Chapter Five

Morphology of the Respiratory Tract

Robert F. Phalen, Hsu-Chi Yeh and Shankar B. Prasad

INTRODUCTION

The respiratory tract is faced with a problem; it must bring large quantities of air into intimate contact with the blood and at the same time defend itself against the countless irritants, oxidants, allergens, carcinogens, pathogens, and other potentially harmful contaminants found in the atmosphere. That the average person inhales about 400 million liters of air in a lifetime while maintaining a healthy lung is a tribute to the architecture of the respiratory tract. (The volumetric rate of intake of air is about 5000 times greater than that of water or food).

The structure of the respiratory tract is being continually elucidated. Research is often specialized and directed at specific levels of organization such as the molecular, cellular, or tissue levels, or at specific regions, the nasal turbinates, the tracheobronchial tree, or the alveoli for instance. In some cases the specialized efforts have been integrated—the mucociliary system is an example—but in other cases the integration of existing morphologic information is far from complete. The current state of understanding of the structure of the mammalian lung has been summarized in several reviews. The 1990 international workshop on Respiratory Tract Dosimetry proceed-

ings (Guilmette & Boecker, 1991) covers anatomy along with particle deposition and clearance. The 1983 American Review of Respiratory Disease supplement entitled "Comparative Biology of the Lung" contains over 20 papers on comparative mammalian lung anatomy and physiology. The series entitled "Lung Biology in Health and Disease" of about 20 volumes edited by Claude Lenfant and published by Marcel Dekker is another source of summary information on the respiratory system. The Handbook of Physiology, Section 3, The Respiratory System (Fishman and Fisher, 1985) also covers many aspects of our knowledge of respiratory-tract structure and function as does Inhalation Toxicology: The Design and Interpretation of Inhalation Studies and Their Use in Risk Assessment (Dungworth et al., 1988).

What follows here is an introduction to the gross and subgross structure of the respiratory system as it relates to inhalation toxicology. The emphasis is on the healthy adult human, with some mention of the events occurring during growth and development, and some information on comparative mammalian airway structure. Much of the information is updated from an earlier chapter by the authors (Phalen and Prasad, 1989).

RESPIRATORY-TRACT REGIONS

The main anatomical structures of the respiratory tract include the

1 nose, consisting of the nares, vestibule, and nasal cavity proper (with the conchae or turbinates);
2 nasopharynx;
3 lips and oral cavity;
4 oropharynx;
5 laryngopharynx;
6 larynx;
7 trachea;
8 bronchi;
9 bronchioles;
10 respiratory bronchioles;
11 alveolar ducts;
12 alveolar sacs; and
13 alveoli.

These structures are commonly grouped into larger regions, or compartments, for the purpose of simplification and mathematical modeling. Several compartmentalization schemes have been proposed, but three very similar models have been particularly useful to inhalation toxicologists. The models are those of Task Groups of the International Commission on Radiological Protection (Morrow et al., 1966; Bair, 1991), the Ad Hoc Working Group to Technical Committee 146-Air Quality of the International Standards Organization (ISO, 1983), the Air Sampling Procedures Committee of the American

Conference of Governmental Industrial Hygienists (Air Sampling Procedures Committee, ACGIH, 1985) and the Task Group of the National Council of Radiation Protection (Cuddihy and Yeh, 1988). These compartmental systems which are largely based on the pioneering morphometric work of Ewald Weibel (1963) are shown in Table 1.

Region 1—containing the airways of the head and neck—begins at the anterior nares and includes the respiratory airway down through the larynx. Particle deposition in this region includes those larger particles whose inertial properties cause impaction in the oral or nasal passages and particles smaller than about 0.5 μm in diameter that diffuse to airway walls. Two pathways, each having a half-time of 4 minutes, were used by the previous ICRP Task Group (Morrow et al., 1966) to describe the clearance of particles which deposit in the nasal airways. The first describes uptake of relatively soluble material into the blood; the second represents physical clearance by mucociliary transport to the throat for subsequent swallowing. Experimental data indicate that the anterior one-third of the nose, where 80% of 7-μm-diameter particles deposit, does not clear except by blowing, wiping, or other extrinsic means, and effective removal of insoluble particles may be slower (Morrow, 1977; Cuddihy and Yeh, 1988).

Region 2—the tracheobronchial region—begins below the larynx and includes the trachea and ciliated bronchial airways down to and including the terminal bronchioles. A relatively small fraction of all sizes of particles that pass through the airways of the head and neck will deposit in the tracheobronchial region. The mechanisms of inertial impaction at airway bifur-

Table 1 Compartmental Models of the Human Respiratory System as Developed by the ICRP Task Group on Lung Dynamics, the International Standards Organization, and the American Conference of Governmental Industrial Hygienists.

Region	Anatomic structures included	Task group region	ISO region	ACGIH region
1	Nose, mouth nasopharynx, oropharynx, laryngopharynx, larynx	Nasopharynx (NP)	Extrathoracic (E)	Head airways region (HAR)
2	Trachea, bronchi, bronchioles (to terminal bronchioles)	Tracheo-bronchial (TB)	Tracheo-bronchial (B)	Tracheo-bronchial region (TBR)
3	Respiratory bronchioles alveolar ducts, alveolar sacs, alveoli	Pulmonary (P)	Alveolar (A)	Gas exchange region (GER)

cations, sedimentation, and Brownian diffusion all cause deposition. Interception can be an important deposition mechanism for fibers. During mouth breathing, the benefits of the collection of larger particles in the nose are largely lost, and the larger particles generally tend to deposit in the tracheobronchial region with higher efficiency. An important characteristic of this region is that it is both ciliated and equipped with mucus-secreting elements, so that in the healthy individual the clearance of most of the deposited particles occurs within 24 hours by mucociliary action to the throat for swallowing. Relatively soluble material may quickly enter the bloodstream.

The rate of mucus movement is slowest in the smaller airways and increases toward the trachea. Particles depositing in the tracheobronchial tree are distributed somewhat differently depending on their size, with smaller particles tending to deposit more distally. Thus, one expects larger particles to clear more quickly. Clearance of material in this region cannot usually be described by a single exponential rate constant (Cuddihy and Yeh, 1988).

Region 3—the gas exchange region—includes the functional gas exchange sites of the lung. It includes respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli. For particles to reach and deposit in this region, they must penetrate the two more proximal regions on inspiration and by either settling, diffusion, or interception come into contact with deep lung surfaces. Since there is gas exchange between tidal residual air, a portion of each breath remains unexhaled, and the times available for deposition may be long for some particles. Clearance from this region is not completely understood, but several mechanisms are believed to exist, including

1 the dissolution of relatively soluble material with absorption into the systemic circulation,
2 direct passage of particles into the blood,
3 phagocytosis of particles by macrophages with subsequent translocation, and
4 transfer of particles to lymphatic channels, vessels, and nodes.

The three-region model does have some rather important drawbacks. For example, the detailed pattern with which particles deposit within a given region is usually not addressed. The assumption that deposition within a given region is uniform may eventually lead to improper estimation of risk. For example, bifurcations in the tracheobronchial region can be sites of high regional deposition. Also, there is not adequate separation of the region between the terminal bronchioles and the alveolar ducts and sacs. This junctional region contains respiratory bronchioles that are unique in structure in that they have both air conducting properties and gas exchange properties. Here, deposition of inhaled particles appears to be greater than in more distal regions, presumably because of lack of penetration of air beyond the respiratory bronchioles. Clearance from the respiratory bronchioles is not well un-

derstood. Since this portion of the gas exchange region is often the site of airway disease in humans, it should not be overlooked by the toxicologist.

