The Effect of Inflammation on Mucociliary Clearance in Asthma*

An Overview

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Mucociliary clearance (MCC) is one of the most important nonspecific defense mechanisms of the respiratory tract, and its impairment is a well-documented feature of chronic respiratory diseases, including asthma. In vitro and in vivo data suggest that several inflammatory mediators influence the mucociliary apparatus. Epithelial damage and functional abnormalities have been described in bronchial asthma, along with changes in mucus-secreting cells and the chemical and rheological properties of airway fluid. Although the mechanisms of MCC impairment in asthma are not clearly understood, data in the recent literature suggest that airway inflammation plays a major role. In this article, we review studies on MCC alterations in light of up-to-date findings on pathogenetic mechanisms in asthma.

(CHEST 2000; 118:1142–1149)

Key words: asthma; inflammation; mucociliary clearance

Abbreviations: CB = chronic bronchitis; ISH = isocapnic hyperventilation; MCC = mucociliary clearance; PAF = platelet-activating factor; PG = prostaglandin; TMV = tracheal mucus velocity

Human lungs represent the largest area (range, 40 to 120 m²) exposed to environmental agents, and the amount of air inhaled into the lungs is about 10 to 20 m³ in 24 h. In the lung, numerous and complex mechanisms maintain cleanliness and sterility, and some are specific, while others are nonspecific mechanisms (eg, mucociliary clearance [MCC] and cough). MCC is one of the most important nonspecific defense mechanisms of the airways. The efficacy of the mucociliary apparatus is due to (1) the morphologic integrity of the cilia structure and mucus components, and (2) the functional efficacy of synchronism and the magnitude of ciliary activity, periciliary fluid depth (sol), and mucus rheological properties (gel).

During a mild airway inflammation such as that occurring in acute viral infections, mucus hypersecretion and changes in the MCC are small and transient. In contrast, in chronic pathologic conditions such as chronic bronchitis (CB), cystic fibrosis and asthma, permanent changes in ciliary structure and function, mucus hypersecretion and/or rheological changes, result in mucus retention.

It is well-documented that MCC is reduced in heavy smokers, and in patients with CB and bronchiectasis. Although MCC also is impaired both in stable patients with asthma and during exacerbations, it is affected to a lesser extent than in patients with CB or bronchiectasis.

In this review, we analyze the MCC functional changes and the contribution of mucus and cilia to the impairment of the mucociliary apparatus in patients with asthma due to the pathologic effects of airway inflammation.

MCC Impairment in Asthmatic Patients and Animal Models

MCC impairment in asthmatic patients was first described by Hilding in 1943 and by Dunnill in 1960. When the authors examined patients who had died of bronchial asthma, they found a reduced number of ciliated cells, goblet cell metaplasia, and large amounts of hyperviscous mucus. On the basis of these findings, the authors suggested that modifi-
cations occurring during asthmatic attacks are associated with a marked ciliary dysfunction and with a decrease of MCC.

To confirm this hypothesis, Santa Cruz et al.\(^{18}\) studied tracheal mucus velocity (TMV) in elderly patients (age range, 57 to 71 years) with obstructive lung disease. These studies, which were carried out by a cinebronchoscopic technique that measures the velocity of Teflon disks placed in the trachea, showed a considerable decrease of TMV. Moreover, Foster et al.\(^{19}\) found a considerable reduction both in mucus clearance and mucus speed in the trachea of symptomatic asthmatic patients. Additionally, Bateman et al.\(^{12}\) in a study of a large group of stable patients with mild asthma and a wide age range, showed that tracheobronchial clearance, evaluated by following the movement of the 5-μm radioaerosol polystyrene particles on a gamma-scanner, was significantly poorer than in the age-matched control group.

In contrast, by using the inhalation of Teflon particles labeled with \(^{99m}\)Tc, Mossberg et al.\(^{20}\) observed no significant reduction in tracheobronchial clearance in a group of asthmatic patients who no longer experienced asthmatic attacks. Since aerosol inhalation was obtained mainly by forced inspiratory maneuvers in the central airways, those findings did not exclude some possible epithelial damage in peripheral airways with a reduction of MCC.

