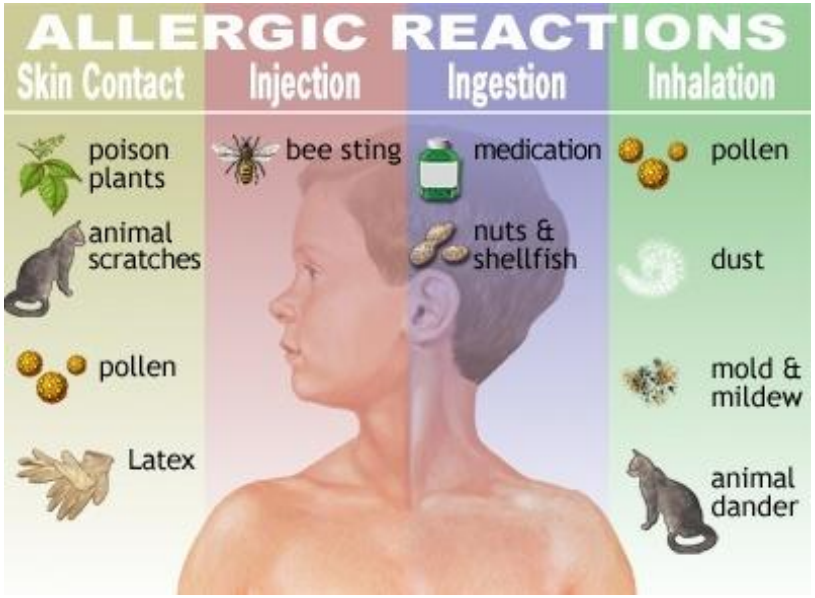
Hypersensitivity type I - IV

Microbiology V

Hypersensitivity

- **Hypersensitivity** is increased reactivity or increased sensitivity by the animal body to an antigen to which it has been previously exposed.
- It is an undesirable reactions produced by the normal immune system
- It includes allergies & autoimmunity (reactions against self antigens).
- Hypersensitivity reaction or intolerance
- They are usually referred to as an over-reaction of the immune system
- These reactions may be damaging, uncomfortable, or occasionally fatal



- Hypersensitivity reactions require a pre-sensitized (immune) state of the host.

- **Allergy** is the response of the immune system to small or harmless substances like dust, pollens, smoke, etc.

