Tumors of the Lung

Volume 24 in the Series
MAJOR PROBLEMS IN PATHOLOGY

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Editor's Foreword

For years, pathologists have attempted to find in the morphology of lung cancers features that can be used to sort them into groups with predictable behavior patterns. In spite of our having made considerable progress in understanding the histogenesis and the direction of cellular differentiation of the various types of lung cancer, no subsets have emerged as having uniquely favorable natural histories, and only small cell cancers of the lung have proved to be susceptible to adjuvant cytotoxic chemotherapy.

As we attempt to further delineate the contribution of cytogenetic abnormalities and the effect of environmental carcinogens on the genesis of lung cancers, and as we continue our search for effective chemotherapeutic agents, the need for accuracy and precision in classification assumes increasing importance. *Tumors of the Lung* provides an answer to this need. It covers in detail the characteristic light microscopic features of all known types and variants of primary lung cancers along with detailed discussion of electron microscopic and immunocytochemical features helpful in their diagnosis and classification.

Drs. Mackay and Lukeman are well known for their work in pathology and cytology of neoplastic diseases of the lung, and both have made many important original contributions to this field. Their great wealth of knowledge and diagnostic expertise is reflected in this well written, comprehensive, and scholarly update on the pathology of lung cancer. The practical experience of Dr. Ordonez in the field of immunocytochemistry is reflected in the sections on this aspect of the study and diagnosis of lung tumors. All physicians who deal with cancer of the lung, particularly surgical pathologists, thoracic surgeons, oncologists, and radiation therapists, will find *Tumors of the Lung* invaluable.

JAMES L. BENNINGTON, MD
Consulting Editor

Preface

If the current trend in the incidence of lung cancer in the United States persists, it is estimated that approximately 200,000 new cases will be diagnosed annually by the year 2000. The frequency of mesothelioma may be diminishing by then, but it is likely to continue at its present rate through the 1990s. Responsiveness to warnings concerning the effects of tobacco and asbestos is producing some improvements in the situation in the United States, but in less developed countries the number of smokers is not decreasing. In North America, the earlier male predominance in lung cancer is being eroded as the incidence curve in females rises.

These trends are continuing in spite of intensive clinical and laboratory studies. Our understanding of the different types of lung carcinoma has improved from two decades ago, methods for early detection are better, and the techniques available to the pathologist are considerably more sophisticated, but the outlook for a patient with lung cancer is still dismal. Significant improvements in the management of small cell carcinoma were achieved with combination chemotherapy, but there has been little further advance in the past decade. Early diagnosis and therapy are the best hope for the patient, and the pathologist plays an important role. To the clinician, the significant subdivision of lung carcinoma is into small cell and non–small cell types; subtyping of the non–small cell tumors is less important in management. However, the pathologist must strive for as much precision as is possible in the diagnosis of lung carcinomas, regardless of their type, since we cannot predict how pertinent this information will be in the future.

Given our inability to cure most patients with lung carcinoma today, it is clearly necessary to intensify therapeutic efforts in the hope of achieving at least gradual improvements in survival. The pathologist plays a pivotal role in this regard, but in order to provide the most information, good biopsy material is essential. The specimens that the pathologist obtains from patients with lung cancer are often less than optimal, and this can lead to an incorrect interpretation or to inability to provide a diagnosis. There is a greater degree of inaccuracy in the diagnosis of primary lung tumors than many pathologists are willing to admit.

In this book, our main objective has been to review the basic histopathology of primary lung tumors. Since the interpretation of lung tumors by conventional light microscopy can be greatly enhanced when the light microscopic findings are correlated with those from immunocytochemistry and electron microscopy, we place emphasis on relating the information these techniques can provide with the basic features seen in histologic and cytologic preparations.

The first World Health Organization classification of lung tumors brought organization where earlier there had been essentially chaos, and the revised version improved on the original in a number of areas. Further modifications were introduced by study groups including the Veterans Administration Oncology Group, the Working Party for the Therapy of Lung Cancer, and the current Lung Cancer Study Group. It can be anticipated that more changes will be instituted as data from pathologic and biologic studies accrue and are shown to be clinically relevant.

Acknowledgments

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Contents

Chapter

1

STRUCTURE AND FUNCTION OF THE RESPIRATORY TISSUES

Some familiarity with the structure and function of the cells that form the respiratory passages is helpful when it comes to interpreting the histopathology of the various tumors that arise in the lung. Most pathologists see the tumor cells in routine cytologic and histologic preparations, but information about their structure and function has been greatly expanded in recent years by ultrastructural studies and immunocytochemistry. Throughout this book, therefore, descriptions and illustrations of tumors of the lung as shown by light microscopy and cytology are correlated with the contributions of special staining procedures and electron microscopy.

