DISEASES OF THE RESPIRATORY SYSTEM 2017

DR HEYAM AWAD

LECTURE 4: BRONCHIAL ASTHMA

DEFINITIONS

Asthma is a chronic disorder of the airways, usually (but not always) caused by an immunological reaction, which is marked by episodic bronchoconstriction due to increased airway sensitivity to a variety of stimuli; inflammation of the bronchial walls; and increased mucus secretion.

The disease is manifested by *recurrent episodes* of wheezing, breathlessness, chest tightness and cough. These symptoms are usually associated with widespread but variable bronchoconstriction and airflow limitation that is **at least partly reversible,** either spontaneously or with treatment. Between the attacks, patients may be asymptomatic.

So, asthma is characterized by:

1. **Intermittent and reversible airway obstruction**,

2. **Chronic bronchial inflammation with eosinophils**

3. **Bronchial smooth muscle cell hypertrophy and hyperreactivity,**

4**. Increased mucus secretion.**

IMPORTANT NOTE: in all the obstructive airway diseases we discussed, the obstruction is permanent and irreversible except in asthma where, at least in the early stages, the obstruction is reversible. The reason for this reversibility is that it's mainly caused by constriction of the bronchi due to muscle spasm (muscle contraction), this contraction is caused by inflammatory mediators mainly leukotrienes that are secreted in response to the immunologic and inflammatory response.

EPIDEMIOLOGY OF BRONCHIAL ASTHMA

There has been a significant increase in the incidence of asthma in the Western world over the past 40 to 50 years. More recently, although treatment for asthma has improved, the prevalence of asthma continues to increase in low and middle income countries and in some ethnic groups in which prevalence was previously low.

The reason for this increase is possibly related to the hygiene hypothesis described later in this lecture.

TYPES OF ASTHMA

Asthma may be categorized as atopic (evidence of allergen sensitization and immune activation, often in a patient with allergic rhinitis or eczema) or non-atopic (no evidence of allergen sensitization).

In either type, episodes of bronchospasm can have diverse triggers, such as respiratory infections (especially viral infections), exposure to irritants (e.g., smoke, fumes), cold air, stress, and exercise.

Atopic Asthma.

This is the most common type of asthma and it is a classic example of IgE-mediated (type I) hypersensitivity reaction.The disease usually begins in childhood and is triggered by environmental allergens, such as dusts, pollens, and foods.

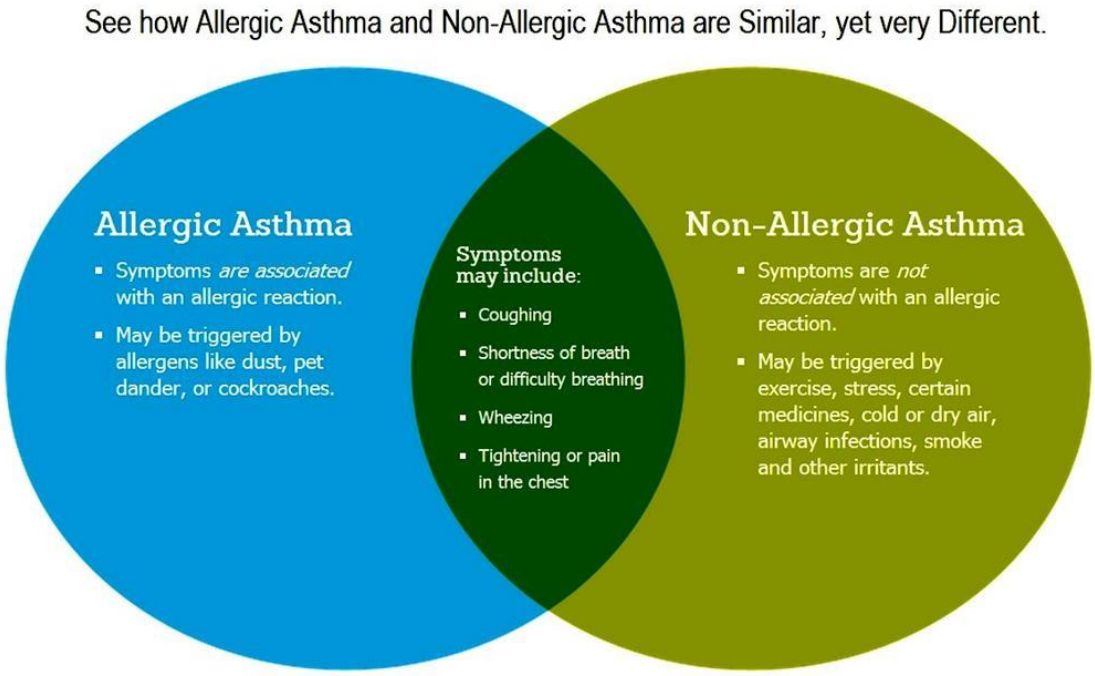
A positive family history of asthma is common, and a skin test with the offending antigen in these patients results in an immediate wheal-and-flare reaction.