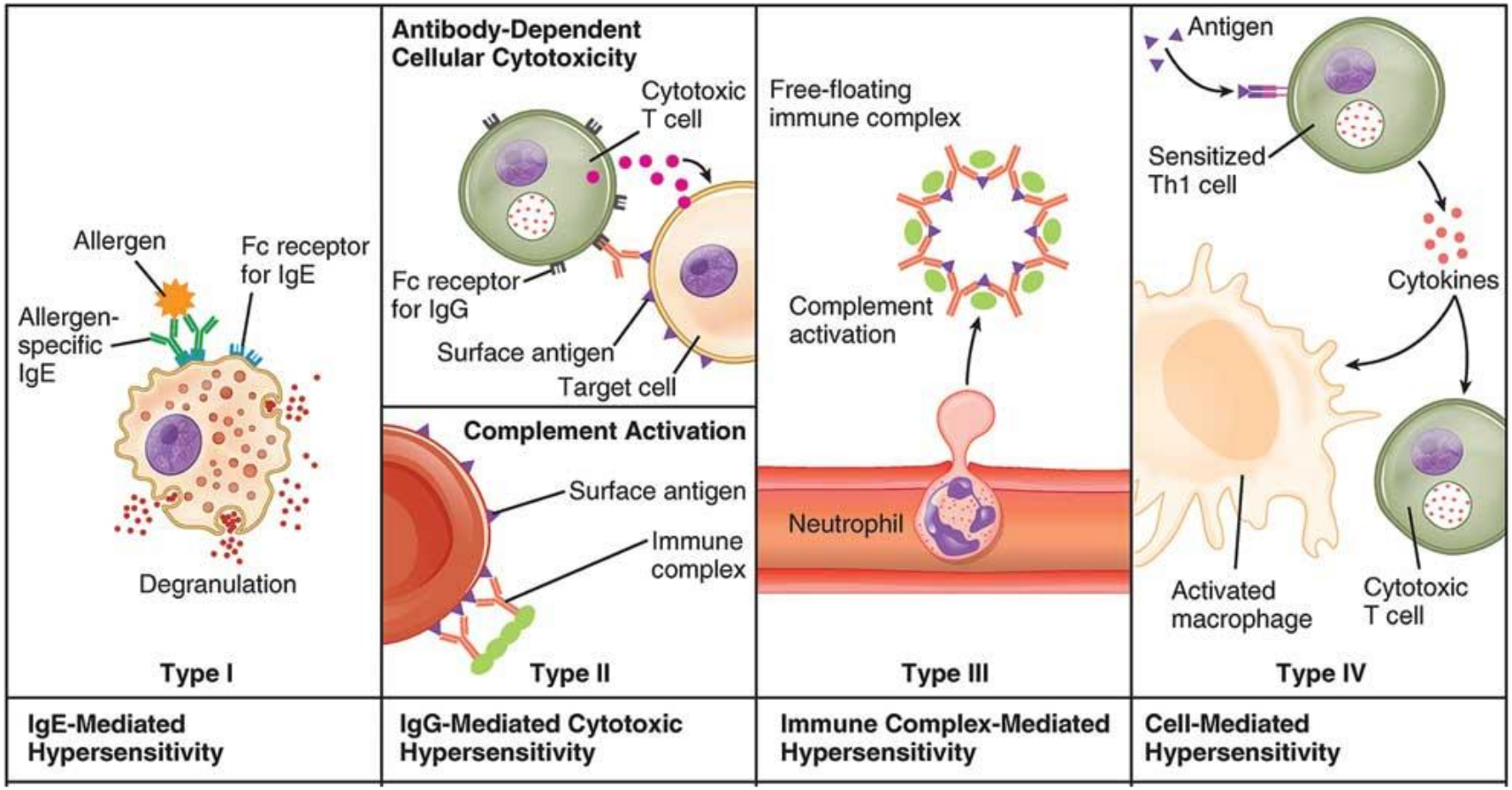
- The Gell and Coombs classification of hypersensitivity distinguishes four types of immune response which result in surrounding tissue damage.

- Based on time required for a sensitized host to develop clinical reactions on re-exposure to the antigen.
- Hypersensitivity reactions are grouped as:

❖ Immediate hypersensitivity – B cell or Antibody mediated

❖ Delayed hypersensitivity- T cell mediated

Gell and Coombs classification of hypersensitivity



Hypersensitivity Types

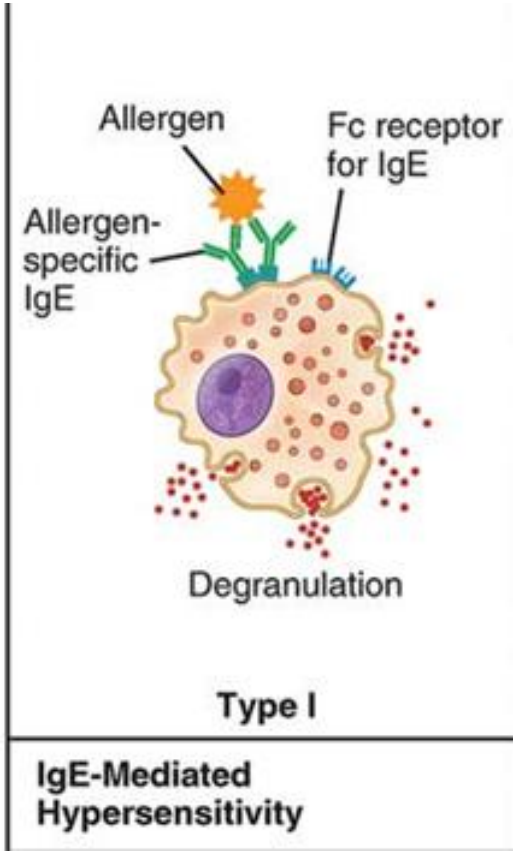
- **Type I: Immediate Hypersensitivity** (Anaphylactic Reaction) Allergy
- **Type II**: Cytotoxic Reaction (Antibody-dependent)
- **Type III**: Immune Complex Reaction.
- **Type IV**: Cell-Mediated (**Delayed Hypersensitivity**)

