Epidemiology and Pathophysiology of Asthma

Zandkarimi Mohammadreza., MD.

Allergist and Clinical Immunologist

- *Epidemiology is the study of the distribution of disease and its causes and consequences, mostly in general populations.*

  Asthma is a non-communicable disease with major public health consequences including high morbidity, and mortality in severe cases.

  Asthma is a disease, characterized by ***chronic airway inflammation*** *and defined by symptoms as:*

  Wheezing ***Shortness of breath***

  Chest tightness ***Cough***

  That vary over time and in intensity, with variable airflow limitation.

Burden Of Asthma

One of the most common chronic diseases worldwide.

Estimated affected individuals - 334 million.

Prevalence is increasing in many countries, especially in children.

Expected to rise to 400 million by 2025.

- *Urbanization, and its associated increase in air pollution, with increases in asthma development and exacerbation.*

From 1950s to 1990s, the values rose at a rate with doubling of prevalence approximately every 14 years.

In the mid 1990s did reports suggest that this increase had slowed down.

The rates of asthma:
Decreased in English-speaking countries and Western Europe
Increased in Africa, Latin America, and parts of Asia.

- *Global epidemic of asthma:*
  Continuing in low to middle income countries
  Subsided in some developed countries

  *Higher **incidence and prevalence in children***
  *Higher **morbidity, and mortality in adults***

  *Childhood asthma more common in **boys***
  *Adult asthma more common in **women***

  In children, rates of asthma worldwide:
  Rising for younger children
  Steady for older children

- ***Excess of asthma in boys during childhood**:*

  1. Boys have smaller airways for a given lung size than girls.

  2. Boys have greater airway hyper-responsiveness to methacholine during childhood, with girls having it in adolescence.

  Likely sex hormones play a role with regard to asthma risk that occurs around puberty.

  Early menarche increases the risk of asthma in girls, likely related, in part, to increasing levels of estrogen and progesterone.

  Asthma incidence then declines in women during menopause, with the exception of those that take hormone replacement therapy, where the asthma incidence is twofold higher.

- *Asthma becomes more common in females until menopause when the differences narrow but never completely reverse.*

2001 to 2003 NHIS survey showed a prevalence of asthma:

9.6%	*7.4%*
male children	*female children*
4.9%	*8.4%.*
adult males	*adult females*

Analysis of the ECRHS data yielded similar results.

- *Allergic diseases predispose to development of asthma through the "**atopic march**," where infants with AD with or without food allergy progress to AR and ultimately asthma.*

  Clinicians be cautious in labeling all early childhood wheezing as asthma, because some have wheezing with respiratory infections because of reduced airway function.

- *For children, asthma may impair airway development and reduce maximally attained lung function.*
  Lung function deficits may persist into adulthood.

  Adult asthma may accelerate lung function decline and increase the risk of fixed airflow obstruction.
  Effect of early onset greater than late onset asthma.

  Therefore, our focus should be on improving not only short-term symptoms, but also the long-term respiratory and other health outcomes.

- *ISAAC reported **phase I** studies showed :*
  12-month prevalence of asthma symptoms
  3% - 5% in Indonesia, China, Greece
  >20% in Canada, Australia, New Zealand, UK.

Phase III of the ISAAC reported based on current wheeze:
There was an approximately 20-fold range of prevalence
0% in India to 16% - 20% in Costa Rica.
20% mostly in English speaking countries and Latin America.

- *Prevalence of childhood asthma in high-prevalence Western countries had remained steady or decreased between the two surveys, whereas the prevalence had increased in low-prevalence non-Western countries.*

  Reduced prevalence results from ***removal of environmental risk factors.***

- *The ECRHS assessed geographic variation in asthma among 140,000 adults from 22 countries:*

  Six-fold variation in the prevalence of current asthma was found among the countries.
  >11% in Australia, New Zealand, USA, Ireland, and UK.
  <4% in Iceland, Spain, Germany, Italy, Algeria, and India.

  Current asthma was defined in the ECRHS as "having an attack of asthma in the past 12 months or currently taking medicine for asthma."

