Immunology of the Lung and Upper Respiratory Tract

Edited by
John Bienenstock, M.D., F.R.C.P., F.R.C.P.(C)

Immunology of the Lung and Upper Respiratory Tract

Edited by
John Bienenstock, M.D., F.R.C.P., F.R.C.P.(C)
McMaster University
Hamilton, Ontario
Canada

McGraw-Hill Book Company

New York St. Louis San Francisco Auckland Bogotá Guatemala
Hamburg Johannesburg Lisbon Madrid Mexico Montreal New Delhi
Panama Paris San Juan São Paulo Singapore Sydney Tokyo Toronto

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The editors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide drug dosage schedules that are complete and in accord with the standards accepted at the time of publication. However, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in these schedules is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

IMMUNOLOGY OF THE LUNG AND UPPER RESPIRATORY TRACT

1 2 3 4 5 6 7 8 9 0 VNHVNH 8 9 8 7 6 5 4

ISBN 0-07-005215-8

This book was set in Times Roman by University Graphics, Inc., the editors were Joseph J. Brehm and Stuart D. Boynton, the production supervisor was Avé McCracken. Von Hoffman Press, Inc. was printer and binder.

Library of Congress Cataloging in Publication Data
Main entry under title:

Immunology of the lung and upper respiratory tract.

Bibliography: p.
Includes index.
1. Lungs—Diseases—Immunological aspects.
2. Respiratory organs—Diseases—Immunological aspects.
3. Immunopathology. I. Bienenstock, John. [DNLM:
1. Lung—Immunology. 2. Respiratory tract infections—
Immunology. 3. Lung diseases—Immunology. WF 600 I33]
RC756.I47 1984 616.2'4079 83-25130
ISBN 0-07-005215-8

List of Contributors

DEAN BEFUS, Ph.D.
Associate Professor of Pathology,
Host Resistance Programme,
McMaster University,
Hamilton, Ontario, Canada

JOHN BIENENSTOCK, M.D., F.R.C.P., F.R.C.P.(C).
Professor, Medicine & Pathology,
Chairman, Department of Pathology,
Host Resistance Programme,
McMaster University,
Hamilton, Ontario, Canada

PER BRANDTZAEG, D.D.S., M.S., Ph.D.
Assoc. Professor of Pathology
and Chief, Laboratory for Immunohistochemistry and Immunopathology,
The National Hospital,
Rikshospitalet, Oslo, Norway

NICKOLAS J. CALVANICO, Ph.D.
Associate Professor of Medicine,
Medical College of Wisconsin;
Veterans Administration Medical Center,
Wood, Wisconsin

THOMAS B. CASALE, M.D.
Senior Medical Staff Fellow,
Allergic Diseases Section,
National Institute of Allergy and Infectious Diseases,
Bethesda, Maryland

ROBERT CLANCY, M.B., F.R.A.C.P., Ph.D.
Professor and Chairman of Pathology,
Faculty of Medicine, University of Newcastle,
Newcastle, NSW, Australia

WALLACE A. CLYDE JR., M.D.
Professor of Pediatrics and Microbiology,
University of North Carolina School of Medicine;
Attending Staff, North Carolina Memorial Hospital

BRYAN CORRIN, M.D., F.R.C.Path.
Professor of Thoracic Pathology,
Cardiothoracic Institute,
Honorary Consultant Pathologist,
Brompton Hospital and London Chest Hospital, London, England

JAMES C. CUMELLA, M.D.
Research Assistant Professor,
Department of Pediatrics,
State University of New York at Buffalo,
Children's Hospital of Buffalo

TOM EGWANG, M.Sc.
Host Resistance Programme,
McMaster University,
Hamilton, Ontario, Canada

GERALD W. FERNALD, M.D.
Professor and Assoc. Chairman,
Department of Pediatrics,
University of North Carolina School of Medicine,
Chapel Hill