MCC changes are present in the asthmatic airways of the entire bronchial tree, as was demonstrated by Bateman et al.\(^{12}\) and confirmed by Daviskas et al.\(^{21}\) These results contrast with those obtained by Foster et al.\(^{22}\) who stated that MCC undergoes changes only in the large airways.

The discrepancies between studies are probably due to the different techniques used and different clinical stages of the disease.

Furthermore, clinical exacerbation of asthma can dramatically decrease MCC, and impairment is of longer duration than airflow obstruction. In this regard, Pavia et al.\(^{13}\) showed that in asthma patients who were in clinical remission and were far from acute exacerbation, a significant reduction of MCC still was present when lung function parameters returned to normal values. When Messina et al.\(^{14}\) evaluated MCC by radioaerosol and gamma-camera in a small group of asthmatic patients during acute exacerbation and after hospital discharge, they observed a severe decrease of MCC during the acute phase of disease, along with an improved speed of MCC during the last days of hospitalization and in the period following discharge. The authors suggested that MCC measurement could be useful for the evaluation of bronchial inflammation and the monitoring of therapeutic interaction in asthma.

Finally, the normal physiologic decrease of MCC during sleep\(^{23}\) becomes more pronounced in asthmatic patients,\(^{24}\) and the nocturnal reduction of MCC can improve after therapy with inhaled \(\beta_2\)-agonists\(^{25}\) and methylxanthines\(^{26}\) but does not improve following the administration of oral, slowly released \(\beta_2\)-agonist, as previously reported by Hasani et al.\(^{27}\)

**Effects of Mediators on MCC**

The effects of inflammation have been investigated in animal models of asthma\(^{28}\) as well as on atopic and nonatopic patients.\(^{29}\) Also, several inflammatory mediators have been found and studied in the bronchial fluid of patients (Fig 1).\(^{30}\)

Chemical mediators of anaphylaxis appear to have various and sometimes opposing effects on the two essential components for MCC, cilia and mucus. It appears, however, that the net effect of the various chemicals involved in anaphylaxis is impairment of mucus clearance\(^{31}\) (Table 1).

Mezei et al.\(^{32}\) studied six asymptomatic atopic asthmatic patients for whom the mucus velocity in the trachea, which was evaluated radiographically, was significantly reduced when compared to that of seven healthy subjects. In all patients, TMV was measured immediately and 1 h following an antigen inhalation challenge. The study showed a 28% decrease of TMV from baseline immediately after exposure to the antigen and a 53% decrease 1 h later, when both specific airway conductance and FEV\(_1\)

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**Figure 1.** An old and significant proposed sequence of events leading to the accumulation of airway secretions in patients with asthma. Adapted from Wanner.\(^{30}\)
Mezey et al.32 while also pointing out that inﬂamat-
a
topic asthmatic patients conﬁrmed the results of
1
1
Endothelin 1, 2, and 3

Leukotriene D4

a significant decrease in the percentage of FEV1 was
treated previously with sodium-cromoglycate even if
reduction of mucus velocity when patients had been
returned to normal values. In contrast, there was no
reduction of mucus velocity when patients had been
treated previously with sodium-cromoglycate even if
a significant decrease in the percentage of FEV1 was
evident. Thus, the authors concluded that the mech-
anism of TMV reduction implies a role for mast cell
mediators.

A similar study carried out by Ahmed et al.33 on
atopic asthmatic patients conﬁrmed the results of
Mezey et al.32 while also pointing out that inﬂama-
tory mediators released after antigen challenge re-
duced mucus transport in the trachea. Additionally,
previous treatment with a slow-reacting substance of
anaphylaxis antagonist (FLP-55712) prevented
changes from occurring.

The inﬂammatory mechanism is also evident in
the upper respiratory tract (ie, the nasal and oro-
pharyngeal tract), as observed by Awotedu et al.34 in a
group of asthmatic subjects with and without allergic
rhinitis. By using the saccharine method, the authors
found a signiﬁcant decrease of nasal MCC. Kurashima et al.35 studied the effect of a thrombox-
ane-A2 synthetase inhibitor (OKY-046) on the im-
pairment of nasal MCC by saccharine testing in 19
asthmatic subjects. Since they found an increase of
nasal mucociliary transport after 4 weeks of treat-
ment with the thromboxane-A2 synthetase inhibitor,
they concluded that thromboxane plays an important
role in the pathogenetic mechanism of MCC in
asthma.