DEVELOPMENT OF THE RESPIRATORY TISSUES

The development of the respiratory system[6, 36] is briefly summarized in the following section.

Intrauterine Development

The earliest indication of the impending formation of the larynx and trachea occurs during the fourth week of intrauterine life when a laryngotracheal groove appears in the ventral wall of the primitive pharynx. As the groove deepens, its lips move together to create a tube with the lumen separated from the esophagus but opening into the pharynx at its upper end. Even at this early stage, the lung buds are visible as two outgrowths from the caudal end of the lengthening tube. They expand laterally, and lobules appear, three on the right and two on the left.

Formation of new branches continues through the 16th week of gestation under the inducing influence of the surrounding mesenchyme. The thick epithelium during this period gives the developing lung a glandular appearance. Through the 24th week, branches to the level of the terminal bronchioles are formed and the surrounding mesenchyme differentiates to form the tissues of the bronchial and bronchiolar walls and the accompanying blood vessels. Primitive respiratory bronchioles then begin to form, and alveolar sacs grow out from them. Initially, the alveoli are pouches in the walls of the alveolar sacs and respiratory bronchioles, but they subsequently proliferate by budding.

Postnatal Development

The lungs continue to develop after birth.[45, 82] New bronchi and alveoli are formed, and the alveoli increase in size.[11] The lung weighs only about 60 g at birth, but its volume enlarges some 28 times by the age of 8 years. It has been estimated that an adult lung contains at least 300 million alveoli.

ANATOMY OF THE RESPIRATORY PASSAGES

Trachea

The adult trachea is approximately 10 cm long, and its bifurcation lies slightly to the right of the midline. Because it is constructed from incomplete rings of elastic cartilage and smooth muscle, the trachea can lengthen and shorten quite rapidly. At rest the carina is opposite the sternal angle, but during deep inspiration it descends as far as the level of the sixth thoracic vertebra. The isthmus of the thyroid gland crosses the second, third, and fourth tracheal rings. The esophagus separates the trachea from the vertebral column, and the recurrent laryngeal nerves ascend in the grooves between the sides of the trachea and esophagus. The lower trachea is intimately related to the great vessels, and the remnant of the thymus lies in front of it. The lumen is about 12 mm in the anteroposterior direction and under 2 cm in transverse diameter. In cross section, the trachea is flattened posteriorly where its wall is formed by bundles of transversely oriented smooth muscle fibers.

Bronchi

The right main bronchus is more vertical, wider, and about half the length of the left main bronchus. It gives off the upper lobe bronchus before entering the hilum, where it divides into branches to the middle and lower lobes. The left main bronchus is roughly 5 cm in length, and it divides into its two lobar branches within the hilum.

The primary branches of the lobar bronchi are termed *tertiary bronchi* or *segmental bronchi* because each is associated with a bronchopulmonary segment. The layer of connective tissue that envelops a bronchopulmonary segment will sometimes limit the spread of nonneoplastic processes such as infections, but tumors do not respect such flimsy boundaries.

Plates of cartilage in the wall of the bronchus are more complete than those of the trachea, but their arrangement is not as regular, and distally they gradually become thinner, smaller, and more widely spaced, disappearing completely as the bronchi become bronchioles.

Bronchioles

The first bronchioles are about 1 mm in diameter. With continued branching, they become progressively smaller until they enter the lobules, where each gives rise to about six terminal bronchioles. From a terminal bronchiole, up to three respiratory bronchioles are formed, and at this point the columnar epithelial lining of the respiratory passages terminates and the respiratory tissue itself begins. From the respiratory bronchioles, thin ducts lead into the alveolar sacs.

Alveoli

Alveoli are rather like square rooms with one wall missing. They open directly into respiratory bronchioles and alveolar ducts and sacs, and neighboring alveoli communicate through small pores.[67] An alveolus is roughly 200 μm across.

CELLS OF THE RESPIRATORY EPITHELIUM

The epithelial lining is similar throughout the trachea and bronchi, but changes in the distribution of the various cell types occur toward the periphery. The respiratory epithelium is pseudostratified, and most of the cells bear cilia (Fig. 1–1). The physical properties of respiratory tract secretions play an important role in the nonspecific defense mechanisms of the lung.[53] As many as ten different cell types have been described in animal lungs, but they have not all been identified in the human lung.[9, 10, 38, 39, 69]

It is rare to see mitoses in the differentiated cells of the trachea and bronchi. Surface cells that die or are lost by desquamation are replaced by proliferation of the basal cells. It is not certain whether the endocrine cells are replaced in this manner, although there is evidence that such a mechanism occurs in the gut.[14, 15, 78]

