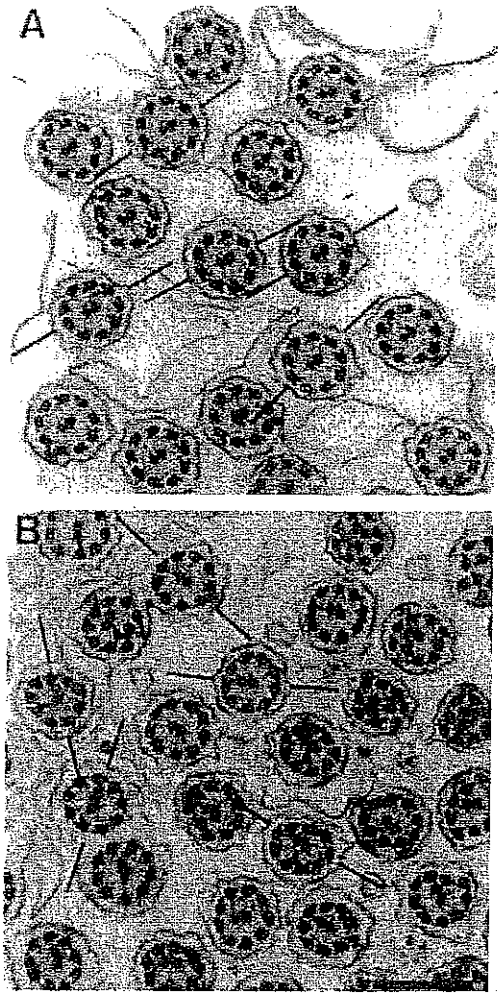

FIG. 2-6. Cilia from a healthy nonsmoking subject **(A)** shows aligned orientation of ciliary axes. Cilia from a patient **(B)** shows random orientation of the ciliary axes and eccentrically located central tubules (*arrowheads*). The ciliary axes are shown for five cilia in each field. (Scale bar: 0.3 μm.) (From de Iongh RU, Rutland J. Ciliary defects in healthy subjects, bronchiectasis, and primary ciliary dyskinesia. *Am J Respir Crit Care Med* 1995; 151:1559–1567, with permission.)

periciliary fluid, or the cilia themselves.[1,40] For example, mucous may become more elastic during viral infections or more viscous during bacterial infections, interfering with its movement.[1,40] Variations in the depth of the periciliary fluid may interfere with the coupling of the cilia to the mucous layer.[1,40] The movement of the cilia may be slow or disorganized. Last, the loss of large surfaces of the ciliated epithelium as a result of viral and bacterial infections may cause stasis of the overlying mucus.[1,40] The best-investigated of these disturbances of function have been the various effects on ciliary function.

Abnormalities of Ciliary Function

Abnormalities of ciliary function may be congenital or acquired. Siewart in 1903 was the first to describe the occurrence of bronchiectasis in a patient with situs inversus, but it was Kartagener, in 1933, who described the triad of clinical features of the syndrome that now bears his name (sinusitis, bronchiectasis, and situs inversus).[8,43] In 1976, Afzelius described a genetic disease caused by immotile cilia ("immotile cilia syndrome").[8] The prevalence was estimated at 1 person in 30,000.[44,45] It was initially thought that immotility of the cilia was the sole pathogenic mechanism, but subsequent studies suggested that the term *immotile cilia* was inappropriate and that in most patients the cilia showed some degree of mobility *in vitro*, although this may well be abnormal.[43,46] The term *primary ciliary dyskinesia* ("dyskinetic cilia syndrome") was then coined to describe the condition.[8,44,46] Over the past 10 years, this has also been noted to be inaccurate; patients with similar clinical features to those of patients with primary ciliary dyskinesia have been recorded whose cilia have near-normal beat frequency, are ultrastructurally otherwise normal, but have random orientation (Fig. 2-6).[47–49] Random orientation at the ciliary tips has also been noted in Young's syndrome, a disease proposed to be a *forme fruste* of cystic fibrosis, but this is thought to be simply a consequence of the abnormal mucus found in this condition.[50]

