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Edited by

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Living organisms must maintain their unique internal biochemical makeup while extracting the substances necessary for survival from a complex, often hazardous external environment. Within the respiratory tract, an elaborate multistaged defense system has evolved to cope with the extraneous substances inevitably taken in along with the required oxygen. Because humans can survive only minutes without oxygen, there is almost continuous intake of air and exposure to the foreign gases and particles it contains. The average adult male inhales 15 kg of air each day, while he consumes only 1.5 kg of food and 2.0 kg of water; very little selectivity can be exercised over the materials inhaled, compared with the control one has over what is ingested.

Depending on where they are deposited, particles inhaled during normal respiration can remain for long periods. They can slowly release toxic substances; microbes can proliferate without warning until irreversible tissue damage has occurred or serious disease has developed. Moreover, the large surface area of the parenchyma (about 70 m² in an adult male) and short diffusing length necessary for rapid gas exchange between the alveoli and the blood in the surrounding capillaries allow for only a very thin tissue barrier (as little as 0.2 μm) to the entry of these microbes and toxic substances into the blood. Because they collect in high local concentrations, the effects from toxic particles can be greater than those from acute exposure to toxic gases, which are often dispersed in respiratory tract fluids and diluted by the continuous exchange of air.

**OVERVIEW**

Simply viewed, the respiratory system's defenses against inhalable particles can be grouped into three lines of defense successively encountered by particles that enter the airways.

The first line of defense for the sensitive deep-lung airways is the progressive mechanical filtering of inspired air through the upper airways; nose, nasopharynx, pharynx, and larynx (during mouth breathing, mouth, oropharynx, and larynx) and the lower airways—the tracheo-bronchial tree. The effectiveness of this filtering determines the relative deposition of particles along the air passages and the extent of their penetration to the vulnerable gas-exchanging structures—the respiratory bronchioles, alveolar ducts, and alveoli—in the periphery of the lung. Receptors in the airways cause constriction of bronchial smooth muscle in response to mechanical or chemical irritation, decreasing the penetration of particles and noxious gases and, in extreme cases, triggering a sneeze or cough, which can actually expel foreign substances from the upper airways or large bronchi of the tracheobronchial tree.

The second line of defense is provided by the fluids that line the airways and gas-exchanging structures and by the clearance mechanisms that physically remove particles from their surfaces. The respiratory tract

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substances that give them detoxifying and bactericidal capabilities. In addition, the secretions that coat the ciliated epithelia of the conducting air passages of the upper and lower airways form the viscoelastic medium in which the cilia beat, propelling particles on a mucociliary "escalator" to the larynx, where they are swallowed and eliminated via the gastrointestinal tract. In the periphery of the lung, the slow but continuous exudation of fluid and its drainage via the airways and the lymphatic system cleanse the respiratory bronchioles and the alveoli. Finally, resident alveolar macrophages scavenge particles from the surfaces of the alveoli, digesting them or removing them via the mucociliary escalator.

The last line of defense is the specific immune defenses of the lung, which are brought into play against biochemically active particles that are deposited in the lung. These defenses are divided into two major effector systems—antibody production (humoral immunity) and lymphocyte-mediated antigen elimination.

These lines of defense are interdependent and coordinated as well. The filtering of inhaled particles determines their pattern of deposition and, hence, the mechanisms available for either neutralizing or removing them. Respiratory tract fluids contribute to the mechanical clearance of particles, have nonspecific bactericidal and detoxifying capabilities, and, in immunized hosts, contain antibodies. The alveolar macrophage carries bactericidal enzymes and antimicrobial antibodies for nonspecific and specific defenses in situ, respectively, in addition to its more primitive function of sequestering or physically removing particles. Finally, the specific immune defenses increase the efficiency of the nonspecific defenses by contributing antibodies to the respiratory tract fluids and by facilitating adherence of organisms to alveolar macrophages and increasing their activity.

**Particles of Concern**

The viable particles of major concern for health effects are pollens and various microorganisms, including bacteria, viruses, algae, molds, yeasts, fungi, rusts, and spores. Inhalation of these particles is related to the whole range of allergic and infectious diseases. Inanimate particles of concern are those that consist of or contain toxic metals, toxic chemical compounds, or radioactive elements. In addition, lung disease has been associated with the inhalation of naturally occurring crystalline and fibrous materials such as silica and asbestos, respectively. Finally, plant and insect debris contain biochemically active substances that can have harmful effects when inhaled.

**Physical Characterization**

Because the diameter, density, and concentration of the particles in an aerosol affect its stability (i.e., the rate at which particles coagulate and how long they remain airborne) as well as its ability to be inhaled and to penetrate into lung airways, particle diameter and density are primary determinants of exposure. Particle density is defined by composition and state of aggregation. This is more complicated for particle diameter, since most solid particles are irregularly shaped and not amenable to measurement of diameter. Consequently, an operational definition of particle diameter based on Stoke's law, called the aerodynamic diameter (or aerodynamic resistance diameter if slip correction is included), is commonly used to characterize the size distribution of particles in an aerosol.

