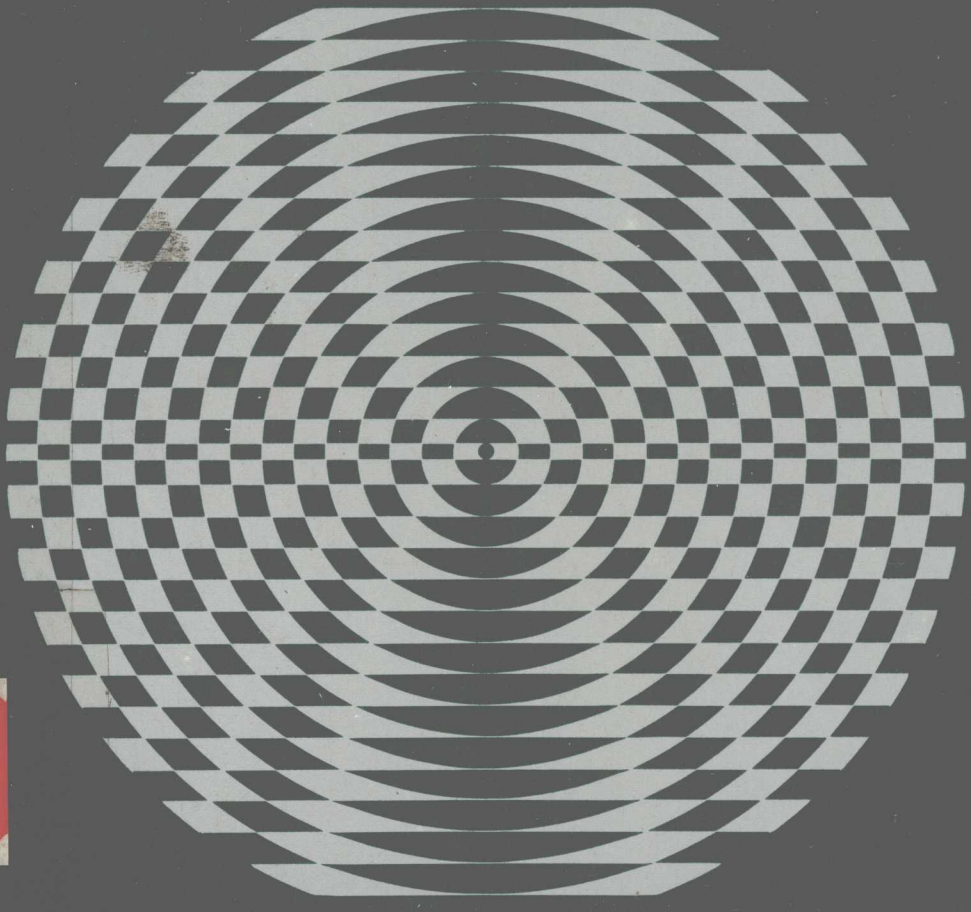
Michael E. Whitcomb

THE LUNG

NORMAL AND DISEASED



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NORMAL AND DISEASED

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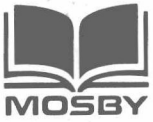

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THE LUNG

NORMAL AND DISEASED

PREFACE

The Lung: Normal and Diseased has been written specifically for students interested in the normal and diseased lung. The organization of the text incorporates concepts used in teaching an introductory course in clinical pulmonary medicine to medical students at The Ohio State University College of Medicine. Traditionally, medical students are taught the structure and function of the normal and diseased lung and the clinical manifestations of the various lung diseases in separate courses (anatomy, histology, physiology, pathology, and pulmonary medicine). Several years ago, the introductory clinical pulmonary disease course at Ohio State was reorganized based on the premise that students are able to understand the clinical features of the various lung diseases better if they first understand the basic structure-function relationships of the normal and diseased lung. The course is organized in such a way that discussion revolves around the three major structural components of the lung—the airways, alveoli, and pulmonary vasculature. The normal structure and function of each component is first reviewed, then the impact of disease on the normal structure-function relationships is discussed. Finally, the clinical, roentgenographic, and physiologic manifestations of the diseases principally affecting each component are described. The diseases are not discussed in great detail, but enough information is provided so that the students can make the association between clinical manifestations common to a number of diseases that primarily affect the same structural component of the lung and basic structure-function relationships. The clinical manifestations of the various lung diseases should be learned in far greater detail during the student's clinical rotations.