The commonest ultrastructural abnormality in patients with primary ciliary dyskinesia is that of absent dynein arms,[8,43] although other defects, such as absence of the nexin links, radial spoke defects, abnormal length of cilia, abnormal arrangements of the tubules, and even absent cilia, have been described (Table 2-1).[8,25,43,44,51–56] As a consequence of impaired ciliary function, inefficient mucous clearance occurs in these patients and predisposes them to develop not only acute and recurrent respiratory tract infections, but also sinusitis and chronic lung disease, including bronchiectasis, as a consequence of repeated infections.[40,43,44]

Primary ciliary dyskinesia is inherited as an autosomal recessive disease.[8] A major aim in the study of the abnormal cilia syndromes is to find the gene(s) responsible for these disorders.[45,57] This may not be an easy task, because several hundred genes are involved in the building of a single cilium.[45] Candidate genes may include those that code for the dynein heavy chains with their phosphorylating sites; those coding for tubulin, making up the microtubules; and those that code for the proteins that bind dynein heavy chains to the tubulins.[45] More than ten genes have been shown to encode different dynein heavy chains.[45] When all these genes have been characterized, it will then be possible to screen patients with suspected ciliary disorders in search of defective genes.[45]

Secondary disorders of ciliary function are said to be relatively common and may well account numerically for much more of the acute and chronic respiratory disease burden.[40] The term *secondary ciliary dysfunction* implies that ciliary structure and function were originally n[illegible]al.[40] Numerous factors are known to be associated with either slow or disorganized cilia.[40] Ultrastructural abnormalities of the cilia have been found in patients with chronic rhinitis, asthma, and

TABLE 2-1. *Ciliary abnormalities in primary ciliary dyskinesia*

Abnormality	Detail	Reference
Dynein arm defects	Absence or reduced number of inner and/or outer arms	[8,43,51]
Tubular defects	Transposition, extra microtubules	[8,43,44,51,53]
	Commonly secondary	—
Radial spoke defects	Absence	[8,43,44,51,54]
Ciliary disorientation	Suspect if mean standard deviation of angle >20 degrees, not reducing after treatment, and present in two sites (nose, bronchitis)	[47,48,49]
Abnormal basal apparatus	—	—
Ciliary aplasia	—	[8,44,52,55,56]
Abnormally long cilia	—	[8,44,55]
No abnormality	Repeat test and do orientation studies	—

Adapted from Bush A, Cole P, Hariri PR, et al. Primary ciliary dyskinesia: diagnosis and standards of care. *Eur Respir J* 1998;12:982–988, with permission.

recurrent bronchitis.[40] In the case of chronic bronchitis, these changes have been noted to become more evident as the disease progresses, and they may well contribute to the impaired mucociliary clearance that is part of the disease process.[58]

Chronic obstructive pulmonary disease (COPD) is most commonly due to cigarette smoking, and both whole cigarette smoke and its aqueous extracts cause cessation of ciliary beating *in vitro*.[40] Chronic smoking may also induce an increased number of abnormal cilia.[4,59] Although patients with COPD due to smoking have delayed mucociliary clearance, differences in studies comparing clearance in healthy smokers and nonsmokers are less clear cut.[40,60] Acute exposure to cigarette smoke *in vivo* gives conflicting results of slowed, unchanged, or even accelerated clearance.[4,40,60,61] Slowing of ciliary beating by cigarette smoke *in vitro* is reversible provided exposure is stopped before ciliostasis occurs, possibly explaining the disparity between some of the data, particularly when comparing *in vivo* and *in vitro* studies.[40,61,62]

Other environmental pollutants, including sulfur dioxide and nitrogen dioxide, have been associated with the development of structural and functional abnormalities of the axonemes.[29,40] A variety of anesthetic gases have been shown to depress ciliary activity, and, in some studies, exposure to high inspired oxygen concentrations has also been associated with impaired ciliary function.[29] Impairment of mucociliary transport may occur as a consequence of physical trauma to the ciliated epithelium, as occurs in intubated patients undergoing mechanical ventilation in the intensive care unit.[3,7,29,63] This is thought to be an important factor predisposing these patients to nosocomial pneumonia.[3,63] Nutritional factors may also be important. For example, loss of cilia has been noted to be one of the early consequences of vitamin A deficiency, and this is said to be responsible for the known susceptibility to tracheobronchial infections among vitamin A–deficient individuals.[64] Alcohol causes pronounced inhibition of ciliary function, and this is thought to be one of the mechanisms by which patients who abuse alcohol are predisposed to pulmonary infections.[4,65] A number of acquired structural defects of the axoneme have been noted in these secondary ciliary disorders, in addition to the occurrence of random orientation.[51,66–70]