Ciliated Cells

Most of the epithelial cells in the trachea and bronchi are ciliated (Fig. 1–2). Each cell is columnar, but it tapers toward its base (Fig. 1–3), which is a necessary modification to

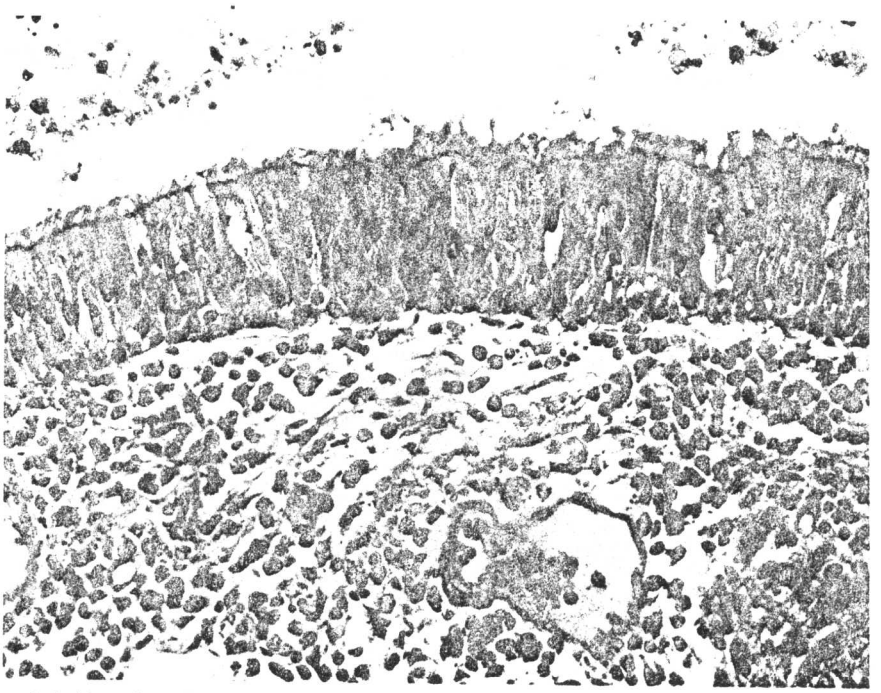


Figure 1–1. Normal respiratory epithelium. Most of the cells are ciliated. The reserve cells form an almost continuous row.

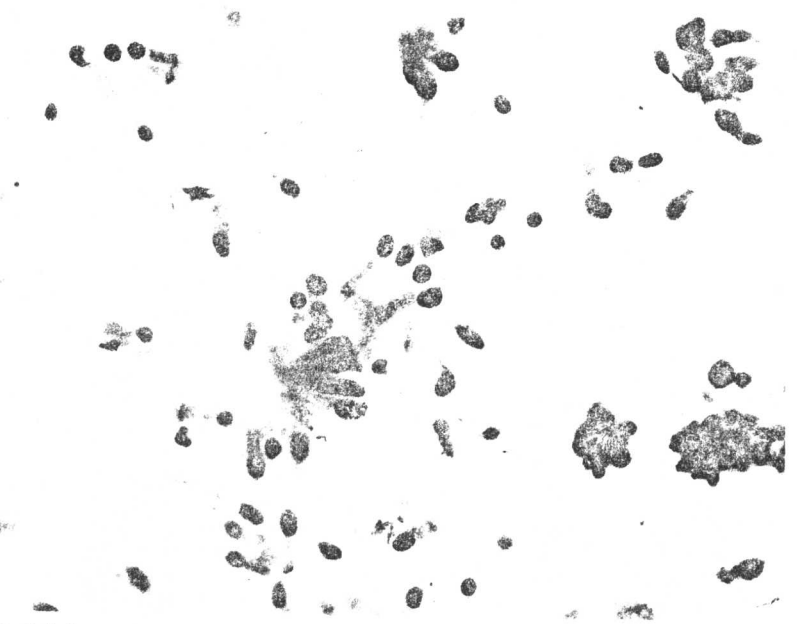


Figure 1–2. Cells from a bronchial brushing. Ciliated columnar cells and small groups of basal cells are present.

