Respiratory Infections

Second Edition

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CHAPTER 2

Nonspecific Host Defenses: Mucociliary Clearance and Cough

Charles Feldman

The primary function of the lungs is to breathe, and with each breath microorganisms and various other potentially toxic agents are moved in and out of the airways.[1,2] The airway surface is a major interface between an individual and the environment. In its attempt to enter the human body and cause infection, an invading microorganism has to overcome a myriad of specific and nonspecific host defenses including both immune and nonimmune mechanisms.[3] Among the nonimmune mechanisms protecting the airways are mechanical barriers, such as airway angulation and the epiglottis; aerodynamic filtration of the airways; airway reflexes such as cough, sneeze, and bronchoconstriction; and the mucociliary transport mechanism.[2–4] Between the posterior two-thirds of the nasal cavity and the nasopharynx, and from the larynx to the terminal bronchioles, the airways are lined by a specialized ciliated respiratory epithelium. Together with the specialized secretions of the goblet and mucous cells, this mucociliary clearance mechanism provides the first line of defense of the airways and is largely responsible for keeping the lower respiratory tract sterile.[3,4] The coordinated movement of the cilia moves the layer of mucus above the cell surface toward the oropharynx, where it can be expectorated or swallowed.

If the mucociliary escalator fails, secretions accumulate in the airways. This may be associated with increased susceptibility to bacterial colonization of the normally sterile lower respiratory tract and may act as the first step in the development of a lower respiratory tract infection.[1] In addition, accumulation of mucus in the airway may also be associated with airflow obstruction and with enhanced airway deposition of inhaled aerosols and pollutants, thereby predisposing to greater injury by these agents. Impaired mucociliary function has been noted to occur in a number of infective and noninfective disorders of the lungs and is thought to play an important role in disease pathogenesis in a number of diverse conditions.[1]

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This chapter discusses mucociliary clearance and the various components of this system, including mucus, periciliary fluid, and the cilia themselves, and highlights various aspects of bacterial and host interaction with this system. It also discusses cough and its role as a backup to the functions of the mucociliary escalator.

AIRWAY MUCOSA

The epithelium lining the airways in humans consists of many different cell types with both individual and overlapping functions.[5] Ciliated cells predominate and are interspersed with a variety of secretory cells (Fig. 2-1). The surface of a ciliated cell has approximately 200 cilia that are an extension of the cell surface and whose motor is a tubulin-based axoneme. The average length of cilia is approximately 6 μm, and this length is under genetic control.[6] Their average diameter is 0.1 to 0.2 μm. Each cilium is surrounded by six shorter microvilli of approximately 1 μm in length and 0.1 to 0.3 μm in diameter.[7] The ciliated cells are in physical contact with each other through tight junctions and in chemical communication through gap junctions.[7] Airway secretory cells include the mucous (goblet) cells, the serous, Clara and dense-core granulated cells of the surface epithelium, and the mucous and serous acinar cells of the submucosal glands.[5] Secretions from these different cells mix with various macromolecules, electrolytes, and water to form the respiratory tract fluid.[5] Other cells found in the respiratory tract include nonciliated cells, such as the brush cells, and the basal cells. The brush cells form a small part of the epithelium, and although they have no cilia, some have microvilli and may serve an absorptive function, a sensory function, or even participate in ciliogenesis.[6,7] The basal cells probably function to attach the columnar cells to the basal lamina. The epithelium varies both in the size of the ciliated cells (varying from pseudostratified columnar to cuboidal) and in the distribution of the cell types from the larger to the smaller airways.[5,7]