Importantly, several respiratory pathogens have been found to produce factors that slow ciliary beating *in vitro*. The true significance of these factors *in vivo* is uncertain, but investigators using an *in vivo* experimental model have been able to produce reduced tracheal mucus velocity using some of these fractions.[40] Viral infections are associated with delayed mucociliary clearance, due largely to loss of ciliated epithelium.[40] For example, during influenza infections, the bronchial epithelium shows degeneration and desquamation of cells.[40] However, viral infections have also been shown to cause defects in the ciliary microtubules associated with cytopathic changes in the epithelial cells and progressive loss of ciliated cells from the epithelium.[3,71] The synergistic role of viruses in predisposing to bacterial infections of the airways is multifactorial and includes loss of ciliated cells, slowing of ciliary beating, increased mucous production, altered mucus rheology and ion transport, and a change in epithelial cell receptors for bacteria.[1]

Bacteria–Host Interactions with Ciliary Function

Several bacteria associated with either acute or chronic respiratory infections in humans, including *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, some strains of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bordetella pertussis*, and others have been documented to produce factors that perturb the mucociliary mechanism and cause injury to ciliated epithelium *in vitro*.[40,68,72] By these means, it is thought that these organisms perturb mucociliary clearance during infections.

Wilson and coworkers noted that the phenazine pigments of *P. aeruginosa*, pyocyanin, and 1-hydroxyphenazine slowed cilia in a dose-dependent manner.[73] Pyocyanin caused a gradual onset of progressive ciliary slowing, ultimately associated with widespread ciliostasis and epithelial damage, whereas 1-hydroxyphenazine caused a rapid onset of ciliary slowing that was reversible.[73,74] Marked ciliary dyskinesia was seen with the latter. Using radiolabeled erythrocytes in anesthetized guinea pigs, they also documented that these toxins slowed tracheal mucous velocity.[1,74] The phenazine pigments have been noted

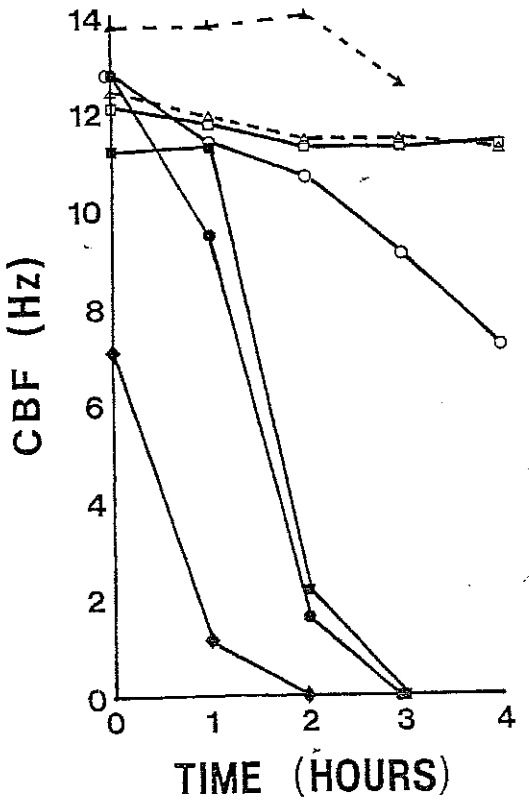

FIG. 2-7. The effect of native pneumolysin purified by high-pressure liquid chromatography from *Streptococcus pneumoniae* on ciliary beat frequency (CBF) of human respiratory epithelium *in vitro*. Open and solid symbols represent data obtained from different biopsies. Experiment 1: solid triangle, control (phosphate buffered saline [PBS]); solid diamond, 50 μg of pneumolysin per mL; solid circle, 25 μg per mL; and solid square, 10 μg per mL. Experiment 2: open triangle, control (PBS); open circle, 5 μg of pneumolysin per mL; open square, 1 μg per mL. (From Steinfort C, Wilson R, Mitchell T, Feldman C, et al. Effect of *Streptococcus pneumoniae* on human respiratory epithelium in vitro. *Infect Immun* 1989;57:2006–2013, with permission.)