JORDAN N. FINK, M.D.
Professor of Medicine,
Chief, Allergy-Immunology Section,
Medical College of Wisconsin;
Associate Chief of Staff/Research,
Veterans Administration Medical Center,
Wood, Wisconsin

JACK GAULDIE, Ph.D.
Associate Professor of Pathology,
Host Resistance Programme,
McMaster University,
Hamilton, Ontario, Canada

ERWIN W. GELFAND, M.D.
Professor of Pediatrics,
University of Toronto,
Immunologist-in-Chief,
Hospital for Sick Children,
Toronto, Canada

PETER M. HENSON, Ph.D., BVM&S, MRCVS
Staff Scientist, Department of Pediatrics,
National Jewish Hospital/National Asthma Center;
Professor of Pathology and Medicine,
University of Colorado School of Medicine, Denver

GARY W. HUNNINGHAKE, M.D.
Professor of Medicine,
Director of the Pulmonary Disease Division,
University of Iowa College of Medicine,
Iowa City

GEORGE J. JAKAB, Ph.D.
Associate Professor of Environmental Health Sciences,
The Johns Hopkins School of Hygiene and Public Health,
Baltimore, Maryland

PETER K. JEFFERY, Ph.D.
Senior Lecturer in Thoracic Pathology, Department of Lung Pathology, Cardiothoracic Institute, Brompton Hospital, London, England

KENT J. JOHNSON, M.D.
Associate Professor of Pathology,
The University of Michigan Medical School,
Ann Arbor

MICHAEL A. KALINER, M.D.
Head, Allergic Diseases Section,
National Institute of Allergy & Infectious Diseases,
Bethesda, Maryland

H. BENFER KALTREIDER, M.D.
Associate Professor of Medicine,
University of California, San Francisco;
Chief, Respiratory Care Section,
Veterans Administration Medical Center,
San Francisco

A. B. KAY, M.D., Ph.D.
Professor and Director,
Department of Allergy & Clinical Immunology,
Cardiothoracic Institute,
Honorary Consultant, Brompton Hospital,
London, England

ROBERT H. KELLER, M.D., F.A.C.P.
Associate Professor of Medicine,
Director, Marcus Center for Immunology and Allergy Research,
Medical College of Winsconsin,
Milwaukee

HOWARD M. LEDERMAN, M.D., Ph.D.
Research Fellow,
Division of Immunology,
Hospital for Sick Children,
Toronto, Canada

POPE L. MOSELEY, M.D.
Fellow in Clinical Medicine,
University of Iowa College of Medicine,
Iowa City

ROBERT A. MUSSON, Ph.D.
Staff Scientist, Department of Pediatrics,
National Jewish Hospital/National Asthma Center;
Assistant Professor, Department of Pathology,
University of Colorado School of Medicine, Denver

PEARAY L. OGRA, M.D.
Professor of Pediatrics and Microbiology,
State University of New York at Buffalo;
Director, Division of Infectious Diseases,
Children's Hospital of Buffalo

HERBERT Y. REYNOLDS, M.D.
Professor of Medicine and Chief Pulmonary Section,
Department of Medicine,
Yale University School of Medicine,
New Haven, Connecticut

MARGARET TURNER-WARWICK, D.M., Ph.D.
Professor of Medicine,
Cardiothoracic Institute,
Brompton Hospital,
London, England

PETER A. WARD, M.D.
Professor and Chairman of Pathology,
The University of Michigan Medical School,
Ann Arbor

ROBERT C. WELLIVER, M.D.
Associate Professor of Pediatrics,
State University of New York at Buffalo;
Children's Hospital of Buffalo

JUDITH B. WILLOUGHBY, Ph.D.
Assistant Professor of Pathology,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland

WILLIAM F. WILLOUGHBY, M.D., Ph.D.
Associate Professor of Pathology,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland

K. RANDALL YOUNG, JR., M.D.
Fellow in Pulmonary Medicine,
Department of Medicine, Yale University School of Medicine,
New Haven, Connecticut

Preface

Immunology now covers an enormous area of Biology. When I started to study immunology in 1964, it was possible to expect that one could obtain a good grasp of all the areas of current and highest interest. One only has to open an immunological journal now to put a lie to this hope.