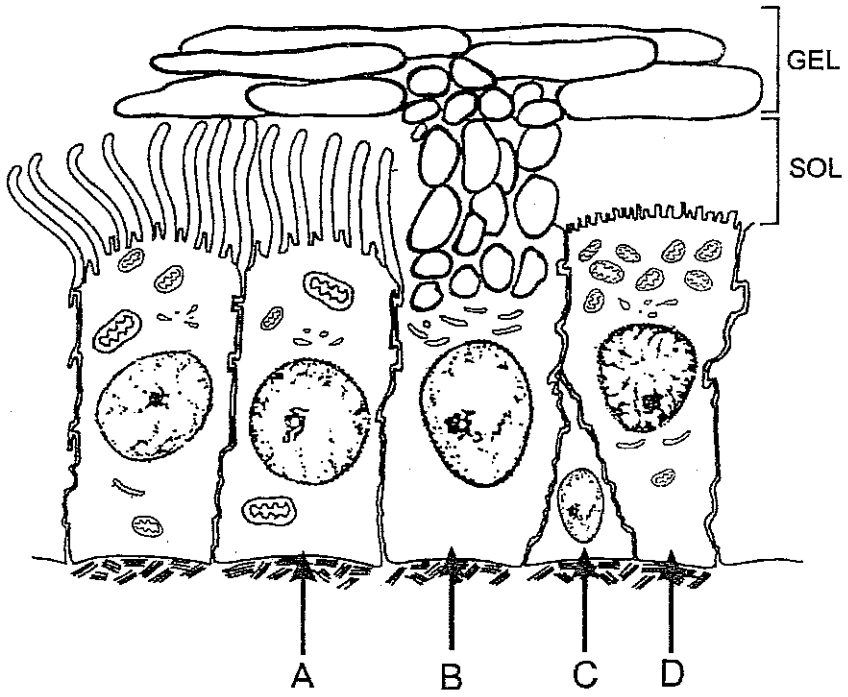

FIG. 2-1. A line drawing shows some of the main cells found in human ciliated respiratory epithelium. **A:** Ciliated columnar cell with cilia and microvilli on its surface. **B:** Goblet cell secreting mucus. **C:** Basal cell. **D:** Nonciliated (brush) cell.

CILIA

Ciliary Structure

Both the upper respiratory tract (including the nasal passages, sinuses, middle ear, and turbinates) and the lower respiratory tract are lined by a ciliated epithelium. The detailed ultrastructure of mammalian cilia has been elucidated (Fig. 2-2). Cilia are cylindric finger-like organelles, the cytoskeletal framework or axoneme of which contains nine pairs of filaments/subfibers (A and B microtubules) around the periphery with two central filaments, contained within its own cell membrane (the so-called 9 + 2 arrangement).[4,6–10] The position of the central pair of tubules indicates the orientation of the cilium.[10]

The microtubules are constructed primarily from heterodimers of alpha- and beta-tubulin arranged in protofilaments.[7,9,10] The A microtubule is made up of 13 protofilaments, and the B microtubule is made up of 10 to 11 protofilaments.[7,9,10] There is also a group of microtubule-associated proteins, called *tektins*, that interact with the tubulin subunits and appear to give structural integrity to the microtubules.[7,9] Adjacent doublets are linked to each other by nexin links and