to have diverse proinflammatory interactions with human phagocytes, which may intensify both bacterial and neutrophil-mediated epithelial injury. *P. aeruginosa* proteases and rhamnolipid and its lectins (agglutinin I and agglutinin II) also inhibit ciliary beating, and the former toxins cause epithelial disruption in addition.[1,28,75] A 1996 study showed that the beat direction of cilia from sites of infection, particularly that of *P. aeruginosa*, was disoriented and that the degree of disorientation closely correlated with the delay in mucociliary clearance.[1,74] Treatment with antibiotics and topical corticosteroids decreased the ciliary disorientation and improved mucociliary clearance.[1,74] That study suggested that growth of cilia may be affected by bacterial infection, either as a direct consequence of bacterial infection or due to the induced inflammation.[1,74]

Studies with *S. pneumoniae* have documented that its protein toxin, pneumolysin, is responsible for the effects on ciliated epithelium.[76] Pneumolysin has distinct cytotoxic and complement-activating moieties, resident in separate domains on the molecule, and it appears that its effects on ciliated epithelium are associated with the cytotoxic region.[28] *In vitro* studies have demonstrated that pneumolysin causes dose-dependent ciliary slowing in human nasal brushings, even in the absence of cell ultrastructural changes (Fig. 2-7).[76] Pneumolysin has many additional proinflammatory activities. For example, in an experimental model of lobar pneumonia, pneumolysin alone induced the salient histologic features of pneumococcal infection in the rat lung, and prior immunization with Freund's adjuvant and pneumolysin reduced the severity of the pneumonia.[28]

We do not have the ability to test these *in vitro* observations accurately *in vivo*. However, *P. aeruginosa* phenazine pigments have been found in the sputum sol phase of patients with cystic fibrosis and bronchiectasis, who are colonized with this organism, in sufficient concentrations to inhibit ciliary beating *in vitro*.[28] The cellular mechanisms by which these toxins may cause ciliary dysfunction and epithelial disruption have been investigated further. A study using sheep trachea suggested that the mechanism of epithelial injury with pyocyanin may be related to enhanced release of reactive oxidants from polymorphonuclear leukocytes present within the epithelial surface.[77] In contrast, studies using human nasal ciliated epithelium have suggested that the mechanism of ciliary slowing is due to depletion of intracellular cyclic AMP and ATP, and the effects do not appear to be mediated through polymorphonuclear leukocytes.[78] Ciliary slowing could be prevented by agents that increase intracellular cyclic AMP and by the cyclic AMP analog, dibutyryl cyclic AMP, and these agents also delay the onset of epithelial disruption.[78] *M. pneumoniae* has been shown to attach to cilia and to cause ciliolysis by disrupting the necklace region, possibly due to release of hydrogen peroxide.[3,68]

The epithelial damage seen in infections, particularly chronic infections, is not mediated by bacterial products alone. A number of host-derived factors have been noted to cause ciliary dysfunction and epithelial injury *in vitro* and may be contributing to disease pathogenesis. Enzymatically generated oxidants and reagent preparations of hydrogen peroxide (H_2O_2) and hypochlorous acid have been shown *in vitro* to cause ciliary dyskinesia and slowing at concentrations ≥100 μm, with complete ciliostasis occurring at higher concentrations (Fig. 2-8).[28,79] Although activated human phagocytes may be an important source of these reactive oxidants, it has been recognized that the pneumococcus itself produces H_2O_2 in significant amounts, and this appears to be an important virulence determinant of this organism.[28] In an experimental model, it was noted that low concentrations of H_2O_2 inhibited ciliary activity in a reversible, nonlethal, dose-dependent fashion, possibly through the action of second messengers including protein kinase [illegible] whereas higher concentrations were cytotoxic.[80] Experimental studies have also shown that mucus contains at least one glycoprotein that scavenges H_2O_2 in a concentration-dependent fashion and