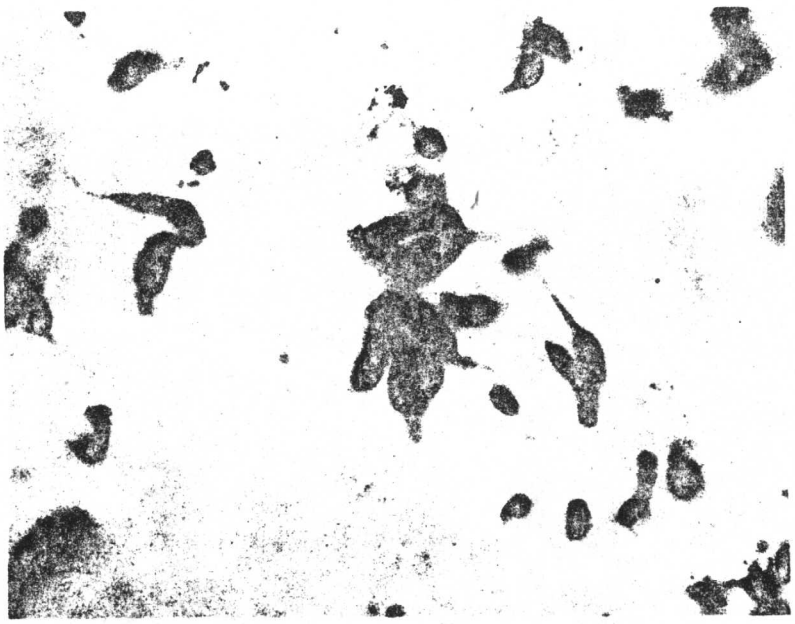


Figure 1–3. Ciliated epithelial cells from a bronchial brushing: the cytoplasm tapers below the level of the nucleus.

make room for the basal and endocrine cells located at this level. The ciliated cell contains lakes of glycogen in its basal cytoplasm, and a well-developed Golgi complex is positioned above the nucleus. Some 250 cilia protrude from the apical surface together with a small number of microvilli.

A cilium is longer and thicker and has a more elaborate internal construction than a microvillus (Fig. 1–4).[2] Each cilium is about 6 μm long, and it contains a system of microtubules (its axoneme) that are arranged in nine peripheral pairs with one central doublet. The microtubules continue below the level of the apical cell membrane into the basal body of the cilium, a cylindrical structure that closely resembles the centriole from which it is derived. The row of basal bodies in the apical cytoplasm produces a linear density that cytologists refer to as the terminal bar (Fig. 1–5). A tapering, striated rootlet of contractile filaments extends down from the basal body into the cytoplasm. The cilia are surrounded by watery periciliary fluid that bathes their surface. The actual mucus layer lies above this fluid, and only the tips of the cilia penetrate it.

In a variety of nonneoplastic conditions and many tumors, occasional cells possess a rudimentary cilium, either confined within the cytoplasm where it invaginates the endoplasmic reticulum or protruding from the surface covered by cell membrane. These aberrant cilia are common and merely represent disordered centriolar activity. They do not provide an indication of the cell type and are of no value in differential diagnosis.

Abnormal cilia have been described in many conditions, including the immotile cilia syndrome.[1, 3, 21, 22, 58] The anomalies include cilia with aberrant numbers of microtubules and compound cilia that are larger than normal with increased numbers of microtubules (Fig. 1–6). The practice of obtaining a biopsy specimen of respiratory mucosa from the nasal cavity or nasopharynx in order to examine the cilia with the electron microscope is controversial since similar abnormalities to those seen in the immotile cilia syndrome can be found in infectious and other nonneoplastic disorders. In a study of 22 specimens of hyperplastic, metaplastic, and dysplastic human bronchial mucosa, Gonzales and associates[23] found a variety of atypical ciliary structures, including abnormal configurations of the plasma membrane, varying amounts of matrix, disorganization of basal bodies, and alterations in the pattern of the microtubules. More than one deviation was present in a single case, and there was no

