ASTHMA

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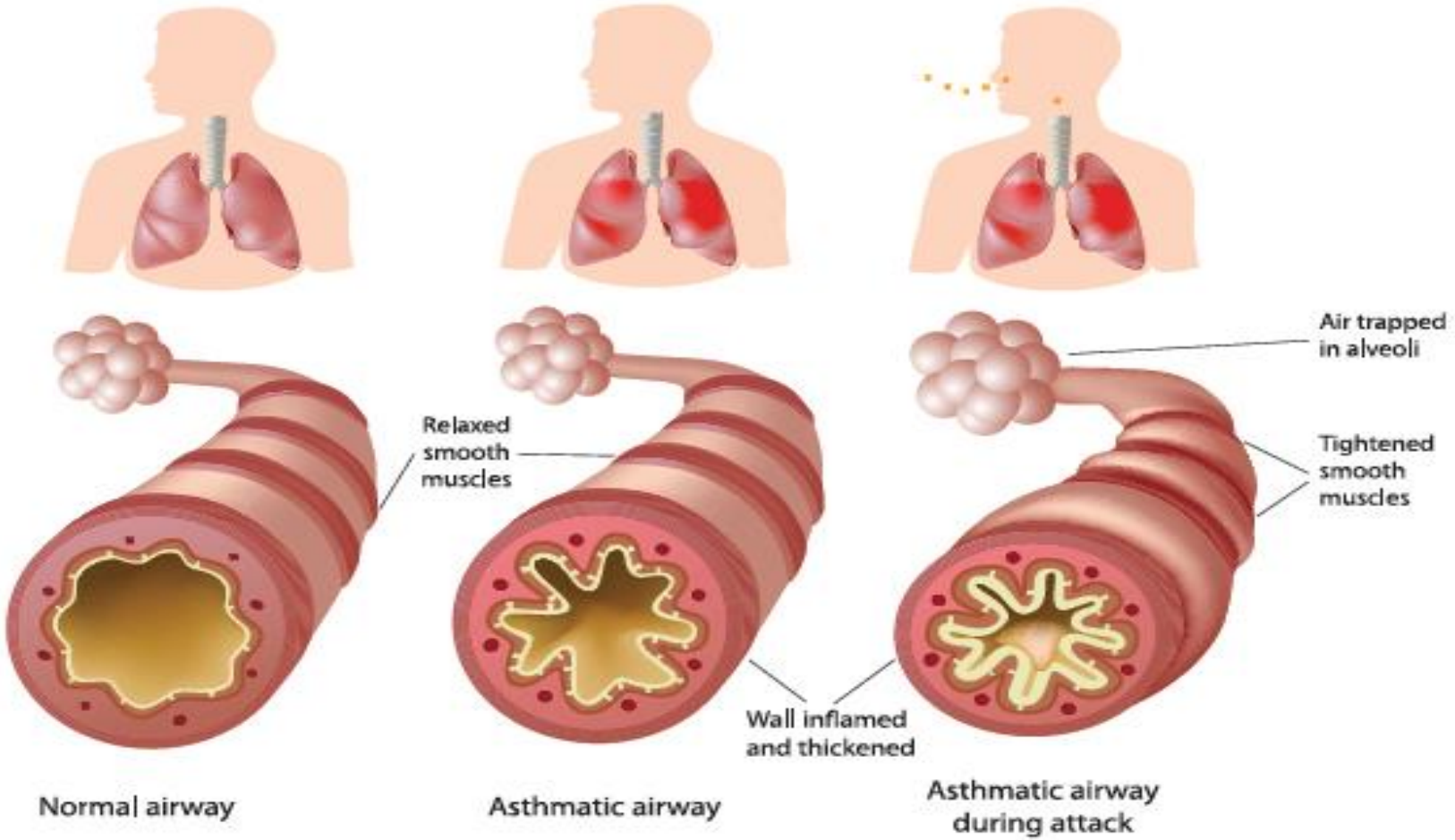
- Asthma is a syndrome characterized by airflow obstruction that varies markedly, both spontaneously and with treatment.

- Asthmatics harbor a special type of inflammation in the airways that makes them more responsive than nonasthmatics to a wide range of triggers, leading to excessive narrowing with consequent reduced airflow and symptomatic wheezing and dyspnea.

How bronchospasm constricts the airway

These illustrations compare a normal airway (left) to an asthmatic one (middle) and an asthmatic airway during an asthma attack (right).



■■PREVALENCE

- Asthma is one of the most common chronic diseases globally and currently affects **~300 million** people worldwide, with **~250,000** deaths annually.

- The prevalence of asthma has risen in affluent countries over the last 30 years but now appears to have stabilized, with **~10–12% of adults and 15% of children affected by the disease**.

- Most patients with asthma in affluent countries are atopic, with allergic sensitization to the house dust mite *Dermatophagoides pteronyssinus* and other environmental allergens, such as animal fur and pollens.

- Asthma can present at **any age**, with a peak age of **3 years**.
- In childhood, twice as many males as females are asthmatic, but by adulthood the sex ratio has equalized.

- Long-term studies that have followed children until they reach the age of 40 years suggest that many with asthma become asymptomatic during adolescence but that asthma returns in some during adult life, particularly in those with persistent symptoms and severe asthma.

- A rise in asthma mortality seen in several countries during the 1960s was associated with increased use of short-acting inhaled β2-adrenergic agonists (as rescue therapy), but there is now compelling evidence that the more widespread use of inhaled corticosteroids (ICS) in patients with persistent asthma is responsible for the decrease in mortality in recent years.

