Asthma
Clearing the Way

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Asthma is a chronic inflammatory disorder of the airways. In genetically susceptible individuals, this inflammation eventually leads to recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and/or in the early morning. These symptoms are associated with variable airflow limitation that reverses either spontaneously or with treatment. Non-pulmonary symptoms suggesting atopy (such as rhinitis, conjunctivitis, and eczema) are common, but not specific to asthma patients. Asthma is associated with an increase in airway responsiveness to a variety of non-specific stimuli, such as methacholine, dry air, exercise, or hypoosmolar solutions.

Inflammation, and its resultant effects on airway structure, is considered to be the main mechanism leading to the development and maintenance of asthma. Therefore, the main thrust of asthma therapy is to limit exposure to triggering factors (viruses, airborne pollutants, allergens), to reduce the inflammatory process using anti-inflammatory agents, and to use smooth muscle relaxants if needed (Table 1).

Billy's case

Billy, 56, is a lifelong non-smoker who developed asthma at the age of eight. He has not been with his asthma treatment for the past 10 years and has made multiple emergency department visits.

Physical exam shows the typical findings of airflow obstruction with wheeze on tidal breathing. Chest X-rays show hyperinflation. A computed tomography airway scan is done and shows the right upper lobe bronchus wall to be twice as thick as reference values. On skin testing, he is highly atopic to house dust mites, animal dander, and tree pollen.

In 2003, after multiple courses of prednisone and six months of high-dose inhaled steroids, his forced expiratory volume in one second is 30% predicted, ratio 0.36.

Examinations/history

Examinations

- Auto antibody profile: Negative
- Serum IgE: 1449 µg/L (elevated)
- Aspergillus precipitating antibody: Negative

Old medical records

- FEV_1: 45% predicted in 1985
- FVC: 74% (ratio 0.61)

Ig: Immunoglobulin
FEV_1: Forced expiratory volume in one second
FVC: Forced vital capacity

Table 1

Asthma control using clinical and physiologic parameters

Parameter	Frequency or value
Daytime symptoms	< 4 days/week
Nighttime symptoms	< 1 night/week
Physical activity	Normal
Exacerbations	Mild, infrequent
Absence from work or school	None
Need for short-acting beta-2 agonist	< 4 doses/week*
FEV_1 or PEF best;	> 85% of personal ideally 90%
PEF diurnal variation	< 15% diurnal variation**

*May use 1 dose/day for prevention of exercise-induced symptoms.
**Diurnal variation is calculated by subtracting the lowest PEF from the highest and dividing by the highest PEF multiplied by 100.

FEV_1: Forced expiratory volume in one second
PEF: Peak expiratory flow obtained with a portable peak flow meter

What is remodelling?

Airway remodelling is the change in the composition, quantity, and organization of the cellular constituents of the airway wall. It results from chronic injury and repair and may be partially reversible or irreversible. Data suggest remodelling contributes to airways hyperresponsiveness (AHR), fixed airway narrowing, and asthma severity. Currently, it is unclear whether remodelling in asthma is a normal response to an abnormal injury or an abnormal repair response. Some aspects of remodelling occur very early in the development of asthma, possibly even at a presymptomatic stage.

Airway responsiveness is regulated by several mechanical factors: parenchymal interdependence, wall thickness and compliance, smooth muscle properties, airway lining surface forces, and airway plugging. The airways in people with asthma undergo epithelial damage, sub-basement membrane thickening, smooth muscle hypertrophy and hyperplasia, mucus metaplasia, increased vascularity, and increased matrix glycoproteins. As a result, these patients have thicker airway walls, more goblet cells, fragile epithelium, more smooth muscle, and more subepithelial collagen (Figures 1 and 2).

AHR correlates with increased subepithelial fibrosis and increased proteoglycan deposition. In general, people with asthma show a greater annual decrease in forced expiratory volume in one second (FEV_1) than controls. All fatal asthma patients have a substantial luminal content of

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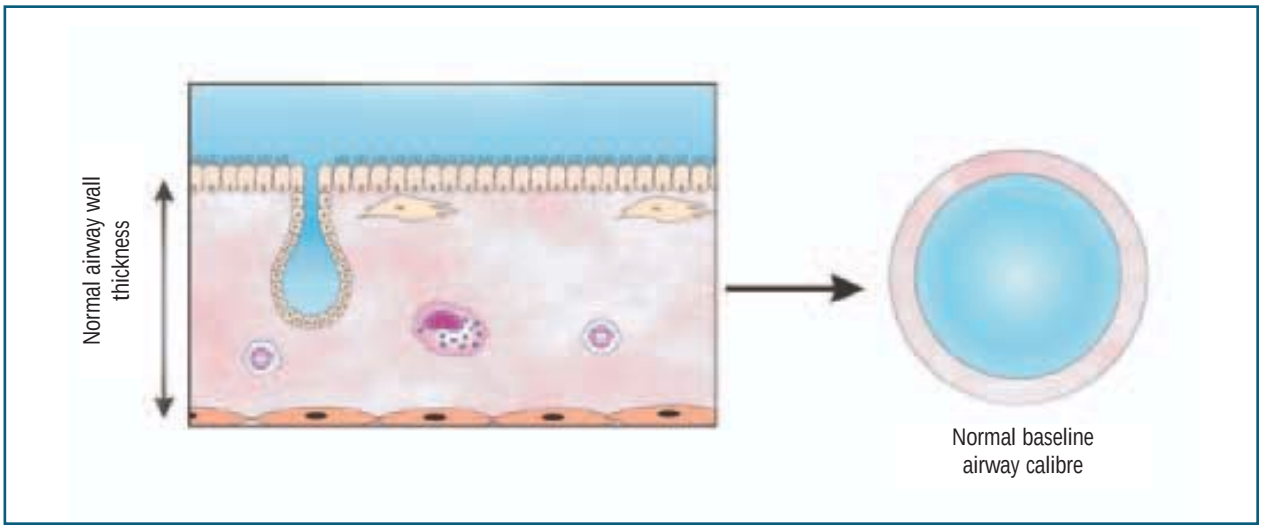

Figure 1. Airway wall in a person without asthma.

cells and mucus. Luminal plugging is as important as airway smooth muscle shortening in causing airway narrowing in severe asthma. Epithelial damage impairs ciliary function and cell debris increases mucus viscosity; these result in impaired airway clearance.