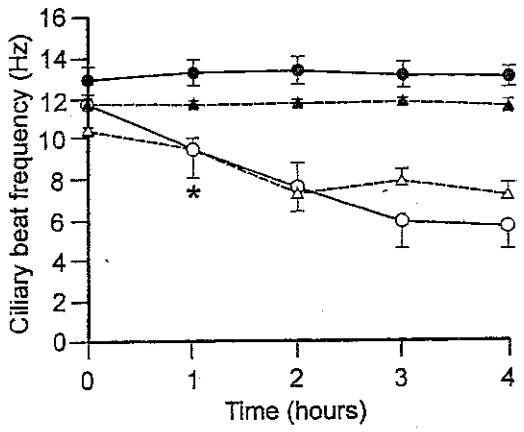

FIG. 2-8. The ciliary beat frequency of human nasal ciliated epithelium over 4 hours of exposure to the glucose (5 mM) and glucose oxidase reactive oxidant-generating system (open circles with unbroken line, 100 mU per mL; open triangles with dotted line, 25 mU per mL), with respective controls shown in filled symbols. The onset of dyskinesia is indicated by the asterisk. (Reprinted from Feldman C, Anderson R, Kanthakumar K, et al. Oxidant-mediated ciliary dysfunction in human respiratory epithelium. *Free Rad Biol Med* 1994;17:1–10, with permission from Elsevier Science.)

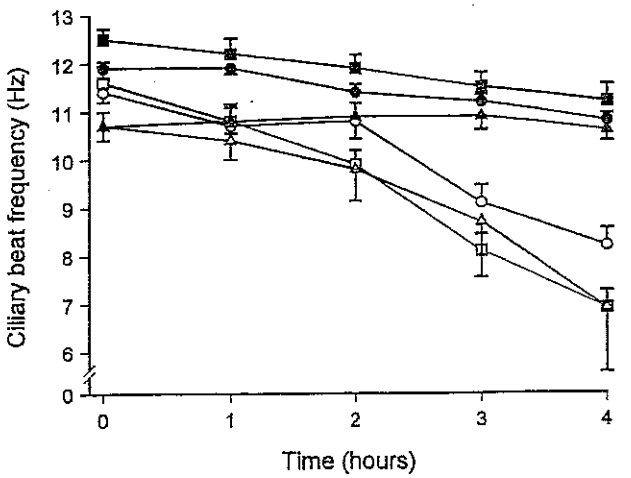

FIG. 2-9. The effects of bioactive phospholipids, platelet-activating factor (PAF), lyso-PAF, and lysophosphatidylcholine on ciliary beat frequency of human ciliated epithelium *in vitro* over 4 hours. The open circular, square, and triangular symbols represent experimental systems containing lysophosphatidylcholine, PAF, and lyso-PAF, respectively, and the matched closed symbols represent the corresponding bioactive phospholipid-free control systems. (From Feldman C, Anderson R, Theron AJ, et al. Roxithromycin, clarithromycin, and azithromycin attenuate the injurious effects of bioactive phospholipids on human respiratory epithelium in vitro. *Inflammation* 1997;21:655–665, with permission.)

may exist to protect ciliated epithelium from reactive oxidants released by luminal phagocytes.[81]

As noted in the section Control of Ciliary Beating, the endogenously produced bioactive phospholipids, including PAF, lyso-PAF, and lysophosphatidylcholine may play a role in noninfective inflammatory disorders of the airways and appear to be important putative mediators of asthma. These bioactive phospholipids have been noted to cause significant dose-dependent slowing of ciliary beating and epithelial injury at concentrations ≥1 μg per mL (Fig. 2-9).[82] These effects are enhanced in the presence of polymorphonuclear leukocytes, probably due to enhanced reactive oxidant production by these cells, induced by the bioactive phospholipids.[82] PAF-activated guinea pig eosinophils have also been shown to disrupt guinea pig tracheal epithelium and affect ciliary function, at least partly due to enhanced reactive oxidant production.[28]

Elastase is another neutrophil product that damages epithelium. High concentrations (500 μg per mL) progressively reduce ciliary beat frequency and cause marked epithelial disruption, whereas lower concentrations (20 μg per mL) also cause epithelial disruption but without slowing ciliary beating.[28] Free elastolytic activity has been shown to be increased in purulent sputum. Enzymes such as collagenase and cathepsin G may be released from neutrophils during host cell–bacterial interactions and can overcome the capacity of inhibitors, such as alpha$_1$-antiproteinase in the pulmonary secretions, to neutralize their effects on airway epithelium.[40]

