Understanding and Teaching the Mechanisms of Asthma

Christopher H. Fanta, M.D.
Partners Asthma Center
Brigham and Women’s Hospital
Harvard Medical School

Objectives

• Distinguish episodic symptoms of asthma from chronic bronchial hyperresponsiveness

• Focus on the inflammatory basis of asthma: chronic eosinophilic bronchitis

• Consider potential reasons for the increasing prevalence of asthma
Begin at the Beginning

- Patient: “What does it mean to have asthma?”
- Educator: “Well, asthma is a disease of the bronchial tubes in which …”
- Patient: “What are bronchial tubes?”

The Airways

from MedicineNet.com
Asthma as Reversible Narrowing of the Bronchial Tubes

- Bronchial smooth muscle (involuntary muscle) constriction
  - Bronchospasm; bronchoconstriction
- Airway wall swelling
Late Asthmatic Response to Allergen

Before allergen challenge

Bronchoscopic View

EAR = Early asthmatic response
LAR = Late asthmatic response
Triggers of Asthmatic Reactions

Universal
- Exercise (esp. in cold air)
- Viral resp. tract infections
- Irritants (fumes, smoke, etc.)
- Medication (beta-blockers)
- Strong emotion

Unique to Some
- Allergens
- Aspirin/NSAIDs
- Sulfites

Key Concept: Bronchial Hyperresponsiveness ("Twitchy Airways")

- Distinguishes asthmatic airways from normal airways
- Is present all the time in asthma, even when one feels entirely well
- Asthma is a chronic susceptibility to airway narrowing in response to triggers in our environment.
What Causes Asthmatic Airways to be “Twitchy”? 

- Unknown
- In part, an inherited tendency
- In part, airway wall inflammation
Allergic-Type Inflammation in Asthma: The Players

Lymphocytes: Captains of the immune response

-- TH₂ lymphocytes: signal other cells (interleukins)
-- B lymphocytes: make the allergy protein, IgE

Mast cells: make inflammatory chemicals ("mediators") like histamine and leukotrienes

Eosinophils: make more of the inflammatory mediators

Arachidonic Acid Pathway

Membrane Phospholipids

Phospholipase A₂

Arachidonic Acid

Cyclooxygenase

Prostaglandins
Thromboxanes

5-lipoxygenase

Leukotrienes C₄, D₄, E₄

Cysteinyl leukotriene receptor
Arachidonic Acid Pathway

**Membrane Phospholipids**

- Phospholipase A<sub>2</sub>

- **Aspirin**
  - **NSAIDs**
  - **Cyclooxygenase**
  - **5-lipoxygenase**

- **Arachidonic Acid**

- **Prostaglandins**
  - C<sub>4</sub>, D<sub>4</sub>, E<sub>4</sub>

- **Thromboxanes**

- **Leukotrienes**
  - Cysteinyl leukotriene receptor

Mast Cell Priming/Activation by IgE

Eosinophil Recruitment in Asthma

What is Asthma?

Asthma is a chronic eosinophilic inflammation of the bronchial tubes in which the airways narrow too much and too easily in response to environmental stimuli.

What Asthma is Not

Chronic bronchitis and emphysema (COPD): permanent, largely irreversible slowing of exhalation due to long-term cigarette smoking

Acute bronchitis: acute, temporary (non-allergic) inflammation of the bronchial tubes, usually due to an infection

Who Gets Asthma?

- Children of atopic parents, esp. mothers
- Children with infantile atopic dermatitis (eczema) and food allergy
- Positive skin tests at age 3 confer increased risk of persistent asthma in school age
Allergens Relevant to Development of Asthma

- Dust mites (linear dose-response relationship)
- Cat dander (bell-shaped dose-response relationship)
- Mold
- Cockroach (especially inner cities)

Occupational Asthma

- Repetitive exposure to workplace stimulus leads to new onset of asthma.
- Persons with occupational asthma develop non-specific airway hyperresponsiveness.
- Occupational asthma only sometimes resolves with removal from the workplace exposure.
Less Likely to Develop Asthma/Allergies

- Having an older sibling or going to daycare
- Having positive PPD skin test or evidence of other respiratory infections
- Exposure to high levels of endotoxin (found in animal feces)

T-Cell Response and Asthma

Factors favoring the Th1 phenotype
- Presence of older siblings
- Early exposure to day care
- Tuberculosis, measles, or hepatitis A infection
- Rural environment

Factors favoring the Th2 phenotype
- Widespread use of antibiotics
- Western lifestyle
- Diet
- Sensitization to house-dust mites and cockroaches

The Asthma “Epidemic”

- In the United States, more than 22 million persons have asthma, including more than 6 million children.
- The annual prevalence of asthma in the U.S. increased from 3.1% in 1980 to 5.5% in 1996, a 74% increase.

Epidemiology of Asthmatic Attacks

- 4000 deaths/year
- 500,000 hospitalizations/year
- 2 million ED visits/year
Disparities in the Asthma Burden

- African-Americans and Hispanics are 3 times more likely to be hospitalized for asthma or die from asthma than white Americans.

Inner-City Asthma: Hospitalization Rates in Boston by Neighborhood

Can One “Outgrow” One’s Asthma?

- Childhood asthma often resolves spontaneously in adolescence (approx. 2/3)
- Recurrence of asthma is early adulthood is common (approx. 20%)
- Remission of adult asthma is rare (<10%).
Conclusions

- Asthma is a chronic allergic-like inflammation of the airways.
- It is characterized by *persistent* hyper-responsiveness and *episodic* narrowing of the bronchi.
- It is increasingly prevalent in Westernized societies, but its associated morbidity and mortality can be controlled.