- **Major risk factors for asthma deaths**
- poorly controlled disease with frequent use of bronchodilator inhalers,
- lack of or poor compliance with ICS therapy,
- previous admissions to hospital with near-fatal asthma.

TABLE 281-1 Risk Factors and Triggers Involved in Asthma	
ENDOGENOUS FACTORS	**ENVIRONMENTAL FACTORS**
Genetic predisposition	Indoor allergens
Atopy	Outdoor allergens
Airway hyperresponsiveness	Occupational sensitizers
Gender	Passive smoking
Ethnicity	Respiratory infections
Obesity	Air pollution (diesel particulates, nitrogen oxides)
Early viral infections	Diet
	Dampness and mold exposure
	Acetaminophen (paracetamol)
Triggers	
Allergens	
Upper respiratory tract viral infections	
Exercise and hyperventilation	
Cold air	
Sulfur dioxide and irritant gases	
Drugs (β-blockers, aspirin)	
Stress	
Irritants (household sprays, paint fumes)	

ATOPY

- Atopy is the major risk factor for asthma, and non-atopic individuals have a very low risk of developing asthma. Patients with asthma commonly suffer from other atopic diseases, particularly **allergic rhinitis, which may be found in >80% of asthmatic patients, and atopic dermatitis (eczema).**

GENETIC PREDISPOSITION

- The most consistent findings have been associations with polymorphisms of genes on **chromosome 5q**, including the T helper 2 (Th2) cells interleukin (IL)-4, IL-5, IL-9, and IL-13, which are associated with atopy.

INFECTIONS

- Although viral infections (especially **Rhinovirus)** are common as triggers of asthma exacerbations, it is uncertain whether they play a role in etiology.

- There is some association between **respiratory syncytial virus** infection in infancy and the development of asthma, but the specific pathogenesis is difficult to elucidate, as this infection is very common in children.

- Atypical bacteria, such as *Mycoplasma* and *Chlamydophila*, have been implicated in the mechanism of severe asthma, but thus far, the evidence is not very convincing of a true association.

DIET

- **low** in antioxidants such as :
- vitamin C
- vitamin A,
- magnesium,
- selenium, and
- omega-3 polyunsaturated fats (fish oil)

- **high** in :
- **sodium** and **omega-6** polyunsaturates are associated with an increased risk of asthma

- **Vitamin D deficiency** may also predispose to the development of asthma. However, interventional studies with supplementary diets have not supported an important role for these dietary factors.

- **Obesity** is also an independent risk factor for asthma, particularly in women, but the mechanisms are not yet clear.

AIR POLLUTION

- Air pollutants such as **sulfur dioxide, ozone, and diesel particulates** may trigger asthma symptoms, but the role of different air pollutants in the etiology of the disease is not yet clear

- Indoor air pollution is also important with exposure to **nitrogen oxides from cooking stoves** and exposure to **passive cigarette** smoke. There is some evidence that maternal smoking is a risk factor for asthma, but it is difficult to dissociate this association from an increased risk of respiratory infections

ALLERGENS

- Domestic pets, particularly cats, have also been associated with allergic sensitization, but early exposure to cats in the home may be protective through the induction of tolerance

OCCUPATIONAL EXPOSURE

- Chemicals such as toluene diisocyanate and trimellitic anhydride, may lead to sensitization independent of atopy. Individuals may also be exposed to allergens in the workplace such as small animal allergens in laboratory workers and fungal amylase in wheat flour in bakers. Cleaners commonly develop occupational asthma owing to exposure to aerosols of cleaning liquids

OBESITY

- Asthma occurs more frequently in obese people (BMI >30 kg/m2) and is often more difficult to control. Although mechanical factors may contribute, it may also be linked to the pro-inflammatory adipokines and **reduced anti-inflammatory adipokines** that are released from fat cells.

INTRINSIC ASTHMA

- A minority of asthmatic patients (~10%) have negative skin tests to common inhalant allergens and **normal serum concentrations of IgE**. These patients, with non-atopic or intrinsic asthma, usually show later onset of disease (**adult-onset asthma**), commonly have concomitant **nasal polyps**, and may be **aspirin-sensitive**

- There is recent evidence for increased **local production of IgE in the airways**, suggesting that there may be common IgE-mediated mechanisms; staphylococcal enterotoxins, which serve as “superantigens,” have been implicated. Type-2 innate lymphoid cells (ILC2) may drive the **eosinophilic inflammation** in these non-allergic patients.

PHARMACOLOGIC AGENTS

- **Betaadrenergic blockers** commonly acutely worsen asthma, and their use may be fatal. The mechanisms are not clear but are likely mediated through **increased cholinergic bronchoconstriction.** All beta blockers need to be avoided and even selective β, β2 blockers, or topical application (e.g., timolol eye drops) may be dangerous.

- **Angiotensin-converting enzyme inhibitors** are theoretically detrimental as they inhibit breakdown of kinins, which are **bronchoconstrictors**; however, they rarely worsen asthma, and the characteristic cough is no more frequent in asthmatics than in non-asthmatics. **Aspirin** may worsen asthma in some patients (aspirin-sensitive asthma is discussed under “Special Considerations”).

EXERCISE

- The mechanism is linked to hyperventilation, which results in **increased osmolality in airway lining fluid and triggers mast cell mediator release, resulting in bronchoconstriction.** Exercise-induced asthma (EIA) typically begins after exercise has ended, and recovers spontaneously within about 30 min

- It may be prevented by prior administration of **β2-agonists** and **antileukotrienes**, but is best prevented by regular treatment with **ICS**, which reduce the population of surface mast cells required for this response.

HORMONES

- premenstrual worsening of asthma related to a fall in progesterone and in severe cases may be improved by treatment with high doses of progesterone or gonadotropin-releasing factors. Thyrotoxicosis and hypothyroidism can both worsen asthma, although the mechanisms are uncertain.