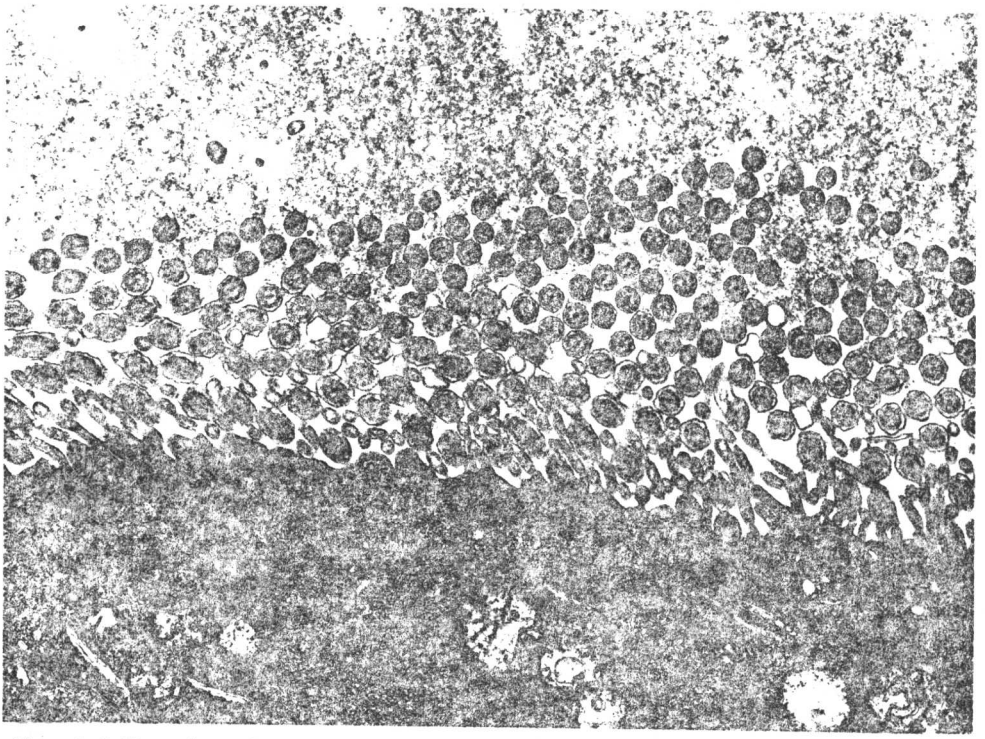


Figure 1–4. The surfaces of two adjacent ciliated cells are shown. Most of the cilia are cut in cross section. Some microvilli and a number of basal bodies can be seen. (× 5,500).

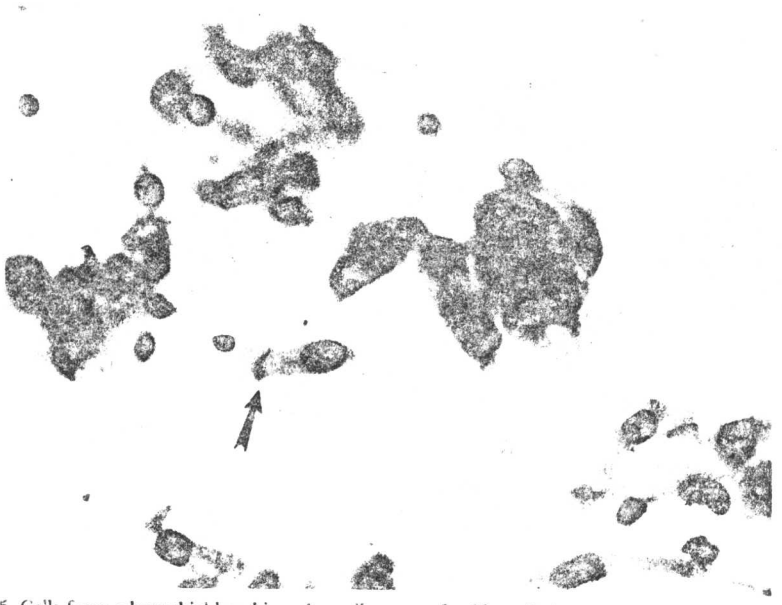
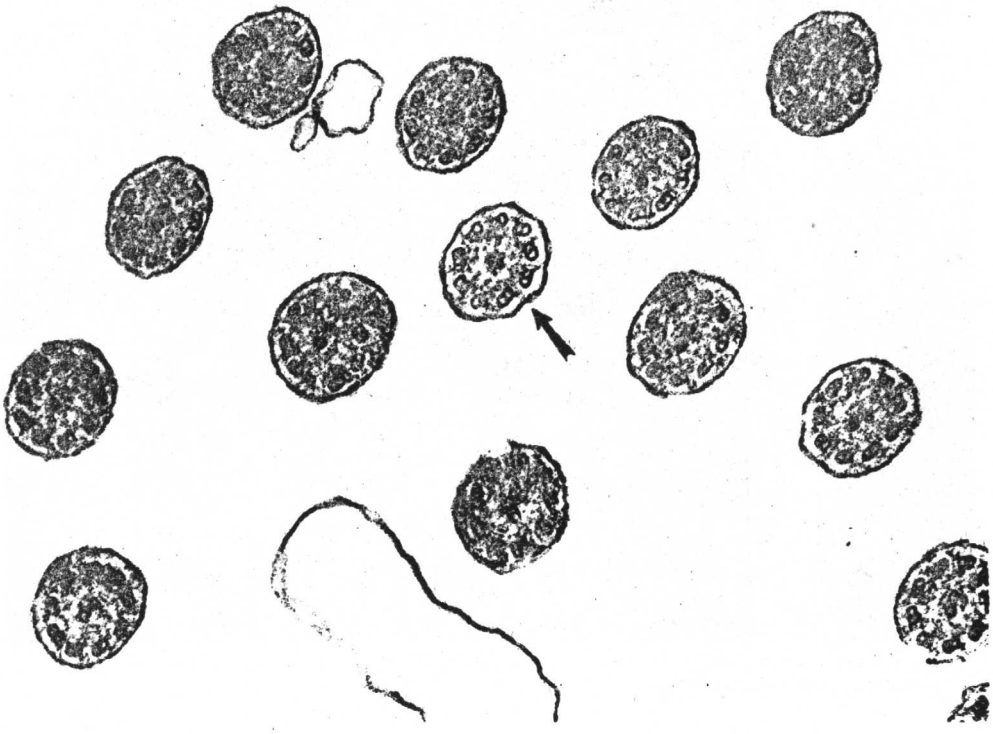