Unfortunately, no single text covers all of this information in a way that is appropriate for students and in a size they find practical. *The Lung: Normal and Diseased* was written to fill this need and to help students expand their knowledge of lung diseases throughout the clinical portion of the curriculum. This text is divided into five major sections. The first three sections cover, respectively, the airways, gas-exchanging parenchyma (alveoli), and the pulmonary vasculature. The

initial chapters in each section discuss the normal and abnormal structure-function relationships of the component of the lung under consideration and then describe the diseases that most appropriately fit into each section. Most diseases fit easily into this classification system. However, this approach does result in some departures from tradition. For example, emphysema is discussed in the section on alveolar wall diseases. In a more traditional physiologic classification scheme, emphysema is usually discussed along with certain airway diseases as an "obstructive lung disease." However, emphysema is truly a disease of the alveolar wall. In my experience, students are better able to understand and learn the clinical features of this disease when it is presented in this context, rather than associating it with asthma, chronic bronchitis, or other airways diseases.

Sections four and five cover the topics of respiratory failure and pulmonary infections. The initial chapters in both sections describe functions of the whole lung (gas exchange and ventilation and the pulmonary defense mechanisms) that are relevant to the clinical entities discussed in subsequent chapters. This is appropriate, since respiratory failure and pulmonary infection are, in a sense, simply pathophysiologic states resulting from altered ventilation and gas exchange or altered pulmonary defenses regardless of the specific causes of the lung disease.

As with any organizational scheme, the approach used in this text has some unavoidable inconsistencies. However, I believe that the organization of the text allows students to learn the clinical features of lung disease within a conceptual framework which allows them to actually *understand* the disease process far better than if diseases are presented in a more traditional physiologic or roentgenographic classification system. Although these classification systems serve a useful purpose for individuals with substantial knowledge of lung diseases, I believe that students approaching clinical pulmonary medicine for the first time are able to understand the subject better when the diseases are presented in a system based on the structure-function relationships of individual components of the lung or the lung as a whole.

Michael E. Whitcomb

CONTENTS

Section one

THE AIRWAYS

Chapter 1

NORMAL STRUCTURE AND FUNCTION

STRUCTURE

The tracheobronchial tree, or airways, consists of a series of branching tubes whose main function is to conduct gases into and out of the lung. In addition to serving as conducting tubes, the airways also provide certain defense mechanisms that protect both the airway mucosa and the alveolar surface from a multitude of environmental noxious agents. These functions should be kept in mind when considering the varied structure of the airways at different points along the tracheobronchial tree.

Sequential division of the airways results in approximately twenty-two to twenty-five generations of airways. The combined cross-sectional area of two subdivisions of a parent trunk is always greater than the area of the parent airway. As a result, the total cross-sectional area of the airways increases substantially with each succeeding generation (Table 1). The importance of the increase in determining certain characteristics of flow in the airways will be discussed later.

The trachea and main stem bronchi are mediastinal structures that lie outside the confines of the lung. The remaining subdivisions of the tracheobronchial tree are intrapulmonary structures. The first fourteen intrapulmonary generations lie within the supporting interstitial connective tissue of the lung and are not in intimate contact with gas-exchanging parenchynal tissue. The remaining airways are closely surrounded by lung parenchyma. The terminal bronchioles, approximately the sixteenth generation, are the last airways to have a continuous mucosal lining. At least three generations of respiratory bronchioles lie beyond the terminal bronchioles. The respiratory bronchioles have a discontinuous mucosal lining with alveoli intermittently protruding directly from the wall of the airway. Beyond the respiratory bronchioles are a variable number of alveolar ducts whose walls are

completely lined with alveoli. The alveolar ducts terminate in alveolar sacs (Fig. 1-1).