A particle falling through the air under the force of gravity (gravitational sedimentation) accelerates until it reaches a velocity at which the force of gravity is just balanced by the viscous resistive force exerted by the air (Stokes' law). This velocity is known as the terminal settling velocity. Thus, with the exception of fibers, the aerodynamic diameter of a particle, however shaped, is taken as the diameter of a unit density sphere that would have the identical terminal settling velocity. Although it is possible to determine effective aerodynamic diameters for fibers in the same way (as a general rule, fibers with length-to-diameter ratios greater than 10 have an effective diameter three times their actual diameter), the extreme length of fibers affects their deposition in the narrow branching passages of the lung and must be taken into account: fibers tumble and physically intercept the walls of the airways. Hence, the size of fibers must be specified by both length and diameter.

Since even an aerosol of the most homogeneous particles has a distribution of diameters, the width of...
that distribution must also be specified. Naturally occurring aerosols are usually log-normally distributed, so geometric standard deviation ($G_d$) is used. An aerosol is called monodisperse if $G_d$ is less than 1.2, or if, in a given situation, the size range is narrow enough that the particles can be treated as if they all have the median diameter.

Half the particles of an aerosol have diameters smaller than the median diameter (count median diameter, CMD) but, because particle mass is proportional to the cube of the diameter, the collective mass of the particles smaller than the CMD may be only a small fraction of the aerosol's total mass. Since the amount of toxic material a particle contains is proportional to its mass rather than its diameter, mass median diameter (MMD) is often specified. This is the particle diameter for a particle whose mass falls at the median of the particle mass distribution of the aerosol. Atmospheric aerosols found over urban regions tend to be distributed bimodally: a fine mode centered at about 0.3 μm (MMD) and a coarse mode centered at about 7 μm (MMD) or larger. Mass median aerodynamic diameter (MMAD) corresponds to the unit density equivalent aerodynamic diameter.

For hygroscopic aerosols, particle size as a function of humidity must also be specified. This is an especially important consideration for particle deposition in the respiratory tract, where the air is saturated with water. Aqueous particles containing solutes absorb water as they penetrate the airways, continuously growing and changing their deposition characteristics. Although the deposition mechanisms described in the next section are valid for any particle, hygroscopic or not, an estimation of the deposition of a hygroscopic aerosol would need to take particle growth into account by integrating over the particle size–versus–humidity function.

**THE FIRST LINE OF DEFENSE: PARTICLE FILTERING BY THE AIR PASSAGES**

Most inhaled particles with an aerodynamic diameter greater than 2 μm are deposited along the conductive air passages of the upper and lower respiratory tract; they are mechanically filtered from the air before they can reach the delicate gas-exchanging membranes within the alveolar region. Because the secondary defenses (especially the clearance mechanisms) are very different for the two regions, the anatomic distribution of this deposit, as well as its total mass and chemistry, must be considered before any health effects can be estimated.

Although a particle is physically characterized by its density, diameter, and shape, this is not enough to predict its deposition in the lung. The dimensions of the air passages and the pattern of air flow must also be taken into account. The intricacies of mathematic models of particle deposition are beyond the scope of this chapter, but we can briefly describe the lung and try to convey an understanding of the interaction between physical deposition mechanisms and general features of lung structure.

**Lung Morphology**

In general, lung morphology is determined by two major constraints: (1) limited access for protection from the environment and (2) a large surface area interface for air-blood oxygen and carbon dioxide exchange. The evolutionary solution to both constraints is the rapidly branching network of cartilage and smooth muscle tubes that constitutes the tracheobronchial tree.

The human tracheobronchial tree has what is known as an asymmetric dichotomous branching pattern (i.e., each segment [the "parent"] gives rise to two daughter branches) [1]. The major daughter is larger (about 30 percent) and forms a smaller (about 20 percent) angle with the parent than the minor daughter. Because of this asymmetry, the number of branchings (generations) along different paths from the trachea (generation $= g = 0$) to the alveoli varies from 7 to 24. Through each successive generation, the airways become smaller, but, because of the exponential growth in the number of airways, the total volume and surface area increase rapidly. The gas-exchange region beyond the termination of the tracheobronchial tree of an average adult contains approximately 300 million alveolar air sacs, with a total gas-exchange surface area the size of a tennis court.

To avoid the computational complexity that is introduced by tracheobronchial tree asymmetry, most calculations of particle deposition have used the simpler, symmetric morphometric model of the lung defined by Weibel [2], which represents an average path. In this model, the airways and their generations are as follows: trachea ($g = 0$), main bronchi ($g = 1$), lobar bronchi ($g = 2$ to 3), segmental bronchi ($g = 4$), bronchi with cartilage in their walls ($g = 5$ to 10), terminal bronchi ($g = 11$), bronchioles with smooth muscle walls ($g = 12$ to 15), terminal bronchioles ($g = 16$), respiratory bronchioles ($g = 17$ to 19), and alveolar ducts ($g = 20$ to 23), with 21 alveoli ($g = 24$) per duct.

