12 Oct 2023,
BT 304
Lecture 28

Type III (*immune complex mediated*) Hypersensitivity

- Similar to Type II, IgG or IgM involved and destruction is complement-mediated.
- Difference is that antigen is SOLUBLE.
- Soluble antigen and antibody combine to form complexes.
- Usually complexes cause no symptoms, quickly disappear from the circulation.
- Size of complexes produced seems important in determining whether they will be eliminated quickly from the body or retained long enough to cause damage.
- In some individuals the immune complexes persist in circulation causing clinical symptoms, some of them serious.

Type III (*immune complex mediated*) Hypersensitivity…

- Mechanism
  - ***Soluble immune complexes*** which contain a greater proportion of antigen than antibody penetrate blood vessels and lodge on the basement membrane
  - At the basement membrane site, these complexes activate the complement cascade.
  - During complement activation, certain products of the cascade are produced,`attract neutrophils to the area. *Such substances are known as chemotactic substances.*
  - Once the polymorphs reach the basement membrane they release their granules, which contain lysosomal enzymes which are damaging to the blood vessel.
  - This total process leads to the condition recognized histologically as vasculitis.

Type III (*immune complex mediated*) Hypersensitivity…

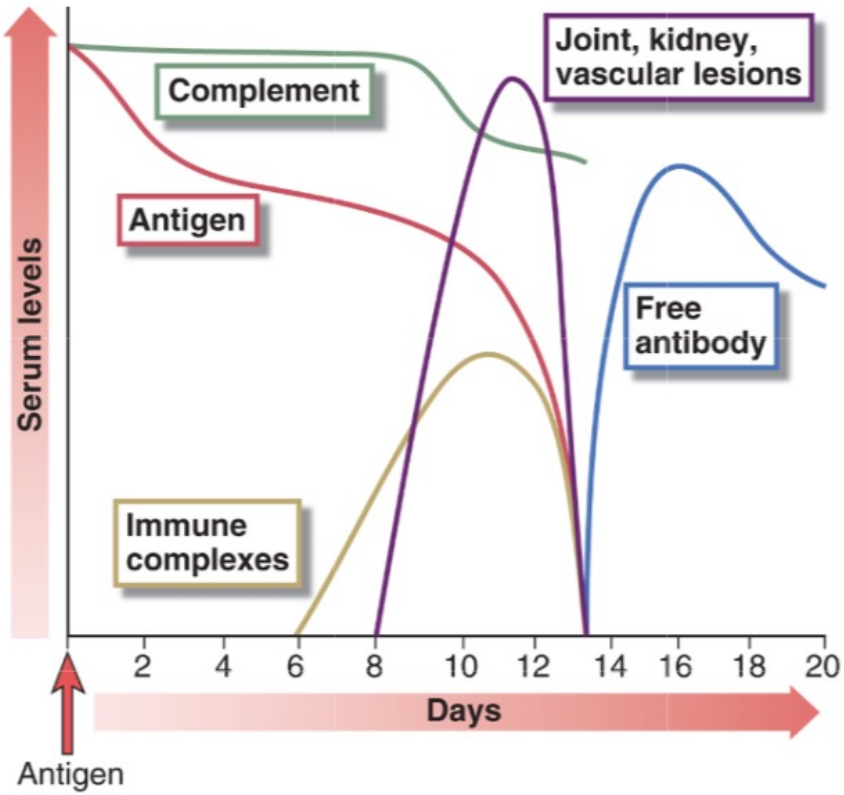
- Tissues most frequently affected are:
  - Glomerular basement
  - Vascular endothelium
  - Joint linings
  - Pulmonary alveolar membranes
- Classical clinical symptoms of immune complex disease are due to blood vessel involvement, i.e., vasculitis.
- Blood vessels of joints and the kidney are most frequently affected, giving rise to symptoms of arthritis and glomerulonephritis.