In view of the burgeoning amount of new knowledge of the immunology of the lung, it seemed appropriate to try to bring it together in a multi-authored work. I suggested the areas and topics which together should provide a working overview. Since so much has been written on asthma and since this is a small part of the contribution by immunologists to our understanding of health and disease associated with the lung, this area has been covered briefly (but I think very well). The long chapter on tonsils and nasal mucosa was not further subdivided because I agreed with the author that the readership hopefully will include a variety of people such as ENT specialists, interested specifically in the upper respiratory tract, who might find this type of information useful if contained within a single chapter.

In the course of my own development, I was lucky enough to work with Dr. Tom Tomasi who has made a major contribution to our understanding of immunology and who opened the door on what has come to be termed mucosal immunology. I did not work very much on the lung until I came to McMaster, where I began to realize that the lung possessed major similarities to the gut and I began to tell the

students that "the lung is a gut that breathes." This comment has engendered some pithy retorts by respirologists which are probably best left to the imagination. Nevertheless, the similarities of embryological derivation, mucosal immunological attributes, and many other aspects still suggest to me that there is much to be learned from such a comparison.

This book is for all students of immunology and respirology who seek a better understanding of the physiology of the lung and I hope that it will interest not only people in many branches of medicine, but also biologists, veterinarians, and so on.

My real hope is that among the readers of this book, there will be individuals who will feel stimulated enough about the subject to pursue further some of the concepts contained in it.

John Bienenstock

Contents

Chapter 1

Structural Analysis of the Respiratory Tract

Peter K. Jeffery
Bryan Corrin

INTRODUCTION

The lining of the respiratory tract is continuous with the skin and with the lining of the alimentary tract, from which the lower respiratory tract develops in utero. In contrast to the alimentary tract, the way ambient air moves frequently and freely over the respiratory lining makes it particularly susceptible to the gaseous environment. In humans at rest, the volume of air entering the nares each day is about 10,000 to 15,000 L. The respiratory lining is generally thinner than the skin: it appears pink owing to underlying blood vessels and velvety owing to surface irregularity of the various cell types that make up the lining epithelium.

While air moves in two directions, secretions produced in the lungs move cranially, together with any foreign material which may have impinged on the airway wall. In upright humans, lung secretions generally move against gravity, although in the upper lobes there are many airways that drain downwards, aided by gravity. In the upper respiratory tract ciliary movement acts similarly, so that secretions formed in the sinuses drain to the nasopharynx, much of this also against gravity.

ANATOMY OF THE RESPIRATORY TRACT

The larynx is conventionally considered to mark the boundary between the upper and lower portions of the respiratory tract: the upper extends from the external nares to the larynx and the lower from the larynx to the visceral pleura.

P. K. J. wishes to thank the Cystic Fibrosis Trust and the Medical Research Council of Great Britain for personal support.

Upper Respiratory Tract

The upper respiratory tract consists of the nose and the pharynx. The nose is formed by two cavities lying on either side of a median septum. The superior part of the nose is entirely surrounded by bone; posteriorly it opens into the nasopharynx, which continues into the oro- and laryngopharynx. Each nasal cavity is wider below than above and wider centrally than at either its anterior or posterior ends. On each lateral wall there are three turbinates, which run roughly horizontally and, under each is a channel. Following the pharynx is the larynx, which serves as a valve protecting the lungs and as the organ of phonation. An extraordinary degree of control is maintained over the size of its opening and the tautness of its vocal cords. Opening off the upper respiratory tract is a system of air sinuses, which give resonance to the voice and lighten the skull, and two eustachian tubes, which are responsible for maintaining air in the middle ear. Air may move in and out of these diverticula, and secretions formed here must drain to the nasal cavities.