When viewed tangentially, the wall of an airway can be divided into mucosal and submucosal layers. The components of these layers vary markedly at different points along the tracheobronchial tree. The varying histologic features of the airways have functional significance and will be considered in some detail.

TABLE 1
Dimensions of the tracheobronchial tree and lung parenchyma at different levels

Structure	Number	Total cross-sectional area
Trachea	1	5 cm^2
Subsegmental bronchi	38	66 cm^2
Terminal bronchioles	4×10^4	116 cm^2
Terminal respiratory bronchioles	6×10^5	1000 cm^2
Alveoli	300×10^6	70 m^2

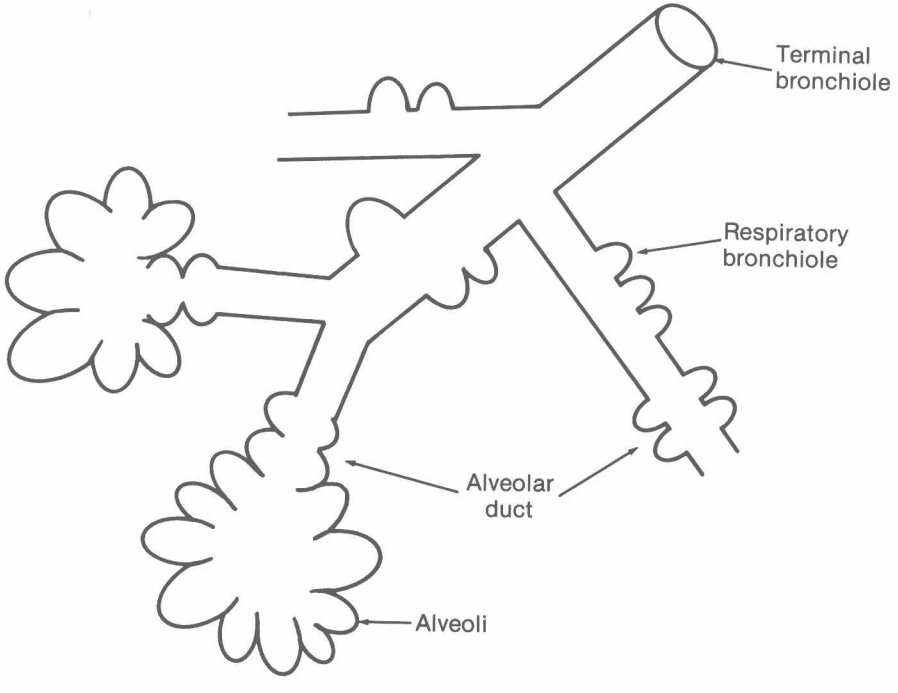

Fig. 1-1. Schematic representation of the structure of the distal airways and alveoli demonstrating the presence of respiratory epithelium (alveolar sacs) in respiratory bronchioles and alveolar ducts.

Mucosa

The mucosa consists of the epithelium, a basement membrane, and the lamina propria. The cells of the epithelium are attached to the basement membrane. The lamina propria lies below the basement membrane and contains lymphocytes, plasma cells, occasional polymorphonuclear leukocytes, and numerous mast cells. An elastic tissue layer forms the boundary of the lamina propria.

A number of different cell types have been identified in the epithelium at some point along the tracheobronchial tree. The functional significance of some of these cells is unknown, and they will not be discussed in any detail. The large airways are lined by a pseudostratified columnar epithelium (Fig 1-2), which consists predominantly of *ciliated cells* and *goblet cells* (Fig. 1-3). Approximately five ciliated cells exist for every goblet cell. The main purpose of the ciliated cells is to propel airway secretions toward the larynx, whereas the goblet cells are actively involved in the synthesis and secretion of mucus (Fig. 1-4). *Nonciliated serous cells* also appear to be distinct cells of the epithelium. The exact function of these cells is unknown, but they may be involved in synthesis of a protein necessary for the transport of a specific immunoglobulin (IgA) onto the airway surface. All these cells are attached to the underlying basement membrane by fine, cytoplasmic foot processes.