Figure 1–5. Cells from a bronchial brushing. A small group of goblet cells is present. In the ciliated cell indicated by the arrow, the dense line in the apical cytoplasm *(terminal bar)* is produced by the basal bodies of the cilia.



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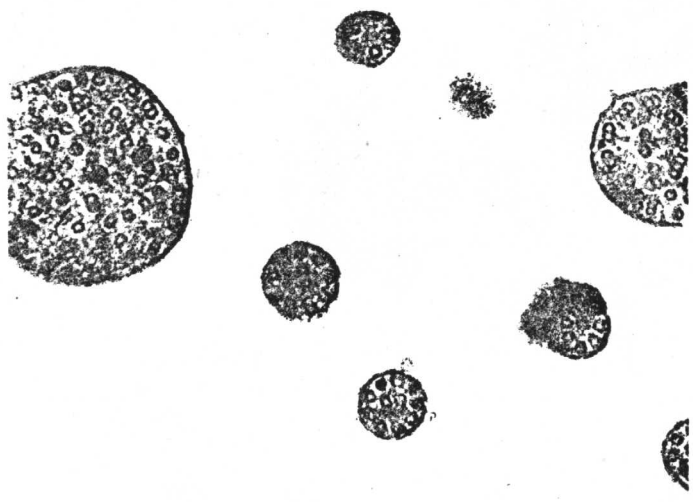

B

Figure 1–6. *A.* The pattern of the microtubules that form the axoneme of a cilium is only seen to good advantage in a true transverse section. In the cilium indicated by the arrow, the central doublet is missing. *B.* Markedly abnormal cilia from a patient who had clinical symptoms of the immotile cilia syndrome. (× 62,000).

evidence of a correlation between the type of ciliary deformation and the extent of the dysplastic process. These abnormal cilia evidently are the result of disordered regeneration of damaged cells, and diagnostic significance should not be attributed to them unless the clinical context is that of the immotile cilia syndrome.

Goblet Cells

The number of goblet cells has been estimated as roughly 7,000/mm² of respiratory surface, but the frequency varies at different levels of the respiratory tract and it is increased in some pathologic conditions.[12, 37] In chronic bronchitis, the number of goblet cells may be much greater than normal. Goblet cells are abundant in the trachea, particularly its lower portion, and in contrast are relatively sparse in the bronchioles.

Like the ciliated cells of the respiratory epithelium, goblet cells taper as they approach the basal lamina (Fig. 1–7). Goblet cells accumulate mucin in droplets, which coalesce to become over 1 μm in diameter. The droplets are electron lucent, but they have a fine granularity and may contain a dense core that, at low magnification, can simulate an endocrine granule. When the goblet cell is full of mucin, its luminal end protrudes above the surrounding ciliated cells, and the mucin is discharged into the lumen through breaches in the apical cytoplasm.[66] Some cytoplasm is lost in this apocrine type of secretion, and shreds of cell membrane left adhering to the surface of the cell are quickly detached. In this way, the cell membrane adjusts to the changes in cell volume. While the cell is accumulating mucus, a few microvilli project from the apical surface.

Surface Serous Cells

Serous cells contain large electron-dense granules. They have been described in animals, but identical cells have not been documented in human respiratory epithelium.