GROSS ANATOMY

Nose, Nasopharynx, and Larynx

The mammalian nose and its immediately postnasal cavities comprise an elaborate organ system that provides for olfaction, detection of airborne irritants, collection of noxious gases and particles, humidification and temperature adjustment of inspired air, and drainage of fluids from the eyes, sinuses, and inner ears. The importance of these functions to maintaining good health also makes the nasopharyngeal region an important target for airborne agents. Despite this fact, the nasal region is often an overlooked region in toxicology. It must frequently deal with air pollutants in their raw unfiltered state at ambient concentrations, and failure of any of its critical functions can lead to serious, even life-threatening conditions.

In humans, the nose contains two channel-shaped nasal cavities that are separated by a cartilaginous and bony septum. The average adult male's nose has an air volume of about 17 cm^3. Each nasal cavity is entered through a naris (nostril) having a cross-sectional area of about 0.7 cm^2 (Landahl, 1950). The nasal cavity is supported by bone, cartilage, and connective tissue that provide sufficient rigidity to prevent total collapse during breathing. The anterior (nearest to the nares) one-third of the nasal cavity is covered with skin much like that on the face that does not have a continuous coating mucus. The posterior two-thirds of the cavity is covered with mucus that moves rearward driven by cilia at an average velocity of about 1.0 cm/min. to a point where it is swallowed. This mucus, produced by goblet cells and glands, is mixed with fluids, including tears, that drain into the nasal cavity from the eyes and sinus cavities of the facial bones. The anterior portion of the nasal cavity is partially covered with hair that traps large inhaled bodies and signals their presence via nerves at the base of the hair follicles.

Posteriorly, the nasal cavity narrows and turns sharply downward. This area—the nasopharynx—is a region of impaction of large particles that eluded previous capture. The nasopharynx, roughly tubular in shape, is joined by the oral pharynx (rear portion of the mouth) a few centimeters down its length. The pharynx then divides at the epiglottis to turn and enter either the larynx and trachea or continues downward to the esophagus. The pharynx is coated with mucus.

The mouth, entered through the variable-size opening between the lips, is divided into two regions—anterior vestibule or labial cavity (including the inner lips, cheeks, and teeth), and a posterior or buccal cavity which joins the oropharynx. The oral cavity is normally about 70–75 mm in length (anteroposterior dimension), 40–45 mm in horizontal dimension, and 20–25 mm in vertical dimension. The tongue has a volume of approximately 60–70 cm^3

(Task Group on Reference Man, 1975). The shape and cross-sectional area of the lip opening are highly variable.

The epiglottis is a muscular flap that moves to cover the entrance to the larynx and trachea during swallowing. Other muscular action also prevents swallowed material from entering the trachea because persons whose epiglottis has been surgically removed can still swallow without choking.

The larynx (or voice box) is a short cavity that has a slit like, variable-size narrowing in its central portion. The narrowing is caused by two pairs of folds in the walls of the larynx. The uppermost folds are called the false vocal cords, and the lower folds the vocal cords. The adult larynx is about 3.5–5 cm long and has a variable cross section that depends on the air flow rate passing through it (Stanescu et al., 1972). The larynx represents a major resistive element to air flow and also forms an inspiratory air jet that leads to particle impaction on the wall of the trachea (Schlesinger and Lippmann, 1976). The larynx is encased by muscle, bone, and cartilage and is lined by a mucus-covered membrane very similar to that found in the rear portion of the nasal cavities and pharynx. In the larynx, mucus is propelled upward for swallowing.

Tracheobronchial Tree

The distal larynx smoothly transitions into the trachea, a flexible tube that, in humans has about 20 roughly U-shaped cartilages set in its wall that prevent its collapse. The gap between the ends of the cartilaginous rings is covered with a flexible muscular sheet of tissue. Thus, in cross section the trachea tends to have a D or O shape, depending on the internal air pressure. During breathing, the trachea elongates on inspiration. The inner walls of the trachea are covered with mucus supplied by goblet cells and mucous glands.

In humans, the trachea divides into two main branches called major bronchi. The bronchi enter the right and left lungs and continue to divide for several generations (averaging about 16 in humans) before alveoli (air sacs) begin to appear in the bronchiolar walls as openings into the lumen. This appearance of alveoli marks the end of the tracheobronchial tree and the beginning of the gas exchange or alveolarized region.

Bronchi and bronchioles (Fig. 1) are roughly circular in cross section, and smooth muscle encircles bronchial airways. The U-shaped cartilages of the trachea are replaced in the bronchial walls by irregularly shaped cartilage plates situated outside the smooth muscle. Further down the tracheobronchial tree, where the tube diameters are about 1.0 mm or less, the cartilage disappears. These tubes are called bronchioles. Bronchioles have mucus-secreting goblet cells but do not have mucous glands in their walls. The outermost layer of the bronchi consists of a mixture of connective tissue and elastic fibers.

