Hypersensitivity

-Hypersensitivity (allergy) is an inappropriate immune response that may develop in the humoral or cell-mediated responses

-Was first termed *anaphylaxis*

-can be systematic, which often leads to shock and can be fatal, or localized, which is various atopic reactions

Types of Reactions

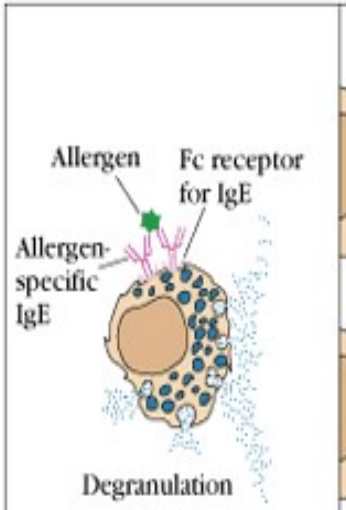
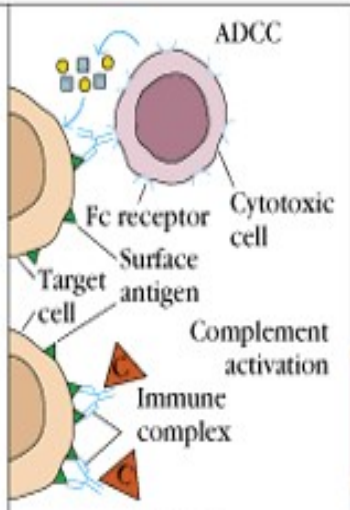
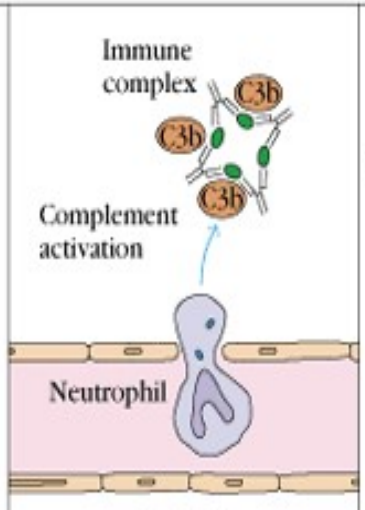
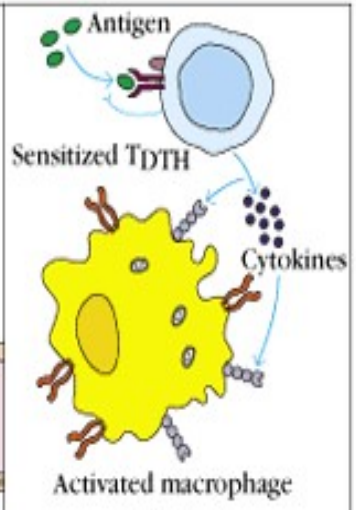
There are four types of reactions:

Type I-IgE mediated

Type II-Antibody-Mediated

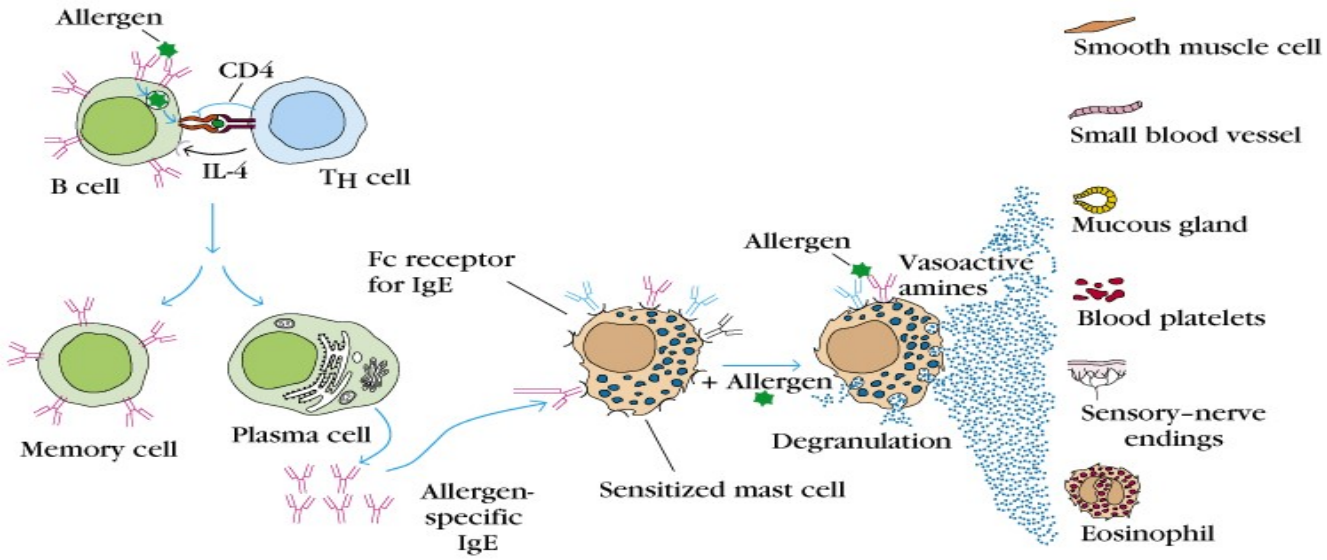
Type III-Immune Complex-Mediated

Type IV-Delayed-Type Hypersensitivity (DTH)

			
Type I	**Type II**	**Type III**	**Type IV**
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_{DTH} cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

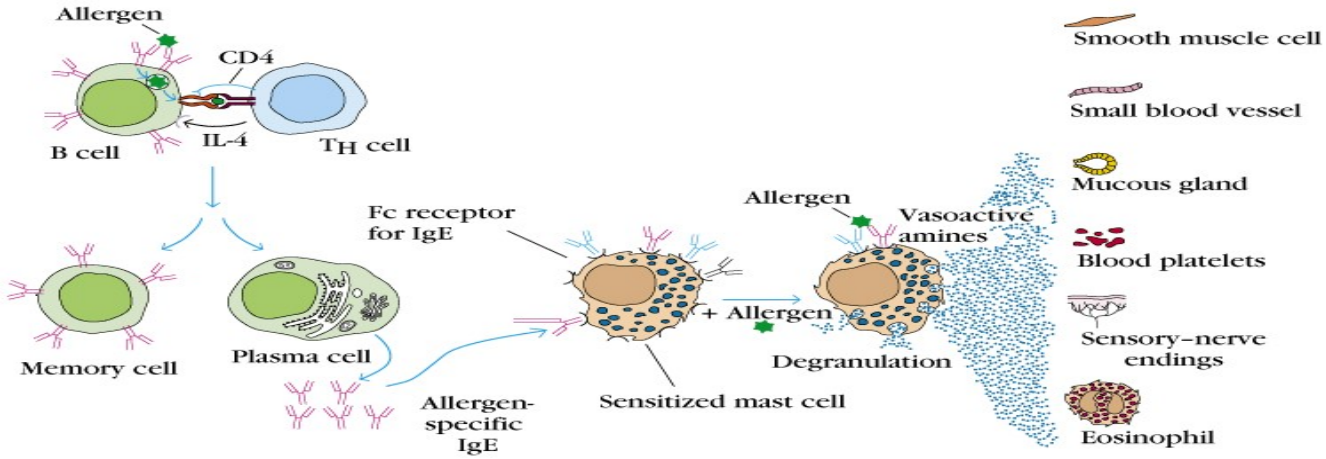
Type I: IgE-Mediated Hypersensitivity

- hmm…that sounds bad …aren't IgE's supposed to be one of the 5 isotypes of "good guys"?
- Of course, the allergen is the true "bad guy" – a non-parasitic antigen capable of stimulating a Type I hypersensitive response.
- It's the secretion and cross-linking of the IgE that causes the problem.
- Let's locate the IgE:

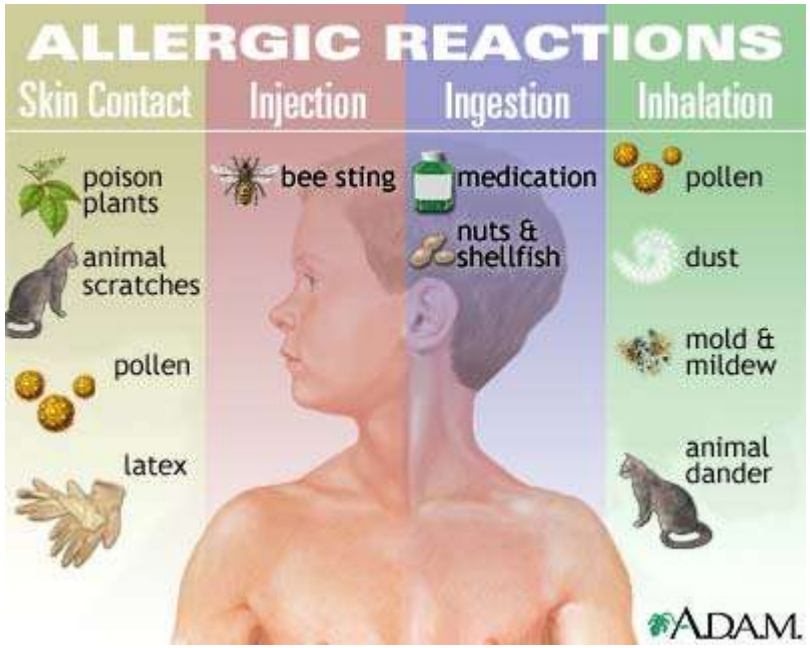


What is the sequence of events in an IgE-mediated hypersensitive response?

1. The plasma cells secrete IgE.
2. These IgE bind to Fc receptors on sensitized mast cells and blood basophils.
3. When the allergen appears again (usually a few weeks after the first exposure), it cross-links the mIgEs and causes degranulation, releasing granules.
4. Mediators within these granules act on the surrounding tissues such as smooth muscle, small blood vessels, and mucous glands.

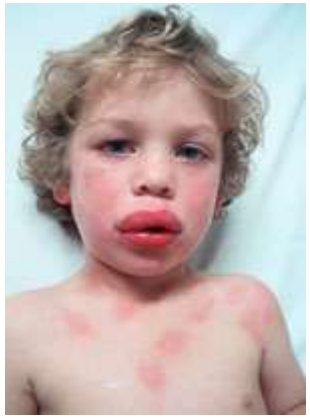


Type I (*Immediate*) Hypersensitivity



Type I (*Immediate*) Hypersensitivity

Anaphylaxis



The chemically active effectors within the granules released via degranulation are called mediators. This group includes:

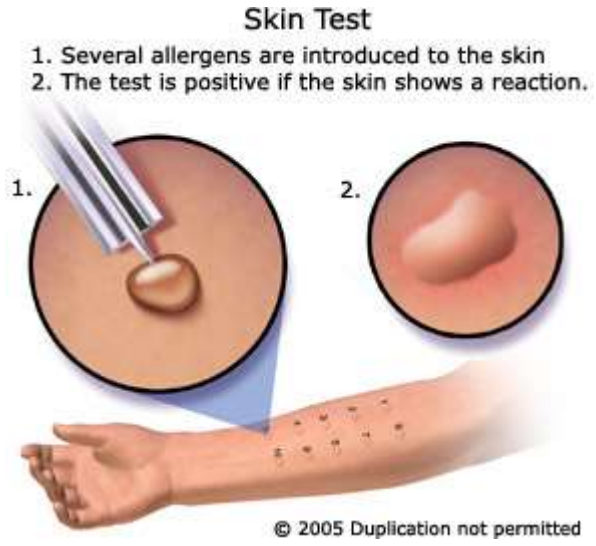
- Histamines
- Leukotrienes
- Prostaglandins
- Cytokines