  The countries with the lowest prevalence of current wheeze (less than 5%) across all age groups included centers:
  Indian, Asia- Pacific, Eastern Mediterranean, and Northern and Eastern Europe.

- ***Risk factors for asthma development and severity:***

  1. ***Genetics****.*

  2. ***Early-life factors****: Prematurity, LBW, breastfeeding, respiratory viral infections, and microbiome.*

  3. ***Life-long factors****: Diet, air pollution, tobacco smoke and occupational exposures.*

Genetic and Familial Factors.

A genetic component of asthma has been recognized, based on the observation that asthma tends to cluster in families.

Heritability estimates for asthma range between 36% and 77%.

Since 1989, more than 100 candidate genes have been described in more than 1000 publications on asthma or an associated disorder.

Twin studies enable the investigations of both the genetic and environmental underpinnings of asthma.

Breastfeeding

The effects of breastfeeding on the development of AD, wheezing disease, and asthma are not clear.

The advantage of breastfeeding include the acquisition of maternal antibodies and immune-competent cells and protection against the early occurrence of lower respiratory tract infections.

Breastfeeding may be a route of exposure to immunologically active substances from the mother, such as:
Tobacco smoke, cow's milk, eggs, wheat allergens, maternal IgE, and sensitized lymphocytes.

Obesity

The prevalence of obesity increased in many countries, particularly in Western and other developed countries in the latter decades of the 20th century.

The rise in obesity parallels the rise of asthma, and a hypothesis has been advanced that obesity could be a risk factor for asthma.

Mechanisms postulated for the association include:

Mechanical effects of obesity

Higher frequency of GER

Upregulation of immunologic and inflammatory correlates of obesity

Shared genetic basis for both conditions

Respiratory Infection

Respiratory infections are common in the first years of life, and provoke wheezing in children.

Importance of previously unknown viruses, such as HRVC.

Lower respiratory tract infections in children, which are caused by HRVs, RSV, parainfluenza viruses, and other pathogens, are universal in childhood.

The prevalence of bronchiolitis is approximately ***20% to 30% in the first year and 10% to 20% in the second year of life.***

Up to 50% of children will have acute wheezing before school age, and 30% to 40% of these will have recurrent wheeze.

- *Enterovirus D68 (EV-D68) is a member of the Picornavirus with severe lower respiratory tract infection.*

  Biologically it is similar to HRVs with many PCR based methods unable to distinguish EV-D68 from HRV.

Microbiome and Bacterial Infection

Hygiene hypothesis was born from the observation that children in larger families had a lower incidence of atopy compared with children from smaller families.

Humans exposed to animal stable and farm environments (rich in microbes) show reduced levels of asthma compared with those in other rural or non-rural environments.

Increased use of antibiotics in children and the increasing prevalence of asthma has led to the hypothesis that antibiotic use may contribute to asthma by altering the normal colonization of the gut microbiome in infants and increasing the atopic, Th2 immune responses.

Allergic Sensitization.

*Between **60% and 80%** of children and young adults with asthma are sensitized to at least one environmental allergen.*

Distinction between atopic and non atopic asthma is important, because atopic asthma in children appears to have a less benign course than non-atopic disease.

Majority of children with wheeze but no atopy lost their symptoms at school age and retained normal lung function at puberty.

Those sensitized to perennial allergens in the first 3 years of life had reduced lung function at school age.

- ***Diet.***

Rising prevalence of asthma and atopic diseases over the past 4 decades can be attributed, in part, to changes in diet and nutrition status.

Dietary constituents involved in the pathogenesis of asthma and allergic disease:

Antioxidants (vitamin E, vitamin C)
Polyunsaturated fatty acids
Folate
Vegetables
Trace minerals(sodium, selenium, zinc, copper)
Mediterranean diet.

Vitamin A
Vitamin D
Fruits
Metals

Work-Related Asthma

OA is a variable airflow limitation or BHR related to exposure to a specific agent or conditions in a particular occupation but not to stimuli outside the workplace.

Agents identified as causes of occupational asthma:

Animal allergens	***Plants***	***Enzymes***
Wood dust	***Drugs***	***Metals***
Oil mists		

Outdoor Air Pollution

Outdoor air pollution can cause exacerbation of preexisting asthma.