The inner lining of the bronchi is pseudostratified columnar epithelium

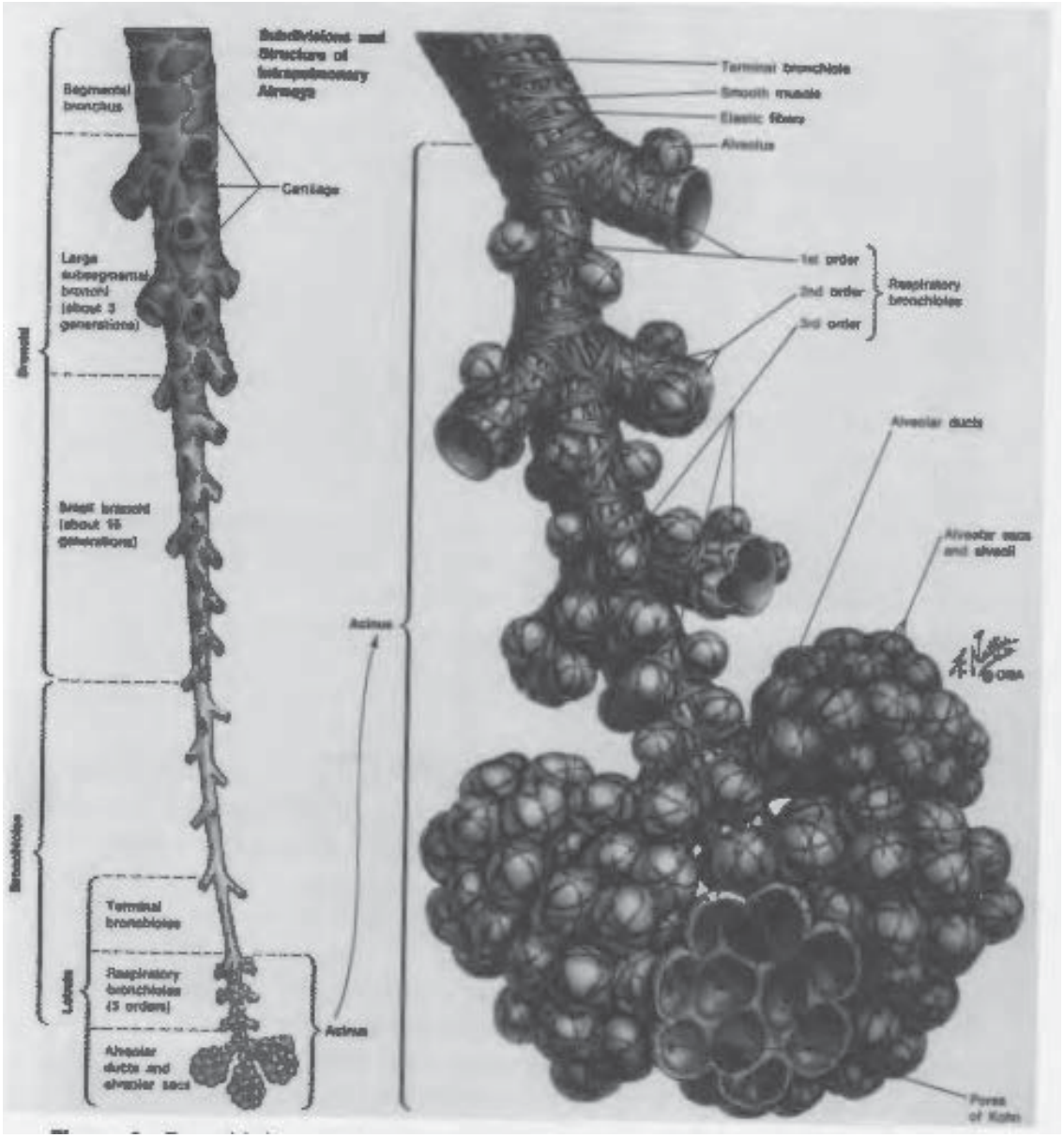

Figure 1 Bronchi, bronchioles, alveolar ducts, alveolar sacs, and alveoli. (Copyright 1979, 1980, CIBA pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reprinted with permission from the CIBA Collection of Medical Illustration illustrated by Frank H. Netter, MD. All rights reserved.)

having ciliated cells, mucus-secreting goblet cells, and underlying mucus-secreting glands. Thus, the tracheobronchial tree possesses an active clearance mechanism because of the propulsion of mucus toward the pharynx. The bronchioles are lined with ciliated columnar epithelium that is not pseudostratified.

The symmetrical tracheobronchial tree model for the human, described by Weibel (1963), is widely used and contains information on airway lengths, diameters, and numbers. Similar, but asymmetric, human models have been

published by Weibel (1963), Horsfield and Cumming (1968), and Yeh and Schum (1980). The fractal (self-similar) nature of the tracheobronchial tree has been recently described (West, 1990). Before B. Mandelbrot introduced the term fractal, K. Horsfield and others explored similar properties of branching systems, including the bronchial airways (Horsfield, 1976).

Respiratory Bronchioles

In humans the terminal bronchioles of the tracheobronchial tree, i.e., those with diameters of about 0.6 mm, branch to form the first-order respiratory bronchioles. These bronchioles continue to divide and branch to give a total of about two to five orders of tubes.

Respiratory bronchioles, as they branch, exhibit an increasing number of alveoli opening into their lumina. These alveoli are thin-walled, are surrounded by blood capillaries, and presumably participate in the gas exchange function of the lung. Because of this gas exchange function, these bronchioles are called respiratory. Within alveoli, ciliated cells are not found, and clearance of deposited debris is presumably by those mechanisms associated with deeper-sited alveoli.

Two major points must be made with respect to the respiratory bronchioles. First, they have been acknowledged as an important site for disease in humans. And second, these structures form part of the "silent zone" of the lung; a region in which respiratory disease is very difficult to detect by conventional pulmonary function testing.

Comparative Tracheobronchial Tree Structure

Substantial variation is recognized in tracheobronchial structure among different species of mammals. The major variations include tracheal length, symmetry of branchings, length-to-diameter ratios for airway tubes, presence or absence of a lobe branching from the mid-region of the trachea, shapes of the air flow dividers at branches, the number of generations in the bronchial tree, and the presence or absence of respiratory bronchioles.

When examining replica casts of the airways, two basic types of structure are seen in mammals (Fig. 2). Most mammals have a very asymmetric tracheobronchial branching structure characterized by long tapering airways, each having numerous small branches (typically making a 60° angle with the major airway). The other type of branching called regular dichotomous or symmetric is characterized by two daughter tubes at each branch that are nearly equal in diameter and branching angle. In reality, perfectly symmetrical bronchial trees have not been seen, but the human's structure is remarkably close. Highly asymmetric branching is seen in most other species including the dog, rabbit, guinea pig, rat, mouse, and others. In general, branching becomes more symmetric as one progresses deeper down the bronchial tree.

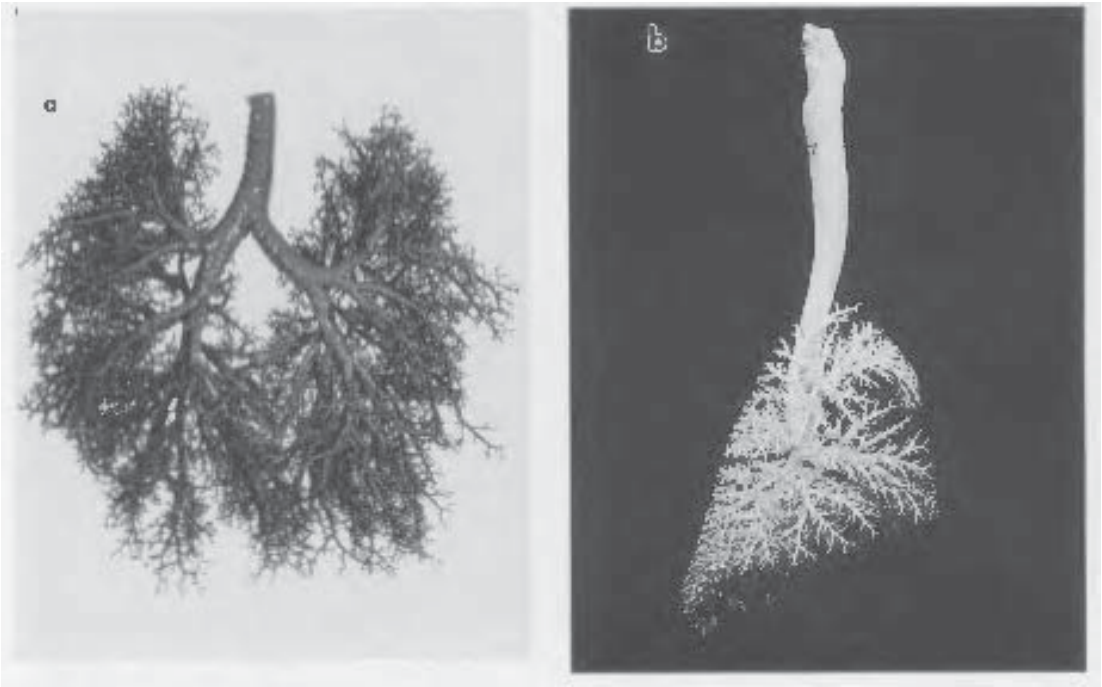

Figure 2 Replica silicone rubber casts of the tracheobronchial airways of the (a) human, and (b) dog. These casts demonstrate the more regular dichotomous and a more monopodial (asymmetric) branching system, respectively. Photographs supplied by the Inhalation Toxicology Research Institute.

Another striking variation is seen in the number of divisions of respiratory bronchioles. Animals that have an average of about 4 or more divisions include humans, monkeys, dogs, goats, and ferrets. The rabbits, guinea pigs, and golden hamster have about 1–2 orders of respiratory bronchioles. Respiratory bronchioles are essentially absent in laboratory rats, and probably in mice.

