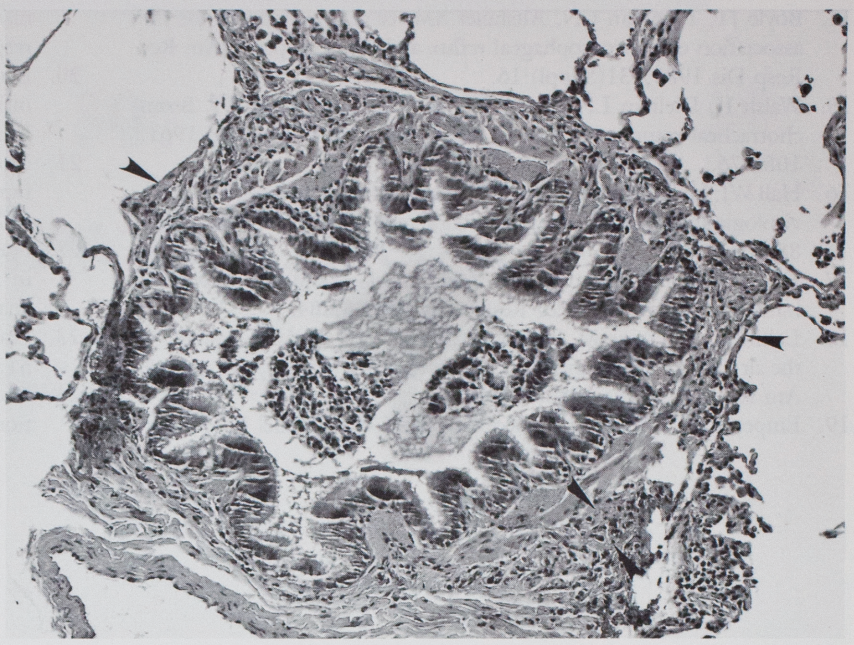

FIGURE 29-9. Bronchiole from a lung biopsy specimen obtained from a 30-year-old woman 8 months after accidental exposure to perchloroethylene gas. The epithelium is intact but has excess goblet cells. There is mucus in the lumen and chronic inflammation plus slight fibrosis (*arrows*) in the wall. The basement membrane is normal. (H & E stain; low magnification.)

be seen in atopic asthma; therefore, it may represent a route of access for agents causing bronchospasm,[18] and several efforts have been made to demonstrate airflow impairment during acute viral infections.[16,19,20] It appears that such impairment does not occur in previously normal individuals, although exacerbation of preexisting asthma has been observed.[19,20] When bronchial provocation tests are performed, however, airways have been shown to be hyperreactive during and for several weeks after infections such as influenza or respiratory syncytial virus,[20,21] and even after a common cold.[20]

OCCUPATIONAL ASTHMA

Occupational asthma has been a controversial term, but obstructive respiratory symptoms have long been known to occur in association with many occupations (see Chap. 17). In some instances, atopic hypersensitivity to an agent in the work environment is the mechanism, and in such cases, the morphology would be similar to that illustrated previously (see Color Fig. 29-1; see Figs. 29-2 through 29-7). In other situations, the work environment contains substances that can act as direct releasers of histamine or other smooth muscle constrictors; these would include cotton and grain dust exposures. The morphology in these cases is more in the form of goblet cell metaplasia, mucus secretion, and chronic inflammation in the bronchi and bronchioles. Eosinophils are inconspicuous. Color Figure 29-2 presents the morphology of a bronchiole in a long-term, nonsmoking cotton worker who had intermittent work-related dyspnea for many years and eventually had persistent airflow obstruction. The morphology is that of a nonspecific chronic small airway disease.[22,23] This lesion is seen often in cotton workers and seems to be more severe in those who do not smoke.[22]

Many other occupational exposures have been associated with respiratory symptomatology.[24] Some of these involve toxic gases such as sulfur dioxide or ozone, whereas others are dusts or aerosols for which mechanisms of action are still unknown.[1] Airway morphology has not been observed in most of these. However, a case seen at the Duke University Medical Center involved a patient who was accidentally exposed to perchloroethylene gas in a cotton mill and experienced severe dyspnea and wheezing. Figure 29-9 is from a lung biopsy specimen from this patient, obtained 8 months after the accident. It revealed widespread bronchiolar involvement. The symptoms persisted for more than 3 years after the episode.