Weibel tabulated the numbers of airways in each generation and their mean diameter and length. He also computed the total cross-sectional area, the total volume, and the cumulative volume for each generation. Given a respiratory pattern, Weibel's tabulated dimensions can be used to compute the air velocity in the airways of any given generation and estimate particle deposition.

**Particle Deposition in the Lung**

There are five major mechanisms by which particles are deposited in the respiratory tract: gravitational sedimentation, impaction, brownian diffusion, electrostatic deposition, and interception. Gravitational
sedimentation, as we saw earlier, is the settling of particles onto airway surfaces under the force of gravity. Deposition by impaction occurs at airway bifurcations when a particle, owing to its momentum and the aerodynamic forces exerted on it by the stream of air in which it is carried, fails to make the turn into either of the daughter branches and impacts on the bifurcation. For particles smaller than 0.5 μm diameter, the gravitational and inertial effects that cause sedimentation and impaction no longer control deposition. Because of their small mass, these particles are subject to the random thermal kinetic buffeting (brownian motion) of the gas molecules in the air around them and diffuse to the walls of the air passages—hence, deposition by brownian diffusion. The relative importance of these three mechanisms—gravitational sedimentation, impaction, and diffusion—for deposition in a given airway depends on the size of the particle, its density, and the velocity of the air moving through that airway. In reality, air turbulence tends to blur the distinctions among the three mechanisms and to exert a major influence on deposition. If the particles are freshly generated by mechanical disintegration or are sprayed as liquid droplets, they may be highly charged and are deposited by electrostatic image forces that they induce on the airway surfaces. Finally, if the dimensions of the particle are of the order of the dimensions of the airway, it may be deposited by physical interception with the airway walls. This is an important deposition mechanism, but only for fibers.

Sedimentation and impaction are the most important deposition mechanisms for particles larger than 1 μm. Both increase in proportion to particle density and the square of particle diameter, and both decrease as airway diameter increases. With increasing air velocity, however, deposition from impaction increases while sedimentation decreases. For this reason, deposition in the large airways (where air velocities are high) is due predominantly to impaction, then shifts to sedimentation in the small airways, as total airway cross section increases and air velocity drops. The two mechanisms are also distinguishable for their respective dependency on airway length and branching angle. Sedimentation increases with airway length and is independent of branching angle; deposition from impaction increases with the branching angle and is independent of airway length.

It follows that slow, deep breathing enhances sedimentation and leads to relatively uniform deposition of particles throughout the respiratory tract, whereas rapid, shallow breathing increases impaction in the large airways, producing a centralized particle deposition pattern. Though rapid, shallow breathing may protect the gas-exchange regions, it creates high local particle concentrations, or “hot spots,” around the bifurcation carinas of the large airways, where the particles impact. Significantly, it has been observed that bronchial carcinomas tend to occur in these same airways [3].

Deposition of particles through brownian diffusion starts to become significant for particles with diameters smaller than 1 μm. A unit density sphere of 1 μm has a terminal sedimentation velocity of 33 μm per second and a diffusion displacement rate of about 13 μm per second, whereas a 0.5-μm unit density sphere has sedimentation and diffusion rates of 9.5 μm and 20 μm per second, respectively. Like deposition by sedimentation, deposition by diffusion increases with increasing airway length and decreases when air velocity or airway diameter increases. It is greatest in the gas-exchanging structures, where velocities are very low, giving particles time to diffuse to the surrounding surfaces.

Interception is important only for fibers, since their length can be an appreciable fraction of the diameter of the air passages. Because of the large cross section they present for lateral movements, fibers tend to align themselves with airstream lines, effectively resisting impaction and sedimentation, and allowing them to penetrate to the peripheral gas-exchanging structures. Though usually aligned with the stream lines, turbulence can disrupt airflow and causes the fibers to flip end over end. In the periphery of the lung, where fiber lengths are significant in relation to airway dimensions, this flipping results in interception with the walls.

While it is possible to estimate total and regional deposition by calculating deposition in each generation and making the appropriate summations, the result is subject to great uncertainty and error. Air turbulence caused by airway branching and surface irregularities and the flow reversal between inspiration and expiration introduce indeterminate factors, which make exact calculations of air flow and particle deposition impossible. In addition, individual variability in tracheobronchial tree dimensions introduces further uncertainty in the application of such results to any living subject, because the specific airway morphometry is unknown. Consequently, data obtained from experimental studies of human volunteers provide the most accurate estimates of regional and total deposition. Figures 14-1 through 14-3, respectively, show total, tracheobronchial, and alveolar deposition (mouth inhalation) data compiled from several such studies, along with curves generated from empirical and theoretical predictive models [4-12]. The variability of deposition among individuals is apparent from the scatter of the data points.