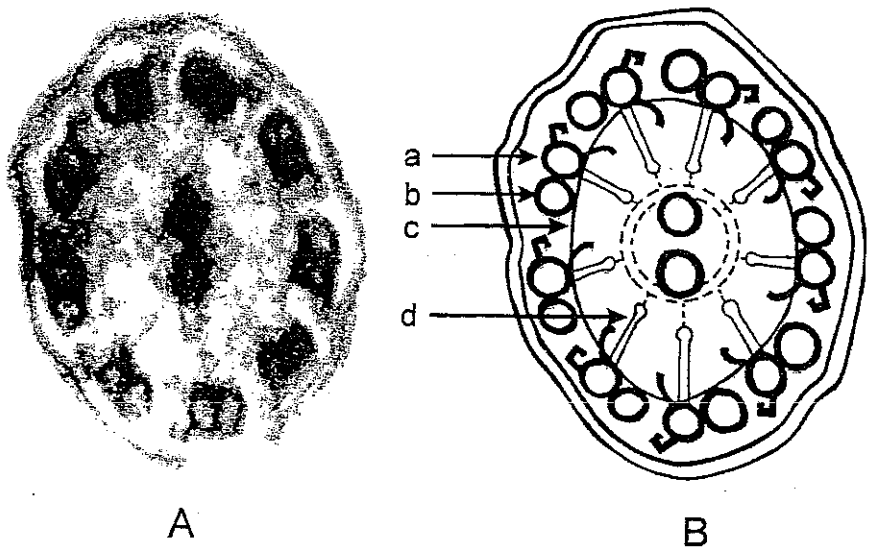

FIG. 2-2. A transmission electron micrograph **(A)** (400,000× magnification) and a comparative line drawing **(B)** of a human cilium. The line drawing shows the **(A)** microtubule with inner and outer dynein arms (a), the **(B)** microtubule (b), the nexin link (c), and the radial spoke (d).

connected to the central pair complex via radial spokes.[8,9] Little is known about the nature and function of nexin links, which appear to provide an elastic structural linkage between adjacent doublets and may provide elastic recoil during the relaxation phase of the beating cycle.[10] The function of the radial spokes is incompletely understood, but they may help to maintain the proper spacing of the doublets and also regulate dynein activity.[9,10] Bridges also exist between the ciliary membrane and the outer doublets along the entire length of the cilium. Each A microtubule has inner and outer dynein arms that extend clockwise.[8,10]

The outer dynein arm in the cilium supplies the energy for the beating of the cilia. Ciliary dynein is a two- or three-headed bouquet-like molecule of molecular weight 1 million to 2 million d.[9] Each head contains a heavy-chain adenosinetriphosphatase.[7,9] On the microtubules, dynein is compacted into the arm-like structure.[9] At the base of the cilium, the nine outer doublets end in the basal body, or centriole, which is anchored to the cytoskeleton and is an organizational site for the microtubules.[9] The basal body has a foot, which points with its narrow end in the same direction as the effective stroke of the cilium.[6,7] Because the basal feet of a cell point in the same direction, the effective stroke of all cilia have a common orientation, but the orientation of neither the basal feet nor the cilia is absolutely identical.[6–8]

Also near the base of the cilium, the axoneme is connected to a special transmembrane complex called the *ciliary necklace*.[7,9] Just above this region is a zone in which calcium shock produces severing of the axoneme, probably by activating a calcium contractile protein localized in this area.[9]

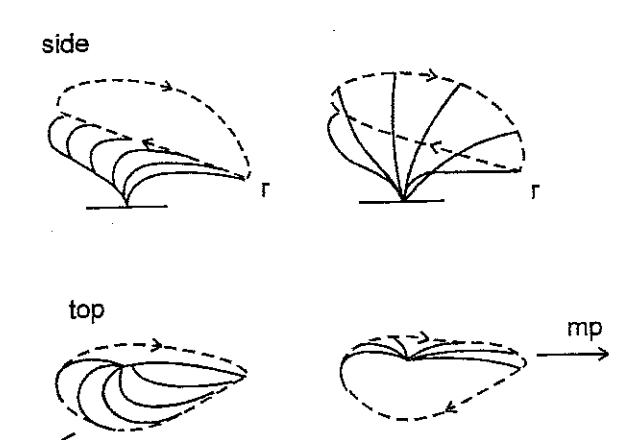

FIG. 2-3. The beat cycle of a rabbit tracheal cilium seen from the side and from above. In the recovery stroke (*left*), the cilium starts from the rest position (r) and unrolls clockwise (*in top view*) to the left, and in the effective stroke (*right*), it remains extended and bends over to reach the rest position at the right. Mucus is propelled (mp) toward the right, and the metachronal wave (mw) is propagated toward the lower left. (From Sleigh MA, Blake JR, Liron N. The propulsion of mucus by cilia. *Am Rev Respir Dis* 1988;137:726–741, with permission.)