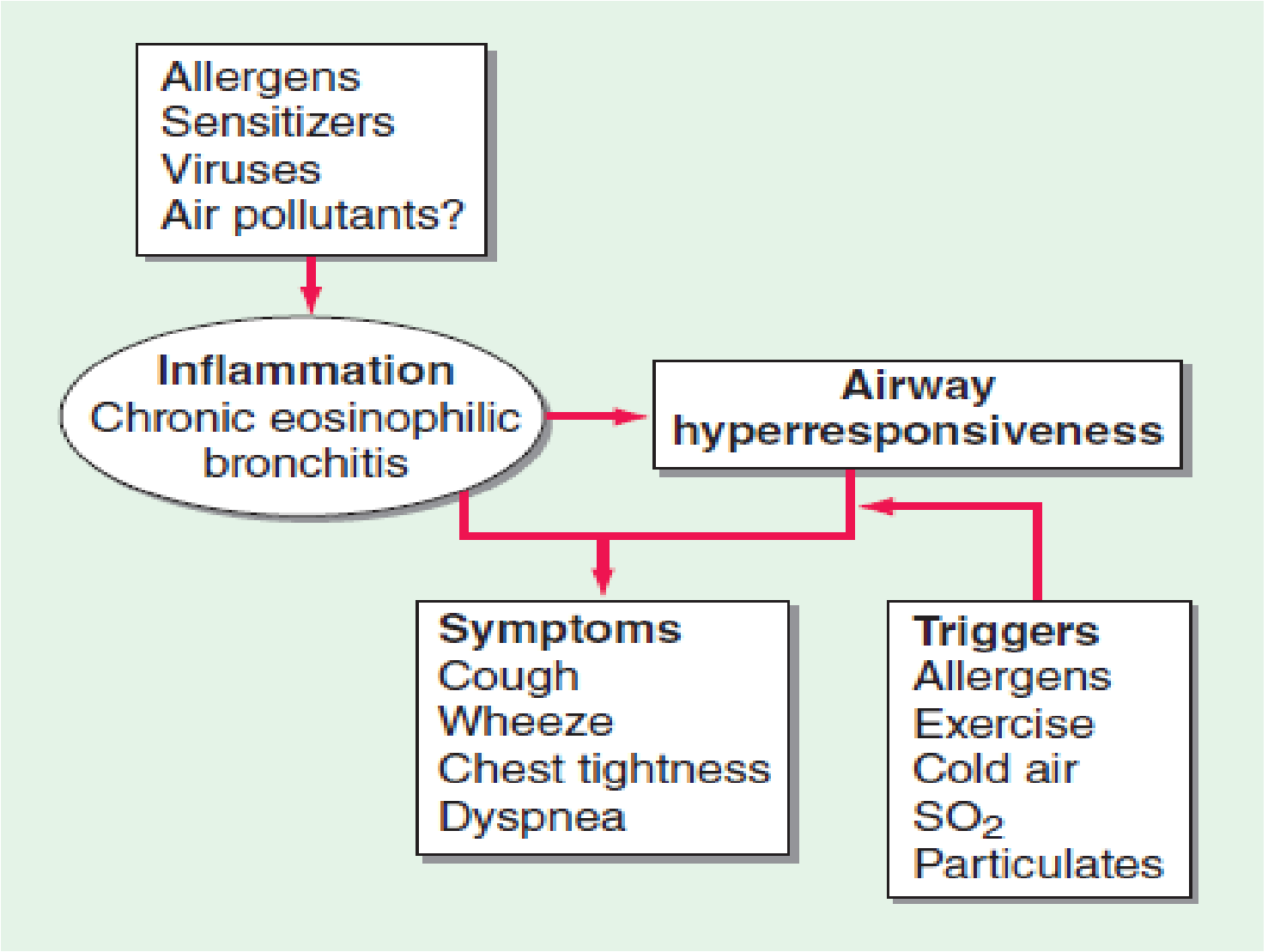
GASTROESOPHAGEAL REFLUX

- Gastroesophageal reflux is common in asthmatic patients as it is increased by bronchodilators. Although acid reflux might trigger reflex bronchoconstriction, it rarely causes asthma symptoms, and antireflux therapy usually fails to reduce asthma symptoms in most patients.
- **STRESS** Many asthmatics report worsening of symptoms with stress

PATHOPHYSIOLOGY

- Asthma is associated with a specific chronic inflammation of the mucosa of the lower airways. One of the main aims of treatment is to reduce this inflammation.

- Early closure of peripheral airway results in lung hyperinflation (air trapping) and increased residual volume, particularly during acute exacerbations and in severe persistent asthma.



IGURE 281-2 Inflammation in the airways of asthmatic patients leads to airway yperresponsiveness and symptoms. SO_2, sulfur dioxide.