Levels of NO2, SO2, PM, CO, O3 were significantly associated with exacerbation in adults.
NO2, SO2, PM significantly associated with exacerbation in children.

Air pollution might cause new-onset asthma.

Indoor Allergens and Air Pollution

Indoor pollution includes:

- ***Combustion-sourced emissions from stoves and ovens***
- ***Space heaters fueled by gas or kerosene***
- ***Wood-burning stoves***
- ***Tobacco smoking***
- ***Volatile organic compounds***
- ***Furnishings***
- ***Allergens from insects***
- ***Molds, mites, rodents, and pets.***

Tobacco Smoke

Active smoking *increases* ***nonspecific responsiveness*** *of the airways, by inducing* ***inflammation or narrowing*** *airway caliber in older people.*

Smokers also tend to wheeze *more frequently than nonsmokers, and wheezing tends to* ***decline after cessation*** *of smoking.*

Increased airway responsiveness in active smokers also tends to abate after smoking cessation.

Natural History and Course of Asthma

The natural history of asthma is a concern for affected children, their parents, the clinicians providing care, and researchers.

Most children with mild intermittent asthma will outgrow their asthma, or have mild episodic asthma.

The risk of asthma persistence increases with:

Severity ***Sensitization*** ***Smoking***

Genetics ***Female sex***