Normal Ciliary Function

During ciliary motion, the dynein arms projecting from the A microtubule interact transiently with the B microtubule of the adjacent outer doublet, causing the latter doublet to slide toward the tip of the axoneme.[9,10] Different patterns of sliding on the various sides of the cilium provide the different shapes of the cilium at the different stages of its movement. Cilia beat in metachronal waves at a rate of approximately 15 to 20 Hz.[9,10] The cilia beat in the more watery periciliary fluid layer just below the thick mucous layer.[4] They engage the mucus mechanically or chemically by means of "hooks" or "claws" that project from their tips and that propel the mucus along in a coordinated propulsive wave. Approximately three to seven hooks are found on the tip of each cilium, and they are 25 to 35 nm long.[6,7]

Airway cilia have a special beating cycle (Fig. 2-3).[6] In the fast, effective ("power") stroke the cilium moves fully extended in an arc, almost perpendicular to the cell surface, engaging the mucous layer above. After the effective stroke, the cilium rests for a short period before beginning its recovery stroke.[6] In the slow recovery ("preparatory") stroke, the cilium withdraws, swinging almost 180 degrees backward, bending to the right, which allows it to retract under the mucous blanket. Respiratory mucus couples the energy of cilia to the movement of foreign particles up the airway.[4] As the cilium swings backward in its recovery stroke, it pushes against other cilia that are in the resting phase, stimulating them to begin their recovery stroke.[6] This is thought to be one of the most important factors in the propagation of the metachronal wave. Ciliary beat frequency appears to be slower in the peripheral airways compared to that of the larger airways and nose.[4,8,10–12] In experimental studies, a similar gradient has been noted for mucus movement.[12]

Control of Ciliary Beating

The control of the ciliary beat function, and, in particular, the coordinated wave pattern, is complex. Although previously neural mechanisms were not thought to be involved, preliminary evidence from 1998 suggests that in the mammalian tracheobronchial tree, sympathetic and parasympathetic neural transmission may control ciliary activity and mucociliary transport.[6,7,13] Experimental studies suggest that at least two independent mechanisms controlling ciliary beat frequency exist: one using calcium and the other related to cyclic adenosine monophosphate (AMP).[7,9,14–18] The release of calcium from internal stores or the influx of calcium into the cell causes an increase in ciliary beat frequency.[7,14,16,17] Mechanical, chemical, and hormonal influences may affect ciliary beat function, but some effects shown in studies may be "mucous" rather than "ciliary" effects, and it is often difficult to distinguish between the two. Mechanical stimulation, which physiologically can be initiated by the presence of

mucus, stimulates ciliary beat frequency by permitting extracellular calcium to enter via cell membrane channels and thus increasing intracellular calcium.[9,16]

A cyclic AMP-dependent kinase is also involved in the control of ciliary beating.[9,18] Adrenergic drugs use this pathway to increase ciliary beating.[16] These agents bind to the beta receptors, and this activates adenylate cyclase through G proteins and increases intracellular cyclic AMP levels.[9,16,19] Methylxanthines are also ciliostimulatory.[20] They are weak phosphodiesterase inhibitors and may increase cyclic AMP levels in the cells through this mechanism. In addition to stimulating ciliary beat frequency, these agents augment net ion secretion and promote mucous secretion in the lower airways.[20] In contrast, adenosine inhibits adenylate cyclase through a specific alpha$_1$-receptor, and consequently decreases cyclic AMP and ciliary beat frequency.[21]

Several studies have provided evidence that nitric oxide may affect epithelial function in the airway, measured as ciliary beat frequency *in vitro* and mucociliary transport *in vivo*.[7,22,23] Inhibitors of nitric oxide synthase block the increase in ciliary beat frequency produced by various ciliostimulators.[22] The nasal concentration of nitric oxide is low in patients with primary ciliary dyskinesia, Young's syndrome, and other acquired conditions, and it has been suggested that measurement of nasal nitric oxide concentrations may be a useful diagnostic screening test for these disorders.[23–25]