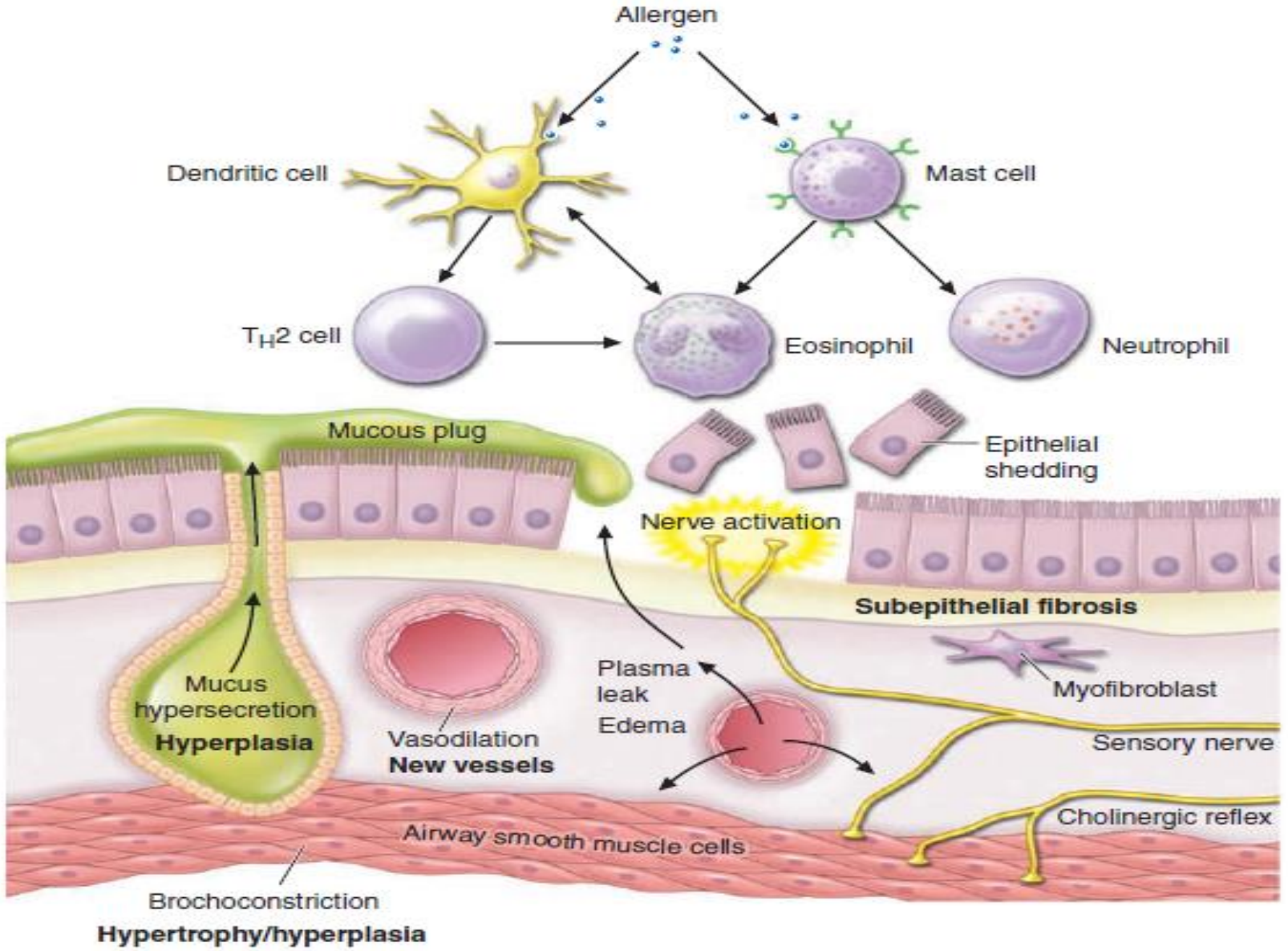


FIGURE 281-3 The pathophysiology of asthma is complex with participation of several interacting inflammatory cells, which result in acute and chronic inflammatory effects on the airway.