Lymphoid tissue in the upper respiratory tract comprises the nasopharyngeal and palatine tonsils. The former is a median nodule forming part of the lining mucosa of the roof of the nasopharynx. It is a diffuse aggregate of lymphoid cells with predominantly pseudostratified covering epithelium thrown into folds; when enlarged it takes on a glandlike structure, hence the term *adenoids*. There are two palatine tonsils situated in the lateral walls of the oropharynx. In contrast to the nasopharyngeal tonsil, they are less diffuse and are covered by a stratified, squamous, nonkeratinizing epithelium invaginated to form deep crypts.

Lower Respiratory Tract

Airway Branching and Definitions The lower respiratory tract is composed of a tree of successively branching airways. The larynx opens into a single tube called the *windpipe* or *trachea*, which soon after entering the thorax divides to form two main *bronchi*, one to each lung. Enclosed within the visceral pleura, the two lungs fill their respective pleural cavities. Medially they abut the mediastinum, below they rest on the diaphragm, and elsewhere they are enclosed by the rib cage. On the medial surface the main bronchovascular structures connect the hilum of the lung with the mediastinum, and at this point the visceral pleura is reflected off the lung to become the parietal pleura. In humans deep oblique fissures divide the lungs into upper and lower lobes, and on the right a transverse fissure further separates a middle lobe from the upper lobe. The right and left main bronchi divide similarly to give a total of five lobar bronchi. Each lobe is divided into *segments*, 19 in all, a segment being the smallest bronchopulmonary unit which can be distinguished and excised separately by the surgeon. Each segment is imperfectly divided into lung *lobules*, which are lung units demarcated by incomplete fibrous septa. The pattern of airway branching is described as one of asymmetrical dichotomy, and from trachea to alveolus there are 8 to 23 generations of airways depending on the distance from the hilum to pleural surface.

In the trachea, supportive cartilage is present in the form of irregular, sometimes branching, crescentic rings (16 to 20 in humans), all of which are incomplete dorsally; the dorsal gaps are bridged with fibrous tissue and bands of smooth muscle. The designation of intrasegmental airways by size is unsatisfactory because this varies with each division and with the phase of inspiration or expiration and state of muscle contraction. Airways are best designated by structure and position along a pathway (i.e generation or order of division). Those airways distal to the trachea that have supportive cartilage in their walls are by definition *bronchi*. In large bronchi the cartilages are irregular in shape but are frequent enough to be found in any cut plane of the airway; in "small" bronchi they are less abundant and may be missed in section. Those airways distal to the last cartilage plate form the *bronchioles*. The last divisions have their ciliated lining epithelia interrupted by occasional alveoli and are called

respiratory bronchioli; this is the first site at which gaseous exchange occurs and is also where the ciliary escalator begins. The generation proximal to the first-order respiratory bronchiolus is called the *terminal bronchiolus*, the last purely conductive airway. A single terminal bronchiolus with its succeeding branches of respiratory bronchioles (generally three orders), two to nine orders of alveolar ducts, and their alveolar sacs together form the *acinus*, which is about 1 cm across and forms the basic respiratory unit of the lung. The summed cross-sectional area for each generation of airways increases logarithmically and, at the periphery, resistance to air flow is negligible. Because of this, gas flow velocity falls rapidly in the respiratory bronchioles and gas mixing in the last few airways is largely by diffusion. Diffusion across tissue is less efficient than in the gas phase, but at the surface of the alveolar walls gas transfer is maximized as the inspired gas is spread over an area of about 70 m^2.

Bronchial Smooth Muscle Smooth muscle, present only in the dorsal intercartilaginous gap of the trachea and extrapulmonary bronchi, completely encircles the intrapulmonary bronchi internal to their supportive cartilage. It is geodesic, comprising two sets of fibers, which wind along the bronchial tree as opposing spirals. The arrangement is such that as the muscle contracts, the airway both shortens and constricts. There are variations in muscle-to-muscle contacts: muscle fibers are separated from each other in guinea pig and dog airways while frequent connections of the nexus (gap junction) type are seen in humans. The latter type of junction implies electrical coupling and is similar to that often found in the gastrointestinal tract. With regard to the motor innervation of muscle, reviewed by Richardson and Ferguson (1979), electron microscopic studies fail to show synaptic contact of nerve with muscle. While some nerve varicosities lie outside the muscle, others may share a common investment of basement membrane with muscle and yet show no further synaptic specialization.