Parenchyma

Parenchyma is a term that relates to the primary functional tissue of an organ as distinguished from its supporting framework or secondary tissues. When applied to the lung, the parenchyma relates to the alveoli and does not include the trachea and bronchial tree which are often viewed as merely conductive airways for the purpose of delivering air to and from the gas exchange region. Major structural elements of the parenchyma of the lung include alveolar ducts, alveolar sacs, alveoli, alveolar capillaries, and the pulmonary lymphatics.

The alveolar duct is a tubular structure whose walls are completely covered with alveoli. It usually branches to either two other alveolar ducts or two blind-ended tubes called alveolar sacs. With respect to the total number of ducts and sacs, Weibel's (1963) figures of 7×10^6 ducts and 8.4×10^6 sacs are probably reliable. The dimensions of the pulmonary acinus, which con-

sists of a terminal bronchiole and the structures supplied by it, have been described by Schreider and Raabe (1981).

Although often depicted as spherical, the alveoli more closely resemble incomplete polyhedra. The open face of the alveolus is exposed to the air in either a respiratory bronchiole—an alveolar duct, or an alveolar sac—the closed portions being surrounded by a network of fine blood capillaries. Thus, in the alveolus the atmosphere and the blood are brought into intimate contact where equilibration of CO_2 and O_2 can take place. In addition to the surrounding capillary net, alveoli are partially surrounded by elastic and nonelastic fibers that provide mechanical support. Alveoli, capillaries, and fibers are embedded in an interstitium or connective tissue. The average diameter of the adult's approximately 300 million alveoli is about 200–300 μm (Task Group on Reference Man, 1975).

CELLS AND TISSUES OF THE RESPIRATORY TRACT

Ciliated Mucosa

The tissue that lines the rear of the nose, larynx, trachea, bronchi, and bronchioles is ciliated mucosa (Fig. 3). As the name implies, such tissue is characterized by the presence of cells with numerous tiny hairlike projections (cilia) and by the presence of individual cells and glands that secrete the components that make up mucus (a sticky viscoelastic fluid). The cilia beat in a coordinated fashion (resulting in movement of the overlying mucus) toward the glottis where it is swallowed.

The ciliated cells of the human respiratory system have cell nuclei and are columnar in shape—about 10–15 μm in diameter and 20–40 μm in height. The ciliated cells are attached at their bases to a basement membrane, and new replacement cells appear to form beneath the mature cells and move upward to replace cells that are lost. At the top surface, protruding into the lumen of the airway, there are 15 to perhaps 100 or more filamentous cilia that are 5–15 μm long and about 0.2 μm in diameter. The cilia bend and then lash forward at rates up to several hundred cycles per minute. It is the coordinated beating of cilia on adjacent cells that propels the mucus.

Interspersed among the ciliated cells are columnar goblet cells similar in size to the ciliated cells but lacking cilia and having a narrow base (and thus a drinking-goblet shape). These cells, also attached to the basement membrane, manufacture mucus and, when filled, open at the top and discharge their contents onto the airway surface. Beneath the basement membrane there are glands consisting of clusters of mucus-secreting cells that secrete into a duct that leads to the epithelial surface. The action of the ciliated mucus-secreting tissues is responsible for sweeping surfaces of the airways free of particulate contamination. This function depends on the quality and quantity of mucus and the quantity and synchronization of cilia. Viral and

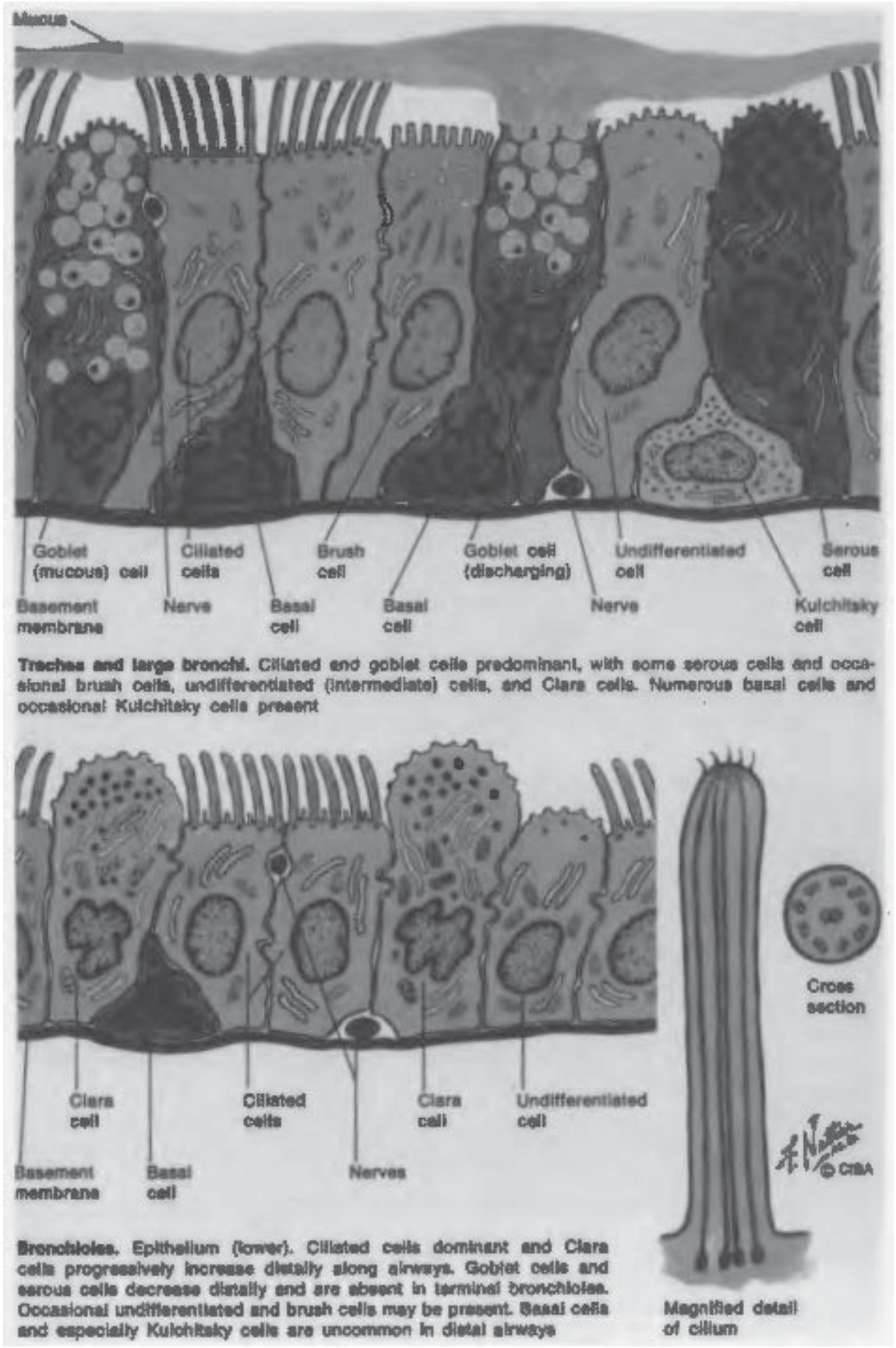

Figure 3 Cells of bronchial walls. (Copyright 1979, 1980, CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reprinted with permission from The CIBA Collection of Medical Illustrations illustrated by Frank H. Netter, MD. All rights reserved.)

bacterial infections as well as various toxicants can lead to oversecretion or undersecretion of mucus and to loss or paralysis of cilia. During such states sneezing and coughing become the major clearance mechanisms that serve to clear the mucociliary epithelium. Often thought to be an annoying symptom, coughing can be a health-preserving mechanism for removing mucus, toxicants, and infectious organisms from the respiratory tract.