Type III (*immune complex mediated*) Hypersensitivity

- ***Arthus Reaction***
  - Immunized rabbits to antigen
  - Rabbits when injected intradermally with antigen
  - Localized inflammatory reaction occurred followed by hemorrhagic necrotic lesion.
  - Occurred due to immune complexes depositing in dermal blood vessels.
  - Complement, neutrophils and platelets caused toxic affects.
  - Rare in humans.
- ***Serum Sickness***
  - Due to passive immunization with animal serum, bovine or horse.
  - Vaccines and bee stings may also trigger.
  - Symptoms appear 7 – 21 days after exposure to animal serum.
  - Headache, fever, nausea, vomiting, joint pain, rashes and lymphadenopathy.
  - Symptoms due to antibody being formed at same time antigen is present = immune complexes form.
  - Benign, self limiting, 7-30 days for recovery.

Sequence of immunologic responses in experimental acute serum sickness.

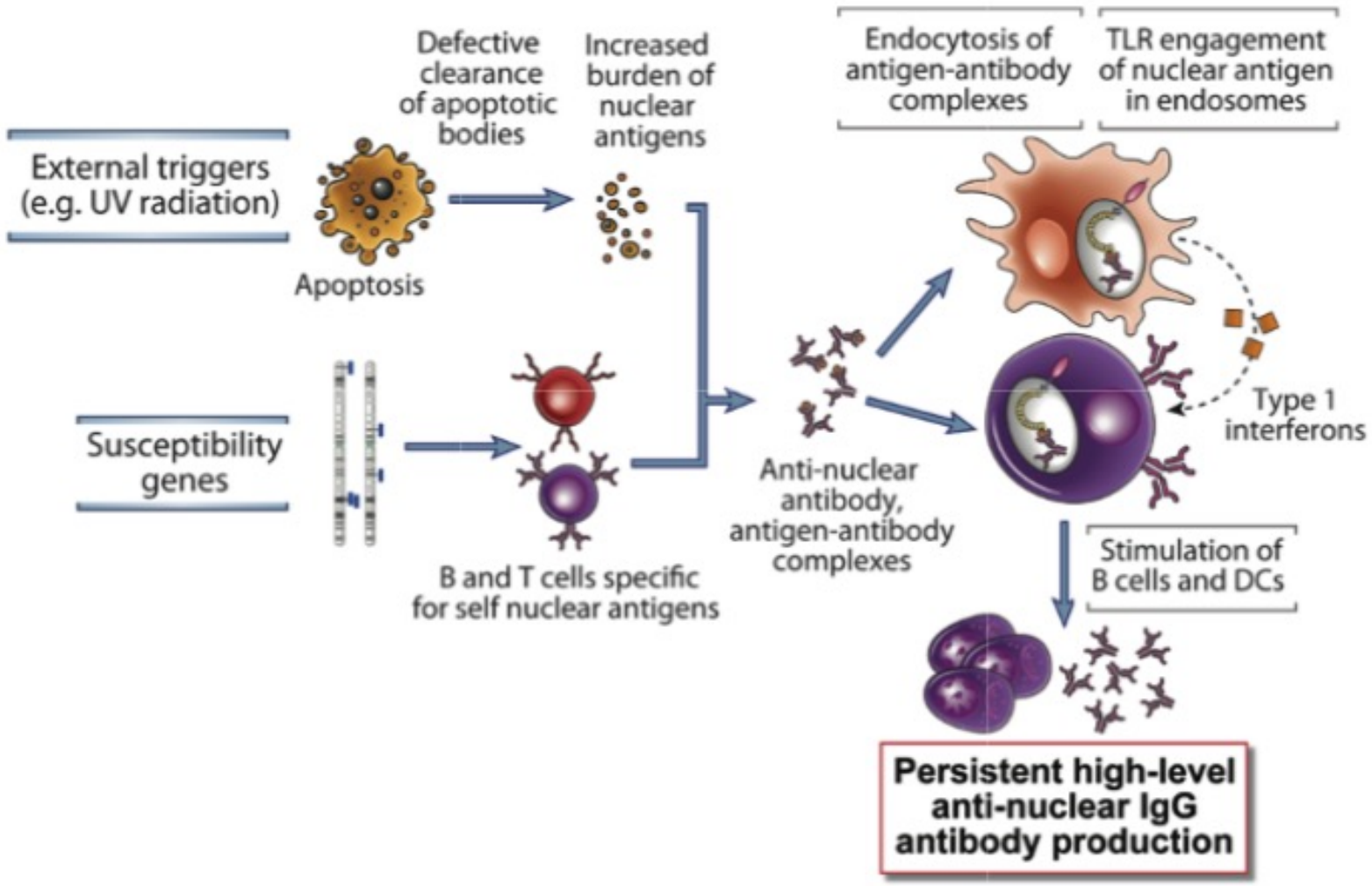
Injection of bovine serum albumin into a rabbit leads to the production of specific antibody and the formation of immune complexes. These complexes are deposited in multiple tissues, activate complement (leading to a fall in serum complement levels), and cause inflammatory lesions, which resolve as the complexes and the remaining antigen are removed and free antibody (not bound to antigen) appears in the circulation



