9.1.4

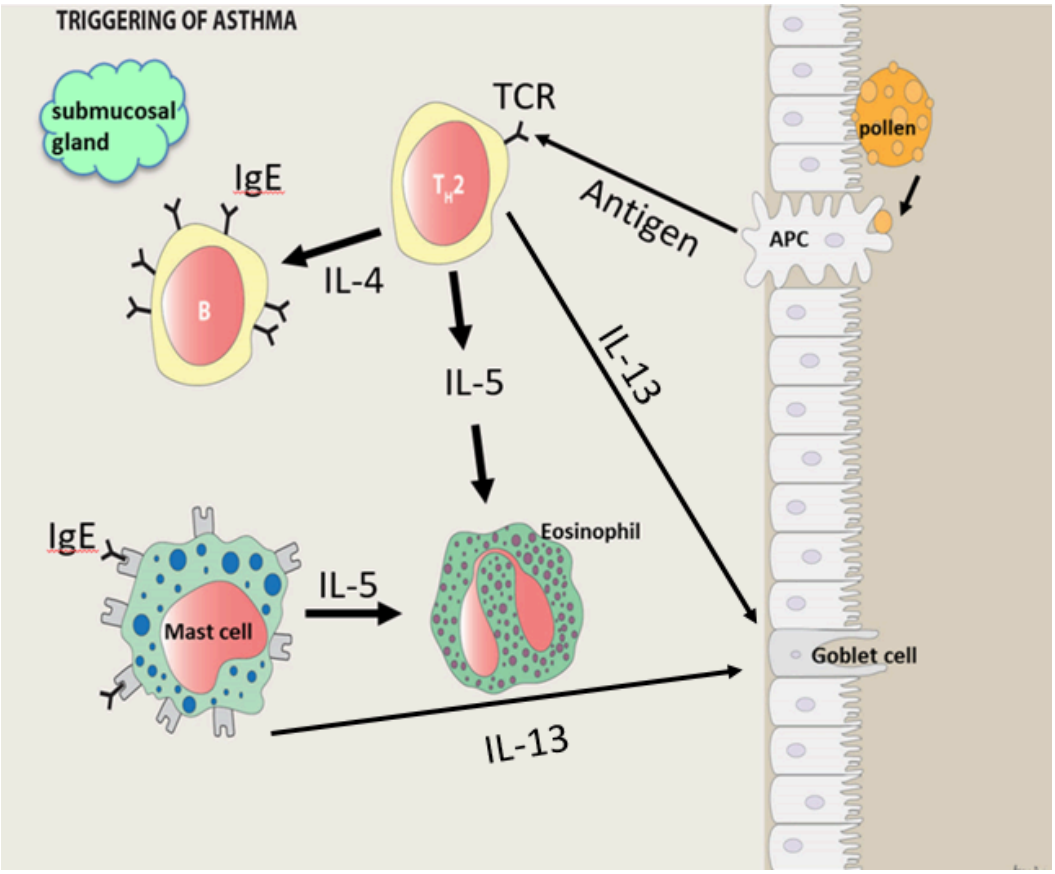
Asthma

Asthma is an obstructive airway disorder caused by an immune reaction. It is characterized by episodic bronchoconstriction, inflammation of the bronchial walls, and increased mucus secretion. The airway obstruction leads to symptoms such as episodic wheezing, dyspnea, a feeling of chest tightness, and a cough. Asthma can be divided into two main categories: extrinsic and intrinsic.

Extrinsic (Allergic or Atopic) Asthma

Extrinsic (or allergic or atopic) asthma is a type 1 hypersensitivity reaction that normally begins in childhood. Family history increases the risk of extrinsic asthma. Common airborne allergens that can trigger allergic asthma include feces of dust mites, cockroach allergens, and animal dander. A skin hypersensitivity test is conducted to diagnose this type of asthma. Potential allergens are injected into the skin. A positive test is the production of an immediate wheel (swelling in the skin) and flare reaction (redness of the skin due to vasodilation).

The pathophysiology of atopic asthma involves an antigen presenting cell (APC) that presents a portion of an allergen like pollen to a naïve T helper cell and also secretes IL-4 which triggers the naïve T-helper cell to differentiate into a T helper 2 cell (TH_2). The TH_2 cell then interacts with a B-cell and releases IL-4 that causes the B-cell to produce IgE antibodies. The Fc region of IgE antibodies bind to mast cells and become their cell surface receptors; this mediates a faster immune response upon subsequent exposure to the allergen. People with allergic asthma typically have high serum levels of IgE. TH_2 cells also release IL-5, which activates eosinophils, and IL-13, which causes submucosal glands to secrete mucus (see figure below).