The Alveolus

As previously mentioned, the adult human's alveolus (Fig. 4): is a polyhedral structure, about 200–300 μm in diameter, having one face open to the airway. The walls of this structure are formed by very thin alveolar epithelial cells whose nuclei sometimes bulge into the alveolar airspace. In reality, there is more than one type of alveolar epithelial cell. At its thinnest portions, the type I (also called type A) alveolar epithelial cell is about 0.1 μm or slightly less in thickness (Nagaishi, 1972). These cells appear to have relatively smooth surfaces and lie on top of a basement membrane that is about 0.02–0.04 μm thick. Another basement membrane supports the blood capillary endothelial cells. These endothelial cells join to form the capillary wall and are quite similar in size and shape to the thin alveolar cell. The total thickness of the air-blood interface has been measured by Meessen (1960) and reported by Weibel (1964) and by Weibel and Gil (1977) to be between 0.36 and 2.5 μm.

A thicker, roughly cube-shaped cell, the type II (or type B) epithelial cell of the alveolus has a surface covered with small protrusions called microvilli. These microvilli greatly increase the surface area of this cell and imply, along with the presence of inclusions within the cell body, that this cell manufactures and secretes substances onto the surface of the alveolus. Biochemical and other evidence indicates that this cell is involved in the manufacture and secretion of surfactant, a surface-tension-lowering agent that reduces the tendency alveoli have for collapsing (Comroe et al., 1973; Pattle, 1965). Abnormalities in lung surfactant can be related to a variety of disease states. The type II cells, which are capable of mitotic division, may serve as precursors to the type I cell during lung growth and repair.

Other cells present in the alveolar region include the macrophage, alveolar brush cells (type III), and interstitial cells. The alveolar brush cell sits on the alveolar basement membrane and protrudes into the alveolar air space. It has large microvilli on its air-exposed side and has as yet largely unknown functions.

In some areas the basement membranes of the alveolus and capillaries are separated by a space called the interalveolar septum or interstitium. This interstitium contains both elastic and inelastic fibers and cells called fibroblasts. Fibroblasts are irregular-shaped cells that are involved in the formation of connective tissue. Rarely, nerve fibers have been seen in the intersti-

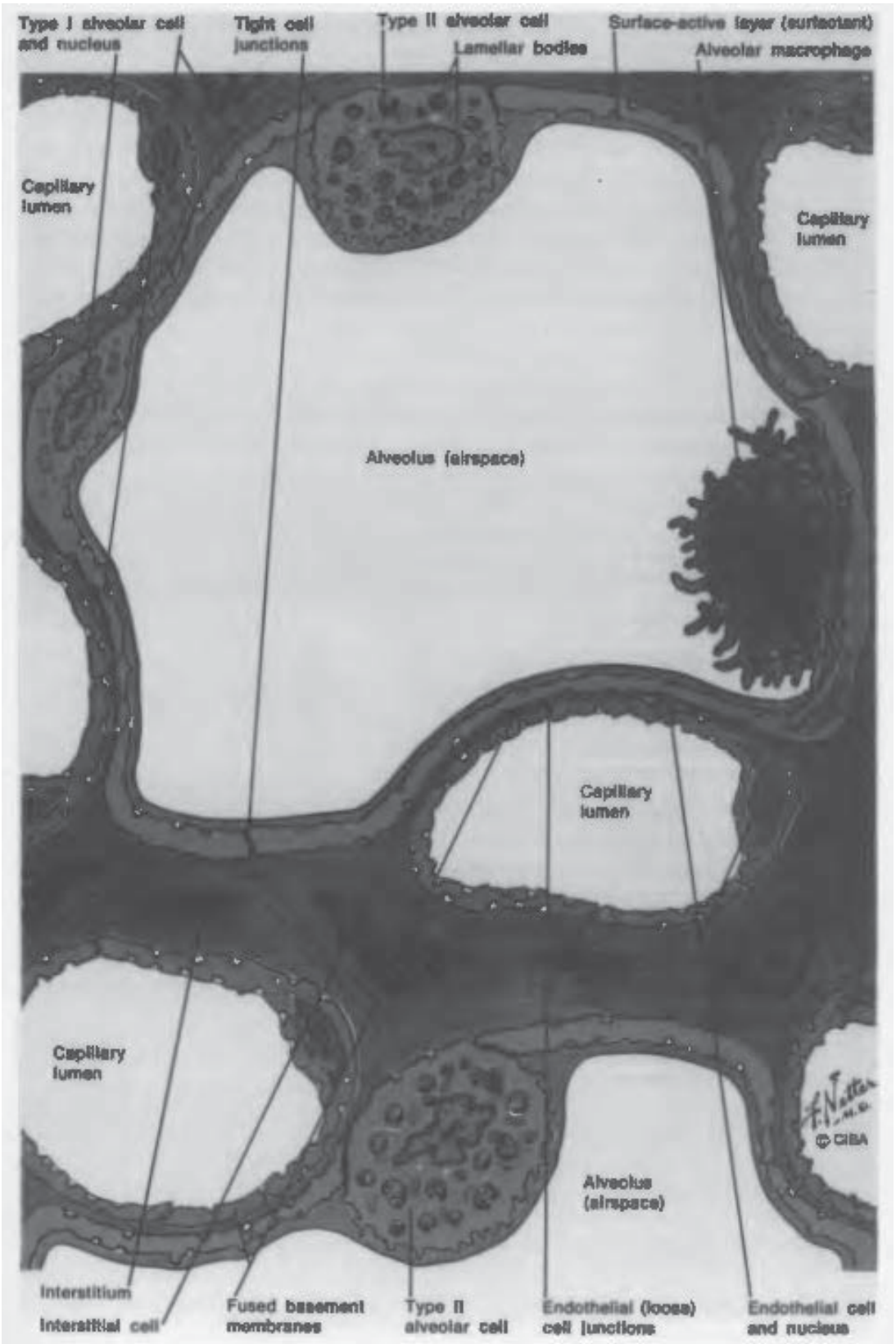

Figure 4 The pulmonary alveolus. (Copyright 1979, 1980, CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reprinted with permission from The CIBA Collection of Medical Illustrations illustrated by Frank H. Netter, MD. All rights reserved.)

tium (Nagaishi, 1972). In pathologic conditions such as edema (fluid accumulation) and infection, the interstitial space may become enlarged owing to the presence of excess fluid and cells such as blood leukocytes (white cells).

Alveolar walls are frequently observed to have pores that appear to connect the airspaces of adjacent alveoli. These pores, called pores of Kohn (Fig. 1), were discovered by Adriani in 1847 according to Miller (1947). Little information is available on their shapes, numbers, or dimensions.

The Macrophage

Alveolar macrophages are relatively large nucleated cells that possess the ability to move and to engulf foreign materials. Roughly similar to the familiar amoeba, macrophages can change shape presumably by

1 liquefaction of their cell membrane,
2 subsequent flowing of the cell contents, and
3 re-formation of their surface membrane.

Phagocytosis and pinocytosis are two terms used to describe the engulfment of substances in varying states by cells such as macrophages. Phagocytosis refers to the incorporation of solid materials; pinocytosis refers to the incorporation of liquid droplets. A third term—endocytosis—includes both phagocytosis and pinocytosis.