Using available data on regional particle deposition and measurements of airway sizes as a function of age, Martonen [13] developed a model for tracheobronchial deposition as a function of age, for both iron oxide (Fe₂O₃), a nonhygroscopic aerosol, and sulfuric acid (H₂SO₄), a very hygroscopic aerosol. The efficiency of tracheobronchial deposition decreases with increasing age (Fig. 14-4). For a hygroscopic aerosol such as H₂SO₄, hygroscopic growth within the airways occurs as the droplets approach equilibrium with the higher-than-ambient air tem-
Figure 14-1. Total deposition (fraction inhaled) as a function of particle size (MMD, d < 0.5 μm, MMAD, d > 0.5 μm). The studies of Chan and Lippmann [4] used a tidal volume of = 1 L and a breathing frequency of 14 breaths per minute. Stahlhofen and coworkers [9] used a 1.5 L tidal volume at = 15 breaths per minute. The data of Swift's group [10], and the predictive curves of Heyder and coworkers [6], Yu [12] and Davies and coworkers [5] are included for comparison. (From Chan TL, Lippmann M. Experimental measurements and empirical modeling of the regional deposition of inhaled particles in humans. *Am Ind Hyg Assoc J* 1980;41:399.)

Figure 14-2. Tracheobronchial (TB) deposition, fraction of aerosol entering the trachea, as a function of particle size (MMD, d < 0.5 μm; MMAD, d > 0.5 μm). The studies of Chan and Lippmann [4] used a tidal volume of = 1 L and a breathing frequency of 14 breaths per minute. Stahlhofen and coworkers [9] used a 1.5 L tidal volume at = 15 breaths per minute. The superimposed curve is an estimate of median deposition for an earlier study by Lippmann [7]. (From Chan TL, Lippmann M. Experimental measurements and empirical modeling of the regional deposition of inhaled particles in humans. *Am Ind Hyg Assoc J* 1980;41:399.)

Figure 14-3. Alveolar (gas-exchanging region) deposition, fraction inhaled, as a function of particle size (MMD, d < 0.5 μm; MMAD, d > 0.5 μm). The studies of Chan and Lippmann used a tidal volume of = 1 L and a breathing frequency of 14 breaths per minute [4]. Stahlhofen and coworkers [9] used a 1.5 L tidal volume at = 15 breaths per minute. The predictive curves of Yu [12] and the ICRP Task Group [11] have been superimposed for comparison. (From Chan TL, Lippmann M. Experimental measurements and empirical modeling of the regional deposition of inhaled particles in humans. *Am Ind Hyg Assoc J* 1980; 41:399.)

Figure 14-4. Tracheobronchial deposition of dry Fe$_2$O$_3$ particles and hygroscopic sulfuric acid droplets in the human lung at various ages. (From Martonen TB. Acid aerosol deposition in the developing human lung. In: Masuda S, Takahashi K (eds). *Aerosols: Science, Industry, Health and Environment*. Oxford: Pergamon, 1990.)
temperature and humidity. When the original droplet size is larger than 0.7 μm, hygroscopic growth increases tracheobronchial deposition; for droplets smaller than 0.5 μm, hygroscopic growth can reduce tracheobronchial deposition.

During mouth breathing, particles that penetrate to the gas-exchange region represent approximately 15 percent of the particles inhaled when the size of the particles ranges from 0.1 μm (MMD) to about 1.7 μm (MMAD), with a shallow minimum of 12 percent at 0.4 μm (MMD). Starting at about 0.7 μm (MMAD), this fraction rises to a maximum of approximately 50 percent for a particle diameter of 3 μm (MMAD), then falls to zero by 10 μm (MMAD). Particles with MMAD larger than 10 μm are filtered from the inspired air by the upper and lower airways, and do not reach the gas-exchange structures.

Although most experimental studies have used mouth breathing, deposition for nose breathing can be described generally. For inhaled particles smaller than 0.7 μm diameter, the fraction that are deposited in the gas-exchange region is similar to that for mouth breathing. As particle diameter increases above 0.7 μm (MMAD), however, the deposition fraction for nose breathing, unlike that for mouth breathing, increases only a little, reaching a peak of about 25 percent at 2.5 μm (MMAD) and then falling to zero by about 8 μm (MMAD). Clearly, nose breathing provides significantly greater protection than mouth breathing against particles of 1 μm diameter or larger.

In actuality, the situation is more complicated. Although some 15 percent of the population are habitual mouth breathers, most people breathe predominantly through the nose until the ventilation rate reaches about 40 L per minute. At higher flow rates, the amount of inhaled air is split almost evenly between mouth and nose. Miller and co-investigators [14] called such people "normal augmenters." Using an empirical deposition model based on available regional deposition data, they calculated tracheobronchial deposition at various flow rates for both normal augmenters, and habitual mouth breathers. Tracheobronchial deposition declines with flow rate in normal augmenters up to 30 L per minute, and then, owing to increased impaction in the upstream nasal airways, jumps abruptly as part of the inhaled air bypasses the more efficient filtration of the nasal passages (Fig. 14-5).

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**Figure 14-5.** Tracheobronchial deposition of particles for normal augmenters (panel A) and mouth breathers (panel B) as a function of aerodynamic particulate diameter for minute ventilation, \( V_{E} \), ranging from a resting level (10 L min\(^{-1}\)) to heavy exercise (60 L min\(^{-1}\)).