Basal, or *germinal cells,* and *intermediate cells* are scattered along the basement membrane. These cells do not reach the surface of the airway and are thus responsible for the pseudostratified appearance of the bronchial epithelium. These cells appear to be precursors of the ciliated and goblet cells. *Argyrophilic cells* (Kulchitsky cells) have also been identified within the basal cell layer. These cells contain neurosecretory granules and appear to have the potential to synthesize a number of bioactive polypeptides. Their significance in the normal lung is unknown, but they are extremely important in certain airway diseases.

The columnar epithelium gradually becomes cuboidal in distal airways. Goblet cells are not present in small bronchioles, whereas *Clara cells* first appear in these airways (Fig. 1-5). Although their exact function has yet to be elucidated, Clara cells are rich in secretory granules and are probably the source of at least one component of the fluid lining the smallest airways. These airways do not have

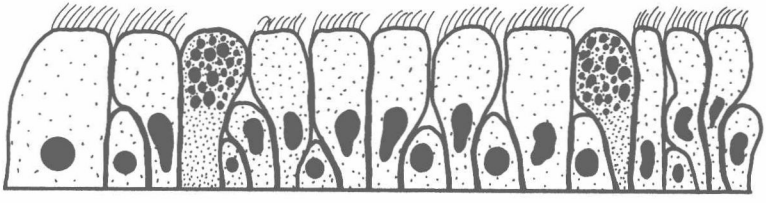

Fig. 1-2. Schematic representation of the pseudostratified columnar epithelium lining the large airways.