TABLE 16-3 PRINCIPAL MEDIATORS INVOLVED IN TYPE I HYPERSENSITIVITY

Mediator	Effects
Primary	
Histamine	Increased vascular permeability; smooth-muscle contraction
Serotonin	Increased vascular permeability; smooth-muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases	Bronchial mucus secretion; degradation of blood-vessel basement membrane; generation of complement split products
Secondary	
Platelet-activating factor	Platelet aggregation and degranulation; contraction of pulmonary smooth muscles
Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)	Increased vascular permeability; contraction of pulmonary smooth muscles
Prostaglandins	Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation
Bradykinin	Increased vascular permeability; smooth-muscle contraction
Cytokines	
IL-1 and TNF-α	Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells
IL-2, IL-3, IL-4, IL-5, IL-6, TGF-β, and GM-CSF	Various effects (see Table 12-1)

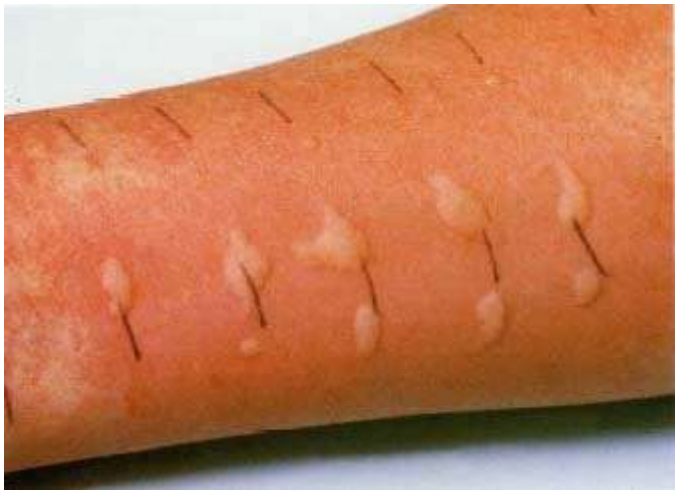
Type I (*Immediate*) Hypersensitivity

Doctors sometimes use skin tests to diagnose allergies.



Type I (*Immediate*) Hypersensitivity

The reactions shown here demonstrate allergic response.



Type II-Antibody-Mediated Cytotoxic Hypersensitivity

- Involves the antibody mediated destruction of cells
- Can mediated cell destruction by activating the complement system to create pores in the membrane of the foreign cell
- Can also mediated by *Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)* where the Fc receptors bind to Fc receptor of antibody on the target cell and promote killing