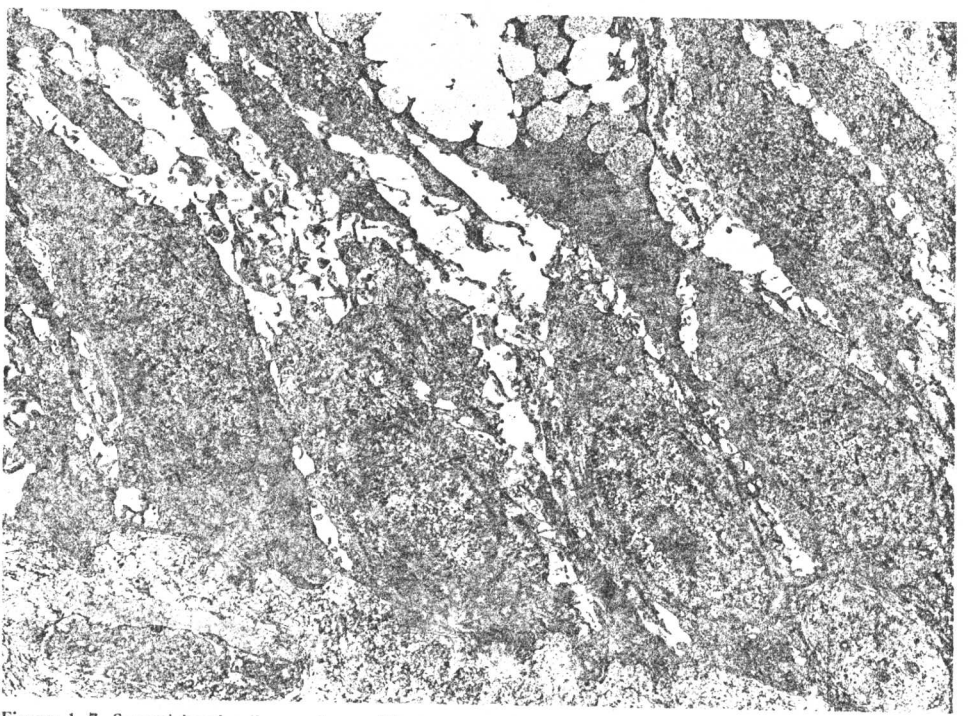

Figure 1–7. Several basal cells are shown. They rest on the basal lamina, and slender bundles of cytokeratin filaments are present in the cytoplasm. The lower part of a goblet cell can be seen: the cytoplasm tapers below the level of the nucleus, and the distended cytoplasm above the nucleus is filled with droplets of mucin. (× 4,000).

Brush Cells

It is also not certain that brush cells, which have been described in animals,[10] occur in the human respiratory mucosa. The animal cell is suspected to have an absorptive function. Brush cells are columnar, and they contain cytoplasmic glycogen and filaments and have many long slender microvilli with microfilament cores that extend down into the apical cytoplasm, an appearance similar to that seen in cells lining the gastrointestinal tract. Since occasional lung adenocarcinomas have microvilli of this type, it is conceivable that brush cells do exist in the human bronchi, but if so they must be present only in small numbers. An alveolar brush cell has been described in the rat lung.[60]

Endocrine Cells

The endocrine cells of the respiratory mucosa are currently of particular interest because of histogenetic implications with regard to bronchial carcinoid and small cell lung carcinoma.[5, 28] Paradoxically, some non–small cell lung carcinomas also contain cells with cytoplasmic granules of endocrine caliber.

Pulmonary endocrine cells have been studied extensively in animals and humans,[6, 24, 54, 55, 57, 63, 68, 81] and they have been given many synonyms, including Feyrter cells, argyrophil cells, and Kulchitsky cells. Endocrine cells are present throughout the trachea and bronchi, and they extend into the bronchioles and the ducts of peribronchial glands. They are present in greater numbers in the fetal lung,

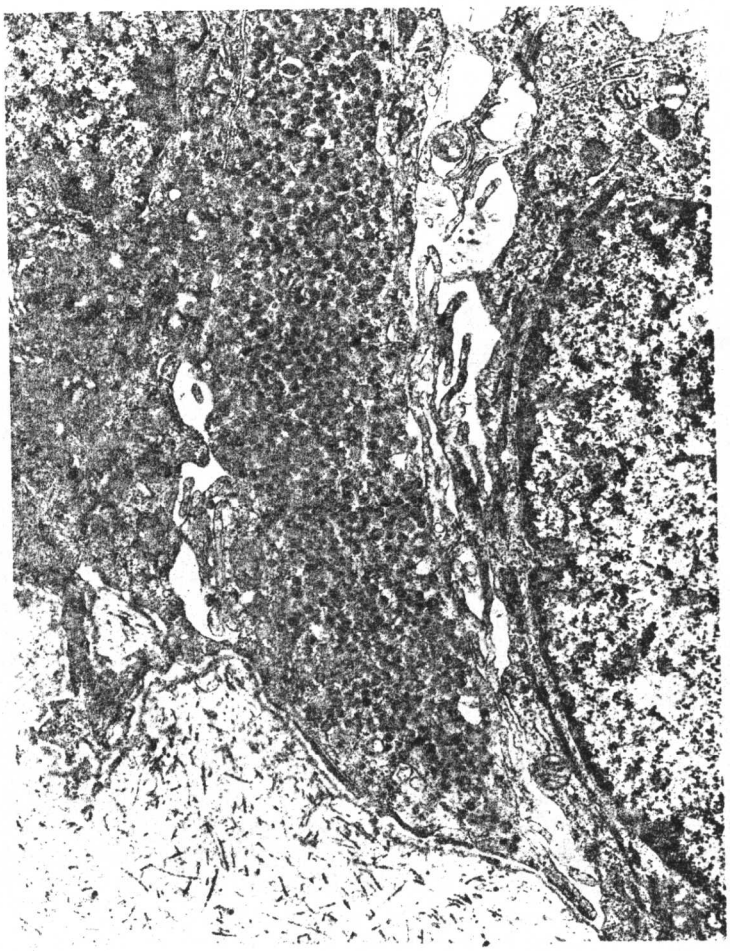

Figure 1–8. An endocrine cell from bronchial epithelium rests on the basal lamina and contains many small dense-core granules. (× 12,000).