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**The Second Line of Defense: Lung Fluids and Clearance**

**Upper and Lower Airways**

**Fluid Lining.** The fluid that lines the upper and lower airways is a mixture of tissue transudates and the secretions of submucosal cells and the goblet cells, which are interspersed with the ciliated cells of the surface epithelium. Its major macromolecular components—and the ones responsible for the characteristic viscoelastic properties necessary for mucociliary clearance—are the long-chain glycoprotein...
molecules, or mucins. These molecules constitute 2 to 3 percent of normal tracheobronchial secretions (95 percent is water) and consist of polysaccharide units linked to a polypeptide core. The relative amounts of additional attached groups of fucose, N-acetyl-neuraminic acid, and sulfates distinguish the different mucins and probably contribute to their buffering capacity, as well as providing a source of sulfhydryls for oxidant neutralization. The physical entanglement of these long glycoprotein molecules is probably the main source of the rheologic (i.e., viscoelastic) properties of mucus.

The submucosal mucous glands, the major source of airway mucus, consist of mucous and serous cells lining a common secretory duct leading to the epithelial surface. Both the quantity and composition of the secretions are influenced by the autonomic nervous system. The same mechanical or chemical irritations that stimulate the contraction of airway smooth muscle cause a discharge of airway secretions. Once secreted, this “mucocoid” separates into two phases. The continuous beating of the cilia takes place within a low-viscosity sol underlying a discontinuous viscoelastic gel phase in which the long-chain mucopoly saccharide molecules are concentrated [15].

The goblet cells, cells distended with mucus and so named because of their shape, are found in the epithelia of both upper and lower airways but are most numerous in the large proximal airways of the tracheobronchial tree. Though they produce mucus, their collective secretory output is not nearly as copious as that of the submucosal mucous glands, and they do not respond to autonomic stimulation. They probably serve as local repositories of mucus and help to maintain a baseline level of secretory output, responding only to local stimuli. Clara cells (nonciliated bronchiolar epithelial cells), found mainly in the terminal bronchioles, also contribute to respiratory tract fluids; however, their secretion has yet to be fully characterized.

Other components of the fluid lining the upper and lower airways are the immunoglobulins IgA and IgG, lysozyme, albumin, lactoferrin, transferrin, α1-anti-trypsin, haptoglobin, α1-antichymotrypsin, the salivary α1- and β1-C-globulins, and α1-acid glycoprotein. IgA, the predominant species of immunoglobulin, is extremely important in mucosal defense against antigens. It is secreted locally as well as being provided by serum transudate along with IgG and albumin. Lysozyme is also produced locally, but the specific sources of the rest are uncertain.

**Mucociliary Clearance.** Except for the anterior nares and the posterior nasopharynx, most of the nasal and bronchial epithelia are ciliated; there are about 200 cilia per cell, each approximately 5 μm long (Fig. 14-6). Coating the epithelia and just covering the cilia is the sol phase of the respiratory tract fluid. Within this sol, the cilia beat about 1000 times per minute in a metachronous or wavelike pattern, drawing their energy from the dephosphorylation of adenosine triphosphate (ATP). Overlying mucous gel is propelled by means of a fluid coupling between it and the sol underneath as well as by contact with the tips of the beating cilia. Patches of the mucous gel, along with any intermingled particles and other debris, are carried out of the airways on this mucociliary escalator. Particles deposited in the anterior nasopharynx are swept forward to the unciliated nares to be removed mechanically or by nose blowing, whereas those deposited elsewhere in the nose (and all of the particles deposited on the ciliated epithelium of the tracheobronchial tree) are swept toward the pharynx and swallowed.

Local transport velocities in both the nasopharyngeal region and the tracheobronchial tree vary widely: values of less than 1 mm per minute to more than 20 mm per minute have been reported. Although most measurements of mucous transport in the tracheobronchial tree have been confined to the trachea, measurements in smaller bronchi and estimates based on mucus thickness and tracheobronchial tree surface area indicate a velocity gradient from the 5 to 10 mm per minute or so observed in the trachea to estimate 10 μm per minute in the smallest ciliated airways.

In general, the transport velocity observed in any given location depends on the arrangement of cilia and on the viscoelastic properties and thickness of both sol and gel phases of the respiratory tract fluid. Too much or too little fluid, or fluid with suboptimal viscoelastic properties, would affect the coupling between the cilia and the mucous gel and impair mucociliary transport. (Patients with bronchitis, for example, have an excess of bronchial secretions and defective mucociliary clearance.) There are also areas where the arrangement of cilia is such that wave patterns conflict and transport is impaired (e.g., in the nasal passages and at the carina of airway bifurcations).

Impaired transport, combined with the tendency of particles to become impacted in these locations, could make airway bifurcations especially vulnerable [3]. Fortunately, both nasal passages and the bifurcations of the large bronchi are the areas where irritant receptors are concentrated and the areas most effectively cleared by sneezes and coughs, respectively.