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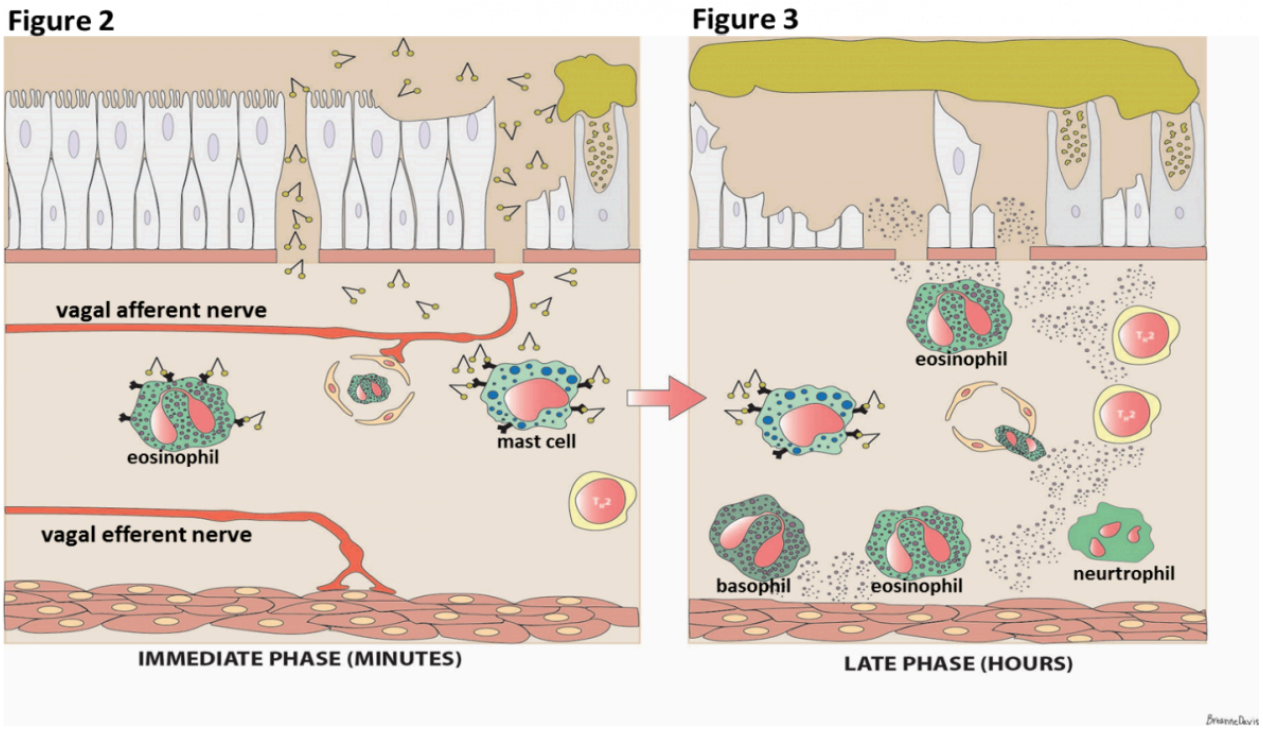
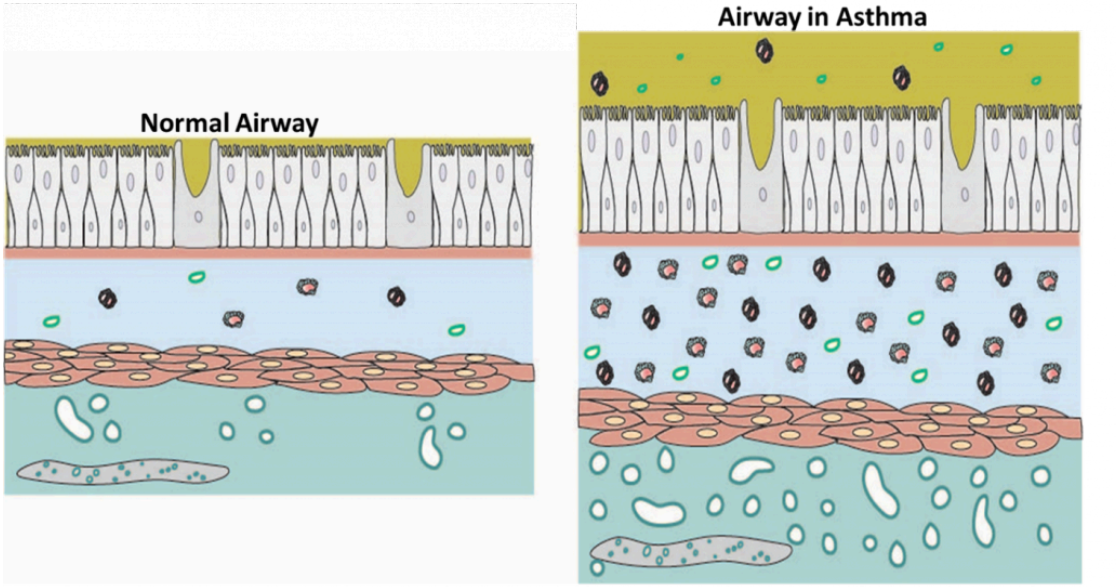
On subsequent exposure to the same allergen, there is an early and late asthmatic response:

- In the early or immediate response, the allergen binds to the IgE mast cell receptor and causes the release of histamine and cytokines like eosinophil chemotactic factor and IL-5 (which recruits and activates eosinophils). Histamine acts as a vasodilator and increases vascular permeability. IL-13 released from TH_2 cells and mast cells cause increased mucus production by goblet cells. Released cytokines can also trigger intrapulmonary parasympathetic nerves to release acetylcholine which also increases bronchoconstriction and mucus secretion. Leukotrienes made from arachidonic acid by immune cells also contribute to bronchoconstriction and vascular permeability.
- In the late response several hours later, further inflammation occurs due to the damage done by recruited leukocytes such as eosinophils, neutrophils, and basophils. Eosinophils are particularly damaging as they release toxic substances like major basic protein and eosinophil cationic protein onto the bronchial epithelial cells that cause further injury and inflammation.



Immediate and Late Phases of Allergic Asthmatic Reaction *Images by BYU-I Student 2018*

Repeated asthmatic episodes bring about more lasting changes to the airway in a process called “airway remodeling.” In this remodeling, immune cells like mast cells, macrophages, eosinophils, and neutrophils accumulate underneath a thickened basement membrane. Underlying smooth muscle cells also undergo hypertrophy and hyperplasia. Goblet cells divide and subepithelial mucous glands undergo hypertrophy, producing excess mucus that blocks the airway. Increased airway vascularity is also observed with asthma and provides nutrients for the actively dividing cells and for mucus production.



There are several causes and contributors to the development of asthma:

- It is believed that about 75% of one's risk for developing asthma is associated with genetic factors. Particularly, patients prone to atopy (genetic predisposition to develop hypersensitivity to allergens in the environment) are at increased risk. Some common genetic predispositions are:
  - Polymorphisms in genes that code for cytokines (especially IL-13) and cytokine receptors (especially the IL-4 receptor) are associated with asthma.
  - Certain class II HLA alleles that are associated with an increase in the production of IgE after pollen exposure.
  - Variants in genes that code for beta-2 adrenergic receptors are associated with hyper-responsiveness of the airway.
- Higher ratios of TH_2 (associated with allergies) vs TH_1 (associated with fighting infections) lymphocytes in the cord blood of neonates may be a strong predictor for later development of asthma.
- Exposure to secondhand smoke in utero.
- Having frequent lower respiratory tract viral infections such as RSV as a child increases the risk for developing persistent asthma.
- Those that grow up in an industrialized environment like cities are more likely to develop asthma. Airborne pollution acts as an allergen to bias the T helper cell to differentiation toward the TH_2 subtype that is associated with allergies. Life in the city also decreases a child's exposure to microbial antigens.
- The "hygiene hypothesis" describes that "being too clean" during childhood years increases the risk for atopy and asthma. This hypothesis explains that children exposed to decreased amounts of bacteria and endotoxins during the first two years of life tend to develop less TH_1 lymphocytes and more TH_2 lymphocytes. This shift in balance increases the risk for developing asthma. Evidence for this hypothesis is quite significant, as a decreased incidence for developing asthma is seen in the following: children attending daycare in the first 6 months of life, children in larger families, children with older siblings, children having an early exposure to cats and dogs, and children given fewer antibiotics at a young age. However, it is probably not the best idea to encourage purposeful introduction of pathogens to children because of the risk of commutable diseases.