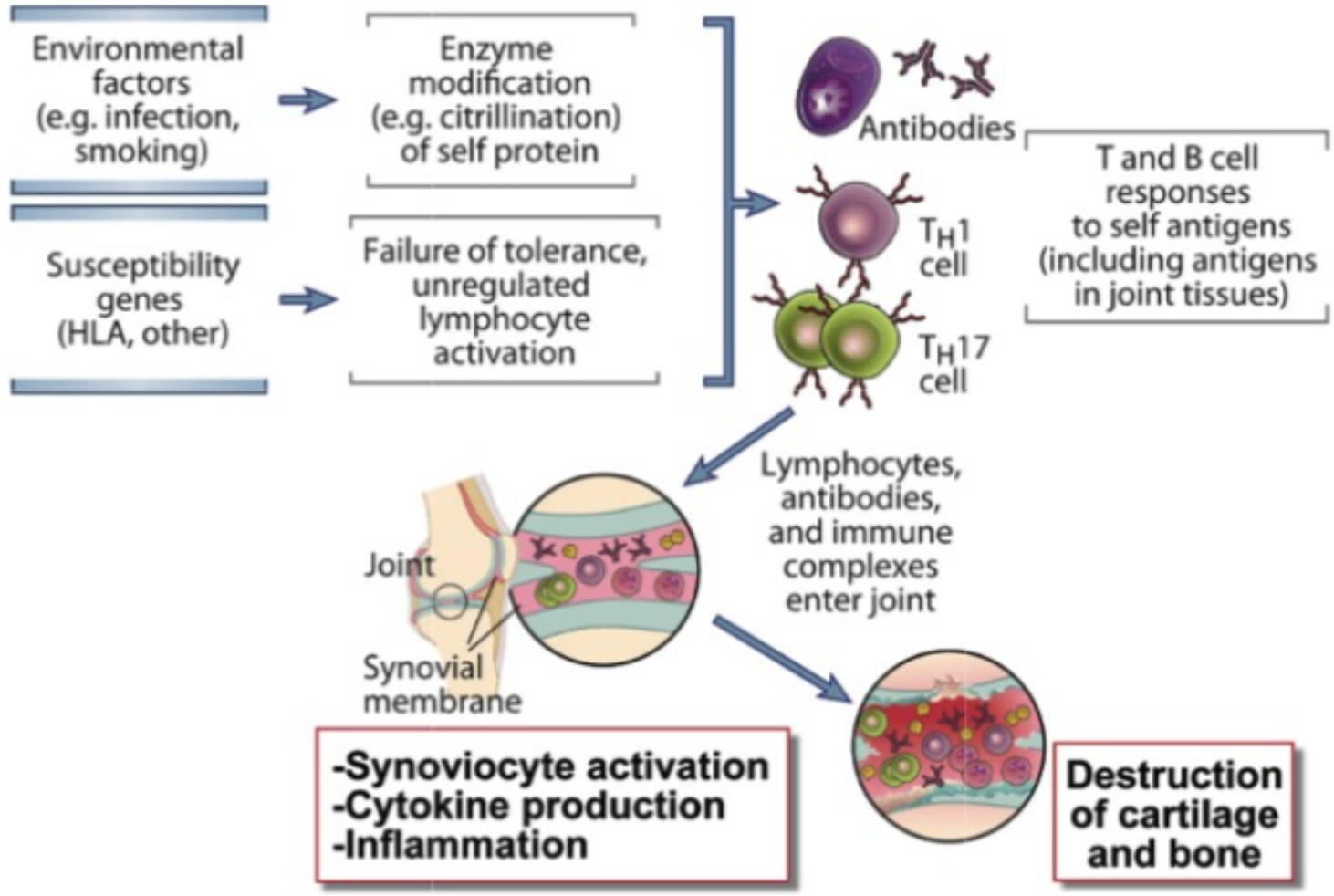
Type III (*immune complex mediated*) Hypersensitivity