Innervation The distribution of the gross nerve supply to the tracheobronchial tree is similar in many species and has been largely determined by silver staining methods. In the trachea and main bronchus, nerve bundles and ganglia are found mainly in the posterior membranous portion of the airway. On entering the lung, the nerve bundles divide to form distinct peribronchial and perivascular plexuses (species differences exist in the extent and immediacy of this division). The peribronchial plexus then further divides to form extra- and endochrondrial (subepithelial) plexuses; this division depends on the quantity and extension of supporting cartilage in succeeding generations of intrapulmonary airways (e.g., little in rats, more in humans). In general, the more distal single bronchiolar plexus has fewer fibers and ganglia than plexuses of airway generations of a higher order; nerve bundles are, however, found in the bronchiolar region and early light microscopic reports of alveolar innervation, which have now been confirmed by electron microscopy in both animals and humans, show the depth to which nerve fibers penetrate the lung (Meyrick 1971; Fox 1980). The airways and alveolar wall may also receive both motor (efferent) and sensory (afferent) fibers (see below).

The efferent innervation has, in general, excitatory and inhibitory components affecting bronchial smooth muscle, blood vessels, and submucosal glands. Morphologic and physiologic studies now indicate that motor fibers also pierce the surface epithelium of certain species (Jeffery 1982). The neural control of bronchial epithelium, glands, and muscle appears to be more complex than originally proposed, and the discovery of new neurotransmitters (purines and peptides) will no doubt prove to be of biological significance (Uddman, 1978; Wharton 1978; Said 1980).

The afferent endings present in both surface epithelium and the underlying submucosa are of broadly three types based on their position, pattern of firing, adaptation to maintained stimulus, and axonal myelination (Widdicombe 1974; Jeffery 1982*a*): type I receptors are rapidly adapting

and comprise cough and "irritant" receptors; type 2 are the slowly adapting pulmonary stretch receptors thought to give rise to the Hering-Breuer reflex; and type 3 are pulmonary juxtacapillary receptors present deep in the lung (Richardson 1981).

Arteries and Veins In humans the trachea receives systemic blood through branches of the inferior thyroid arteries, which anastomose with bronchial arteries. The walls of the bronchi are supplied by systemic bronchial arteries derived from the descending aorta, and each airway is also accompanied by a branch of the pulmonary artery. The pulmonary arteries divide with the airways and also send off supernumerary branches that do not accompany airways. There is considerable reserve in the pulmonary vascular bed and many vessels may be lost in disease or surgically without significantly affecting pulmonary vascular resistance. Most small pulmonary arteries enter an acinus with the bronchiole and are thus found at the center of the acinus. The pulmonary capillaries form a meshwork situated in the alveolar walls and regroup at the periphery of the acinus to form pulmonary veins. The pulmonary veins run in the interlobular septa initially but then join the artery and bronchus proximal to their entry into the lobule. Blood drains from the trachea via the thyroid venous plexus and middle and inferior thyroid veins, and from the bronchi via the hilar bronchial veins or pulmonary veins deep in the lung. However, marked species variations exist in this overall anatomic arrangement.