A vast number of substances, both endogenous and exogenous, and including inflammatory mediators, chemical agents, and pharmaceutic preparations, may affect ciliary function and have been fully described in previous reviews.[7] Many inflammatory mediators, such as the leukotrienes and prostaglandins, stimulate ciliary beating *in vitro*, causing a decrease in overall mucociliary transport as a consequence of the associated inflammation and stimulation of mucous hypersecretion.[26,27] A particular exception among the inflammatory mediators are the bioactive phospholipids, as well as eosinophilic major basic protein, which slow ciliary beating.[28] Ciliary beat frequency is also sensitive to temperature, being decreased at lower temperatures.[6,29]

Measurement of Ciliary Function

A number of tests have been described for testing the overall function of the mucociliary apparatus.[30] The saccharin test is simple and inexpensive, and frequently is used as a screening tool before the referral of patients for formal assessment of ciliary function.[25,30] The test is performed by placing one-fourth of a saccharin tablet anteriorly on the inferior nasal turbinate and measuring the time needed for the patient to taste the saccharin. A time of 30 minutes or less is considered to be normal.

Although it would be best to study ciliary function *in vivo*, such technology is not available, and methods at the time of this writing are difficult to perform and interpret. Ciliary beat frequency is measured *in vitro*, usually in a watery environment and by the use of a number of techniques, including a photodiode or phototransistor technique, a stroboscope, a high-speed camera, and an auditory clicking device.[29,30] Several techniques are also used for sampling of tissue from the respiratory tract, including surgical biopsy, nasal lavage, scrapings, brushings, and imprints.[30] A simple noninvasive nasal brushing technique has been found to be useful.[25,30] Studies have shown that nasal cilia are, in general, well representative of lower respiratory tract cilia.[31] A simple diagnostic algorithm has been developed for the workup of patients with suspected primary ciliary dyskinesia and this would be of use in any patient with a suspected disorder of ciliary function (Fig. 2-4).[25]