- Chronic immune complex diseases are naturally occurring diseases caused by deposits of immune complex and complement in the tissues.
  - Systemic Lupus Erythematosus (SLE)
  - Acute glomerulonephritis
  - Rheumatic fever
  - Rheumatoid arthritis

Model for the Pathogenesis of SLE



Model for the Pathogenesis of RA



Type IV (*delayed*) Hypersensitivity

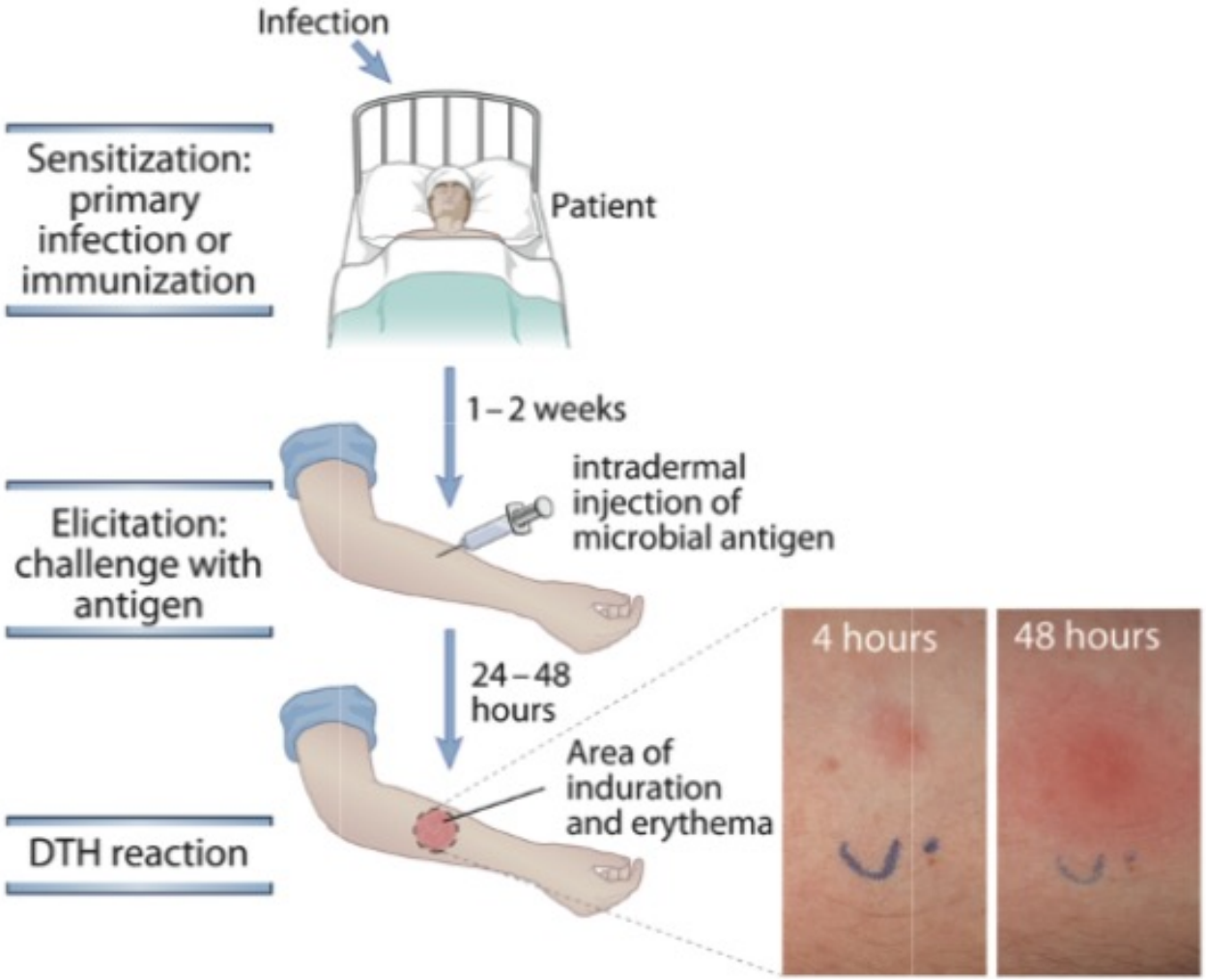
- Used to describe the signs and symptoms associated with a cell mediated immune response.
- Results from reactions involving **T lymphocytes (particularly CD4+)**.
- Characteristics of this phenomenon are:
  - Delayed, taking 12 hours to develop.
  - Causes accumulation of lymphocytes and macrophages.
  - Reaction is not mediated by histamine.
  - **Antibodies are not involved in the reaction.**