Macrophages are found on the surfaces of the alveoli in the deep lung, but they are not a fixed part of the alveolar epithelial wall. They are credited with maintaining the sterility of the lung by virtue of their ability to engulf and kill infectious microorganisms such as bacteria. Macrophages also engulf particles that deposit in the deep lung. It appears that these pulmonary alveolar macrophages undergo chemotaxis—movement in response to chemical stimuli. Chemotaxis may be positive (toward the stimulus) or negative (away from it).

The process of phagocytosis has been described as occurring in seven sequential steps (Stossel, 1976):

1 target recognition,
2 reception of the message to initiate phagocytosis,
3 transmission of the message to an effector,
4 attachment of the macrophage membrane to the target,
5 formation of the pseudopodia,
6 engulfment by the pseudopodia, and
7 fusion of the pseudopodia with the macrophage cell body.

Failure of any of these subprocesses could result in the inactivation of the function of the macrophage in providing for defense of the lung.

Macrophages have an amazing efficiency in engulfing particles. Within minutes of deposition of an inhaled particle, the pulmonary alveolar macrophage is seen to have begun ingestion. These cells also appear to be able to phagocytize even when packed nearly full of debris. On the other hand, certain dusts are clearly toxic to the macrophage and result in their death or debilitation. Macrophages appear to efficiently engulf a relatively narrow size range of particles (Fenn, 1921, 1923). Holma (1969) suggested a diameter of 1.5 μm for maximally efficient uptake by macrophages. He found that phagocytic uptake had an upper particle diameter limit of 8 μm, a size that usually does not penetrate to alveoli. Fibers are exceptions in that alveolar deposition occurs for particles whose lengths exceed the limits for phagocytosis. Physiologically realistic models that quantitatively describe particle clearance sequestration by macrophages are under active development and validation (Stöber et al., 1994). The macrophage also plays an important role in immunological responses (Dinarello, 1985).

Mucus-Secreting Glands

Mucus-secreting glands are present in the nose and tracheobronchial tree (Fig. 5). These glands are present in great numbers in large airways and become more sparse moving down to smaller airways, finally disappearing at the level of the bronchiole. Along with goblet cells, these glands produce the mucus that covers the ciliated portions of the respiratory tract. Since these glands lie beneath the mucous membrane, they are called submucosal glands. They have a branched tubuloacinar structure ("acinar" referring to the blind ends of the tubes that branch and form each gland). The tubes into which mucus is secreted join a collecting duct that becomes ciliated just before it enters the bronchial air space. These ciliated ducts appear as pinholes on the surfaces of bronchi, having a maximum surface concentration of about one opening per square millimeter in the trachea (Netter, 1979).

Two types of cell—mucous and serous—rest on a basement membrane and line the tubules. Serous cells are found lining the blind ends of the tubules, and mucous cells line the more proximal portions. The secretion of these cells—mucus—is primarily an acid glycoprotein, which is both viscous and elastic.

THE LYMPHATIC SYSTEM

The lymphatic system of lungs play an important supportive role in maintaining liquid homeostasis, respiratory defenses, and in the clearing of inhaled toxicants and particulate matter. The large flow of lymph from the interstitium of the lungs toward the blood also helps in removing the excess fluid from the tissue spaces.

The lymphatics of the lung are subdivided into a superficial and a deep

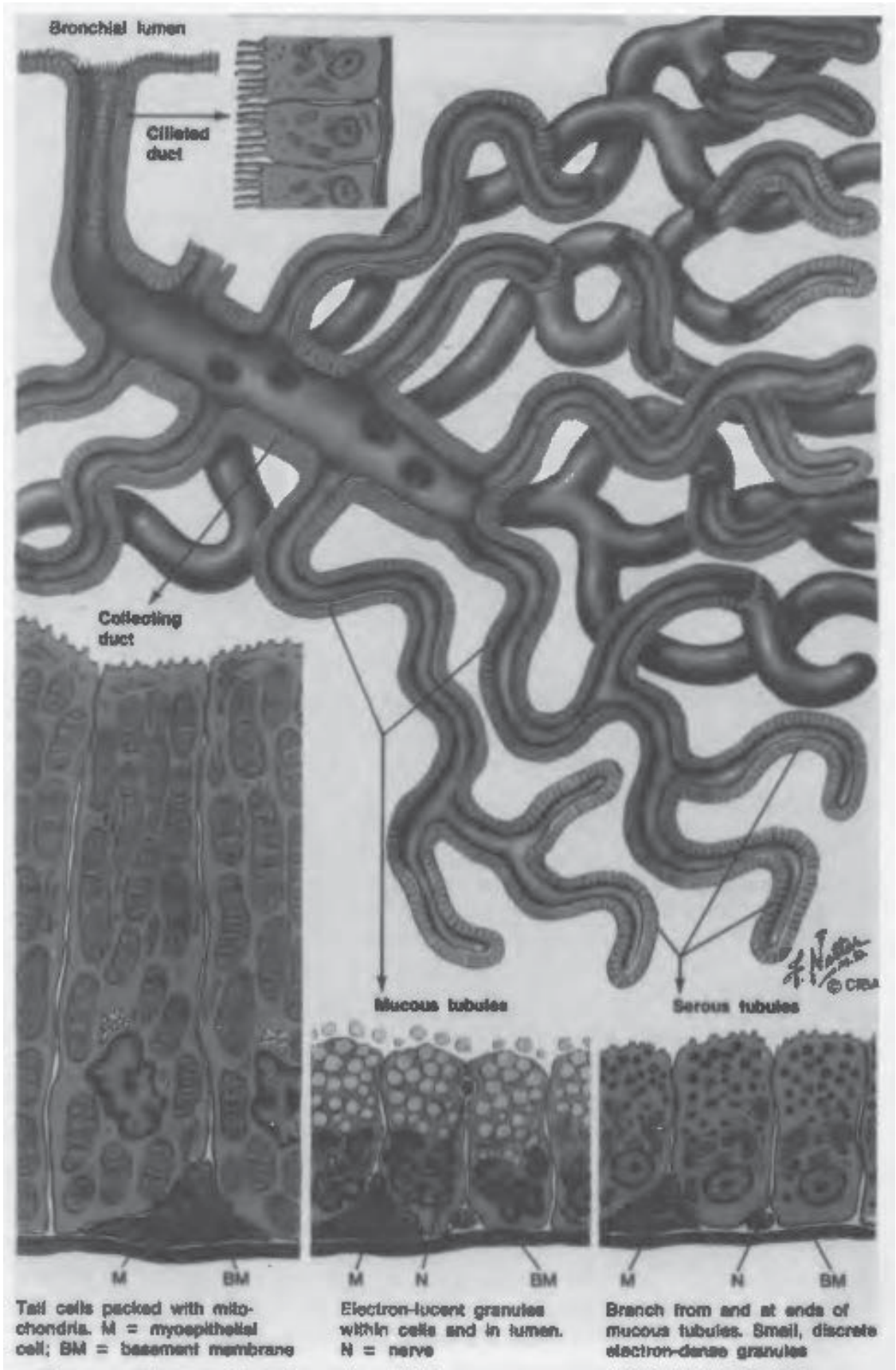

Figure 5 Submucosal glands of bronchial walls. (Copyright 1979, 1980, CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reprinted with permission from The CIBA Collection of Medical Illustrations illustrated by Frank H. Netter, MD. All rights reserved.)

plexus depending on their location. The former is located in the connective tissue of visceral pleural layer and the latter in the peribronchovascular connective tissue. These are interlinked by vessels in the interlobular septa with a potential for bidirectional flow. In addition, the lymphatics line pulmonary arteries, veins, and bronchi and converge at the pulmonary hilus into the hilar lymph nodes. There are lymphatic vessels between the alveoli and lung capillaries. The pumping motion of the lungs (and in some regions valves) facilitate lymph flow.