REFERENCES

1. Sheffer AL. Guidelines for the diagnosis and treatment of asthma. USPHS Publication No. 91. Bethesda, MD: National Heart, Lung, and Blood Institute, 1991:3042.
2. Murray JF. The normal lung. Philadelphia: WB Saunders, 1976:77.
3. Dayman H. Mechanics of airflow in health and in emphysema. J Clin Invest 1951;30:1175.
4. Pratt PC, Klugh GA. Peribronchiolar radial traction measured. USPHS Publication No. 1717. Washington, DC: U.S. Public Health Service, 1968:125.
5. Pratt PC. Intrapulmonary radial traction: measurement, magnitude and mechanics. USPHS Publication No. 1897. Washington, DC: U.S. Public Health Service, 1969:159.
6. Miller JA, Pratt PC, Capp MP. Human bronchial and bronchiolar compressibility measured by postmortem bronchography. Lab Invest 1973;29:465.
7. Pratt PC. Emphysema and chronic airways disease. In: Dail DH, Hammar SH, eds. Pulmonary pathology. New York: Springer-Verlag, 1987:651.
8. Pratt PC. The role of chest radiography in diagnosis and exclusion of emphysema. Am J Med 1987;82:998.
9. Foster WL, Pratt PC, Roggli VL, et al. Centrilobular emphysema: CT–pathological correlation. Radiology 1986;159:27.
10. Stevenson DD, Simon RO. Aspirin sensitivity: respiratory and cutaneous manifestations. In: Middleton E, Reed C, Ellis EF, et al, eds. Allergy principles and practice. St. Louis: CV Mosby, 1988.
11. Kerrebijn KF, ed. Similarities and discrepancies between asthma and chronic obstructive pulmonary disease. Am Rev Respir Dis 1991; 143(Suppl):1150, 1420.
12. Dunnill MS. Pulmonary pathology. New York: Churchill-Livingstone, 1987:61.
13. Glynn AA, Michaels L. Bronchial biopsy in chronic bronchitis and asthma. Thorax 1960;15:142.

14. Boyle JT, Tuchman CN, Altshuler SM, et al. Mechanisms for the association of gastroesophageal reflux and bronchospasm. Am Rev Resp Dis 1985;131(Suppl):16.
15. Walsh JJ, Dieltein LF, Low FN, Burch GE, Mogabab WJ. Bronchotracheal response in human influenza. Arch Intern Med 1961; 108:376.
16. Hall WJ, Hall CB, Speers BS. RSV virus infection in adults: clinical, virologic and serial pulmonary function tests. Ann Intern Med 1978; 88:203.
17. Hers JF, Muller J. Broad aspects of the pathology and pathogenesis of human influenza. Am Rev Respir Dis 1961;83:84.
18. Laitinen LA, Heino M, Laitinen A, Kava T, Haahtela T. Damage of the airway epithelium and bronchial reactivity in patients with asthma. Am Rev Respir Dis 1985;131:599.
19. Empey EW, Laitinen LA, Jacobs L, Gold WM, Nadel JA. Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. Am Rev Respir Dis 1976;113:131.
20. Laitinen LA, Kava T. Bronchial reactivity following uncomplicated influenza A infection in healthy subjects and in asthmatic patients. Eur J Respir Dis 1980;61:51.
21. Minor TE, Dick EC, DeMeo AN, et al. Rhinovirus and influenza type A infections as precipitants of asthma. Am Rev Respir Dis 1976;113:149.
22. Pratt PC, Vollmer RT, Miller JA. Epidemiology of pulmonary lesions in non-textile and cotton-textile workers: a retrospective autopsy analysis. Arch Environ Health 1980;35:133.
23. Pratt PC. A rationale for evaluation of byssinosis. N C Med J 1990; 51:447.
24. Rosenman KD. Asthma and work: how do you diagnose the situation? Chest 1991;100:1481.