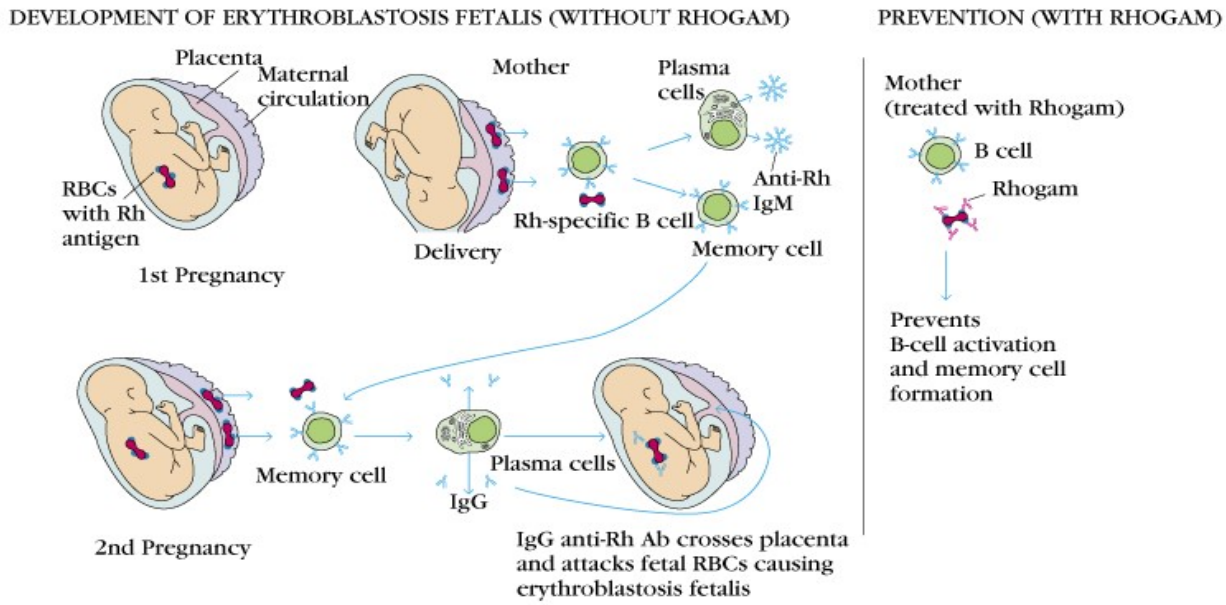
Transfusion reactions:

- Antibodies of the A,B, and O antigens are usually of the IgM class (these antigens are call *isohemagglutinins*)
- For example an A individual produce isohemagglutinins to B-like epitopes but not to A epitopes because they are self
- Person who are transfused with the wrong blood type will produce anti-hemmagglutinins causing complement mediated lysis
- Antibodies are usually of the IgG class

- Transfusion reactions can be delayed or immediate but have different Ig isohemagglutinins
- Immediate reactions has a complement-mediated lysis triggered by IgM isohemagglutinins
- Delayed reactions induce clonal selection and the productions of IgG which is less effective in activating the complement
    - This leads to incomplete complement-mediated lysis
- Cross-matching can detect antibodies in the sera to prevent this

Hemolytic Disease of the Newborn

- This is where maternal IgG antibodies specific for fetal blood group antigens cross the placenta and destroy fetal RBC's
- *Erythroblastosis fetalis*-severe hemolytic disease of newborns
  - Most commonly develops when an Rh^+ fetus expresses an Rh antigen on it's blood that and Rh^- mother doesn't recognize



Erythroblastosis fetalis

- During the 1st pregnancy small amounts of fetal blood pass through the placenta but not enough to induce a responses
- During delivery larger amounts of fetal blood cross the placenta causing an activation of B-cells that are Rh specific thus leading to memory B-cells (anti-Rh antibodies)
- The IgM antibody clears the Rh^+ cells from the mother
- In subsequent pregnancies with an Rh^+ fetus, the Rh^+ RBC cross the placenta activating the memory B-cells
- These in turn cross the placenta and damage the fetal RBC because they are seen as "foreign"
- This type of reaction can be prevented by administering antibodies against the Rh antigen within 25-48 hours after the 1st delivery
- *Rhogam*-is the antibody that is injected
  - it will bind to the fetal RBC that enter the mother's circulation and facilitate the clearance of them before B-cell activation
  - In subsequent pregnancies the mother is unlikely to produce IgG anti-Rh antibodies
  - If the mother doesn't receive this injection there are other ways to treat this, depending on the severity

Drug-Induced Hemolytic Anemia

- This is where certain antibiotics can absorb nonspecifically to the proteins on RBC membranes
- Examples: penicillin, streptomycin
- Sometimes antibodies form inducing complement-mediated lysis and thus progressive anemia
- When drug is withdrawn the hemolytic anemia disappears