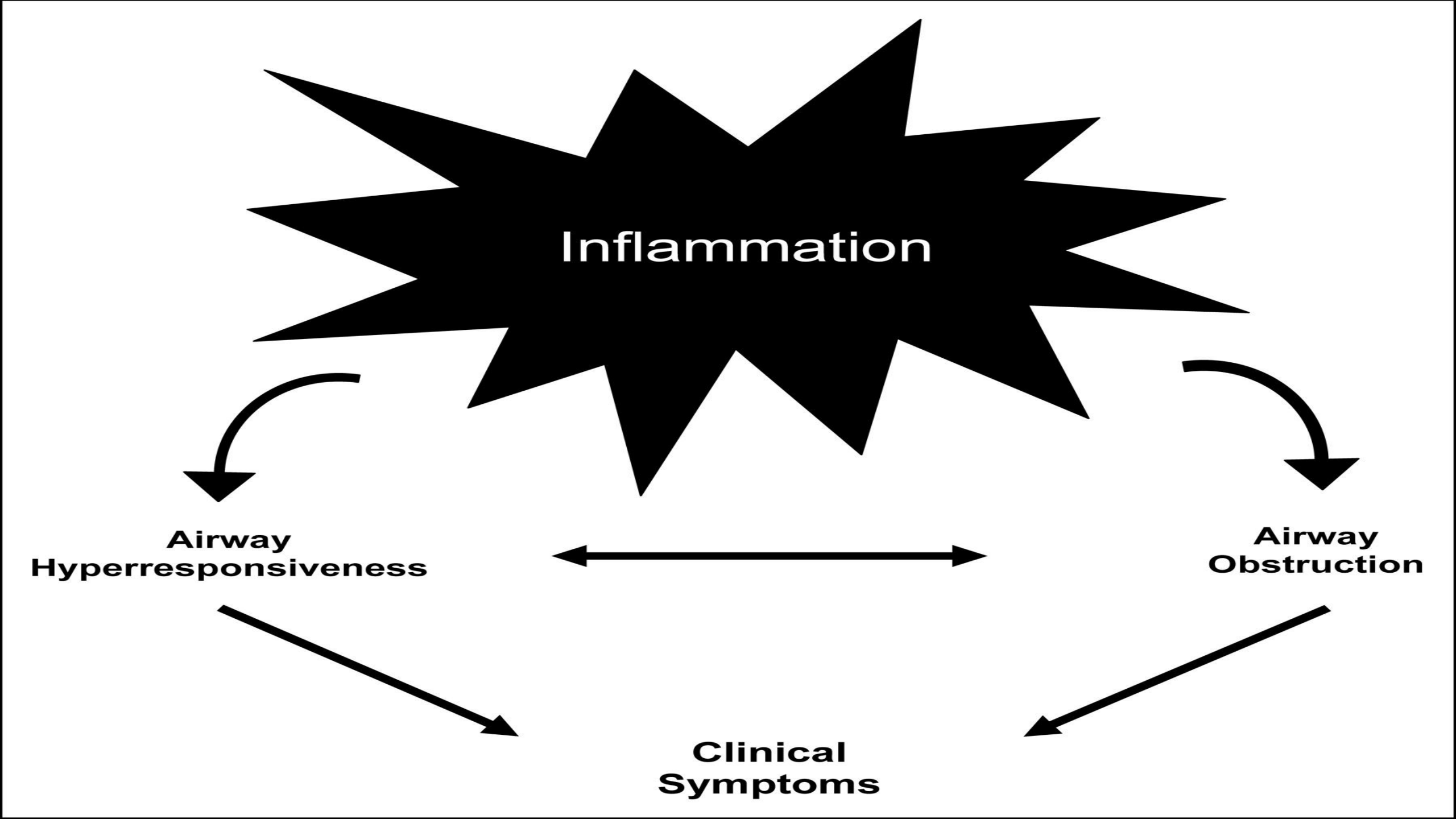
Pathophysiology of Asthma

- *Asthma is a complex clinical syndrome characterized by:*

Variable airflow obstruction

Airway hyper-responsiveness

Cellular inflammation


Inflammation
Airway Hyperresponsiveness
Airway Obstruction
Clinical Symptoms

- ***Airflow Limitation***

Induced by airway inflammation

Bronchoconstriction*- Bronchial smooth muscle contraction that quickly narrows the airways in response to exposure to a variety of stimuli.*

Airway hyperresponsiveness*- An exaggerated bronchoconstrictor response to stimuli.*

Airway edema*- As the disease becomes more persistent and inflammation become more progressive, edema, mucus hyper secretion, and formation of mucus plugs limit airflow.*

- ***Remodeling***

Reversibility of airflow limitation may be incomplete in some patients.

Persistent changes in airway structure:

Sub-basement fibrosis

Mucus hypersecretion

Injury to epithelial cells

Smooth muscle hypertrophy

Angiogenesis

Pathology
Cellular Inflammation

Persistent airway inflammation is also a feature of asthma across the severity spectrum and is almost always accompanied by:

Increased airway smooth muscle
Thickening of the subepithelial lamina reticularis
Matrix deposition in the airway wall
Increase in microvessels and neural networks
Mucous metaplasia with increased submucosal glands