Agents Attenuating the Effects of Bacteria on Ciliated Epithelium

As noted earlier in the section Control of Ciliary Beating, a number of mediators and various pharmaceutic agents have been shown to affect ciliary beat frequency, and several of these agents have been shown *in vitro* to attenuate the effects of bacteria, bacterial products, and various other toxic substances on human ciliated mucosa.[7,28] Although investigators are beginning to elucidate possible mechanisms, the exact clinical relevance of these observations needs clarification. Salmeterol, a long-acting beta$_2$ agonist, has been shown to reduce pyocyanin-induced slowing of human ciliary beating *in vitro* and to lessen the fall in intracellular cyclic AMP and ATP apparently through stimulation of the beta$_2$ adrenoceptors, as well as to attenuate epithelial damage and loss of ciliated cells induced by *P. aeruginosa* infection without affecting the distribution of the organism on the mucosa.[28,83] Similarly, salmeterol appears to protect the respiratory epithelium against *H. influenzae*–induced damage.[84] Although the mechanism of the cytoprotective action of salmeterol is uncertain, it has been demonstrated that salmeterol antagonizes the proinflammatory, prooxidative activity of the bioactive phospholipids by a membrane-stabilizing mechanism.[28]

Low, sub-minimum inhibitory concentratic ..MIC) concentrations of the antibiotics amoxicillin, loracarbef, and ciprofloxacin have been noted to attenuate the effects of *H. influenzae* on human ciliated epithelium *in vitro*, and erythromycin has been

shown to suppress the production by *P. aeruginosa* of toxins that either damage epithelium or stimulate neutrophil cytotoxicity.[28] The macrolide/azalide antibiotics (roxithromycin, clarithromycin, and azithromycin), which enhance mucociliary clearance by stimulating ciliary beat frequency and inhibiting mucous hypersecretion, have also been noted to attenuate the effects of bioactive phospholipids on human ciliated epithelium, predominantly by inhibition of reactive oxidant production as a consequence of their membrane-stabilizing activity.[28,82]

Some of these interesting *in vitro* observations have been found to have clinical relevance. For example, diffuse panbronchiolitis is a chronic infectious disease of the airways, associated initially with *H. influenzae* and then with *P. aeruginosa* colonization.[85] This condition has been described mainly in patients in the Far East. Although patients with the condition previously were considered to have a poor prognosis, the outcome has improved dramatically with the use of low-dose, long-term erythromycin, probably as a consequence of its antiinflammatory activities.[85] Similarly, use of macrolide antibiotics has been shown to improve asthma control, also possibly as a result of antiinflammatory action.[82]

Abnormalities of Mucus and Periciliary Fluid

Abnormal secretions are the major cause of mucociliary dysfunction in most disorders of the airways. Changes in both mucus and periciliary fluid are usually the result of airway inflammation.[1] Products of activated leukocytes, peptides released from afferent nerves, and inflammatory mediators all contribute to the process.[39] In cystic fibrosis, the primary abnormality is a defect in the cystic fibrosis transmembrane regulator gene that results in decreased chloride secretion into the airway lumen and increased sodium and water reabsorption.[7] This results in the production of very thick viscous mucus due to failed hydration, associated with the inability to maintain an adequate periciliary fluid level with secondary impairment of ciliary beating.[7] Sputum of patients with cystic fibrosis contains a large amount of DNA that originates from the large number of luminal leukocytes that are present as a consequence of chronic colonization and infection of the airways. This adds to the viscosity of mucus and impedes normal mucociliary clearance, even if other components of the transport system are functioning normally.

In chronic inflammatory disorders of the airways, including asthma and COPD, hypertrophy of submucosal mucous glands and hyperplasia of goblet cells are present, which together with airway inflammation lead to excessive luminal secretions.[7,40] The mucociliary transport rates in these patients are decreased.[7] In the case of asthma, a further decrease in transport rates is seen after allergic challenge and appears not to be due to depressed ciliary activity, but rather secondarily to a change in periciliary fluid production and possibly even function, together with alterations in the luminal mucous layer. Leukotrienes appear to be important mediators of these effects in asthmatics.[7] The sol phase from asthmatic sputum samples has, however, also been shown to cause slowing of human cilia *in vitro*.[40]