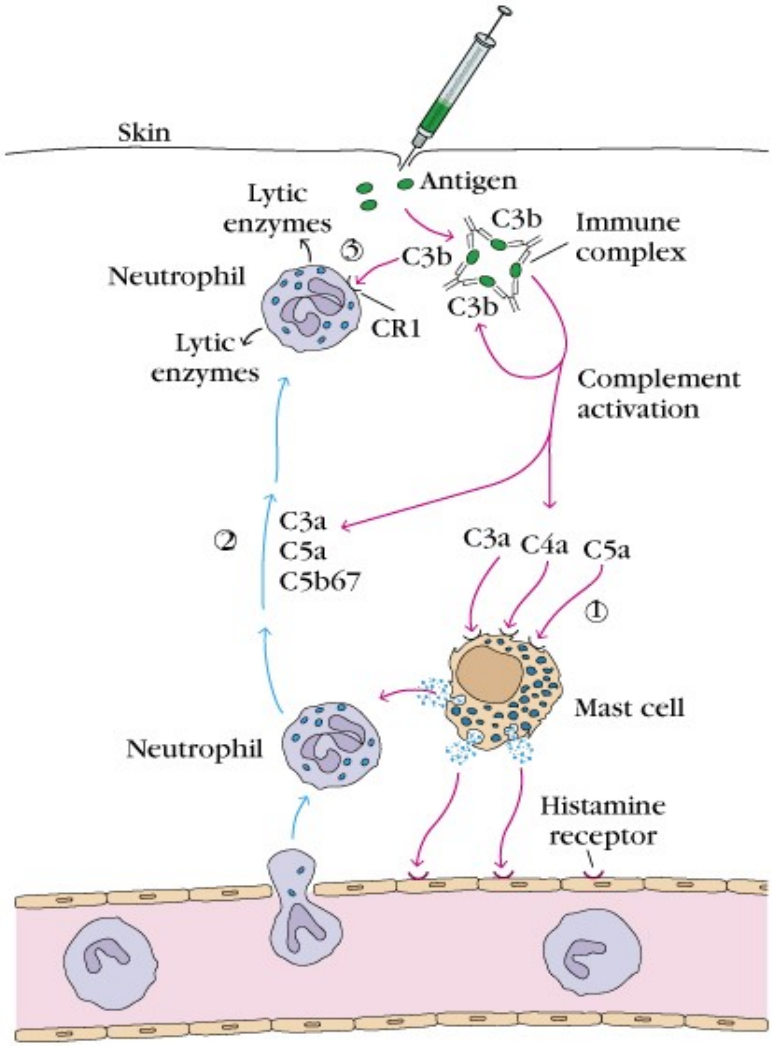
Type III-Immune Complex-Mediated Hypersensitivity

- Reaction with antibodies create immune complexes
- These generally facilitate the clearance of antigen by phagocytosis
- Large amounts of immune complexes can lead to tissue damage (Type III reaction)
- The magnitude depends on the quantity of immune complexes and their distribution
- The complexes get deposited in tissues:
  - Localized reaction is when they are deposited near the site of antigen entry
  - When formed in the blood reaction can develop where ever they are deposited

- Deposition of these complexes initiates a reaction that results in the recruitment of neutrophils
- Tissue is injured by the granular release from the neutrophil (attempted phagocytosis release lytic enzymes that cause the damage)

Localized Type III Reactions:

1. Injection of an Antigen:
   - Can lead to an acute Arthus reaction within 4-8 hours
   - Localized tissue and vascular damage result from accumulation of fluid (edema) and RBC (erythema)
   - Severity can vary from mild swelling to redness to tissue necrosis
2. Insect bite:
   - May first have a rapid type I reaction
   - Some 4-8 hours later a typical Arthus reaction develops



Generalized Type III Reactions:

- Large amounts of antigens enter the blood stream and bind to antibody, circulation immune complexes can form
- These can't be cleared by phagocytosis and can cause tissue damaging Type III reactions