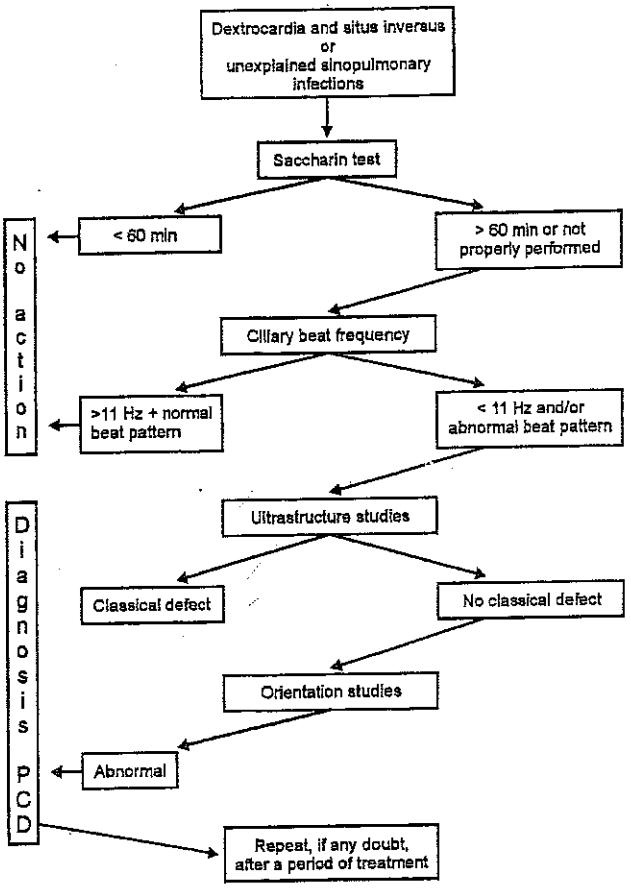

FIG. 2-4. Diagnostic algorithm for primary ciliary dyskinesia (PCD). Step 1: Saccharin test, result <60 minutes in a properly performed test, no action. Step 2: Ciliary beat frequency, result >11 Hz, low index of suspicion for PCD, normal beat pattern, no action. Step 3: Ultrastructural studies, classical abnormality, no further diagnostic tests. Step 4: Orientation studies. Step 5: Repeat samples after treatment unless there is absolutely no doubt regarding the diagnosis. (From Bush A, Cole P, Hariri M, et al. Primary ciliary dyskinesia: diagnosis and standard of care. *Eur Respir J* 1998;12:982–988, with permission.)

PERICILIARY FLUID LAYER

The periciliary fluid is a watery secretion, the depth of which is a little less than the length of the cilium. The cilia beat throughout their entire cycle in this watery layer.[6] The level of this fluid layer is critical to the normal functioning of the mucociliary escalator. If the layer is too deep, the cilia cannot engage the mucous layer, and if the level is too shallow, the mucus itself impedes ciliary beating.[6,7] The periciliary fluid layer also has an important role in mucus hydration after it is secreted by the mucus-producing cells. It appears that the periciliary fluid level is regulated by an active ion transport across the epithelial cells, with a concomitant passive fluid transfer.[7] Capillary action between the cilia may help production and maintenance of the fluid level.

The epithelial cells possess two major ion transport systems that are both adenosine triphosphate (ATP) dependent.[7] One is for chloride secretion and the other is for sodium absorption. Sodium absorption predominates under basal conditions in larger airways in humans.[7] Chloride secretion is achieved through several different chloride channels.[7] Patients with cystic fibrosis have defective function of one of these chloride channels as a consequence of defective phosphorylation of the cyclic AMP-dependent kinase that opens the channel.[7] The failure of the chloride channel and associated increase in sodium absorption result in the thick viscous secretions seen in patients with cystic fibrosis.

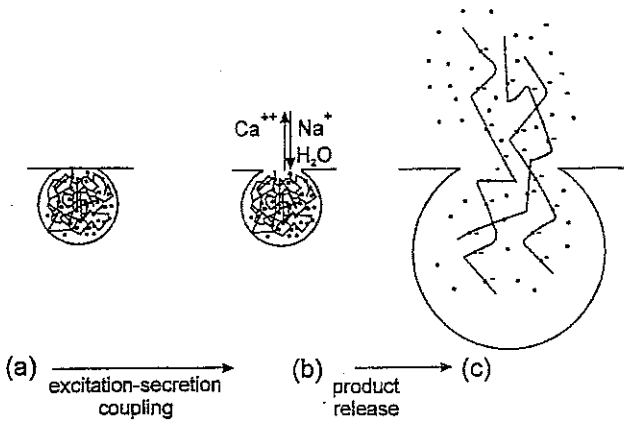

FIG. 2-5. Mechanisms of mucin exocytosis. By analogy to the sequence of activation in muscle contraction, in exocytosis it is convenient to separate the stimulus-coupling steps from the actual mechanical phenomena that drive product release. The stimulus-coupling steps encompass the events that start with receptor activation and lead to the docking of the secretory granule to the plasma membrane, the formation of a secretory pore, and the switching of the pore to high ionic conductance (a). Once a high conductance is established between intragranular and extracellular compartments, Na^+/Ca^{2+} ion exchange follows, triggering a phase transition that turns the mucin polymer from a condensed to a hydrated phase (b). At this stage, electrochemical energy stored in the mucin polymer network is transformed into mechanical energy via electrostatic interactions, driving the final release of secretory products (c). (From Verdugo P. Mucin exocytosis. *Am Rev Respir Dis* 1991;144[Suppl]:S33–S37, with permission.)