Type IV (*delayed*) Hypersensitivity

- Most well known is the Koch Phenomenon
  - Inject tuberculoprotein (*PPD test) intradermally
  - Reaction results in an area of induration of 5 mm or more in diameter and surrounded by erythema
  - Reaction which occurs within 48 hours is a positive.

*Purified protein derivative

Delayed-Type Hypersensitivity (DTH) Reaction

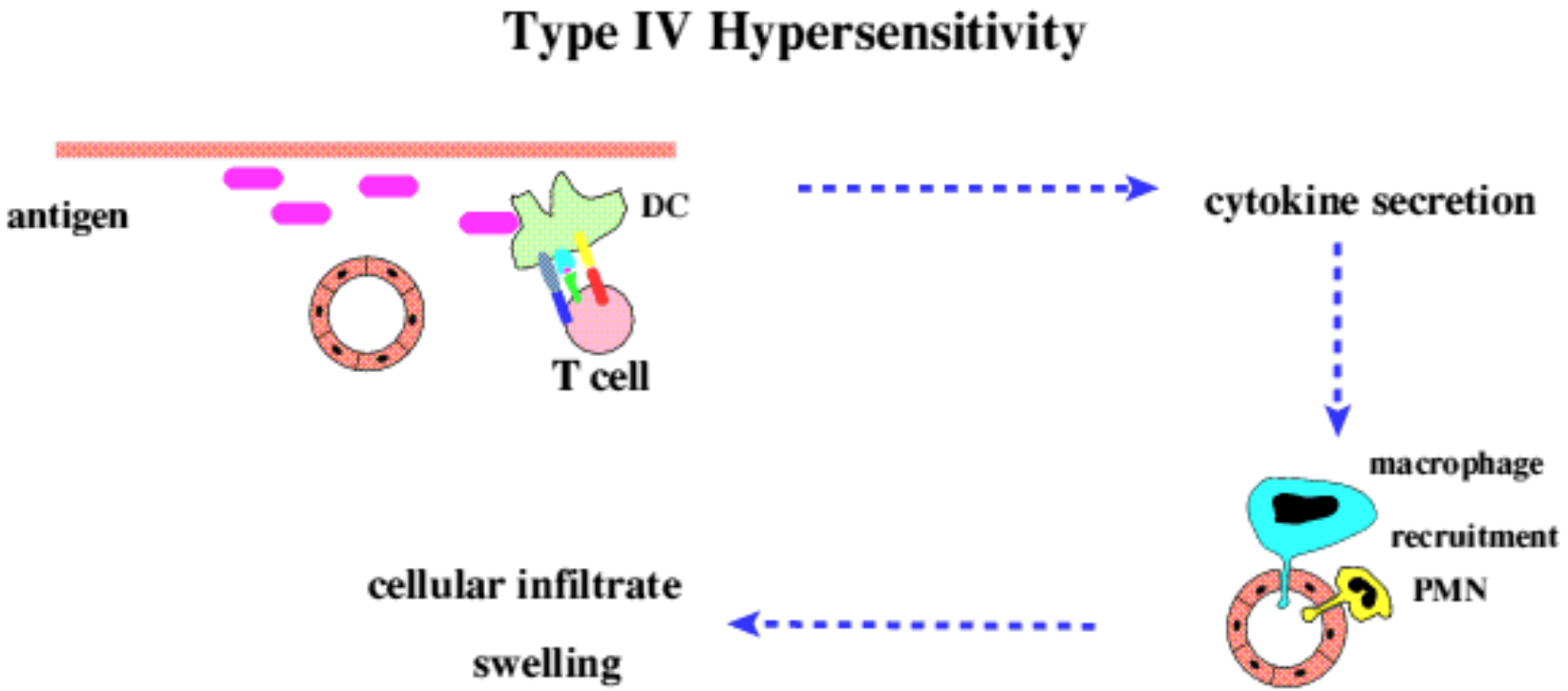