Atopic asthma may also be diagnosed based on high total serum IgE levels or evidence of allergen sensitization by serum radioallergosorbent tests (called RAST), which can detect the presence of IgE antibodies that are specific for individual allergens.

Non-Atopic Asthma.

Individuals with non-atopic asthma do not have evidence of allergen sensitization and skin test results are usually negative. A positive family history of asthma is less common in these patients.

Respiratory infections due to viruses (e.g., rhinovirus, parainfluenza virus and respiratory syncytial virus) are common triggers in non-atopic asthma. Inhaled air pollutants, such as smoking, sulfur dioxide, ozone, and nitrogen dioxide, may also contribute to the chronic airway inflammation and hyperreactivity in some cases.



Drug-Induced Asthma

Several pharmacologic agents provoke asthma; aspirin being the most striking example

Patients with aspirin sensitivity present with recurrent rhinitis and nasal polyps, urticaria, and bronchospasm

The precise mechanism remains unknown, but it is presumed that aspirin inhibits the cyclooxygenase pathway of arachidonic acid metabolism without affecting the lipoxygenase route, thereby shifting the balance of production toward leukotrienes that cause bronchial spasm

Occupational asthma

Occurs due to occupational exposure to smoke , fumes or chemicals, like rubber, cotton and others.

PATHOGENESIS.

Atopic asthma is caused by a **TH2 and IgE** response to environmental allergens **in genetically predisposed individuals.**

A fundamental abnormality in asthma is an exaggerated TH2 response to normally harmless environmental antigens. TH2 cells secrete cytokines that promote inflammation and stimulate B cells to produce IgE and other antibodies.

These cytokines include:
1. IL-4, which stimulates the production of IgE
2. IL-5, which activates locally recruited eosinophils
3. IL-13, which stimulates mucus secretion from bronchial submucosal glands and also promotes IgE production by B cells.

The T cells and epithelial cells secrete chemokines that recruit more T cells and eosinophils, thus exacerbating the reaction.

As in other allergic reactions IgE binds to the Fc receptors on submucosal mast cells, and repeat exposure to the allergen triggers the mast cells to release granule contents and produce cytokines and other mediators, which collectively induce the **early-phase (immediate hypersensitivity) reaction and the late phase reaction.**

The early reaction is dominated by *bronchoconstriction, increased mucus production, variable degrees of vasodilation, and increased vascular permeability.*

Bronchoconstriction is triggered by direct stimulation of subepithelial vagal (parasympathetic) receptors through both central and local reflexes triggered by mediators produced by mast cells and other cells in the reaction.

The late-phase reaction is dominated by recruitment of leukocytes, notably eosinophils, neutrophils, and more T cells.

Although TH2 cells are the dominant T cell type involved in the disease, other T cells that contribute to the inflammation include TH17 (IL-17 producing) cells, which recruit neutrophils.

THE ASTHMATIC ATTACK IS CAUSED BY SEVERAL MEDIATORS MAINLY:

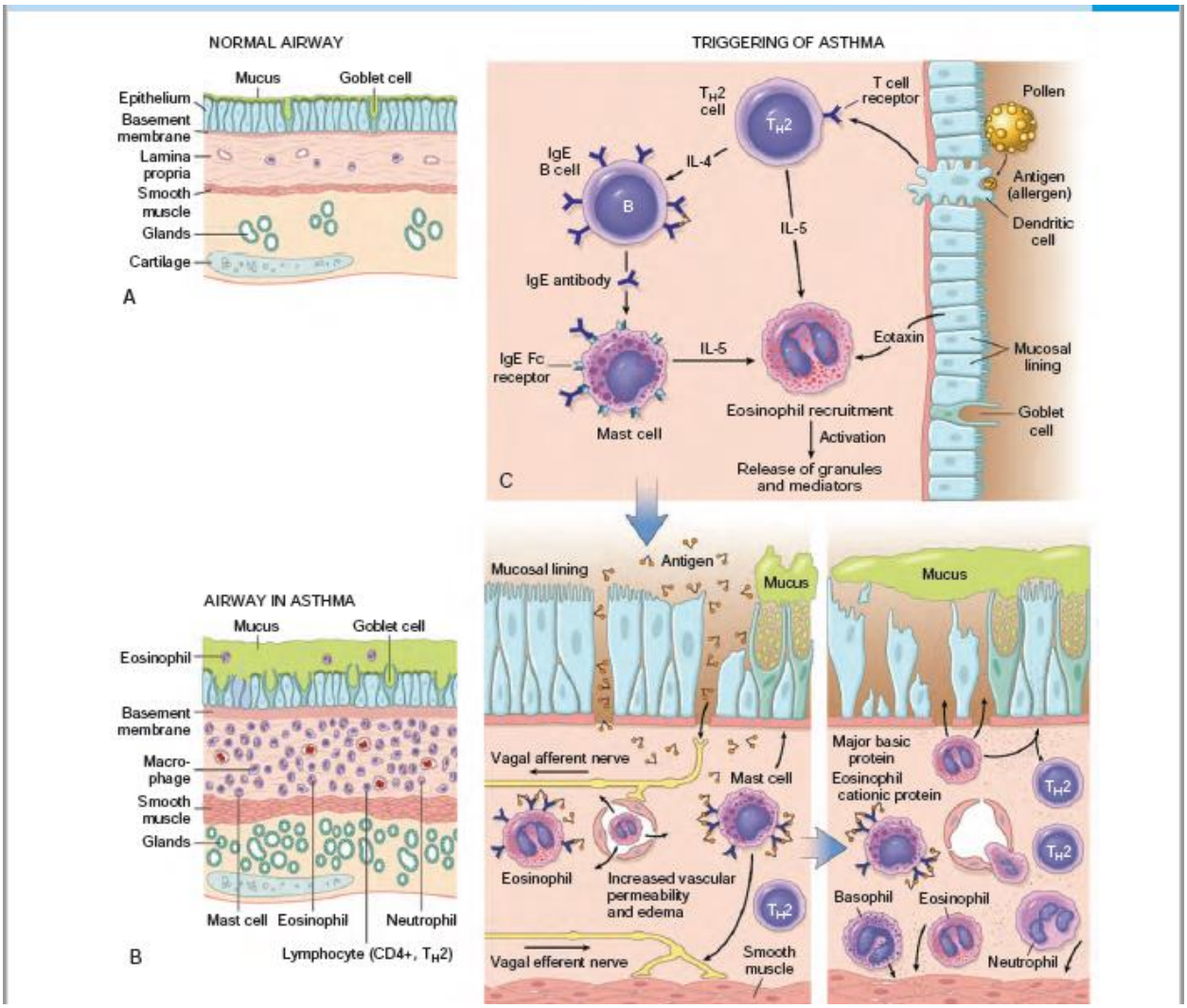
1. leukotrienes C4, D4, and E4, which cause prolonged bronchoconstriction as well as increased vascular permeability and increased mucus secretion

2. acetylcholine released from intrapulmonary parasympatheticnerves, which can cause airway smooth muscle constriction by directly stimulating muscarinic receptors.

3. histamine, a potent bronchoconstrictor;

4. prostaglandin D2, which elicits bronchoconstriction and vasodilatation;

5. platelet-activating factor, which causes aggregation of platelets and release of serotonin from their granules. These mediators might yet prove important in certain types of chronic or nonallergic asthma.



Genetic Susceptibility.

Susceptibility to atopic asthma is multigenic and often associated with increased incidence of other allergic disorders, such as allergic rhinitis (hay fever) and eczema.

The genetic polymorphisms linked to asthma include a locus on chromosome 5q, near the gene cluster encoding the cytokines IL-3, IL-4, IL-5, IL-9, and IL-13 and the IL-4 receptor.

Among the genes in this cluster, polymorphisms in the IL13 gene have the strongest and most consistent associations with asthma or allergic disease.

Also particular class II HLA alleles are linked to production of IgE antibodies against some antigens, such as ragweed pollen.

IL-4 receptor gene variants are associated with atopy, elevated total serum IgE, and asthma.

Environmental Factors.