Measurements of overall nasopharyngeal or tracheobronchial clearance provide more consistent indicators of mucociliary function than local transport rates, because they represent a composite of regional rates, averaging out local variations. Such measurements are provided by experimental studies in which a test aerosol tagged with a T-ray-emitting isotope is inhaled and its clearance is monitored by external detectors. Data from a study in which tracheobronchial clearance was measured are plotted in Figure 14-7A [16]. The percentage of particles retained is plotted as a function of time after inhalation. Tracheobronchial clearance is shown by the fall in reten-
tion during the first few hours, and its completion by the relatively constant retention level after an average of 6 to 8 hours. Although retention curves can be evaluated in many ways, the time to clearance completion has proved the most reliable parameter because it is the least dependent on the distribution of the deposited particles.

Overall, clearance of the ciliated nasopharyngeal region is completed within about 4 hours, and clearance of the ciliated epithelium of the tracheobronchial tree can take as little as 2 or as many as 20 hours. Clearance times for the tracheobronchial tree especially, but also nasopharyngeal region clearance times and tracheal transport velocities, appear to be characteristic of an individual. This might be expected, since both local transport velocities and overall clearance rates depend on the quantity and rheologic properties of the respiratory tract secretions as well as respiratory tract morphology and ciliary function. All of these should be fairly constant and, to some extent, unique to an individual. Because the quantity and quality of respiratory tract secretions are influenced by the autonomic nervous system, mucociliary function can also change dramatically. For example, depending on individual clearance characteristics and sensitivity, acute exposure to an irritant like cigarette smoke usually causes a temporary increase in the tracheobronchial clearance rate. Even as mild a stimulant as tea can speed mucociliary clearance, and the administration of an adrenergic agent like isoproterenol can cause clearance to be completed in less than an hour, whereas atropine essentially halts it. More important than these transient changes, however, is the impairment of tracheobronchial clearance associated with lung disease that is often seen in cigarette smokers. Although this impairment may be secondary to disease-induced changes in respiratory tract secretions or lung morphology, it will certainly exacerbate any disease condition because it constitutes the breakdown of an important defense mechanism.

Gas-Exchanging Structures

Alveolar Fluid. The fluid lining the alveoli, like that lining the conducting passages, is a combination of local secretions and plasma transudates. Its most important components are the lipid secretions (surfactants) associated with the type II alveolar cells, which give it its surface tension-reducing properties. These lipids have been identified as the saturated lecithins, principally dipalmitoyl lecithin, together with the unsaturated lecithins and cholesterol. If the surface ten-
monocytes, that enter the lung interstitium as monocytes from circulating blood. In the interstitium, the monocytes divide and mature into interstitial macrophages. Many of these cells move out onto the alveolar surface, adapting to the highly aerobic environment to become alveolar macrophages, where they maintain the sterility of the lung by engulfing, neutralizing or digesting, and physically removing pathogenic particles (Fig. 14-8).

The macrophages reach sites of particle deposition by chance or through chemical attraction to chemotactic substances released by the particles or to particle coatings (opsonins) containing antibodies (especially IgG), antibody–antigen complexes, or complement formed from alveolar fluid. They can also be drawn by chemotactic substances released by lymphocytes and other macrophages as they interact with the particles, amplifying macrophage response. Once in contact with a particle, the macrophage, often stimulated by the opsonins, rapidly engulfs it. Lysosomes (packets of hydrolytic enzymes) then attach themselves to the phagosomal membrane surrounding the ingested pathogen, the lysosomal membranes become continuous with the phagosomal membrane, and the lytic enzymes kill and digest the pathogen.

Indigestible material remains sequestered in the macrophages and is gradually removed as macrophages migrate from the gas-exchange structures to ciliated airways for clearance via the mucociliary escalator. Often, this material includes antigens, pathogenic particles, or other toxic substances the macrophages are incapable of digesting. Because alveolar clearance is a slow process, and because macrophages live only weeks, the materials can be released when macrophages die, to be taken up again by other macrophages. In this manner, pathogens may persist in the lung indefinitely, causing chronic infection, immunogenic reactions, or toxicity.

Within the interstitium, the interstitial macro-

Figure 14-8. Rabbit alveolar macrophage attaching itself to yeast particle. (Courtesy John G. Hadley, Owens-Corning Fiberglas, and John Adee, Battelle Northwest.)

Alveolar Macrophage. Alveolar macrophages are large (10 to 12 µm) mononuclear phagocytic cells, generally believed to be descendants of bone marrow
Phages provide bactericidal and immune-mediated protection against particles that escape alveolar macrophages and penetrate the alveolar epithelium, as well as sequestering them and removing them via the lymphatics.