Type IV (*delayed*) Hypersensitivity…

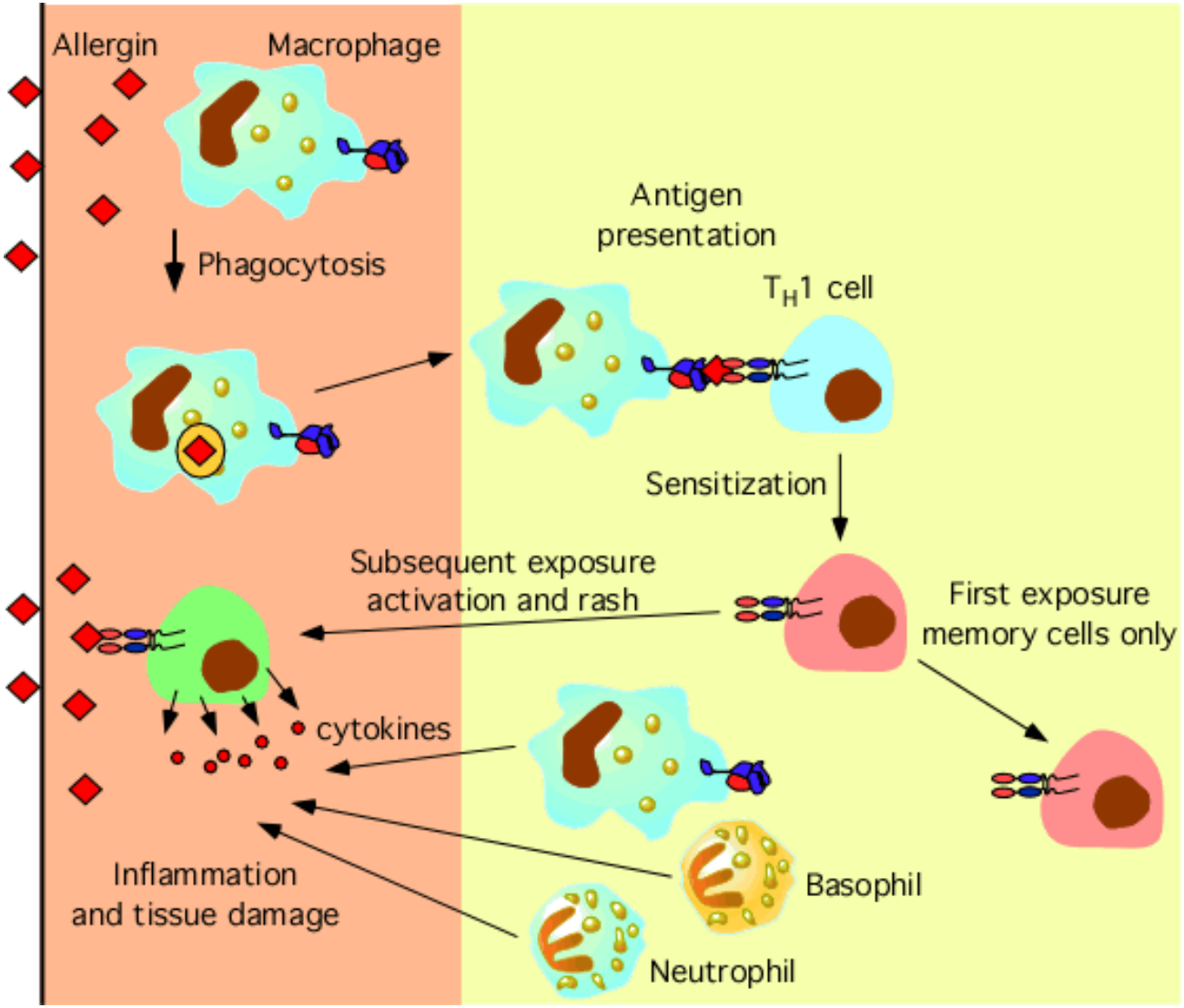
- Contact dermatitis due to contact with chemicals
  - Poison ivy, oak and sumac give off urushiol.
  - Nickel, rubber, formaldehyde, hair dyes, cosmetics
  - Latex allergies
- Hypersensitivity Pneumonitis
  - Response of sensitized T cells to inhaled allergens.
  - Caused by chronic inhalation of microorganisms.
  - Occupationally related – pigeons, farmers