where more than one structural type of granule has been described.[19] Most of the endocrine cells are solitary, but they also form small clusters called neuroepithelial bodies,[26, 27] and these cell groups have been studied in animal lungs and in the human fetal lung.[13, 46–49, 79, 80]

The endocrine cells are broadest at their base where they attach to the basal lamina (Fig. 1–8), and they are intimately sandwiched between neighboring columnar cells so that each is triangular in profile, tapering apically and rarely reaching the lumen. The cytoplasm contains many small dense-core granules, which vary in size between 120 and 250 nm but fall within a narrow range of calibers in a particular cell.

The cells can be identified by light microscopy using argyrophil stains such as Grimelius' silver nitrate method[29, 30] or the Sevier-Munger stain.[76] Argentaffin cells (containing reducing agents capable of reducing silver solutions) apparently do not occur in normal tracheobronchial epithelium.

Attempts have been made to classify the endocrine cells of the lung on the basis of the caliber of their dense-core granules[31–33] and by their functional properties as revealed by immunostaining. It appears that more than one type does occur, but it is difficult to relate the normal cells to those seen in tumors because the neoplastic cells display a variety of immunocytochemical and ultrastructural features.

The immunocytochemical demonstration of cytokeratin and desmoplakin in both the solitary neuroendocrine cells and the neuroepithelial bodies confirms their epithelial nature.[52] Immunocytochemical studies have shown reactivity in both the solitary neuroendocrine cells and in neuroepithelial bodies to general neuroendocrine markers such as neuron-specific enolase,[25] chromogranin,[51] and synaptophysin,[52] as well as some regulatory peptides and specific endocrine products, including bombesin, calcitonin, serotonin,[17, 20, 25] somatostatin,[20] and calcitonin gene-related peptide.[50] Leu-enkephalin has been demonstrated only in solitary endocrine cells.[52]

The function of the solitary pulmonary endocrine cells has not been clearly defined, although they presumably elaborate secretions that affect tissues in their immediate vicinity, such as smooth muscle cells in the walls of the respiratory passages and vessels. Stahlman and Gray[81] examined the lungs of 34 human fetuses and 22 newborns using electron microscopy and identified axons, cholinergic terminals, and nonadrenergic-noncholinergic terminals, including some in contact with endocrine cells and deep within neuroepithelial bodies. They suggest that the function of these cells may include reflex mechanisms integrated with the autonomic nervous system and postulate that the cells may have a tropic role in lung development and regeneration. Lauweryns and Van-Lommel[19] report that the cells in neuroepithelial bodies synapse with both afferent and efferent nerves and conclude that the bodies function as neuroreceptors that are locally modulated by axon reflexes.

Oncocytes

The eosinophilic cytoplasm of oncocytic cells results from the presence of large numbers of mitochondria.[10] Similar mitochondrion-rich cells are found in other tissues, notably endocrine organs such as the thyroid (Hürthle cells) and parathyroid (oxyphil cells), and in salivary tissues (oncocytes). They occur in some tumors of these tissues, and similar cells are seen in low-grade renal neoplasms. In the normal respiratory tract, oncocytes have been observed in the trachea, and varying degrees of oncocytic change can be seen in the duct cells of the bronchial glands (Fig. 1–9).

Basal Cells

Basal or reserve cells are found in the respiratory epithelium as far distal as the bronchioles, but they are more numerous proximally. They may be sufficiently plentiful to form a continuous row along the basal lamina, and some stratification can occur (Fig. 1–10), but usually the layer of basal cells is incomplete. Their presence at the base of the epithelium creates an impression of two distinct rows of nuclei (see Fig. 1–1).

In Figure 1–11, the small, round to polygonal basal cells can be seen sitting on the basal lamina. They are in contact with their neighbors or adjacent columnar epithelial cells at various points along their surface, and small desmosomes connect the apposed cell membranes. The basal cells have very few organelles, but slender bundles of cytokeratin filaments are often evident, and a thin strand of smooth muscle myofilaments can sometimes be found in the cytoplasm close to the attachment of the cell to the basal