Despite their protective function, macrophages can also be involved in lung disease. Enzymes (including collagenase and elastase) released when macrophages are damaged or killed by the ingestion of toxic particles or fibers, can digest lung tissues and contribute to the pathogenesis of lung disease—for example, emphysema and fibrosis. Some particles, especially silica, also cause macrophages to release substances that attract fibroblasts and enhance fibroblast collagen formation [17]. This mechanism is probably the basis for silicosis. Silica particles in the interstitium are taken up by interstitial macrophages. The associated release of chemotactic substances causes them to aggregate and draw other macrophages and fibroblasts into the area. At the same time, the dying macrophages, killed by the toxic silica, release their digestive enzymes. The silica is then taken up by fresh macrophages, creating a degenerative cycle of focal tissue destruction and collagen formation.

The toxicity of long fibers of asbestos seems to be related closely to their length. It may be that alveolar macrophages attempt to phagocytize fibers that they cannot completely engulf. The fibers protrude through the walls of the macrophages, creating breaks through which the enzymes can leak.

**Pulmonary Lymphatics.** The pulmonary lymphatic system is a network of vessels connecting aggregates of immunocompetent lymphoid tissue that drains excess fluids, proteins, and even cells and particles from the pulmonary interstitium. It backs up respiratory tract surface defenses against foreign cells and antigenic particles with both cell-mediated and humoral immune defenses and ties in the lung to the body's systemic immune system. This network is composed of two major plexuses—peribronchovascular and pleural plexus. The peribronchovascular plexus consists of intercommunicating networks located in the connective tissue surrounding the airways, pulmonary arteries, and pulmonary veins, which merge imperceptibly at the level of the bronchioles and arteries. The pleural plexus is a dense network of small lymphatic vessels localized within the connective tissue of the visceral pleura. The twoplexuses are linked by means of small vessels in the interlobular septa as well as by pleural lymphatics that run over the surface of the lung toward the hilus, where they join with the peribronchovascular lymphatics. In the lumen of the vessels, funnel-shaped one-way valves work with vascular and respiratory pressures to maintain slow but steady unidirectional flow of lymph from the periphery of the lung to the larger lymphatic collecting vessels; and finally to the bloodstream via the right lymphatic and thoracic ducts.

Lymphatic "capillaries," arising as blind pouches within lymphoid aggregates at the level of the terminal and respiratory bronchioles and in connective tissue adjacent to alveoli, absorb fluids and particles from the interstitium of the peripheral lung. These vessels are distinguished by their extremely thin walls, interrupted basement membrane, and loose intercellular junctions, which account for the permeability of the lymphatic vessels to serum proteins, cells, and particles. Moving out of the periphery of the lung, the lymphatic vessels feed through more and more highly organized lymphatic tissue. In the walls of the respiratory bronchioles, lymphoepithelial organs bring respiratory epithelium, lymphatic tissue, and blood vessels into proximity. They may serve as functional pathways for the removal of alveolar fluids and particulates from airways to lymphatics. Lymphoid nodules in the walls of medium-sized and large bronchi (bronchus-associated lymphoid tissue, BALT) also provide pathways for the potential interchange of particles and lymphoid cells between air passages and lymphatics for activation of immune defenses. Finally, hilar and tracheobronchial lymph nodes receive the lymphatic drainage for most of the respiratory tract before it reenters the blood.

**Alveolar Clearance.** The respiratory bronchioles, alveolar ducts, and alveoli, unlike the conducting airways, do not have ciliated epithelia. Particles are cleared from the surfaces of these structures, but the process is much slower than in the ciliated airways. In Figure 14-7, particle retention data from a long-term clearance study have been plotted on three different time scales so that the difference between tracheobronchial and alveolar clearance rates can be appreciated [16]. The particles were 4.0-μm (MMAD) polystyrene microspheres, and the retention is expressed as a percentage of initial deposition. Tracheobronchial clearance (Fig. 14-7A) is normally completed in about 6 to 8 hours. The elimination of this material from the gastrointestinal tract can be seen in Figure 14-7B from the abrupt drop in retention on the second and third days after inhalation. By the fourth day, although particles are passing through the tracheobronchial tree and gastrointestinal tract as they clear, only the gas-exchange region of the lung contains a significant fraction of the particles initially inhaled. Finally, Figure 14-7C shows the characteristic two-phase pattern of alveolar clearance observed in healthy persons. Here, the fast phase has a half-time of 19 days, and the slow phase a half-time of 375 days.

Most of the particles that are deposited in the gas-exchange structures, depending on their size and composition, are engulfed by alveolar macrophages. These particle-laden macrophages, as well as the "naked" particles that remain, can then follow one of two major clearance routes: the mucociliary escalator or the alveolar epithelium into the interstitium for clearance via the lymphatics (Fig. 14-9). There are opposing views, but the particle-laden macrophages probably are cleared principally via the airways and naked particles via both routes. It is not known how the macrophages and particles find their way to the mu-
ciliary escalator, but surface tension and viscosity gradients, respiratory movements, and a slow movement of fluid transudate from the alveoli to the airways have all been suggested. The fast alveolar clearance phase is commonly associated with macrophage activity, and it is assumed that particles entering the interstitium clear more slowly; however, no direct correspondence has yet been drawn between the two temporal clearance phases and either clearance route.