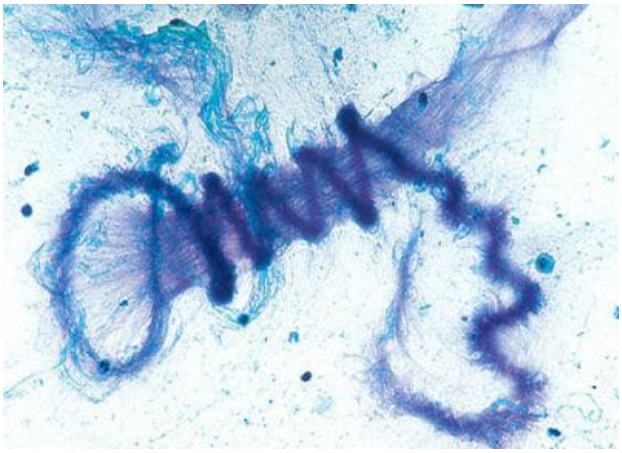
Asthma is a disease of industrialized societies where the majority of people live in cities. This likely has two main explanations. Firstly, industrialized environments contain many airborne pollutants that can serve as allergens to initiate the TH2 response. Secondly, city life tends to limit the exposure of very young children to certain antigens, particularly microbial antigens, and exposure to such antigens seems to protect children from asthma and atopy. This protective effect is even more apparent if the microbial exposure occurred throughout the mother's pregnancy. The idea that microbial exposure during early development reduces the later incidence of allergic (and some autoimmune) diseases has been known as the **hygiene hypothesis.**

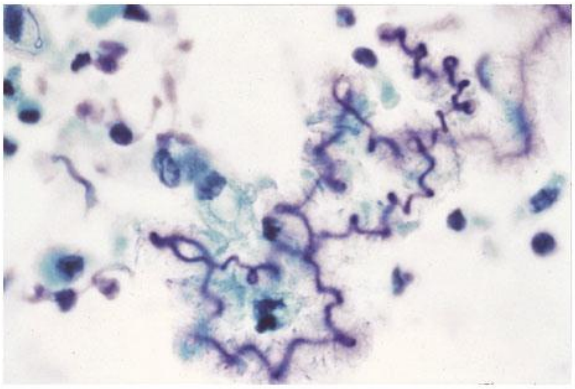
MORPHOLOGY

Gross features: occlusion of bronchi and bronchioles by thick, tenacious mucus plugs, which often contain shed epithelium.

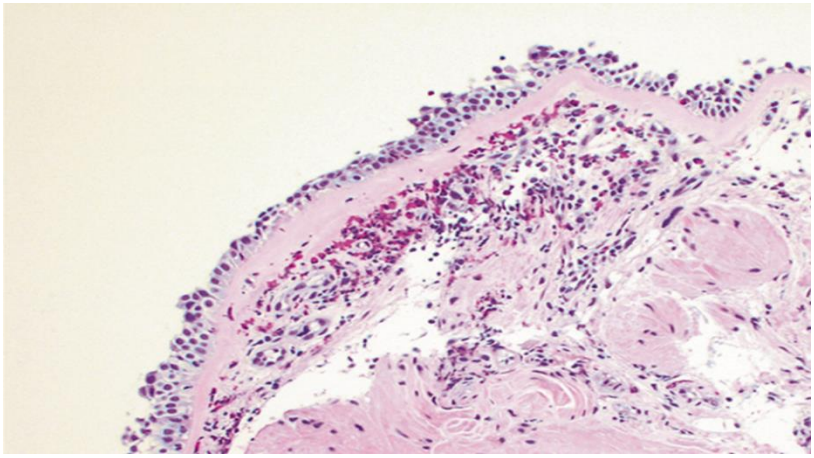
Microscopically:

1. in sputum or bronchoalveolar lavage specimens we see **Curschmann spirals (pic below)**, which may result from extrusion of mucus plugs from subepithelial mucous gland ducts or bronchioles.