Intrinsic (Non-Atopic) Asthma

The pathophysiological mechanisms of **intrinsic (non-atopic) asthma** are not well understood. Intrinsic asthma is not caused by allergies. With this type of asthma, a positive family history is much less common and no evidence for allergen sensitization can be found because allergen skin tests are usually negative. While there is no obvious role of allergens driving the inflammatory processes, there is much similarity to allergic asthma: Blood IgE levels are elevated, the same inflammatory cytokines are released, TH_2 cells dominate (less TH_1 cells), and mast cell/eosinophil activation occurs in a similar fashion. Theories postulate that intrinsic asthma is due to physiological processes that involve immune cell activation by physical irritation (like air particles, flow rates and temperature). Other theories suggest possible "super antigens" that may involve non-specific T-cell activation. There is also the possibility of hapten interactions and autoimmune responses.

Some triggers for non-atopic asthma include respiratory viral infections, air pollutants (like sulfur dioxide, nitrogen dioxide, and ozone from smog), occupational exposure (like fumes from epoxy resins and plastics), organic dusts (like wood and cotton), gasses (like toluene), chemicals (like formaldehyde) and even seemingly harmless actions like exercise and cold exposure. Other triggers may be emotional trauma, changes in hormone levels, and exposure to bronchial irritants such as strong odors and smoke. Some episodes of intrinsic asthma are seasonal.

Certain drugs can also be a trigger for asthma. For example, NSAIDs can induce a classic triad of asthma symptoms including chronic rhinosinusitis, nasal polyps, and bronchial asthma. It is believed that this type of asthma is due to a decrease in the production of a prostaglandin called PGE-2. PGE-2 can inhibit enzymes like 5-lipoxygenase that are responsible for the production of leukotrienes (bronchoconstrictors and vasodilators). Treatment with NSAIDs like aspirin and ibuprofen results in less PGE-2 production and therefore less inhibition of leukotriene production. This results in an increase in leukotrienes which are responsible for the increased bronchoconstriction observed in this type of asthma.

Diagnosis and Treatment of Asthma

The cardinal symptoms of asthma include chest tightness, dyspnea or shortness of breath, coughing that may or may not produce sputum, and wheezing. Classic asthma attacks can last for several hours. Asthma symptoms seem to worsen at night.

Diagnosis is done by assessing the patient's history and symptoms. Determining their family history as it relates to asthma is important. Skin tests can reveal allergic responses to particular allergens. Blood tests can reveal specific IgE antibodies as well as eosinophil counts. Eosinophils in the sputum can also support a diagnosis of asthma.

Pulmonary function tests are also used to diagnose asthma. It would be good to review the following tests from your previous anatomy and physiology courses: **forced expired volume in 1 second (FEV_1)** over **forced vital capacity (FVC)** **(FEV_1/FVC) ratio** and **peak expiratory flow (PEF)**. For someone having an asthmatic attack, you can expect the FEV_1/FVC ratio to be lower than the normal value of 75-80%. This is because it is very difficult for someone with an obstructive lung disease like asthma to exhale quickly because they have increased airway resistance. PEF is a measure of a person's maximum rate of expiration after full inspiration and thus can give an indication if there is an obstruction of the airways. This measurement is obtained using a handheld peak flow meter and can be used for diagnosis or monitoring asthma. If an individual's PEF drops 80% below their personal best, action should be taken to treat the asthma flareup.

Common pharmaceutical treatments for asthma include:

- Bronchodilators such as short-acting beta-2 agonists (SABAs) and long-acting beta-2 agonists (LABAs). These drugs bind to beta-2 adrenergic receptors expressed on bronchiolar smooth muscle cells and induce smooth muscle relaxation leading to bronchodilation. Recall that beta-2 adrenergic receptors are g-protein coupled receptors and the activation of these beta-2 receptors leads to increased cAMP production. Cyclic AMP (cAMP) then activates a kinase that phosphorylates and inhibits a protein required for muscle contraction.
- An enzyme called phosphodiesterase breaks down cAMP. Theophylline is a phosphodiesterase inhibitor that acts to increase cAMP and induce bronchodilation.
- Anticholinergics can be used to block the effects of the parasympathetic nervous system that normally causes bronchoconstriction via muscarinic receptors.
- Inhaled corticosteroids (ICS) have anti-inflammatory effects that can be useful as well.
- Leukotriene receptor antagonists (LTRAs) block the effects of the broncho-constricting leukotrienes while 5-lipoxygenase inhibitors block the production of leukotrienes.
- Omalizumab is an anti-IgE monoclonal antibody used to bind up IgE to decrease its effects on mast cells.