urushiol *– an oily mixture of organic chemicals found in the sap and other parts of plants such as mangoes, poison ivy and the urushi*

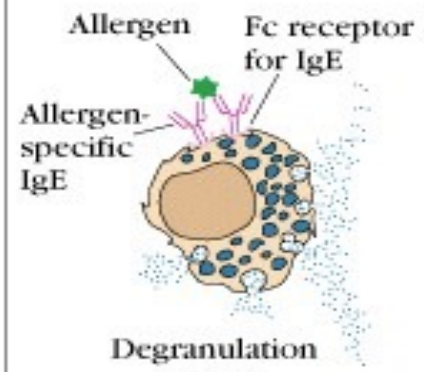
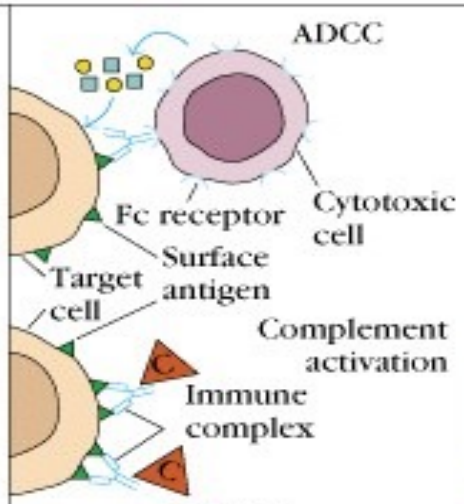
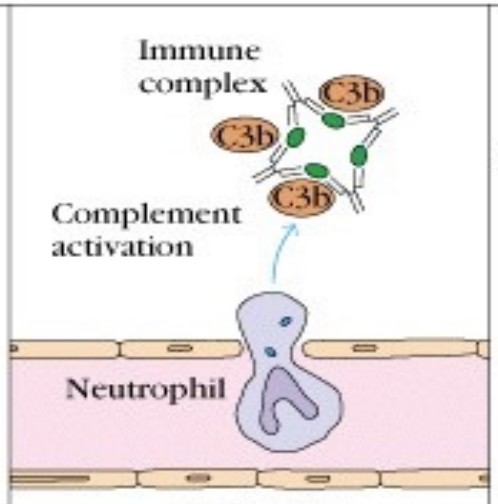
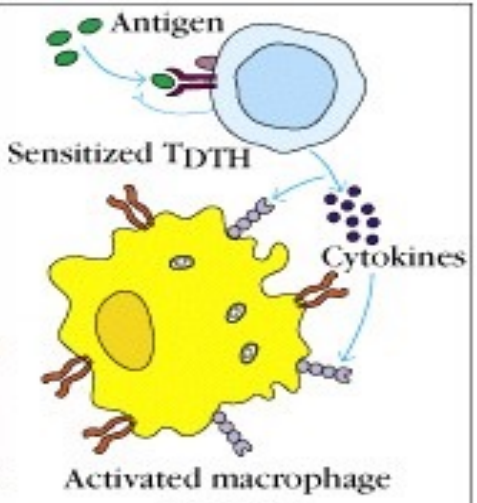
Type IV (*delayed*) Hypersensitivity



Type IV (*delayed*) Hypersensitivity…



Summary

 **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