The major groups of lymph nodes of the lung include:

1 bronchopulmonary lymph nodes around the divisions of lobar bronchi,
2 hilar nodes around the upper and lower bronchi,
3 paratracheal nodes on either side of trachea (more prominent on right side), and
4 the azygos node adjacent to the azygos vein at the junction of right upper lobar bronchus and the right main bronchus.

From these nodes the lymph drains into the thoracic duct on the left side and into the right lymphatic duct on the right side. These in turn drain into systemic venous circulation at the junctions of subclavian and internal jugular veins.

In addition, there are lymphatic vessels along the distribution of internal mammary arteries, intercostal arteries, and the anterior and posterior mediastinum, all of which receive drainage primarily from the chest wall. The lung's lymphatic system is in communication with the lower deep cervical nodes above and with the abdominal nodes below.

Commonly, the lower lobes drain into the hilar nodes while the upper lobes drain directly into paratracheal nodes, although this drainage pattern may show wide variations. One problem associated with this extensive lymphatic system is the spread of bronchogenic carcinoma so readily out of the lung to distant sites.

INNERVATION OF THE RESPIRATORY SYSTEM

The nervous system receives, generates, conveys, stores, and processes information. Portions of the nervous system, found in nearly every tissue of the body, play an important part in the voluntary and involuntary control and coordination of muscles, organs, glands and their subunits, tissues, and cells. In the respiratory system, nerves are responsible for

1 control of muscles for breathing, adjustment of the size of bronchial airways, and control of the cough, sneeze, and gag reflexes;
2 the initiation and control of protective breathing patterns;
3 the control of secretions;

4 adjustment of the distribution of blood flow; and
5 provision of sensory information on odor, irritancy, and the composition of lung tissue fluids and blood.

As for the body in general, much of the information that is carried by the nervous systems of the respiratory tract is not noticed at the conscious level.

Especially important are nerves that trigger the cough reflex; nerves that lead from pressure, stretch, and chemical receptors; and nerves involved in bronchial muscle constriction, protective breathing patterns, and mucous gland secretion. It is clear that the innervation of the respiratory tract is extensive and, in fact, present in nearly every region from the nose down to the alveoli. The interaction of inhaled airborne toxicants with this system is relatively poorly understood.

POSTNATAL LUNG DEVELOPMENT

The mammalian respiratory system goes through a period of significant differentiation and development after birth and the transition to air breathing. The sequence of development appears to be similar in all mammals examined thus far (mice, rats, cats, rabbits, dogs, and humans), but the timing of events varies considerably (Dunnill, 1962; Boyden and Tompsett, 1965; Emery, 1969; Crocker et al., 1970; Hislop and Reid, 1974; Burri et al., 1974; Thurlbeck, 1975; Boyden, 1977). Although most investigators conclude that the full number of tubular airways are present at birth, there is a significant increase in the number of alveoli throughout the period of early maturation after birth (Kerr et al., 1975; Thurlbeck, 1977; Reid, 1977; Jeffery and Reid, 1977; Burri and Weibel, 1977; Brody and Vaccaro, 1979).

In humans the number of alveoli present at birth, estimated at about 20–70 million, increases over about the first 5–10 years of life to the adult complement of about 200–500 million (Thurlbeck, 1975; Reid, 1977); the rate of increase in number decreases with age after birth. Great variability in the number of alveoli is seen at all ages, presumably due to genetic and environmental factors superimposed on differences in counting techniques as well as the difficulty in identifying immature forms of alveoli. The sites of alveolar development, as elucidated in human and laboratory animals studies, include the distal bronchioles (Thurlbeck, 1975, 1977), where saccular protrusions in the bronchiolar wall, which is initially covered by cuboidal epithelial lining cells, are eventually replaced by thin alveolar epithelium (Boyden and Tompsett, 1961). The process of formation of alveoli appears to proceed along these airways in a direction from the distal airways toward more proximal ones.

The tracheobronchial region is perhaps the best understood portion of the respiratory tract with respect to dimensional changes during growth and development. One reason for this is that particle dosimetry models indicate that newborns, infants, and children may receive larger inhalation doses than

adults (Hofmann, 1982a,b; Phalen et al., 1985; Xu and Yu, 1986). Also, the tracheobronchial region has been relatively easy to measure quantitatively through the use of replica silicone rubber casts and dissection techniques.

SUMMARY

The anatomical characteristics of the respiratory tract are continually being elucidated via ongoing research. Although more than a dozen major anatomical structures, from the nose down to the alveoli, have been described. Inhalation toxicologists tend to use a 3-compartment model consisting of the airways of the head, the tracheobronchial airways, and the gas exchange airways. These three regions have characteristic lumen shapes, cell populations, particle clearance mechanisms, and particle deposition characteristics. Although mammalian species show some obvious variability in airway structure, such differences are relatively well understood.

Particulate material that has deposited on airway surfaces is cleared from the airways by several mechanisms; some such as coughing and mucociliary flow act rapidly, and others such as lymphatic drainage and particle dissolution may act very slowly. The nervous system of the respiratory tract has many functions that are toxicologically significant, including control of breathing depth and frequency, triggering of the cough reflex, and control of mucus production.

At birth, mammalian lungs undergo a transition to air breathing. This transition is followed by a period of lung development which includes the addition of alveoli. In humans, lung development is initially rapid, but 5–10 years may be required before the full number of alveoli is present. An area of considerable uncertainty which is important in inhalation toxicology is the observed individual-to-individual variability in lung anatomy, lung defenses, and rate of maturation.

REFERENCES

Air Sampling Procedures Committee, American Conference of Governmental Industrial Hygienists (ACGIH): Particle Size-selective Sampling in the Workplace. Cincinnati: American Conference of Governmental Industrial Hygienists, 1985.

Bair, WJ: Overview of ICRP respiratory tract model. Radiat Prot Dosim 38:147–152, 1991.

Boyden, EA: Development and growth of airways. In: Development of the Lung, edited by WA Hodson, pp. 3–35, New York: Marcel Dekker, 1977.

Boyden, EA, Tompsett DH: The postnatal growth of the lung in the dog. Acta Anat 47:185–215, 1961.

Boyden, EA, Tompsett DH: The changing patterns in the developing lungs of infants. Acta Anat 61:164–192, 1965.

Brody, JS, Vaccaro, C: Postnatal formation of alveoli: Interstitial events and physiologic consequences. Fed Proc 38:215–233, 1979.

Burri, PH, Weibel, ER: Ultrastructure and morphometry of the developing lung. In: Development of the Lung, edited by WA Hodson, pp. 215–268. New York: Marcel Dekker, 1977.

Burri, PH, Dbaly, J, Weibel, ER: The postnatal growth of the rat lung. Anat Rec 178:711–730, 1974.

Comroe, JH, Forster, RE, Dubois, AB, et al.: The Lung, 2nd Ed. Chicago: Year Book, 1973.

Crapo, JD, Barry, BE, Gehr, P, et al.: Cell numbers and cell characteristics of the normal human lung. Am Rev Respir Dis 126:332–337, 1982.

Crocker, TT, Teeter, A, Nielsen, B: Postnatal cellular proliferation in mouse and hamster lung. Cancer Res 30:357–361, 1970.

Cuddihy, RG, Yeh, HC: Respiratory tract clearance of particles and substances dissociated from particles. In Inhalation Toxicology: The Design and Interpretation of Inhalation Studies and Their Use in Risk Assessment, edited by D Dungworth, G Kimmerle, J Lewkowski, R McClellan, W. Stöber, pp 169–193. New York: Springer-Verlag, 1988.