An important initial event in the pathogenesis of most infections is the attachment of bacteria to epithelial surfaces and associated structures, as is discussed more fully in Chapter 4. It appears from *in vitro* studies that the first interaction of most bacteria with the airways' epithelium is with the mucous layer. Factors perturbing mucociliary clearance may enhance bacterial colonization of the mucus in the airways, which may be an important precursor to acute and chronic infections of the lower respiratory tract. A number of bacteria that cause bronchial infections or colonize the respiratory tract (e.g., in patients with COPD or bronchiectasis) elaborate extracellular substances that stimulate mucous secretion *in vitro*. For example, *P. aeruginosa* proteases and rhamnolipid have been shown in an experimental model to stimulate mucous production *in vivo*.[1] *S. pneumoniae* and *H. influenzae* have also been noted to stimulate secretion of mucus *in vitro*.[86] *P. aeruginosa* rhamnolipid has also been noted to affect chloride ion transport.[1]

The interactions of *S. pneumoniae* with human ciliated mucosa have been studied in an organ culture *in vitro*.[28] *S. pneumoniae* adhered initially to a thick gelatinous mucous layer and caused progressive ciliary slowing, these effects presumably being due to the pneumolysin. Adherence to epithelial cells or cilia was not seen, and only minor and patchy epithelial damage was noted. Later, epithelial disruption was recorded with separation of tight junctions through which these organisms appeared to invade.[28]

Similarly, *H. influenzae* also initially associated with the mucous layer of the epithelial surface, and later with damaged epithelium, which appears to be a prerequisite for the association of this organism with respiratory epithelium.[28] In the same organ culture model, *P. aeruginosa* adhered preferentially to mucus, damaged epithelium, and exposed basement membrane.[28] Bacterial adherence to mucus occurs via specific interactions between adhesin structures on bacterial surfaces and receptors in the mucus.[1,87–91] Airway mucus is rich in potential receptors for bacteria,[87] and studies are under way to determine the specific bacterial and host structures involved.[1,87,88,92,93] Although under normal circumstances this avid adherence to mucus may serve as a mechanism to trap bacteria and remove them from the airways, in cases of chronic colonization, such as occurs in cystic fibrosis, bronchiectasis, and diffuse panbronchiolitis, this may serve a deleterious role.[88]

COUGH

Cough is a relatively common reflex that is activated when the normal mucociliary apparatus is severely impaired or is overwhelmed by inhaled particles or secretions.[10] Under these conditions, energy derived from airflow is needed to move the mucus. Cough is elicited when sensory receptors in the upper and lower airway epithelium are stimulated by mechanical and chemical stimuli.[10,94–97] Mechanical receptors are sensitive to touch and displacement, and chemical receptors are sensitive to noxious gases and fumes.[98] Receptors are thought to be wide-

spread and are said also to be found in the sinuses, tympanic membranes, pericardium, diaphragm, and stomach.[10,96,98] Whether they have a physiologic role in eliciting the cough reflex is uncertain. Three types of receptors in the lungs are believed to be involved in the cough reflex, including rapidly adapting (irritant) stretch receptors, slowly adapting stretch receptors, and the bronchial C fiber receptors.[10,94,95,97] These are all distributed throughout the tracheobronchial tree.

Stimulation of the rapidly adapting receptors in the airways appears to elicit the cough reflex and may also induce mucous secretion, in turn stimulating cough, although some question of their importance in the cough reflex exists.[10,94,97,98] The role of the C fibers is not clear. Although stimulation of these receptors inhibits cough, it also induces mucous secretion, which then stimulates cough.[10] The role of the slowly adapting receptors appears to be the stimulation of the expiratory muscles.[10] Afferent impulses from the irritant receptors enter the brain via the vagus, trigeminal, glossopharyngeal, and superior laryngeal nerves.[10,95,96,98] The efferent pathway causes activation of the glottic, diaphragm, intercostal, and abdominal muscles.[98] Debate is still ongoing as to whether a discrete cough center exists in the brain.[98]