Not all inﬂammatory mediators can impair and
decrease MCC in asthma. In fact, Wanner et al.28
found that histamine and acetylcholine can increase
the transport of mucus in dog tracheas. This ﬁnding
was conﬁrmed further by consecutive studies made
on sheep trachea strips. The authors found a de-
crease of surface liquid velocity secondary to perfu-
sion with a platelet-activating factor (PAF) and an
antigen. On the contrary, after acetylcholine perfu-
sion, an increase of surface liquid velocity in a
concentration-dependent manner occurred.36

Polosa et al.37 evaluated the strong effect of brady-
kinin, a vasoactive nonapeptide with secretagogue
properties, on the secretory cells of dog airways and
of nasal mucosa in vivo, and they suggested that it
acts as a mediator in the pathogenesis of bronchial
asthma. They conﬁrmed previous data by Yeates et al.,38 demonstrating that in healthy subjects this
compound increases MCC with respect to a control
group treated with a placebo.

**AIRFLOW OBSTRUCTION AND MCC**

Despite the fact that MCC is impaired in asth-
matic patients, there is no clear evidence that the
severity of disease, as reﬂected by airflow obstruc-
tion, is correlated with the degree of impairment of
MCC.39

The pathologic modiﬁcations that occur in bron-
chial asthma, most importantly bronchial ﬂow ob-
struction, can be included among the possible causes
of MCC impairment. Studies in animal models
showed that the induction of a ﬂow-limitation seg-
ment determined the reduction in mucociliary
movement.40 This ﬁnding also was conﬁrmed in
humans. It is believed that ﬂow limitation is caused
by repetitive coughing in the segmental and subseg-
mental bronchi,41,42 and that coughing may decrease
MCC in central airways.43

In 1978, Mezey et al.32 when studying TMV in
subjects affected by bronchial asthma with a wide
baseline FEV1 range, observed that after antigen
challenge the decrease of TMV was not correlated
to the fall in FEV1. Moreover, although sodium crom-
glycinate treatment did not prevent the bronchocon-
striction that was induced by antigen challenges, an
increase of mucus transport was observed. Since,
with the same cumulative antigen dose, speciﬁc
airway conductance and FEV1 decreased less than
without cromolyn pretreatment, a partial protection
against bronchoconstriction is suggested. The au-
thors concluded that bronchial obstruction did not
cause MCC changes.

### Table 1—Effects of Inflammatory Mediators on MCC, Ciliary Beat Frequency, and Mucus Secretion*

<table>
<thead>
<tr>
<th>Inflammatory Mediators</th>
<th>MCC</th>
<th>Ciliary Beat Frequency</th>
<th>Mucus Secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>↑</td>
<td>↑ (↓)</td>
<td>↑</td>
</tr>
<tr>
<td>SRS-A</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-Hydroxyeicosatetraenoic acid</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Leukotriene C4</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Leukotriene D4</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboxane A2</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAF</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophil major basic protein</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Eosinophil cationic protein</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil elastase</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral protease</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mast cell chymase</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGs</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>VIP</td>
<td>↑</td>
<td>↑ (↓)</td>
<td></td>
</tr>
<tr>
<td>Neurokinin A</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance P</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsaicin</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cathepsin G</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement C3a and C5</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelin 1, 2, and 3</td>
<td>↑</td>
<td>↑ (↓)</td>
<td></td>
</tr>
</tbody>
</table>

*↑ = increase; ↓ = decrease; ↑ (↓) = increase with some reported decreasing effect or no effect.
In addition, O’Riordan et al., in a group of stable asthmatic subjects with varying degrees of bronchial obstruction, observed that patients with significant decreases of MCC were affected by airflow limitation during tidal breathing. However, they did not find any correlation between obstruction and decreasing MCC. Also, in a later study, the same group did not experience any MCC reduction during methacholine-induced challenge.44