Dinarello, CA: An update on human interleukin 1: From molecular biology to clinical relevance. J Clin Immunol 5:287–297, 1985.

Dungworth, D, Kimmerle, G, Lewkowski, J, McClellan, R, Stöber, W (eds): Inhalation Toxicology: The Design and Interpretation of Inhalation Studies and Their Use in Risk Assessment. New York: Springer-Verlag, 1988.

Dungworth, DL, Phalen, RF, Schwartz, LW, Tyler, WS: Morphological methods for evaluation of pulmonary toxicity in animals. Annu Rev Pharmacol Toxicol 16:381–401, 1976.

Dunnill, MS: Postnatal growth in the lung. Thorax 17:329–333, 1962

Emery, J (ed): The Anatomy of the Developing Lung. Suffolk, U.K.: Heinemann, 1969.

Emery, JL: The postnatal development of the human lung and its implications for lung pathology. Respiration 27 (Suppl):41–50, 1970.

Fenn, WO: The phagocytosis of solid particles. I. Quartz. J Gen Physiol 3:575–593, 1921.

Fenn, WO: The phagocytosis of solid particles. IV. Carbon and quartz in solutions of varying acidity. J Gen Physiol 5:311–325, 1923.

Fishman, AP, Fisher, AB (eds): The Respiratory System, Section 3, Handbook of Physiology. Bethesda, MD: American Physiological Society, 1985.

Guilmette, RA, Boecker, BB (eds): Respiratory Tract Dosimetry: Proceedings of a Workshop held in Albuquerque July 1–3, 1990. Ashford, Kent: Nuclear Technology Publishing, 1991 (Also, Radiat Prot Dosim 38, Nos 1–3, 1991).

Hislop, A, Reid, L: Development of the acinus in the human lung. Thorax 29:90–94, 1974.

Hofmann, W, Steinhausler, F, Pohl. E: Dose calculations for the respiratory tract from inhaled natural radioactive nuclides as a function of age. I. Compartmental deposition, retention, and resulting does. Health Phys. 37:517–532, 1979.

Hofmann, W: Mathematical model for the postnatal growth of the human lung. Respir Physiol 49:115–129, 1982a.

Hofmann, W: Dose calculations for the respiratory tract from inhaled natural radioactive nuclides as a function of age. II. Basal cell dose distributions and associated lung cancer risk. Health Phys 43:31–44, 1982b.

Holma, B: The acute effects of cigarette smoke on the initial course of lung clearance in rabbits. Arch Environ Health 18:171–173, 1969.

Horsfield, K: Some mathematical properties of branching trees with application to the respiratory system. Bull Math Biol 38:305–315, 1976.

Horsfield, K, Cumming, G: Morphology of the bronchial tree in man. J Appl Physiol 24:373–838, 1968.

ISO: Air Quality-Particle Size Fraction Definitions for Health Related Sampling, ISO/TR 7708–1983 (E). Geneva: International Standards Organization, 1983.

Jeffery, PK, Reid, LM: Ultrastructure of airway epithelium and submucosal gland during development. In: Development of the Lung, edited by WA Hodson, pp. 87–134. New York: Marcel Dekker, 1977.

Kerr, GR, Couture, J, Allen, JR: Growth and development of the fetal rhesus monkey. VI. Morphometric analysis of the developing lung. Growth 39:67–84, 1975.

Landahl, HD: On the removal of airborne droplets by the human respiratory tract. I. The lung. Bull Math Biophys 12:43–56, 1950.

Meessen, H: Die Pathomorphologie der Diffusion und Perfusion. Verhandl Dsch Ges Pathol 44–98, 1960.

Miller, WS: The Lung. Springfield, IL: Charles C. Thomas, 1947.

Morrow, PE: Clearance kinetics of inhaled particles. In: Respiratory Defense Mechanisms, Part II, edited by JD Brain, DF Proctor, and LM Reid, p. 491–543. New York: Marcel Dekker, 1977.

Morrow, PE, Bates, DV, Fish, BR, Hatch, TF, Mercer, TT: Deposition and retention models for internal dosimetry of the human respiratory tract (report of the International Commission on Radiological Protection: ICRP: Task Group on Lung Dynamics). Health Phys 12:173–207, 1966.

Nagaishi, C: Functional Anatomy and Histology of the Lung. Baltimore: University Park Press, 1972.

Netter, FH: The CIBA Collection of Medical Illustrations, Vol. 7: Respiratory System. Summit, NJ: CIBA Pharmaceutical Corporation, 1979.

Pattle, RE: Surface lining of lung alveoli. Physiol Rev 45:48–79, 1965.

Phalen, RF: Inhalation Studies: Foundations and Techniques. Boca Raton, FL: CRC Press, 1984.

Phalen, RF, Oldham, MJ, Beaucage, CB, Crocker, TT, Mortensen, JD: Postnatal enlargement of human tracheobronchial airways and implications for particle deposition. Anat Rec 212:368–380, 1985.

Phalen, RF, Prasad, SB: Morphology of the respiratory tract. In: Concepts in Inhalation Toxicology, edited by RO McClellan, RF Henderson, pp. 123–140, New York: Hemisphere, 1989.

Reid, L: The Lung: Its growth and remodeling in health and disease. Am J Roentgenol 129: 777–7888, 1977.

Schlesinger, RB, Lippmann, M: Particle deposition in the trachea: In vivo and in hollow casts. Thorax 31:678–684, 1976.

Schreider, JP, Raabe, OG: Structure of the human respiratory acinus. Am J Anat 162:221–232, 1981.

Stanescu, DC, Pattijn, J, Clement, J. Van de Woestijne, KP: Glottis opening and airway resistance. J Appl Physiol 32:460–466, 1972.

Stöber, W, Morrow, PE, Koch, W, Morawietz, G: Alveolar clearance and retention of inhaled insoluble particles in rats simulated by a model inferring macrophage particle load distributions. J Aerosol Sci 25:975–1002, 1994.

Stossel, TP: The mechanism of phagocytosis. J Reticuloendothel Soc 19:237–245, 1976.

Task Group on Reference Man: Report of the Task Group on Reference Man. International Commission of Radiological Protection No. 23, pp. 122–124. New York: Pergamon Press, 1975.

Thurlbeck, WM: Postnatal growth and development of the lung. Am Rev Respir Dis 11:803–844, 1975.

Thurlbeck, WM: Structure of the lungs. In: International Review of Physiology, Respiratory Physiology II, Vol. 14, edited by JG Widdicombe, pp. 1–34. Baltimore: University Park Press, 1977.

Weibel, ER: Morphometry of the Human Lung. New York: Academic Press, 1963.

Weibel, ER: Morphometrics of the lung. In: Respiration, VI, edited by WO Fenn, H Rahn, pp. 285–307. Washington, DC: American Physiological Society, 1964.

Weibel, ER, Gil, J: Structure-function relationships at the alveolar level. In: Bioengineering Aspects of the Lung, edited by JB West, pp. 1–81. New York: Marcel Dekker, 1977.

West, BJ: Physiology in fractal dimensions: Error tolerance. Ann Biomed Engr 18:135–149, 1990.

Xu, GB, Yu, CP: Effects of age on deposition of inhaled aerosols in the human lung. Aerosol Sci Technol 5:349–357, 1986.

Yeh, HC, Schum, GM: Models of human lung airways and their application to inhaled particle deposition. Bull Math Biol 42:461–480, 1980.