An effective cough depends on the ability to achieve high gas flows and velocities through the airway.[98] For a cough maneuver, the glottis is closed for approximately 0.2 seconds after a rapid deep inspiration ranging in volume between 50% of tidal volume and 50% of vital capacity.[10,96,98] The intrapleural pressure rises significantly, the glottis is opened, and a rapid exhalation follows with explosive release of intrathoracic air.[10] Due to dramatic airway compression during cough, as a result of the high pressure gradient between the pleural space and the airway, the airflow velocity reaches up to 280 meters per second in the trachea and approaches sonic velocity.[2,96] This high velocity explains the efficiency of cough in the trachea, which serves to dislodge mucus and other foreign particles and allows them to be expectorated.[10] Cough clearance is essentially a stepwise process mobilizing mucus toward large airways by successive coughs. Repetitive coughs can damage airway epithelium. In addition, the pressures, velocities, and energy produced during vigorous coughing can cause a variety of cardiovascular, central nervous system, gastrointestinal, genitourinary, and various other complications that have been reviewed elsewhere.[96]

The efficacy of cough depends on the fluid dynamic interaction between the mucous layer and airflow. For cough to be effective in moving mucus, the secretions must be dispersed into the expiratory gas.[98] This interaction has been analyzed in the framework of a two-phase gas-liquid flow.[98] Interacting with the mucous layer, the airflow develops shear force on the interface with the mucous layer, the magnitude of which is directly proportional to the kinetic energy of the airflow. To move mucus in the direction of the large airways, the shear force has to overcome the mucous viscosity and gravitational forces.

Depending on the airflow velocity and the characteristics of mucus, the mucous layer moves in different patterns. In small airways, particularly at high airflow velocities, mucus is moved by a squeezing action as alveolar pressure distal to the mucous plug increases. Hence, the so-called annular flow pattern, in which a channel of air forms through the mucous plug, is the major mechanism for mucous clearance from the lower airways.[98] At some of the very high velocities commonly encountered in the larger airways, mucus may be torn off the surface and form droplets that are suspended in the airway lumen.[98] This so-called misty flow is typical during expectoration of mucus from the trachea.[98]

If airflow requirements are met, the effectiveness of mucous clearance depends on the depth of the mucous layer and its rheologic properties.[98] Also, for a given airflow velocity, a critical mucous depth is required for mucus to be moved. The critical depth increases with increasing mucous viscosity, and with constant viscosity the critical depth tends to increase with elasticity. Healthy people cannot clear airway mucus by coughing, because normal mucus is too thin for effective gas-liquid interaction. Elasticity has a negative effect on mucous clearance by cough, but a positive effect on the movement of secretions by ciliary beating.

An alternate explanation to this two-phase gas-liquid flow theory is the hypothesis that the removal of airway secretions by cough may have more to do with stimulation of ciliary activity than dispersion of liquid into gas.[98] This suggests that the high velocity of air during cough may stimulate the mucociliary mechanism either by changing secretions of periciliary fluid or by directly increasing ciliary beating.

A number of factors may adversely influence the efficiency of the cough mechanism, including expiratory and respiratory muscle weakness, changed mucous rheology (particularly an increase in viscosity and elasticity), and altered mucociliary function.[98] Normal function of the mucociliary apparatus is important in the maintenance of an effective cough, because it is needed to transport secretions from the periphery to the more proximal airways, where they can be cleared by cough.[98]

Conversely, a number of both pharmacologic and nonpharmacologic protussive treatment modalities have been described that appear to improve cough clearance, although clinical studies of these agents and techniques that document improvement in patient outcome are lacking.[98,99] Expiratory muscle training, mechanical aids to cough such as compression of the lower thorax and abdomen and chest physiotherapy with postural drainage, vibration, and percussion have been described as being beneficial. The forced expiratory technique of "huffing" that requires the patient to forcibly exhale with the glottis open, from a medium to low lung volume, has been introduced as an alternative to cough for removal of secretions.[98] This technique has the advantage of lower transpulmonary pressure and less airway compression and closure than coughing, and it has been found to be effective in removing secretions in patients with COPD.[98]

CONCLUSION

Mucociliary dysfunction is present in a number of respiratory diseases, especially those that involve the airways, and

is a consequence of the disease process. Although mucociliary dysfunction may itself cause considerable morbidity, the available treatment modalities for this component of the disorder are often not very effective and are usually ignored.[99] Some drug therapy (e.g., beta-adrenergic antagonists) and physical therapy seem to benefit patients with impaired mucociliary clearance, but none of these treatment modalities is very effective alone.[99] A better understanding of factors implicated in mucociliary dysfunction and modalities by which these may successfully be reversed, as investigated in studies such as those which are discussed earlier in this chapter, may help identify novel treatment strategies for this component of various respiratory disorders.

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