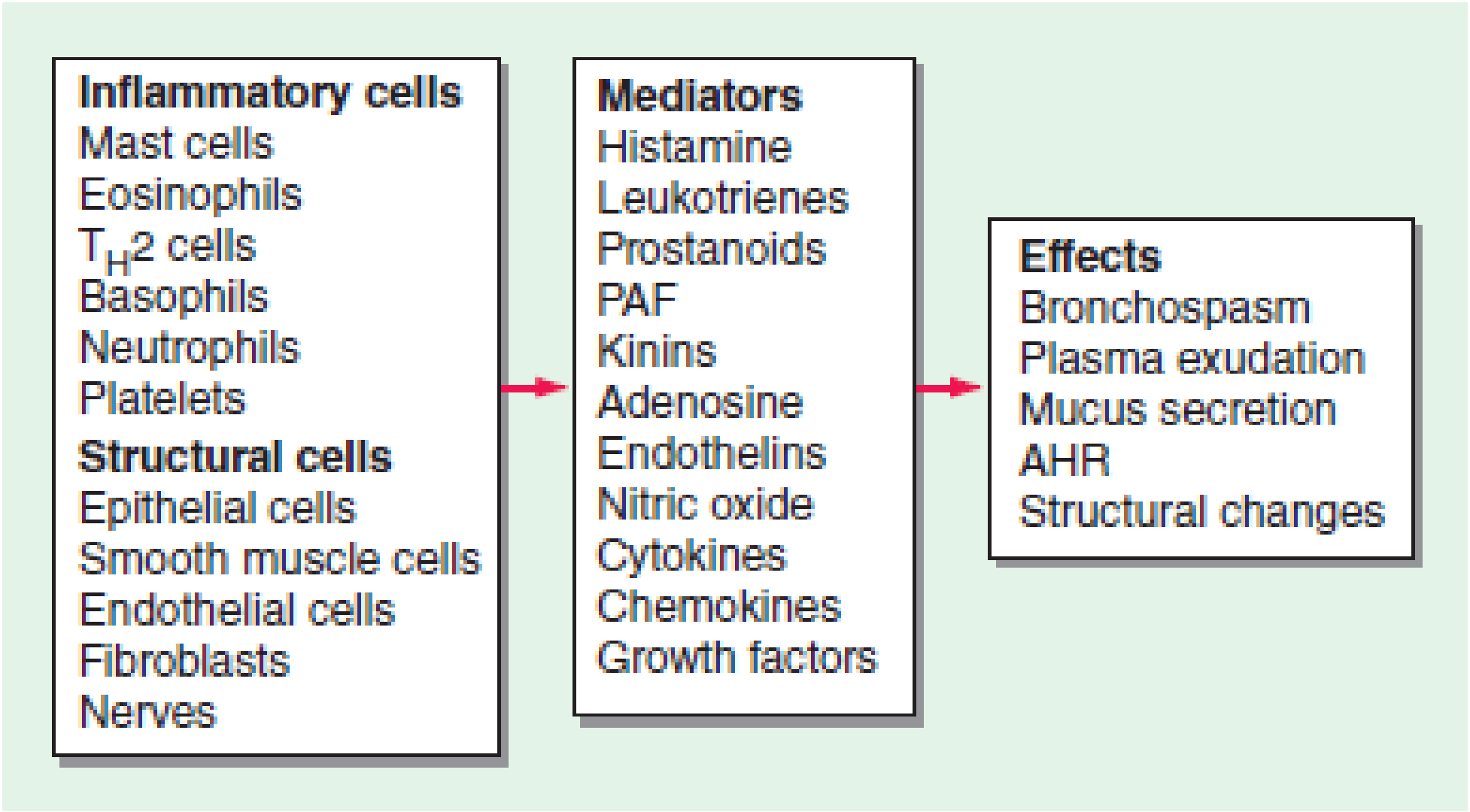
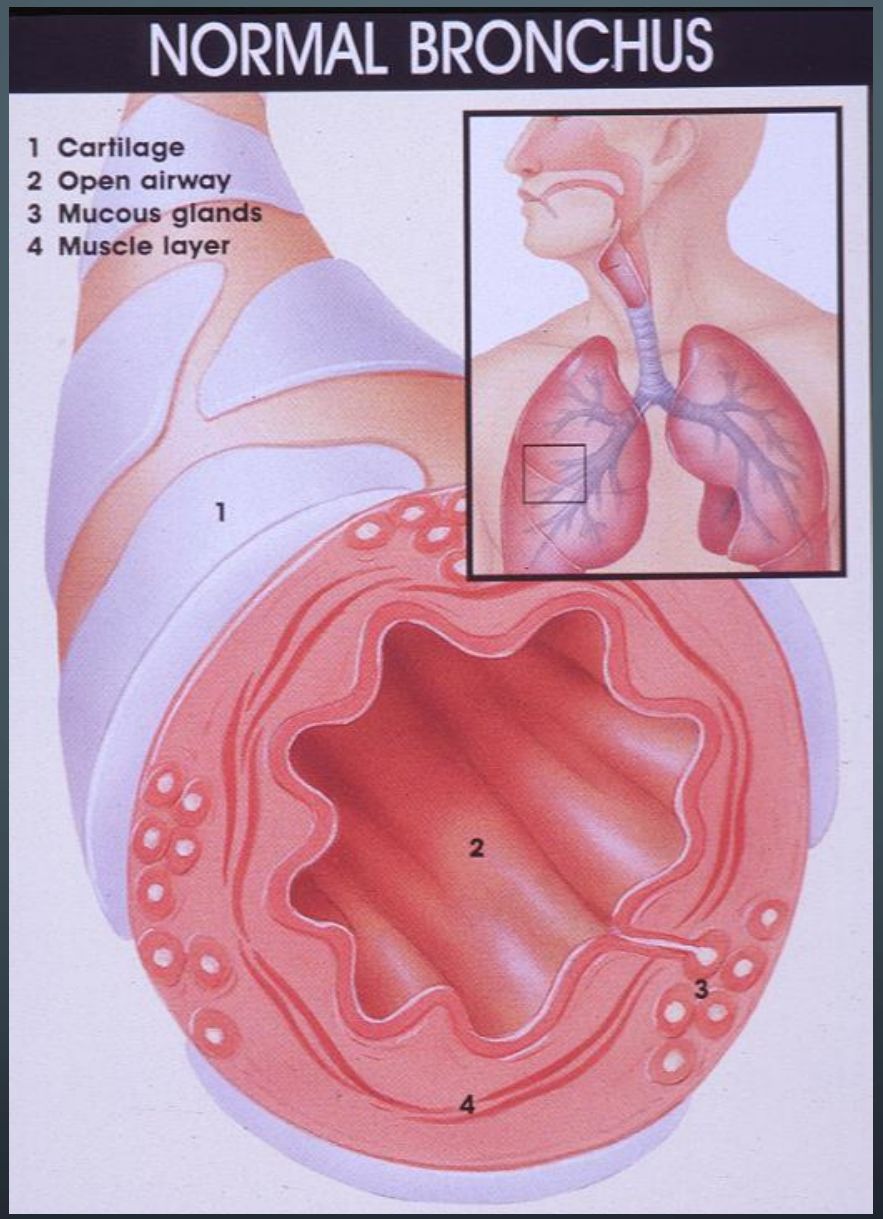


FIGURE 281-4 Many cells and mediators are involved in asthma and lead to several effects on the airways. AHR, airway hyperresponsiveness; PAF, platelet-activating factor.