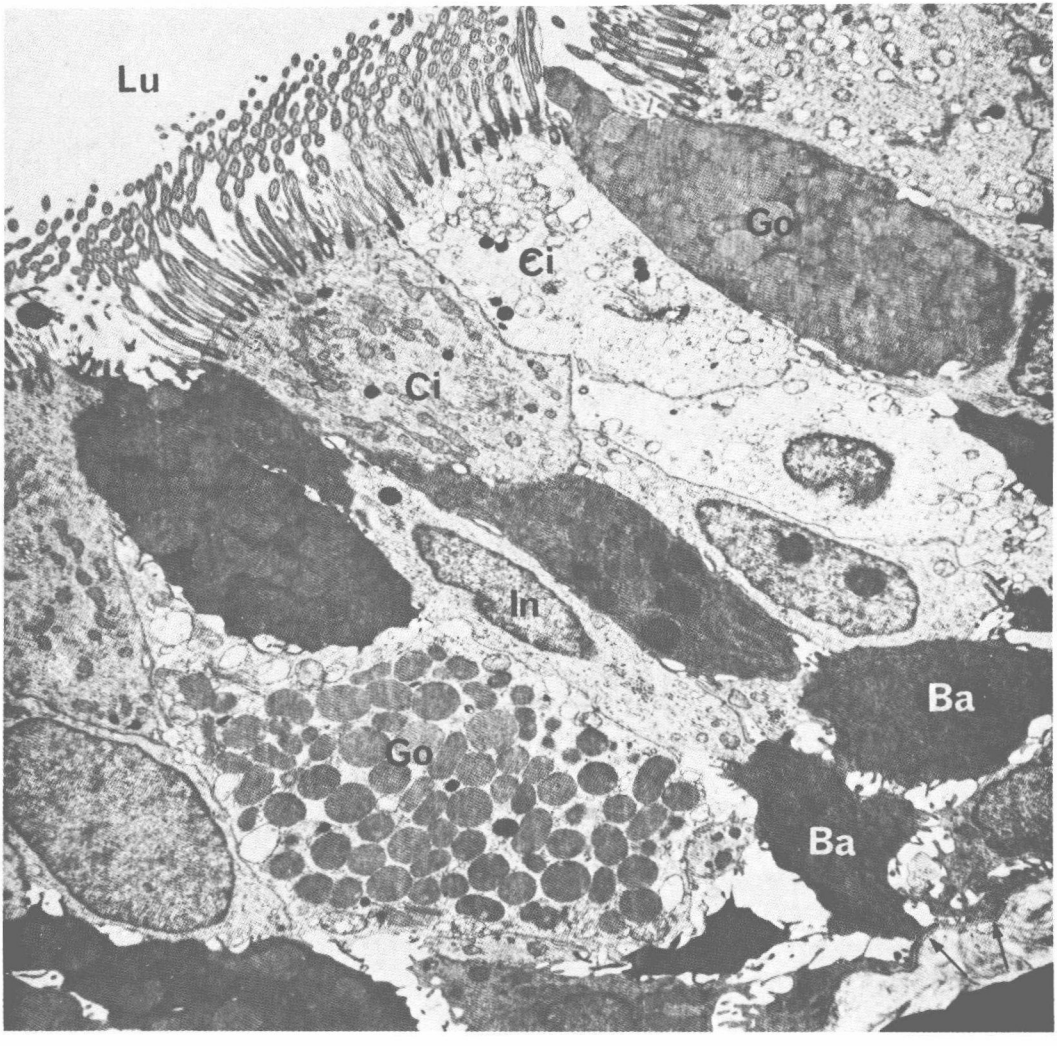

Fig. 1-3. Ultrastructure of the bronchial mucosa. Ciliated (*Ci*), goblet (*Go*), intermediate (*In*), and basal (*Ba*) cells are present. The secretory granules in the goblet cells are abundant. *Lu*, Lumen of the bronchus.

From Breeze, R.G., and Wheeldon, E.B.: REB: the cells of the pulmonary airways, Am. Rev. Respir. Dis. **116**:705, 1977.

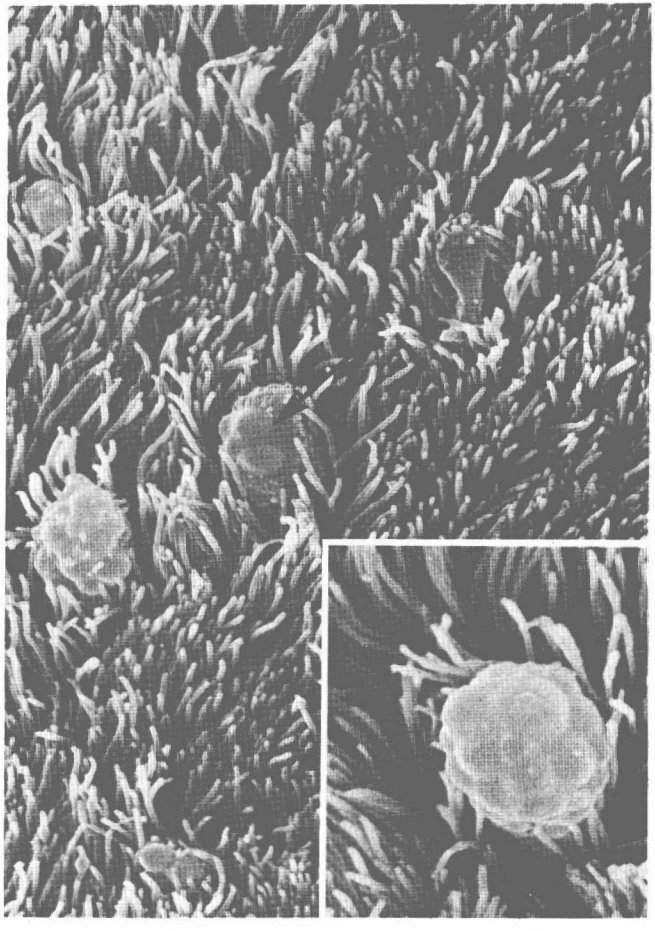

Fig. 1-4. Scanning microscopy of the surface of the bronchial mucosa. The secretions of goblet cells are interspersed in the microvilli of the ciliated cells. The insert shows in greater detail a single goblet cell discharging its secretion.

From Breeze, R.G., and Wheeldon, E.B.: REB: the cells of the pulmonary airways, Am. Rev. Respir. Dis. **116**:705, 1977.