Lymphatics Pulmonary lymphatics have been studied in detail by Lauweryns (1971). They are wide in relation to their wall thickness and are attached to adjacent connective tissue fibers by special anchoring filaments, which hold the lymphatics open when interstitial fluid accumulates, interstitial pressure rises, and compression might be expected. There is considerable reserve in the clearance capability of the pulmonary lymphatics, which may increase their load tenfold when pulmonary edema threatens (Staub 1970). Pulmonary lymphatics are valved structures and, in addition to the above features, have capillaries that differ from those of blood in the poorly developed junctions of their endothelium; adjacent endothelial cells often merely overlap and the endothelial basal lamina is discontinuous. Although they are not found at the alveolar level, their commencement in the regions of bronchioles means that no part of the lung is removed from a lymphatic vessel by much more than 2 mm. The pulmonary lymphatics drain outward to the visceral pleura and inward to the hilum. Lymph from both the pleural and pulmonary lymphatics passes through hilar, tracheal, and mediastinal lymph nodes to join the systemic circulation via the thoracic duct and great veins of the neck.

CELLULAR CONSTITUENTS OF THE CONDUCTIVE AIRWAYS

The conductive airways perform many functions beyond mere conduction of inspired and expired gases: these include warming and humidification of inhaled air and cleansing it of potentially harmful dust particles, gases, bacteria and other living organisms. The more distal respiratory zone is therefore kept free of pollution and infection by airway defense mechanisms that include: (1) nervous reflexes leading to bronchoconstriction and/or cough; (2) ciliary activity; (3) secretion of mucus, lysozyme, lactoferrin, and secretory IgA; (4) cellular immune response and reactions. Figure 1-1 shows that the airway wall comprises epithelial, connective tissue, and muscular and nervous elements arranged as: (1) a lining mucosa of surface epithelium and supporting elastic lamina propria; (2) a submucosa in which lie the glands, muscle, and cartilage plates; and (3) a thin adventitial coat. The surface epithelium, submucosal glands, and lymphoid tissue that contribute to these many functions are considered below.

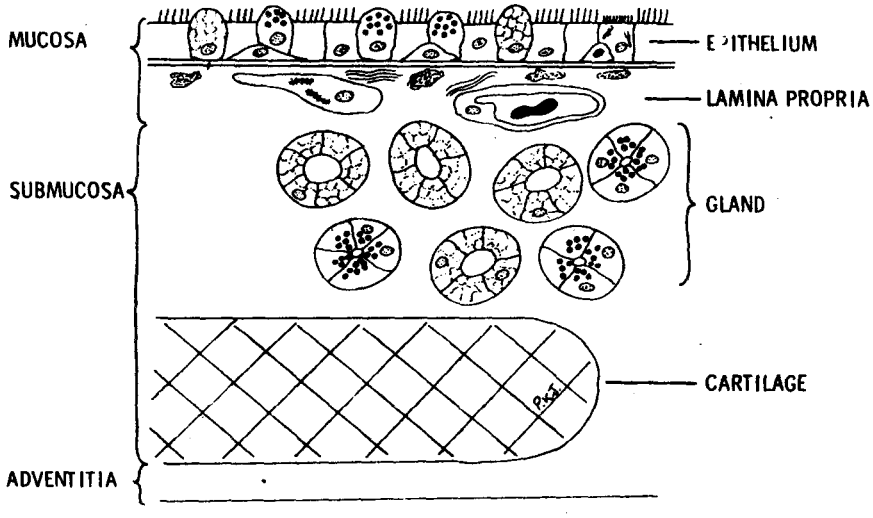

Figure 1-1 Diagrammatic representation of the airway wall.

Surface Epithelium

With the exception of the anterior nares, which are lined by stratified keratinizing squamous epithelium, much of the epithelium of the upper respiratory tract is formed of ciliated, pseudostratified, columnar cells, interspersed with occasional mucus-secreting cells. Patches of nonkeratinizing squamous epithelium are found in the pharynx, while in the larynx such epithelium is found over the anterior surface of the epiglottis, the upper half of its posterior surface, the upper part of the aryepiglottic folds, and the vocal cords. The stratified squamous epithelium covering the vocal cords gives way to one that is ciliated, pseudostratified, and columnar when the trachea is reached (the term *pseudostratified* implying that all cells rest on the basement membrane but not all reach the airway lumen) (Fig. 1-2). In humans this type of epithelium persists throughout the major bronchi, thereafter becoming simple cuboidal. In other species this transition to simple cuboidal occurs more proximally. In the specific pathogen–free rat, for example, it is found at the hilum of the lung (Jeffery 1975). In humans, mucus-secreting cells are regularly found in the tracheobronchial tree but are sparse in bronchioli less than 1 mm in diameter. Again there are species differences: mucus-secreting cells are numerous in the trachea and bronchi of the guinea pig and cat but few are found in these regions in the rat, mouse, hamster, or rabbit while in the cat mucus-secreting cells are additionally found as far distally as the bronchioles (Jeffery 1977*a*).