Cilia: Structure and Functions in Asthma

In asthmatic patients, mucus hypersecretion causes a decrease of ciliary beat frequency with respect to the duration of bronchial inflammation and produces severe structural and functional epithelial damage to the mucociliary apparatus.45

Ultrastructural and in vitro studies have demonstrated that cilia have claw-like projections on their tips that move secretions during the “effective stroke” and return to primary position during the “recovery stroke” by moving slowly in the periciliary fluid (sol phase).46–48

The shedding of airway ciliated epithelium is one of the most significant and frequently occurring morphologic alterations of asthma.49 It is also a characteristic pathologic feature of asthmatic tissue obtained from autopsy,17 bronchial biopsy50 and BAL.51 In this regard, ciliated cells obtained in bronchial biopsy52 and in BAL53 correlate with the degree of bronchial responsiveness, and ciliary destruction is more evident with persistent disease, although it can be reversed with steroid treatment.54

Structural changes, such as ciliary epithelial lesions, with cells that often appear swollen, as well as intercellular space edema have been described in the airway epithelium of asthmatic patients.

Electron microscopy has shown ciliated cells with vacuolization of both the endoplasmic reticulum and mitochondria and a loss of cilia,50,51 along with microtubular discontinuities.55 It is evident that airway inflammation is the cause of these changes, and the more severe the inflammation, the more prevalent the destruction of the mucociliary apparatus.

Although epithelial derangement is a peculiar aspect of bronchial asthma, studies carried out on chicken tracheas showed that epithelial damage of at least 50% of the bronchial ciliary apparatus is necessary to determine an evident decrease of MCC.56 Hence, functional alterations of cilia that can cause MCC modification should be evaluated. In this regard, Mossberg et al.57 assumed that the coordinated ciliary stroke is disturbed when the variation between the stroke direction of cilia is 90°, while Laitinen et al.50 demonstrated that the ciliated stroke deviation exceeded from 45° up to 90° in their asthmatic patients.

Regarding ciliary modifications in asthma, Frigas et al.58,59 were the first research group to hypothesize a functional change by isolating a characteristic protein, called the major basic protein, that can induce ciliostasis, cytolysis, and epithelial mucosa damage in the eosinophils of asthmatic patients. At a later date, Dulfano and Luk60 identified another ciliary inhibitory factor that seems to derive from a specific reaction between a substance present in the sputum and cilia of asthmatics. This seemingly reversible inhibitory effect is probably related to clinical exacerbations and not to functional damage of the cilia or mucosa cells. Similar inhibitory effects of sputum obtained from asthmatics also have been observed with human bronchial explants.

Furthermore, when evaluating ciliated cells that were obtained from the tracheas of allergic sheep in vitro, Maurer et al.61 noted a remarkable increase of ciliary beating, even though TMV was reduced. These results led the authors to conclude that during an allergic reaction, the reduction of mucus transport is not related to a decrease of ciliary beat frequency.

It is important to note, however, that inflammatory mediators do not always exert an inhibitory effect on ciliary function. A study carried out by Wanner et al.62 on sheep tracheas showed that leukotriene C4 and prostaglandin (PG) E1 and PGE2 are potent ciliary stimulators, whereas histamine modestly increases ciliary beat frequency only at high concentrations. Also, Seybold et al.36 showed that the perfusion of acetylcholine and epinephrine caused an increase of ciliary beat frequency in sheep tracheas in a concentration-dependent manner. The same effect was obtained with antigen challenge perfusion, while the opposite was obtained with PAF.

Mucus Secretion in Asthma

The efficiency of MCC depends not only on ciliary activity but also on the amount and rheological characteristics of mucus.63 Respiratory mucus is a complex mixture of secretions from submucosal glands, secretory cells of the epithelial surfaces, tissue fluid transudates, substances produced by specialized cells, and alveolar surfactant. In the tracheobronchial tree, mucus is produced by at least four types of secretory cells, mucous, and serous glands,64 and the “normal” amount of secretion ranges from 10 to 100 mL/d.65

In chronic respiratory diseases, the persistence of airway inflammation can determine epithelial pathophysiologic modifications that produce excessive mu-
hus hypersecretion.66 This significant change is due to the increase of secretory cells and to the hypertrophy and hyperplasia of submucosal glands with respect to normal subjects.17,67,68