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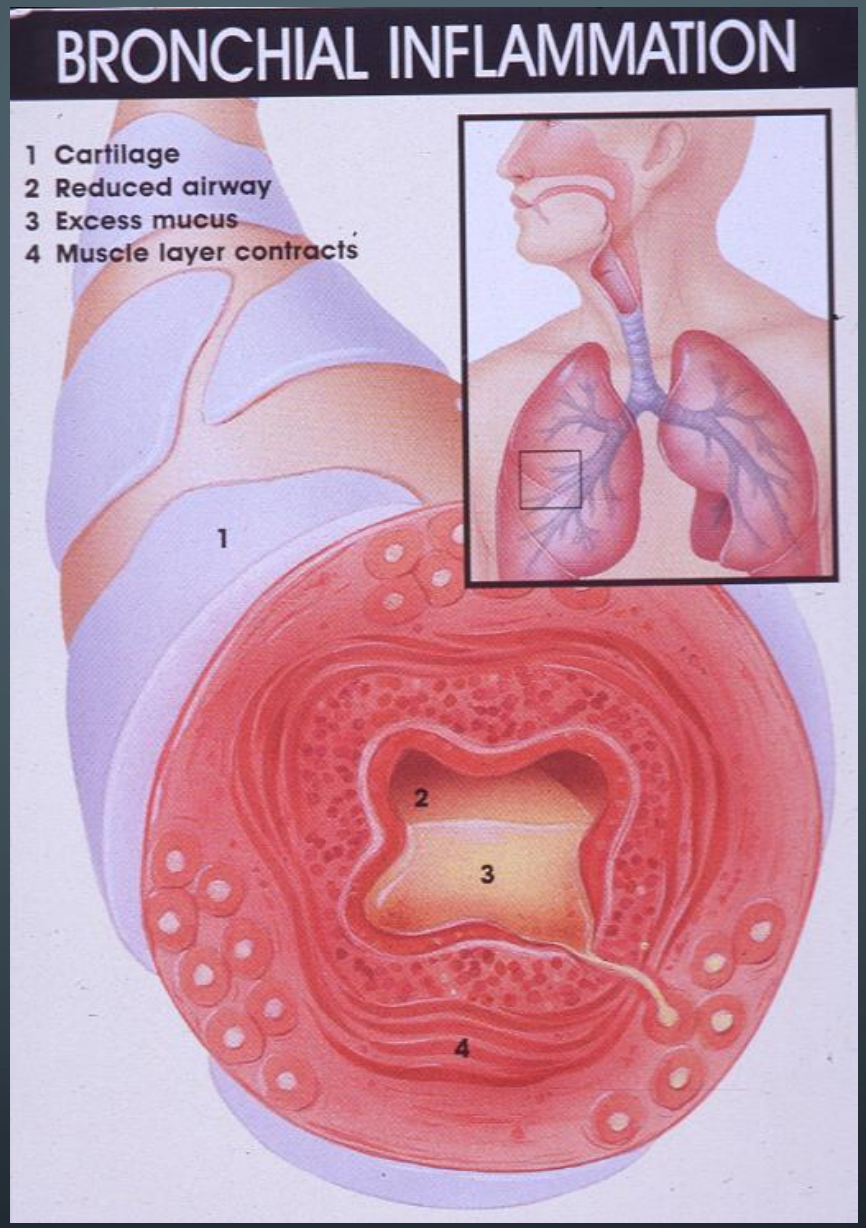

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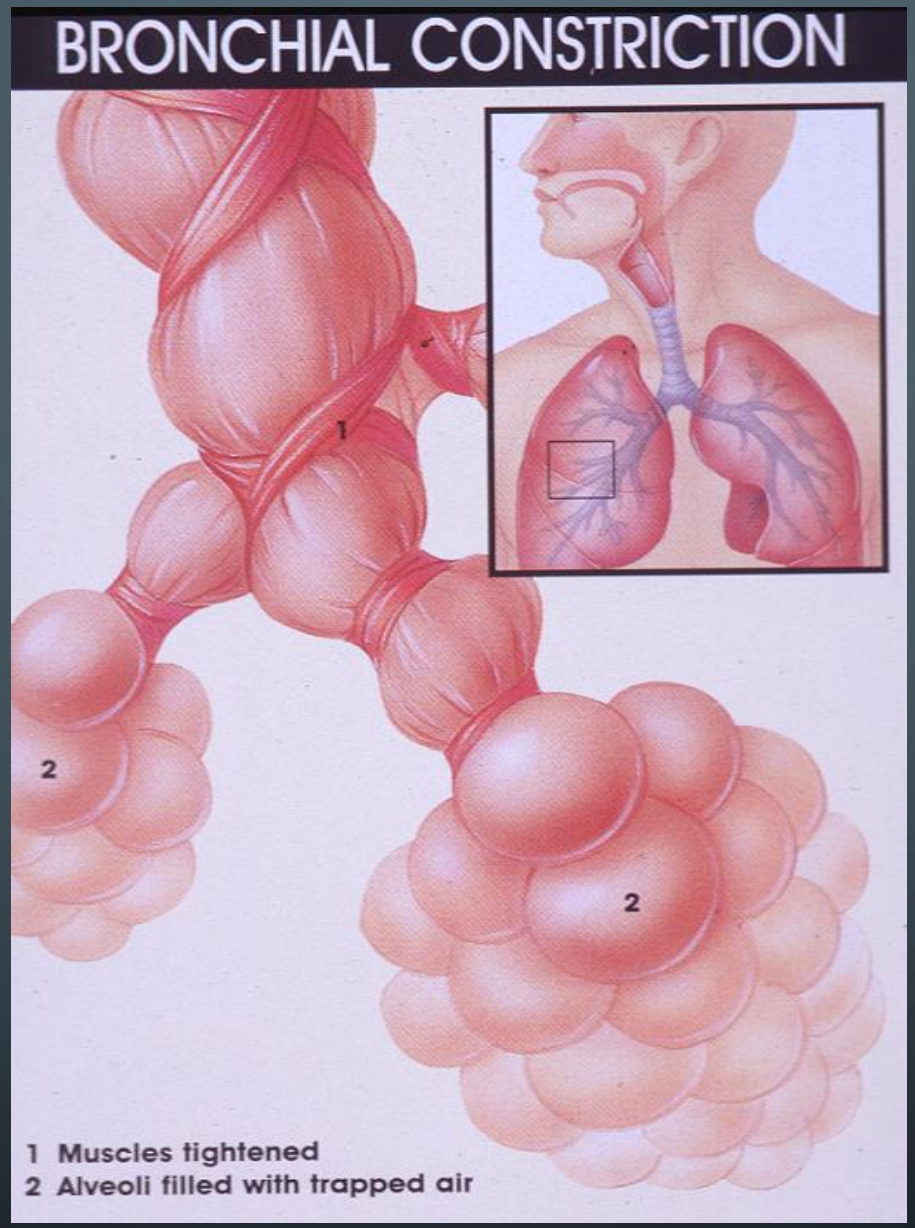