MUCUS

Mucus is a highly complex substance that consists of, among other things, a heterogeneous mixture of water, salts, and glycoproteins that forms a hydrogel.[6,32,33] Some of the additional substances it contains include serum transudate, peptidoglycan, proteolytic enzymes and their inhibitors, immunoglobulins, and lipids. Mucus also contains factors that help prevent bacterial colonization, including secretory immunoglobulin A, which forms an immunologic barrier to bacterial colonization; lysozyme, which is bactericidal; and lactoferrin, which has antioxidant activity and traps iron, which is required by many bacteria.[2,4,6] Mucins, which are glycoproteins, form the main polymeric species in the mucous matrix, particularly in hypersecretory conditions.[32,33]

There is debate regarding the macromolecular composition of normal airway secretions, with some observing that mucous glycoprotein is the major secretory product and others proposing that peptidoglycan is the main glycoconjugate.[32] The detailed structure of the glycoprotein macromolecules has been elucidated, and they have been shown to consist of a protein core with attached carbohydrate side chains made up of different sugars.[32] Some workers believe that the glycoproteins are linked to each other end-to-end by disulfide bonds, forming very large molecules that are intertwined or entangled together with their coils being held together by weak noncovalent bonds.[6] Others suggest that the glycoproteins are cross-linked into a three-dimensional network by intramolecular or intermolecular disulfide bonds.[6]

Mucus is formed within the Golgi apparatus and secreted from vesicles in a concentrated form through exocytosis by a jack-in-the-box mechanism (Fig. 2-5).[34] Mucins, the primary polymeric species in the mucous matrix, are densely packed in secretory granules and undergo massive swelling on exocytosis as a consequence of hydration.[6,7,33,34] Mucins are polyanions, and their condensation requires that their negative charges be rendered neutral by acidic pH or by counter-ion shielding.[34] Counter-ion shielding may be achieved by the high concentrations of calcium in the vesicles that act as a shielding cation to screen the polyanionic residues of mucin, allowing their condensation.[33] Relatively small concentrations of calcium should inhibit mucin swelling.[33]

Although shielding is necessary, it alone does not adequately explain condensation and decondensation.[34] This may best be explained by Tanaka's theory of polymer gel phase transition.[7,33,34] All polymer gels (e.g., mucins) exist only in two phases: a condensed phase and an expanded, hydrated phase.[7,33,34] After the secretory granules fuse with the cell membrane, the calcium ions in the vesicles are probably exchanged with sodium ions from the extracellular space.[34] Because monovalent cations are weaker supporters

of the condensed-phase form, this exchange results in rapid mucin hydration, driven by a Donnan equilibrium process.[34] The volume of gel increases several hundredfold in only 3 seconds. The periciliary fluid layer serves as a water and electrolyte donor in this event. Although the classical *sol* and *gel* layer description of mucus in the respiratory tract is perhaps an oversimplification, the mucous blanket does appear to function in this two-layer system.[4]

Mucus exhibits a number of complex physical properties that are essential for its coupling role to mucociliary transport. It is said to have viscoelastic flow, or rheologic properties, and the glycoproteins are said to be an important determinant of this in mucoid sputum.[4,6,35] The interest in rheologic properties of mucus has led to the development of procedures and instruments for describing these characteristics. The rheologic properties of polymer gels like mucin are determined by their conformation, the polyionic charge, the concentration of their constituent polymers, and also by the interconnections among the polymer chains in the gel's matrix.[33] Critical factors regarding mucous rheology are mucous hydration and mucin molecule length. Mucous hydration depends not only on the amount of water but also on the concentration of salt, cations, and polycations and the pH of the airway liquid.[34]