What are the treatments?

Medications used to treat asthma can be separated into relievers and controllers. The relievers include short-acting beta-2 agonists or inhaled anticholinergics. (The latter are only used occasionally.) The most effective agents in the controller group are the inhaled corticosteroids. Also included in this group are the leukotriene receptor antagonists, non-steroidal medications (cromoglycate), and the long-acting beta-2 ago-

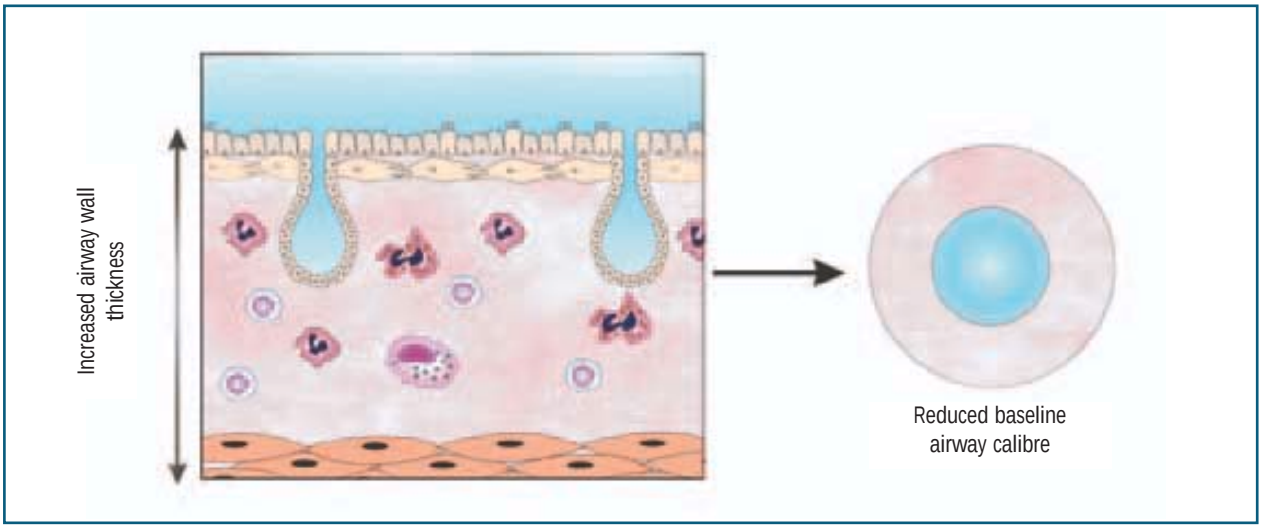

Figure 2. Airway wall in a person with asthma.

nists (salmeterol or formoterol). Formoterol, being rapid-acting, can also be used as a reliever. Immunotherapy is occasionally beneficial.

Is prevention/reversal of remodelling a valid goal?

Initiation of inhaled corticosteroids at diagnosis has been shown to lead to a greater increase in airflow response versus treatment that started two years after diagnosis.[1]

In one study, 35 asthma patients not taking inhaled corticosteroids upon enrolment were treated with high-dose fluticasone (1,500 mcg/day) for one year. AHR improved throughout the study and the authors concluded that two-thirds of the improvement in hyperresponsiveness with inhaled corticosteroid treatment for one year was due to improvement in remod-

Take-home message

How is asthma treated?

- Medications to treat asthma can be divided into relievers and controllers. The relievers include beta-2 agonists. The most effective controllers are the inhaled corticosteroids.
- Initiation of inhaled corticosteroids at the time of diagnosis has been shown to lead to a greater increase in airway response.
- Avoidance of triggers is also key to asthma treatment.

elling.[2] However, it is not certain that inhibition/reversal of remodelling can be achieved with doses of inhaled corticosteroids that are considered safe (free of systemic side-effects). Given that frequent exacerbations may be associated with progression of remodelling, strategies that reduce the rate of exacerbations are indicated (*e.g.*, combination treatment with inhaled corticosteroids and long-acting beta agonists, with an action plan that leads to the early introduction of one- or two-week fourfold increases in doses of inhaled corticosteroids as symptoms increase).

Is long-term remission possible?

Since airway remodelling in asthma plays a significant role in airways hyperresponsiveness and narrowing, the early initiation of environmental control, prevention of exacerbations, and early use of inhaled corticosteroids is warranted. However, it is likely that new approaches to prevent the development of remodelling will be required to achieve long-term remission of asthma. Dx

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2. Ward C, Pais M, Bish R, et al: Airway inflammation, basement membrane thickening and bronchial hyperresponsiveness in asthma. Thorax 2002; 57(4):309-16.

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1. Bai TR, Cooper J, Koelmeyer T, at al: The effect of age and duration of disease on airway structure in fatal asthma. Am J Resp Crit Care Med 2000; 162(2Pt1):663-9.

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