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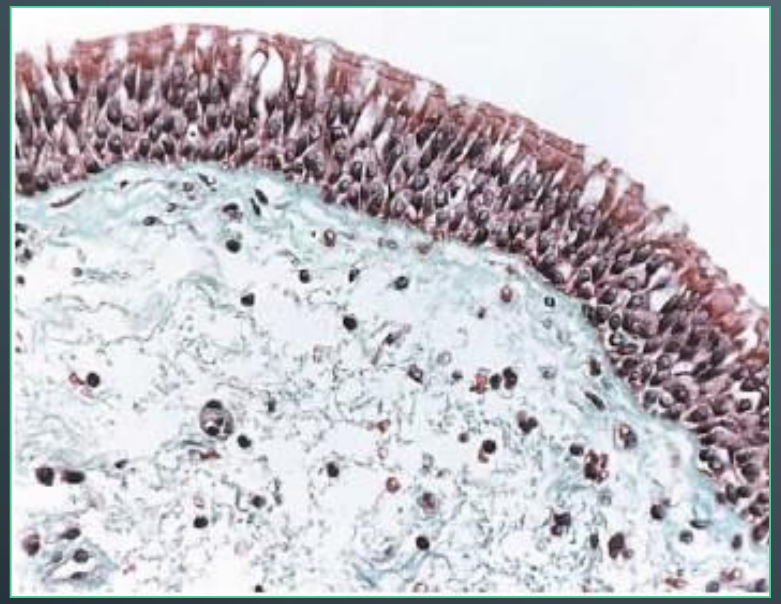
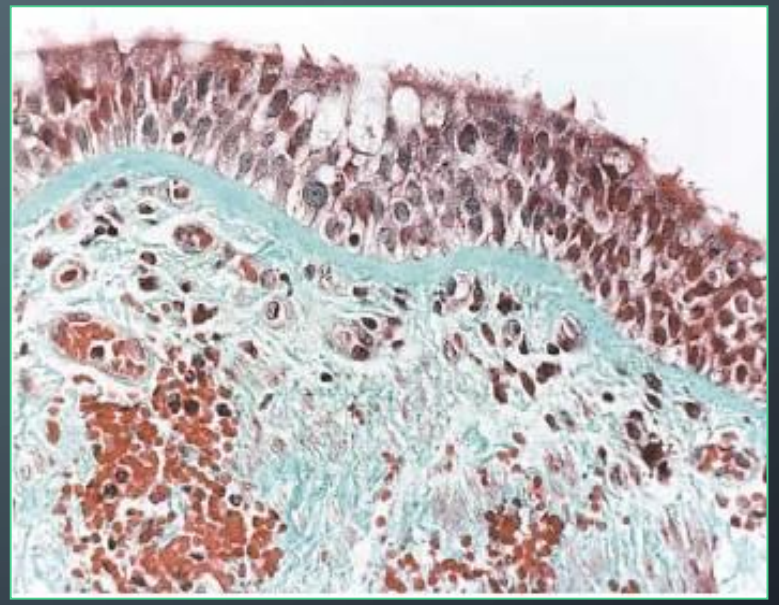
ASTHMA *IS* A CHRONIC INFLAMMATORY DISEASE: PATHOPHYSIOLOGIC CHANGES