Mucus appears in the smaller airways as droplets, rafts, or flakes, and not as a continuous blanket as was previously thought.[6,7,10,36] It is possible that mucus is secreted only in response to stimulation by foreign particles, to transport them out of the lungs.[6] The secreted mucous droplets coalesce and get larger as they migrate out of the lungs, and the thickness of mucus also increases toward the trachea.[6] Airway mucus has a long relaxation time as a consequence of its viscosity, and this allows it to trap and retain foreign particles.[6,7] The transport of mucus is indirectly proportional to viscosity and directly proportional to elasticity.[6] Other physical properties such as surface tension and spinability (thread-forming ability, representing a combination of the characteristics of elasticity and cohesion) are also important in mucous-particle interactions and in mucous transportability.[6] Little is known about how alterations in the structure of mucus change its physical properties, and it is difficult to predict how changes in mucous properties affect mucociliary interactions and mucous transportability.[4]

Several cell types in the respiratory mucosa produce mucous glycoproteins, including the mucous cells in the submucosal glands, the goblet cells in the respiratory mucosa, and possibly even the ciliated cells themselves.[32] The control of mucous secretion has been studied *in vivo* and *in vitro* and has been noted to be complex.[32] Although experimental models show evidence of neural control and neurotransmitters, and chemical mediators have been shown to have an effect, the situation in humans is still somewhat unclear. The submucosal glands receive a dense innervation from the autonomic nervous system, and both cholinergic and adrenergic agonists stimulate macromolecular output.[5,32,35] A peptidergic nervous innervation also exists and appears to modulate airway mucous secretion via peptide neurotransmitters or neurokinins.[35] Various substances, including neuropeptides, inflammatory mediators, bacterial products, and irritants, may modify mucus output.[32] Experimental data suggest that there may be purinergic regulation of mucous secretion from goblet cells[37] and that an important central signaling pathway may exist, mediated by nitric oxide, in response to a variety of inflammation-associated stimuli (including tumor necrosis factor, platelet-activating factor (PAF), histamine, and reactive oxidants) to enhance mucin secretion.[38]

At least eight genes encoding human epithelial mucin have been identified thus far.[5,39] Four of these mucin genes have been found to be expressed in the lung.[39] Mucous gene loci are designated with the letters *MUC*, followed by the number reflecting the order in which the genes were cloned.[39] Both *MUC2* and *MUC5* appear to be major candidates for secreted mucin, because their messenger RNA have been demonstrated in airway epithelial cells.[39] *MUC5* appears to be responsible for normally secreted mucus and *MUC2* for mucus produced during airway inflammation or infection.[39] These preliminary data await confirmation in future studies. Secretions from airway epithelial cells can be stimulated by three types of secretagogues: irritant gases, inflammatory agents, and others, including mechanical strain and neuronal influences.[39]

MUCOCILIARY TRANSPORT

Mucociliary transport in the respiratory tract is essential to normal health and is of particular importance in host resistance to respiratory infections. Effective mucociliary clearance is dependent on the propulsion of mucus by the coordinated beating of cilia.[29] Mucociliary transport depends on the characteristics and normal functioning of each of the components of this system, including the cilia themselves, the periciliary fluid layer, and the mucus.[1,6,40] A number of theoretical models of mucociliary transport have been developed and have become increasingly sophisticated. They reflect the various components of the system. Several mechanisms exist to measure overall mucociliary function.[29,30] These include tests of ciliary function, measurement of the volume and characteristics of the periciliary fluid and mucous layers, and tests that assess the efficiency of mucociliary interaction.[29] The latter would include *in vivo* testing of mucociliary transport velocity and mucociliary clearance rates. A 1998 review described in detail the various experimental models for studying mucociliary clearance.[41] Some studies have shown an inverse relationship between mucociliary clearance and age.[7] The basis for this aging process is unknown. No gender difference appears to be present in mucociliary clearance in humans, but there is suggestion of a genetic determination of clearance.[7,42]

ABNORMALITIES OF MUCOCILIARY CLEARANCE

Abnormalities of the mucociliary escalator may occur as a primary defect or secondary to a disease process and may involve any of the components of the system, including the mucus, the