Hypersensitivity is an increased or inappropriate immune response. Hypersensitivities have been classified into 4 basic types based on the type of immune response they elicit. All 4 types can result in inflammation.

**TYPE I Hypersensitivity**

*Classic allergy*

*IgE mediated trigger for release of chemicals from mast cells.*

Chronic allergic responses result in increased numbers of eosinophils.

Type I allergic reaction is also called **anaphylaxis.**

*E.g.* Hay fever, asthma, bee stings, food allergies.

**I. Allergens** are a subset of antigens that specifically stimulate a type I allergic response. Allergens are small proteins (often enzymes) which are normally innocuous antigens that do not cause pathogenesis or disease. Mucosal exposure and a low dose of antigen/allergen increases the sensitization to that allergen. Allergens elicit a Th2 response with the production of IL-4 and B cells producing IgE antibodies.

**II. Genetic predisposition**

*Atopic* is the term for genetic trait to have predisposition for localized anaphylaxis. Atopic individuals are predisposed to allergies and have higher levels of IgE and eosinophils.

1. Associated with certain chromosomes but not sure which genes yet though many have been implicated.

   *E.g.* Cytokines, FcεReceptor.

2. HLA (Human MHC) alleles. Certain Class II MHC may bind allergic peptides which may be key may be to initiating Th2 response.
III. Mechanisms of allergic response

1. Sensitization. To become sensitized, a person who is exposed to allergen must generate an immune response that results in an IgE isotype. This means the activation of Th2 cells and B cells. IL-4 is necessary to get the isotype switching to IgE. Memory B cells of the IgE isotype will be made but more importantly the IgE antibodies can remain attached to Mast cells for years. The IgE antibodies which normally would be degraded in the blood after a few months are maintained in the body on Mast cells by a high affinity FceReceptor.

2. Secondary exposure. Cells have IgE on surface ready to go. Granules already full of mediators. Allergen binds IgE must cross-link activates signal for mast cell degranulation release of mediators induces anaphylaxis.

Localized anaphylaxis is target organ allergic response to allergen.
A. Airways sensitivity results in sneezing, rhinitis, etc.
B. Digestive tract contact results in vomiting, cramping, diarrhea.
C. Skin sensitivity usually reddened inflamed area resulting in itching.

Systemic anaphylaxis systemic vasodilation of blood vessels and smooth muscle contraction bronchiole constriction. Inflammation results in increased fluid in tissues leading to low blood pressure and shock.
IV. Mediators of Type I Hypersensitivity

1. Primary mediators cause immediate inflammatory response.

**Histamine**
- Constriction of smooth muscles. e.g. bronchiole constriction leads to wheezing.
- Vasodilation/inflammation. e.g. swelling from liquid in tissues, red itchy skin causes hives.
- Activates enzymes for tissue breakdown.

**TNF-α** Causes endothelial cell activation and inflammatory cascade.

2. Secondary mediators cause the late phase reaction which starts within a few hours after exposure to the allergen and can cause symptoms for weeks. The increase inflammation can cause expulsion of contents of intestine or nasal passages. This can include diarrhea, vomiting, sneezing, coughing, phlegm, etc.

A. Leukotrienes and prostaglandins.
   1. Constriction of smooth muscle. 2. Increased vascular permeability. 3. Mucus secretion.
B. Cyokines    IL-3, IL-5, GM-CSF, IL-4, IL-9, IL-13
   1. Promote eosinophil production.
   2. Th2 response
C. More inflammatory cytokines   IL-1, IL-6, TNF-α

Continuation of sensitization cycle
Mast cells control the immediate response and initiate the infiltration of eosinophils and neutrophils which drive secondary response. More IgE production can be further driven by activated Mast cells, basophils, eosinophils.

**Eosinophils**
Eosinophils play key role in secreting mediators to drive late phase reaction and promote inflammation.
Eosinophils make enzymes, cytokines (IL-3, IL-5, GM-CSF), IL-8, LTC4, LTD4, PAF
Eosinophils can provide CD40L and IL-4 for B cell activation that bypasses need for Th activation.

V. Treatment for TYPE I

1. Immunotherapy. Known as desensitization to allergen or allergy shots.
Inject low amounts of allergen increasing dosage over a long period of time to reduce the IgE on Mast cells and produce blocking IgG which binds allergen and causes usual immune elimination of foreign antigens.

2. Pharmocotherapy. Drugs.
Standard therapy---relieve symptoms.
- Antihistamines. These are drugs that block histamine receptors.
- Anti-inflammatories (e.g. aspirin, ibuprofen, naprosyn etc.)
- Corticosteroids. Broad immunosuppressive drugs that inhibit immune responses. (e.g. Prednisone)
TYPE II Hypersensitivity

Antibody mediated cytotoxicity of red blood cells.

1. Transfusion reactions. Antibody mediated response after blood transfusion. Innocuous antigens on red blood cells (e.g. blood group Ags--ABO). Antibody against rbc antigen binds and mediates killing of rbcs via C or ADCC.

2. Drug reactions - drug binds to rbc surface and ab binds to drug and causes lysis of rbcs.


Rh+ baby born to Rh- mother first time fine. 2nd time can have abs to Rh from 1st pregnancy. Ab crosses placenta and baby kills its own rbcs.

Treat mother with ab to Rh antigen right after birth and mother never makes its own immune response.

TYPE III Hypersensitivity

Immune complex mediated.

Ab-ag complexes get deposited in tissues and cause localized inflammatory response. Can be called an Arthus reaction. (e.g. Arthritis, Lupus).

High amount of antibody present exposure to antigen leads to high number of immune complexes that can not be eliminated. Causes mechanical damage and results in inflammation.

TYPE IV Hypersensitivity

Delayed Type Hypersensitivity (DTH)

This is a Th1 cell mediated hypersensitivity. Delayed is relative DTH response takes 48-72 hours.

Th1 cells produce CKs that activate macrophages which can lead to tissue damage, lesions, scarring, and potentially granulomas.

Stages of DTH

1. Sensitization stage.

Development of effector Thelper1 specific to DTH antigen.

Th1 cells are activated by antigen presented by macrophages or skin dendritic cells. These Th cells become memory cells for activation of hypersensitivity reaction capable of triggering inflammatory response.

2. Effector stage. Secondary contact yields what we call DTH.

A. Exposure to antigen causes activation of memory Th cells from previous exposure proliferation and new effector T cell.

B. Influx of macrophages release of CKs. E.g. IL-1, IL-8, IFN-γ, TNFα,

C. Inflammation starts 24-48 hours after contact with antigen.

Small molecules that complex with skin proteins are taken up by APCs and presented to Th cells to get sensitization. Contact dermatitis reactions are DTH responses. (e.g. poison oak).