- *Serum Sickness*-type III hypersensitivity reaction that develops when antigen is intravenously administered resulting in formation of large amounts antigen-antibody complexes and the deposition in tissue
- Other conditions caused by Type III-
  1. Infectious Diseases
     - Meningitis
     - Hepatitis
     - Mononucleosis
  2. Drug Reactions
     - Allergies to penicillin and sulfonamides
  3. Autoimmune Diseases
     - Systematic lupus erythematosus
     - Rheumatoid arthritis

Type IV Hypersensitivity

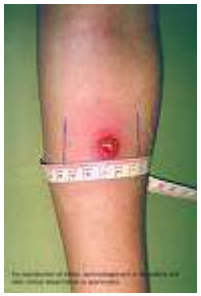
cell mediated hypersensitivity or
delayed type hypersensitivity

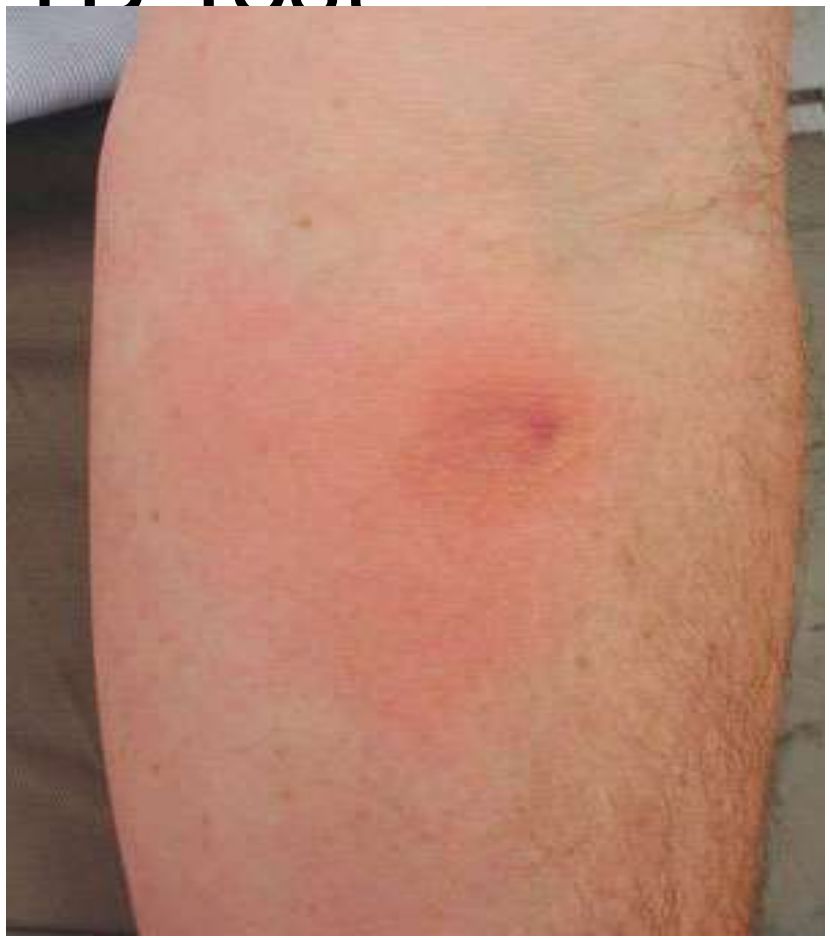
What is delayed type hypersensitivity (DTH)?

- A hypersensitive response mediated by sensitized T_{DTH} cells, which release various cytokines and chemokines
- Generally occurs 2-3 days after T_{DTH} cells interact with antigen
- An important part of host defense against intracellular parasites and bacteria

Type IV (*delayed*) Hypersensitivity

Positive TB Test





Phases of the DTH Response

Sensitization phase: occurs 1-2 weeks after primary contact with Ag

What happens during this phase?

- T_H cells are activated and clonally expanded by Ag presented together with class II MHC on an appropriate APC, such as macrophages or Langerhan cell (dendritic epidermal cell)
- Generally CD4+ cells of the T_H1 subtype are activated during sensitization and designated as T_{DTH} cells