Although asthmatics in the stable phase produce unquantifiable amounts of mucus daily, highly viscous mucus plugs are commonly found at the autopsy of subjects who died of bronchial asthma.69,70

Some histologic findings suggest that the amount of mucus hypersecretion in stable asthmatics can determine airflow limitation in small airways.71

Moreover, mucus can take the place of surfactant even in bronchiolar airways. It contributes to bronchial collapse and reduces bronchial reversibility, as observed during an asthmatic attack, by modifying surface tension properties.72,73

In patients with asthma, plasma exudate is a major component of airway fluid and reflects the degree of inflammation. Plasma exudate may produce an increase of the fluid layer where cilia beat, thus impairing MCC. Protein components of plasma exudate increase mucus production, prevent hydration, and alter mucus viscosity, possibly by mucin-albumin complexes and by the activation of the coagulation system through fibrin formation. Moreover, peribronchial edema may reduce lung compliance and further facilitate bronchoconstriction by uncoupling the bronchial muscle.74

In patients with bronchial asthma, sputum becomes viscous and expectoration is always more difficult than in patients with CB, bronchiectasis, or cystic fibrosis.8,66 Airway secretions adhere to bronchial walls and, although they are quantitatively “normal,” contain large quantities of albumin, lipids, and glycoproteins that alter their rheological characteristics.75 These altered sputum characteristics are responsible for the increased adhesiveness and loss of fluidity, which in turn decreases MCC (Table 2).76

Moreover, immunologic factors, the autonomic nervous system, and the nonadrenergic and noncholinergic pathway alterations of vasoactive intestinal polypeptide releases have all been promoted as possible generators of the hypersecretory mechanism in asthmatics.77–80 Fuller et al81 showed that bradykinin and lysyl-bradykinin, inflammatory peptides that are derived from the effect of kallikrein on kininogenic molecules, stimulated sensitive nonmyelinc fibers (C fibers) in a selected manner. These fibers can cause an increase of mucus secretion by a tachykinin release.

Furthermore, by modifying biochemical components, antigenic challenge can alter mucus rheological properties and mucociliary transport. By studying the trachea of Ascaris-sensitized sheep after antigenic challenge, Phipps et al82 found an increase in the number of glycoproteins in the periciliary fluid and a subsequent interaction with the mucociliary apparatus. This effect is caused by the release of leukotrienes, as demonstrated by the blocking process that Na-cromoglycate and anti-leukotriene sulfopeptide antagonists exert on the secretory mechanism. Other in vitro studies carried out by Marom et al63,84 confirmed the role of potent secretory stimulants of leukotrienes C 4 and D 4, whereas histamine, PGE 2, PGD 2, PGI 1, PGE 1, and PGA 2 have proved to be less effective.

Sperber et al85 evaluated a new, high-molecular-weight, macrophage-derived, mucus secretagogue-68, which was found in BAL fluid, on 37 patients with bronchial asthma who had mucus hypersecretion. The authors hypothesized a direct correlation between hypersecretion and mucus secretagogue-68 values.

Also, excessive amounts of mucus secretion might be caused by an increased transfer of water and electrolytes in the airway lumen, with a reduction of ciliary movement.86 In this regard, Olver et al,87 after antigenic challenge, and Marin et al,88 after histamine challenge, found an increase in the amount of electrolytes in the dog tracheal epithelium. These findings were further confirmed by experiments on sheep trachea strips previously sensitized to Ascaris. In fact, the successive antigen exposure caused a transient but marked flow of H 2 O, Cl −, and Na + throughout the bronchial epithelium.82 Similarly, other compounds such as histamine,88 bradykinins,89 arachidonic acid-derived factors obtained via lipoy-