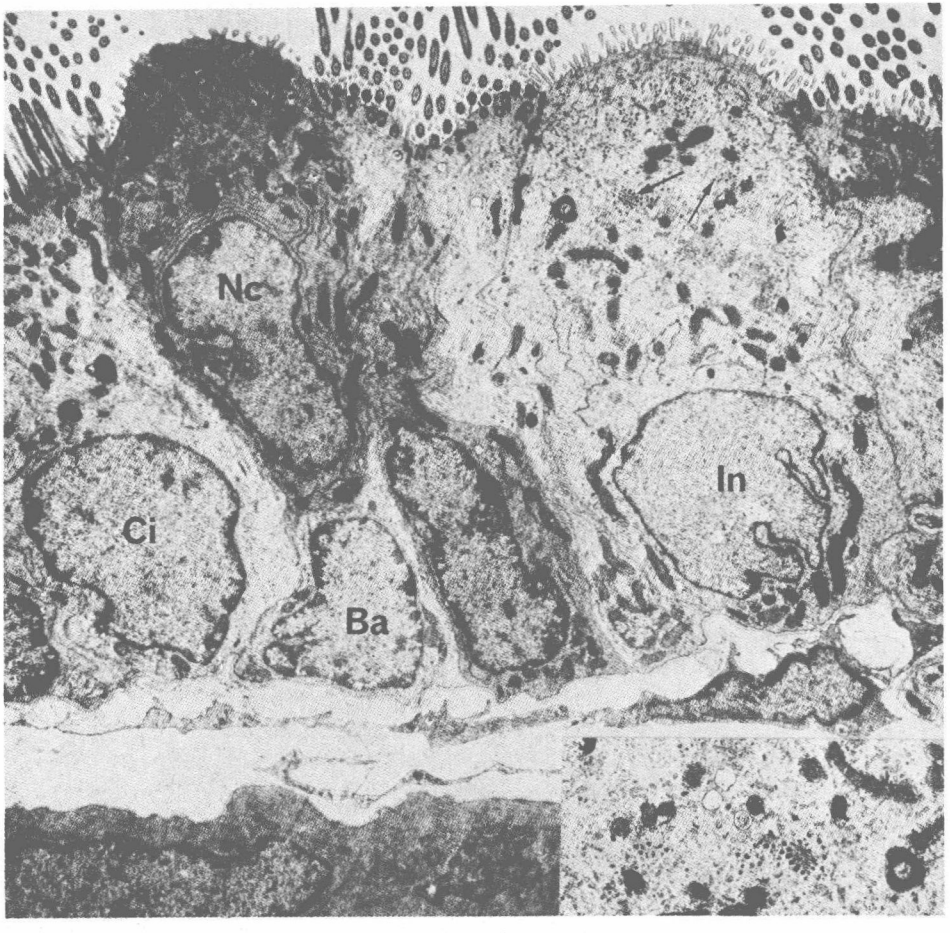

Fig. 1-5. Ultrastructure of the bronchiolar mucosa demonstrating a nonciliated (*Nc*), bronchiolar secretory cell (Clara cell). Ciliated (*Ci*), basal (*Ba*), and intermediate (*In*) cells are also depicted.

From Breeze R.G., and Wheeldon, E.B.: REB: the cells of the pulmonary airways, Am. Rev. Respir. Dis. **116**:705, 1977.

a mucous lining layer reflecting the absence of goblet cells and mucous glands. The cilia of the ciliated cells in these airways are bathed, however, in a watery, protein-rich layer that appears to have surface active properties. Although the source of the various constituents of this fluid is not agreed upon totally, it is agreed that Clara cells are probably important in its production.