TYPE I (Anaphylactic) Hypersensitivity

- **Anaphylaxis** – *ana* = without, *phylaxis* = protection
- It is caused by **IgE** antibodies specific for environmental antigens and is the most prevalent type of hypersensitivity disease.

- The allergen stimulates the induction of CD4+T cells.
- These T cells secrete **cytokines** that cause **IgE** production by plasma cells.

- The IgE molecule will bind to the **Fc receptor** on **mast cell** and **basophils**
- Causes vasodilation increased vascular permeability and vascular spasm.



- This type may occur as a systemic or local reaction:
  - **Systemic reactions:** skin erythema, followed by respiratory difficulty due to bronchial constriction.

  - **Local reactions:** generally on the skin or mucosal surface at the site of Ag exposure.
  - Ex. Allergy to penicillin, *Aspergillus* spores, rupture of *Echinococcus* cyst

- Some antigens (**allergens**), such as insect venom, foods, pollen, and dust mite, can induce the formation of **IgE** antibodies in individuals with a corresponding predisposition.

- The IgE antibodies bind via Fc receptors to **mast cells** (sensitization).

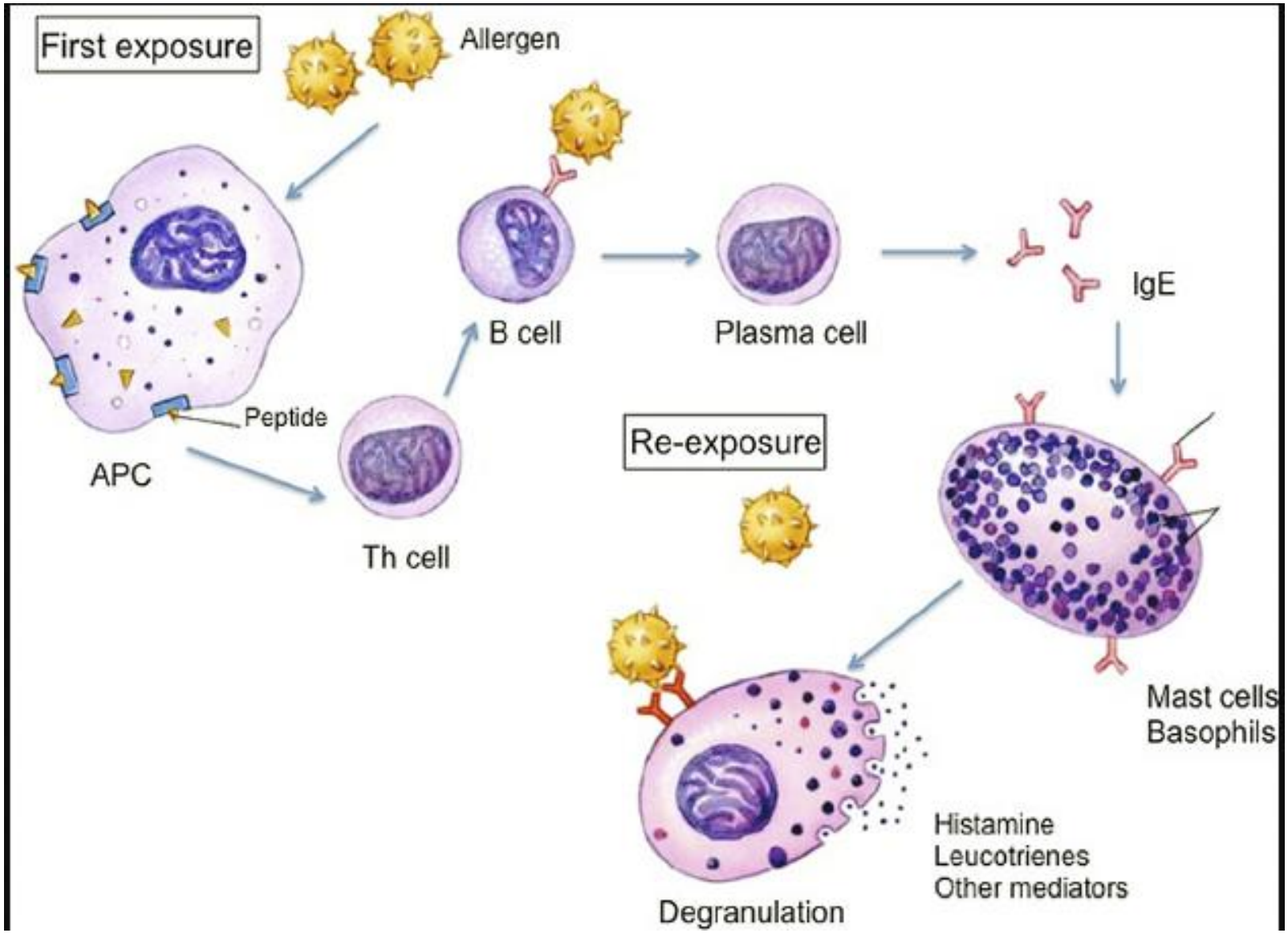
- If the individual is **re-exposed** to the allergen, cross-linkage of the membrane-bound IgE occurs.