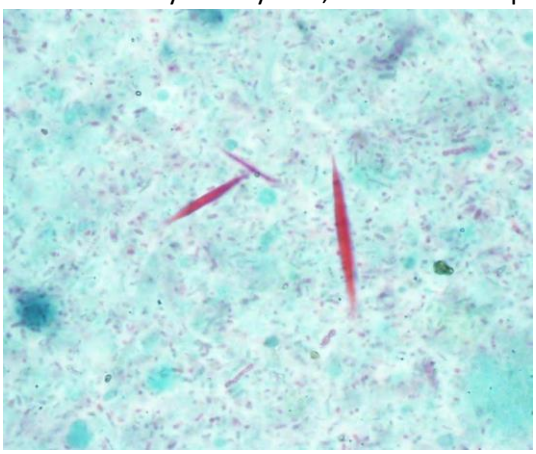


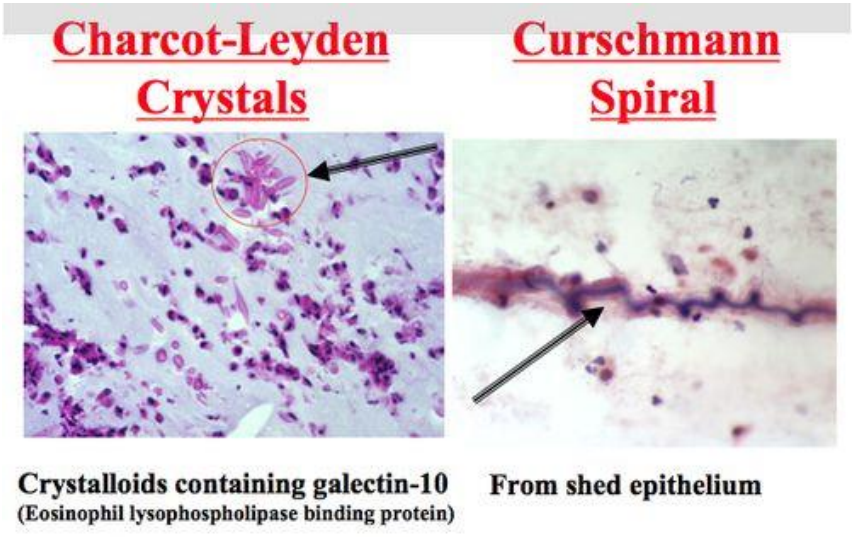


2. numerous eosinophils (the red cells seen in the pic below)



3. Charcot-Leyden crystals; which are composed of an eosinophil protein called galectin-10:

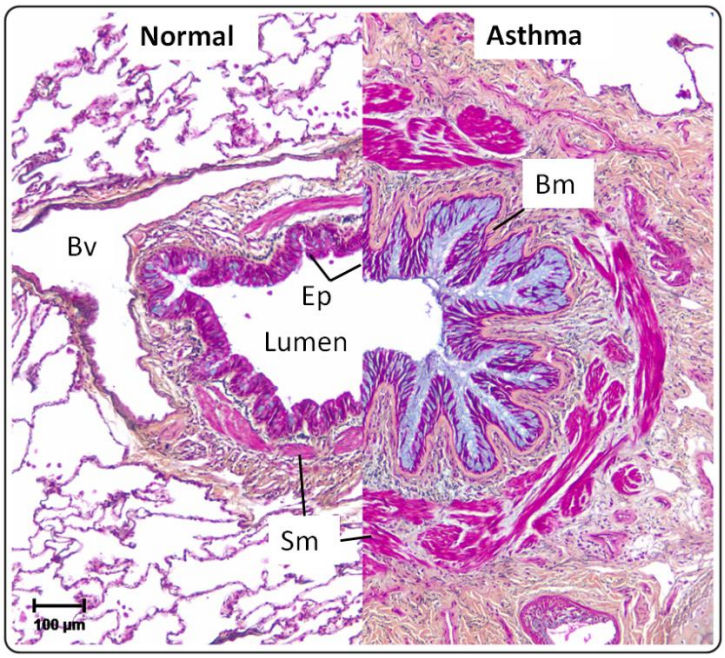




With repeated inflammations the airway undergoes structural changes , collectively called **"airway remodeling"** and these include:

- Thickening of airway wall
- Subbasement membrane fibrosis (due to deposition of type I and III collagen)
- Increased vascularity
- An increase in the size of the submucosal glands and number of airway goblet cells
- Hypertrophy and/or hyperplasia of the bronchial wall muscle

FEATURES OF AIRWAY REMODELLING:



CLINICAL COURSE.

A classic acute asthmatic attack lasts up to several hours. In some patients, however, the cardinal symptoms of chest tightness, dyspnea, wheezing, and coughing (with or without sputum production) are present at a low level constantly. In its most severe form which is called **status asthmaticus,** the paroxysm persists for days and even weeks, sometimes causing airflow obstruction that is so extreme that marked cyanosis or even death ensues.

The diagnosis is based on demonstration of an increase in airflow obstruction (from baseline levels),

Therapy is based on severity of the disease. Up to 50% of childhood asthma remits in adolescence only to return in adulthood in a significant number of patients. In other cases there is a variable decline in baseline lung function.

THANK YOU