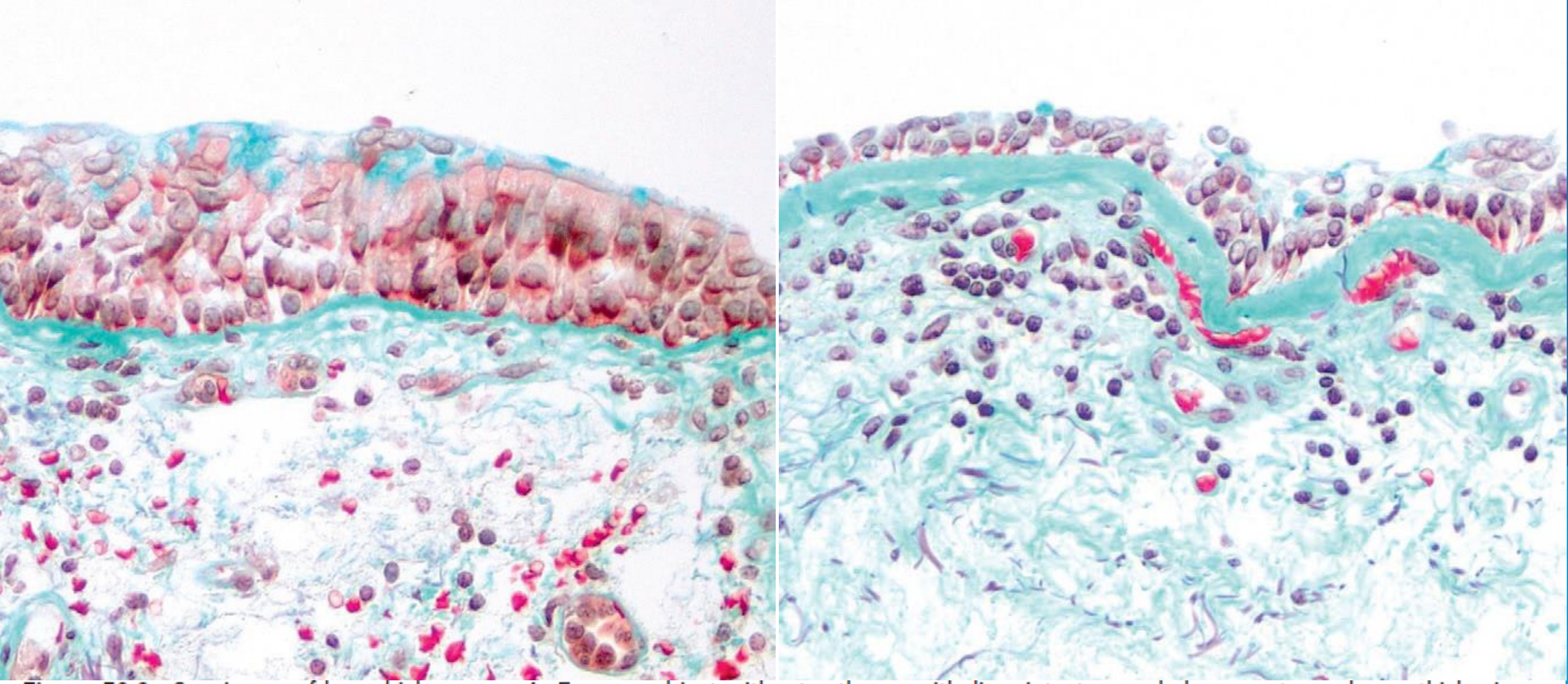


Figure 50-2 Specimens of bronchial mucosa. A, From a subject without asthma: epithelium intact, no sub–basement membrane thickening, and no cellular infiltrate. B, From a patient with mild asthma: evidence of goblet cell hyperplasia in the epithelial cell lining, sub–basement membrane thickening with collagen deposition in the submucosal area, and cellular infiltrate. (Trichrome stain, ×40.) *(From Busse WW, Lemanske RF Jr. Asthma. N Engl J Med 2001;344:350.)*

- ***Mucus plugs*** *in asthmatic airways cause further obstruction.*

  *Mucus plugs are composed of mucins, serum proteins, inflammatory cells, and cellular debris), which include desquamated epithelial cells and macrophages often arranged in a spiral pattern (**Curschmann spirals**).*

  The excessive mucus production in fatal asthma is attributed to hypertrophy and hyperplasia of the submucosal glands and mucous metaplasia in the more distal airways.

- *Compared with nonasthmatic subjects, the airway wall thickness is increased from 50% to 300% in patients with fatal asthma and from 10% to 100% in nonfatal asthma.*

Goblet cell hyperplasia and hypertrophy are one consequence of Th2 inflammation especially through the effects of IL-4, IL-9, and IL-13.

These new blood vessels serve as a conduit for inflammatory cells and a rapid mechanism for increased swelling and edema.

*In the majority of types the inflammatory cell content of the airway walls is mainly **eosinophils** but in the different asthma subphenotypes, also includes neutrophils, lymphocytes, macrophages, mononuclear cells, and mast cells.*

- ***Chronic inflammatory disorder of the airways***

Mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, epithelial cells

Eosinophils are a characteristic feature in asthma*, with the bronchial epithelium and submucosa infiltrated by these cells.*

Virtual absence of eosinophils in some cases of severe or fatal asthma (paucigranulocytic asthma), adding to the concept of disease subphenotypes and heterogeneity.

- ***Alveolar macrophages are the most prevalent cells in human lungs**, that secrete a wide array of mediators.*

  In asthma, the principal role of T cells in the lung is the orchestration of an allergic-type immune response with Th2 cell mostly via secreting Il-4, Il-9, Il-13.

Thank You For Attention