Particles that enter the interstitium can also become sequestered there, within macrophages or bound in connective tissue to remain indefinitely. Relatively inert particles such as soot cause the diffuse pigmentation seen at autopsy in lungs of city dwellers, while toxic materials such as silica and asbestos lead to the lung diseases silicosis and asbestosis.

Although the role of impaired alveolar clearance in the pathogenesis of lung disease is not yet clear, persons with lung disease have defective alveolar clearance. Figure 14-10 shows alveolar clearance in a person with chronic obstructive lung disease. The fast clearance phase has disappeared, and the half-time of the slow phase is significantly increased. Cigarette smokers show a similar long-term clearance pattern: no fast phase and slow phase half-times increased in proportion to pack-years of smoking. Since the effects of inhaled particles are often directly related to their retention time, such alterations in alveolar clearance may have serious consequences that are probably more severe than those resulting from changes in tracheobronchial clearance.

THE THIRD LINE OF DEFENSE: THE IMMUNE SYSTEM

Most antigenic particles that deposit in the respiratory tract do not penetrate the fluid barriers and do not elicit a systemic immune response. As we have seen above, they are enzymatically degraded, neutralized by antibodies already present, and cleared. In addition, the particles that penetrate to the gas-exchange regions are engulfed and deactivated or removed by alveolar macrophages, or interstitial macrophages if they reach the interstitium.

Sometimes, however, these defenses are not sufficient, and the antigens gain access to lymphoid tissue. In the upper and lower airways, they may move to the lymphoid nodules in the walls of the bronchi or directly through the mucosa. In the gas-exchanging structures, they may be taken up by the lymphoepithelial organs in the walls of the respiratory bronchioles or move into the interstitium to lymphatic capillaries for transport to local lymphoid nodules, and, subsequently, to the hilar and tracheobronchial lymph nodes.

Once antigens reach organized lymphatic tissue, the full capabilities of the immune system come into play. Those capabilities can be divided functionally into two major effector systems, cell-mediated immunity and humoral, or antibody-mediated immunity. These systems are related, respectively, to two major subpopulations of lymphocytes, T cells and B cells, which concentrate in lymphoid tissue.
T cells arise from stem cells in the bone marrow and differentiate under the influence of the thymus. They circulate continually, migrating from peripheral blood into lymph nodes and respiratory submucosa and returning to the blood via the large lymphatic vessels and, finally, the thoracic duct. Once sensitized by interaction with antigen, T cells evolve into subsets of effector cells: (1) soluble mediator (lymphokine)-secreting cells; (2) cytotoxic cells; (3) helper cells; and (4) memory cells. Probably most important in the defense of the respiratory tract are the lymphokine-secreting cells. The lymphokines help coordinate the immune response, especially macrophage function, and include macrophage migration inhibition factor, macrophage activation factor, lymphotixin, chemotactic factor, and mitogenic factor. The cytotoxic cells are sensitized T cells that directly kill foreign cells and cells bearing antigens. For example, a heterogeneous population of so-called natural killer (NK) cells is important in resistance against neoplastic cells and cells that harbor viruses. The NK cells interact with interferon to provide nonspecific immune surveillance, especially that associated with histocompatibility. A third subset of sensitized T cells are called helper cells, because of their role in the regulation of antibody production by B cells. Finally, memory cells specific for the challenging antigen remain to provide immunity on later exposure.

B cells are bone marrow-derived lymphocytes that congregate in lymphoid tissues, such as the follicles of lymph nodes, and serve as precursors for the antibody-forming cells that effect humoral immunity. In response to antigen stimulation, and usually in coordination with helper T cells, B cells differentiate into plasma cells, which secrete soluble antibody for dissemination via blood, lymph, and respiratory tract fluids.

There are five major structural types or classes of immunoglobulins, the molecules that function as antibodies: IgA, IgG, IgM, IgD, and IgE. IgA is the predominant immunoglobulin species in the upper and lower airways; most is synthesized locally. It neutralizes viruses and toxins, inhibits microbial growth, agglutinates particles, and, possibly most important, blocks mucosal penetration of antigens. IgG, although it is present throughout the respiratory tract in local secretions, occurs in relatively high concentrations in the gas-exchange structures, provided mostly by serum transude. The respiratory tract's major bacterial opsonin, IgG, agglutinates particles, activates complement, neutralizes bacterial exotoxins and viruses, and lyses gram-negative bacteria. Since little IgM or IgD is found in respiratory tract fluids, their roles are uncertain. It is known, however, that IgM agglutinates particulate antigens, activates complement, and lyses certain bacteria, and that its concentration increases in cases of IgA deficiency; consequently, it may be more important to the defense of the respiratory tract than its low concentration would indicate. IgE is synthesized locally, mainly by lymphoid cells in the bronchial mucosa and the hilar lymph nodes, and is responsible for the symptoms of atopic allergy. It is necessary for the specific interaction of inhaled extrinsic allergens with mediator-containing mast cells.

REFERENCES