Normal Architecture



Bronchial Mucosa From a Subject Without Asthma

Disrupted Architecture

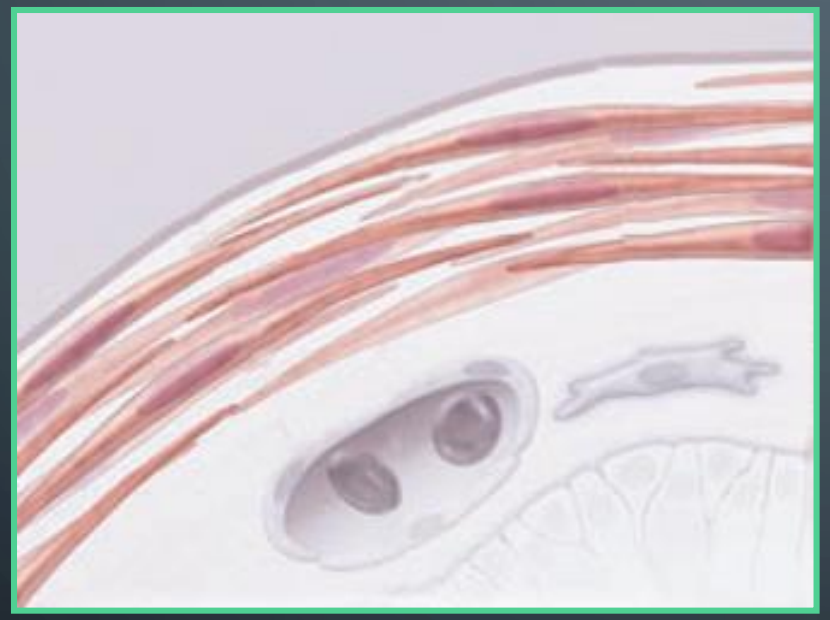


Bronchial Mucosa From a Subject With Mild Asthma

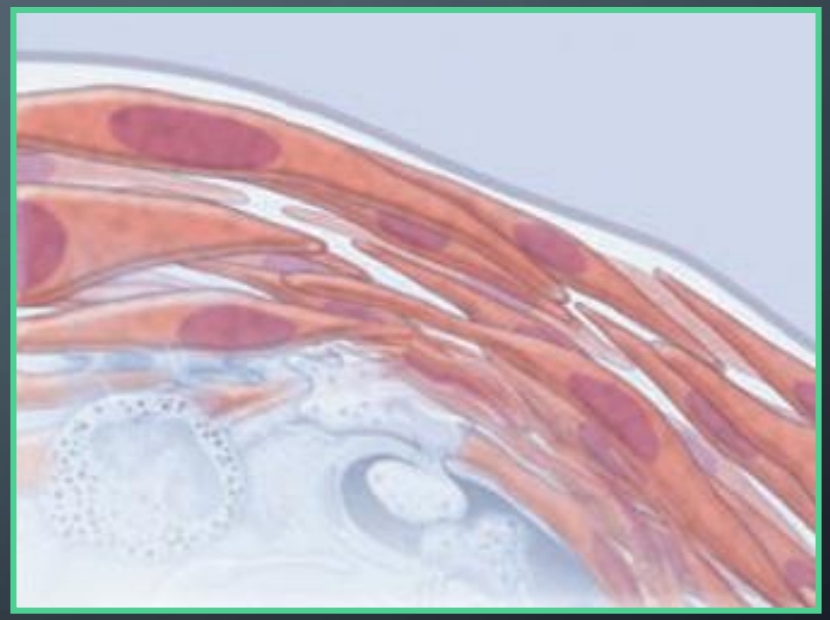
Hematoxylin and eosin stain.
Photographs courtesy of Nizar N. Jarjour, MD, University of Wisconsin.

CONSEQUENCES OF PERSISTENT ASTHMA: SMOOTH MUSCLE HYPERPLASIA

Normal Airway



Asthmatic Airway



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PHYSIOLOGY

- **Limitation of airflow** is due mainly to bronchoconstriction (from mast cell mediators), but airway edema, vascular congestion, and luminal occlusion with exudate may contribute. This results in a **reduction in forced expiratory volume in 1 second (FEV1), FEV1/ forced vital capacity (FVC) ratio, and peak expiratory flow (PEF**), as well as an increase in airway resistance.

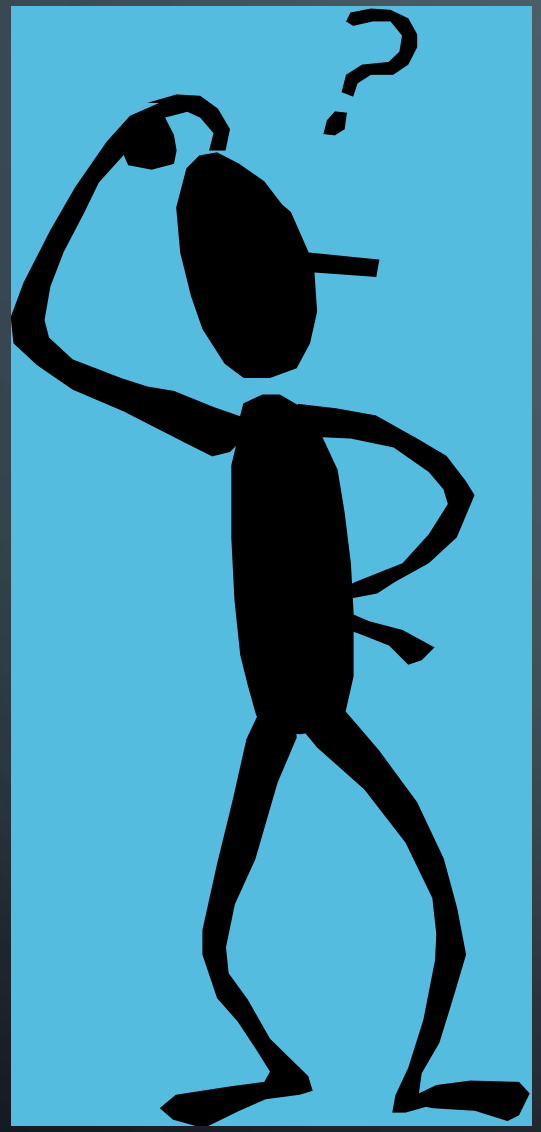
- In more severe asthma, reduced ventilation and increased pulmonary blood flow result in mismatching of ventilation and perfusion and in bronchial hyperemia. Ventilatory failure is very uncommon, even in patients with severe asthma, and arterial PCO_2 tends to be low due to increased ventilation.

AIRWAY HYPERRESPONSIVENESS

- AHR is the characteristic physiologic abnormality of asthma and describes the **excessive bronchoconstrictor response** to multiple inhaled triggers that would have no effect on normal airways.

AIRWAY RESPONSIVENESS

- prevalence of airway **hyperresponsiveness is upward of 20%** in the general population, with women having a higher prevalence than men The prevalence of increased airway responsiveness exceeds the prevalence of asthma by **two- to fivefold**



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Questions??