Lymphoid nodules are important components of the lamina propria at some sites along the tracheobronchial tree (Fig. 1-6). At these sites the epithelium overlying the nodules is modified and consists of flattened, nonciliated cells resembling lymphoepithelium in other areas of the body (Fig. 1-7). This bronchus-associated

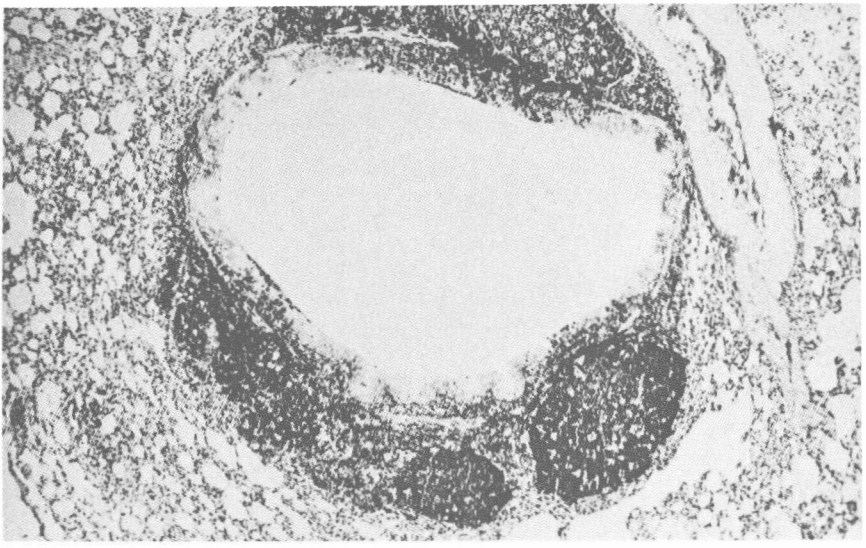

Fig. 1-6. Transverse section of a bronchus demonstrating the presence of bronchus-associated lymphatic tissue (*BALT*).

From Kirkpatrick, C.H., and Reynolds, H.Y.: Immunologic and infectious reaction in the lung, New York, 1976, Marcel Dekker, Inc.

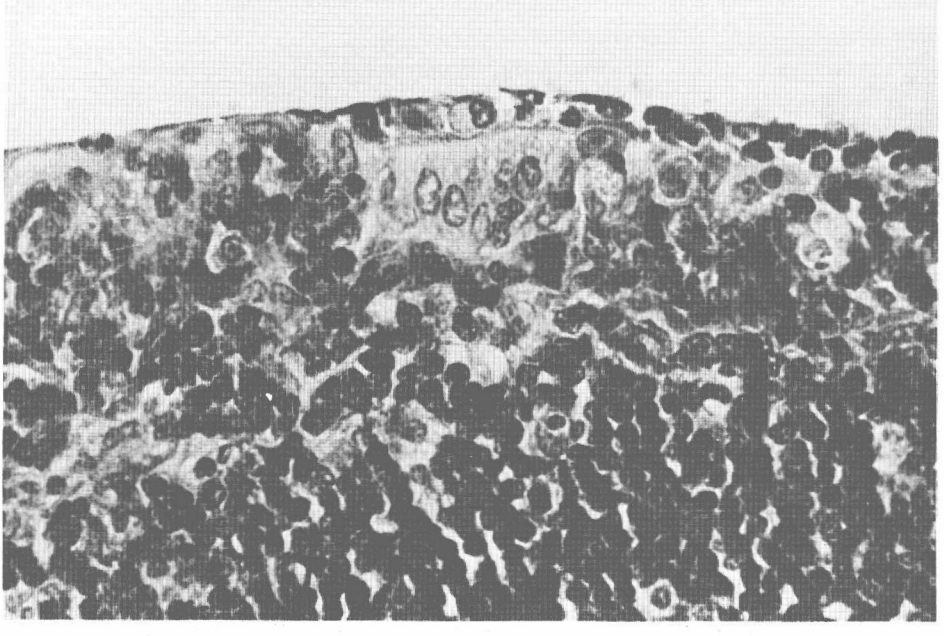

Fig. 1-7. High-power view demonstrating the epithelium overlying the bronchus-associated lymphatic tissue (*BALT*).

From Kirkpatrick, C.H., and Reynolds, H.Y.: Immunologic and infectious reaction in the lung, New York, 1976, Marcel Dekker, Inc.