The various epithelial cells are held together by three types of junction: (1) tight (zonula occludens) and intermediate (zonula adhaerens) junctions, which together form attachment belts or terminal bars, which extend around the lateral surface of cells adjacent to the airway lumen; (2) maculae adhaerens or desmosomes, which are "spot" junctions widely distributed between cells and appear as hemidesmosomes joining basement membrane to epithelial cells; and (3) nexuses or gap junctions, which play a role in cell to cell communication. Normally impermeable, the terminal bar prevents excessive fluid movement across the epithelium but, following irritation by tobacco smoke or ether it appears to become permeable to markers of MW 40,000 placed in

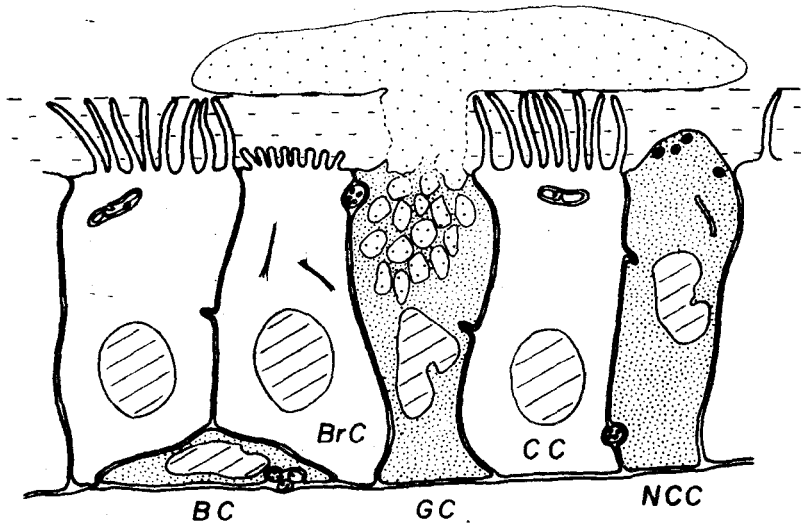

Figure 1-2 Diagrammatic representation of airway surface epithelium to show basal (BC), mucous or goblet (GC), ciliated (CC), nonciliated (NCC), and brush (BrC) cells. Cilia are thought to beat in a low-viscosity or *periciliary* layer, with the secreted mucus only being moved by their tips.

the lumen (Richardson 1976; Boucher 1980). Transport from lumen to submucosa of potentially antigenic molecules in excess of MW 40,000 appears to be by a different route involving epithelial cell transport (Richardson 1976). The localization, synthesis, and transport of secretory IgA has been summarized by Hauptman and Tomasi (1978). The transepithelial passage of IgA is selective and depends upon the epithelial production and coupling of secretory piece to dimeric IgA produced locally by subepithelial plasma cells.

A variety of cell types is recognized in surface epithelium (Jeffery 1975, 1977*b*; Breeze 1977). Eight different epithelial cell types have now been delineated (Table 1-1), while, in addition, cells involved in the immune response and its reactions may migrate through the epithelial basement membrane; some of these remain within the epithelium whereas others are in passage to the airway lumen (McDermott 1982). The terminal processes of nerve fibers whose cell bodies lie deep to the epithelium also pierce the epithelial basement membrane and are thought to initiate airway reflexes such as bronchoconstriction and/or cough (Richardson 1981). Many but not all of the eight surface epithelial cell types are represented in humans, their distribution varying with species (Table 1-2). Ciliated, mucous, Clara, and basal cells are consistently identified in all the mammals shown in Table 1-2, but there are doubts about the occurrence of brush cells and the migratory globule leucocytes in human airways. Some of these cell types will now be considered in more detail.