<table>
<thead>
<tr>
<th>Physical Properties</th>
<th>Normal</th>
<th>CB</th>
<th>Bronchial Asthma</th>
</tr>
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<tbody>
<tr>
<td>Quantity over 24 h, mL</td>
<td>10</td>
<td>24.7 ± 16.3</td>
<td>12.7 ± 8.7</td>
</tr>
<tr>
<td>Color</td>
<td>Colorless</td>
<td>Usually yellow or greenish</td>
<td>Colorless</td>
</tr>
<tr>
<td>Odor</td>
<td>Nonodorous</td>
<td>Varies according to the kind of infection</td>
<td>Usually nonodorous</td>
</tr>
<tr>
<td>pH range</td>
<td>7.45–8.15</td>
<td>6.3–7.9</td>
<td>5.4–7.6</td>
</tr>
<tr>
<td>Viscosity, dyne ⋅ s ⋅ cm −2</td>
<td>&lt; 400</td>
<td>&lt; 400</td>
<td></td>
</tr>
<tr>
<td>Elastic recoil at 100 dyne/cm, SR units</td>
<td>4–8</td>
<td>4–8</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Dulfano and Ishikawa.76
genase cascade,\textsuperscript{90} and PGs\textsuperscript{84} can determine a trans-
epithelial transport of H\textsubscript{2}O and Cl\textsuperscript{−}.

Additionally, decreased amounts of periciliary fluid also might cause the rheological modification of mucus. This observation was confirmed by Daviskas et al\textsuperscript{21} when they evaluated MCC with a radioaerosol technique during and after isocapnic hyperventilation (ISH) in 8 healthy subjects and 10 asthmatic patients. An analysis of initial and postintervention lung radioactivity for the whole right lung and for defined regions showed that MCC was reduced during ISH with dry air and increased after in patients from both groups when compared to the results of ISH with warm humid air and nasal breathing at rest. The authors concluded that MCC changes during and after ISH with dry air might be caused by excessive H\textsubscript{2}O loss, which in turn causes a reduction of the periciliary fluid layer and subsequent hyperosmolarity of the airway fluid.

**CONCLUSION**

In bronchial asthma, morphologic and functional changes that occur in the airways can be due to both inflammatory and/or injury repair mechanisms. In cases of severe disease (ie, in patients who died of asthma), desquamative areas with infiltrative edematous zones and inflammatory cells, such as eosinophils, neutrophils, mast cells, and some mononucleated cells, can be observed.

In addition, pathogenetic mechanisms of asthma define the key role of inflammation in the development of disease. Inflammatory cells as well as different types of asthma mediators in the bronchial wall damage the airway epithelium and cause muscle hyperreactivity and impairment of mucociliary function.

In conclusion, based on findings in the literature, we can state that MCC is abnormal in stable patients and in the acute phase of bronchial asthma and that inflammatory mediators influence MCC, as well as ciliary structure and function and mucus production.

Finally, not enough data are available to be able to weigh the relative contribution of each of the mentioned factors, and further research is needed to better understand the effect of inflammation on the mucociliary apparatus in asthma.

**ACKNOWLEDGMENTS**: We thank Ms. Elizabeth de Young, of the University of Parma Language Institute, for the final text revision.

**REFERENCES**

22. Foster WM, Langenback EG, Bergofsky EH. Lung mucociliary function in man: inter-dependence of bronchial and tracheal mucus transport velocities with lung clearance in
bronchial asthma and healthy subjects. Ann Occup Hyg 1982; 26:227–244


31 Pavia D, Lopez-Vidriero MT, Clarke SW. Mediators and mucociliary clearance in asthma. Bull Eur Physiopathol Respir 1987; 23(suppl):895–945


44 O’Biordan TG, Smaldone GC. Induced bronchoconstriction and mucociliary clearance in asthma [abstract]. J Aerosol Med 1993; 6(suppl):50


58 Frigas E, Loegering DA, Cleich GJ. Cytotoxic effects of the guinea pig eosinophil major basic protein on tracheal epithelium. Lab Invest 1980; 42:35–43


60 Dulfano MJ, Luk CK. Sputum and ciliary inhibition in asthma. Thorax 1982; 37:646–651


66 Lopez-Vidriero MT, Reid L. Bronchial mucus in asthma. In: Weiss E, Segal M, Stein M, eds. Bronchial asthma, mecha-


70 Reid LM. The presence or absence of bronchial mucus in fatal asthma. J Allergy Clin Immunol 1987; 80:415–416


74 Persson CGA. Plasma exudation and asthma. Lung 1988; 166:1–23