Ciliated Cells Ciliated cells (Fig. 1-3) have 200 to 300 cilia per cell, each of which beats at about 1000 times per minute with its effective stroke generally in the rostral direction (Sleigh 1977). The cilia are thought to beat in a periciliary layer of low viscosity, the origin of which is as yet unknown. They move the overlying mucus only by their tips, the interaction of the ciliary

Table 1-1 Mature Airway Epithelium: Cell Types

Epithelial Cells
I. Basal*
II. Luminal*
A. Ciliated
B. Nonciliated
1. Secretory
a. Mucous†
b. Serous†
c. Clara
d. DCG (often basal but sometimes luminal)†
2. Unknown function
a. Special type
b. Brush
C. Indeterminate (covers a mixture of cell types that cannot be clearly classified)
Migratory Cells
I. Lymphocyte†
II. Globule leukocyte/mast cell†
Neural Cells
I. Neuroepithelial bodies
II. Nerve terminals†

*All cells may rest on the basal lamina but only luminal cells reach the surface.

†Some of these cells occur in both surface epithelium and submucosal glands. The appropriate prefix should be applied.

tips and mucus being facilitated by minute terminal hooklets (Jeffery 1975).

Mucous Cells Mucous cells (Fig. 1-4) contain electron-lucent, confluent granules of about 775-nm diameter. The granules are thought to contain an acidic mucin, its acidity due to sialic acid or sulfate groups at terminal positions on the oligosaccharide side chains of the glycoprotein core. The production of the correct amount and viscoelasticity of mucus is important in the maintenance of mucociliary clearance and the degree and type of acidity of the mucus may determine its viscoelastic profile and hence the ease with which it may be shifted by cilia and/or cough. The numbers of mucus-secreting cells increase in disease (e.g., chronic bronchitis) and experimentally following inhalation of sulfur dioxide (Lamb 1968) or tobacco smoke (Jones 1972; Jeffery 1981). In human trachea the normal mean density is estimated at 6800 mucous cells per square millimeter surface epithelium (Ellefsen 1972).

Serous Cells Serous cells have discrete electron-dense granules of about 600 nm diameter. These cells resemble the serous cells of submucosal glands morphologically and have so far been described only in the airway surface epithelium of the specific pathogen–free rat (Jeffery 1975), young hamster (McDowell, personnal communication), "clean" adult cat, and fetal human (Jeffery 1977*a*.). While many have been shown to contain neutral mucin, there is now evidence that some also contain a nonmucoid substance of composition yet to be determined (Spicer 1980).

Clara (Nonciliated Bronchiolar) Cells Clara cells have electron-dense granules of about 580 nm diameter, which are irregular in outline in many species but rounded in humans. The function of this cell has long been in dispute and it has been suggested it may produce bronchiolar surfactant (Niden 1967) or a hypophase component of surfactant (Gil 1971). Furthermore, it has stem cell multipotentiality, as following irritation or drug administration both ciliated and mucous cells may develop from the Clara cell (Jeffery 1973; Evans 1978).

Dense-Core Granulated (DCG) Cells DCG cells are rare cells which are generally basal in position but may have a thin cytoplasmic projection reaching the lumen (Bensch 1968). Clusters of such cells with axonal association (i.e., neuroepithelial bodies) have also been described (Lauweryns 1973). DCG cells have small (120-nm) spherical granules, with an electron-dense core surrounded by an electron-lucent halo. They have been shown to contain biogenic amines (Lauweryns 1982) and peptides such as bombesin (Wharton 1978), which may exert a regulatory role on smooth muscle of both blood vessels and bronchi, mucus secretion, and/or ciliary activity.