- This results in the immediate release of **mediators** (e.g., histamine, kininogen), which induce vasodilation, smooth-muscle contraction, mucus secretion, edema, and/or skin blisters.

- Most allergens are small proteins that can easily diffuse through the skin or mucosa.

- They are frequently proteases and are active at very low doses.
- IL-4 favors differentiation of TH2 cells.

- The exact mechanism that leads B cells to produce IgE is not known


First exposure
Allergen
B cell
Plasma cell
IgE
Peptide
APC
Th cell
Re-exposure
Mast cells
Basophils
Histamine
Leucotrienes
Other mediators
Degranulation

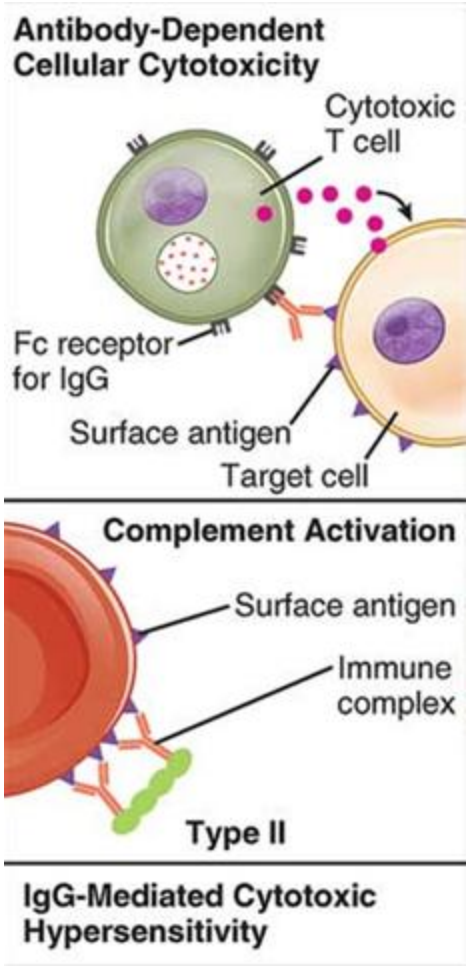
TYPE II Hypersensitivity

- In this type **Ab** are formed against **target Ag** that are **cell membrane** components.
- Not really a hypersensitivity.

- **IgG** and **IgM** antibodies specific for **cell surface** or extracellular matrix **antigens** can cause **tissue injury** by activating the **complement system**, by recruiting inflammatory cells, and by interfering with normal cellular functions.

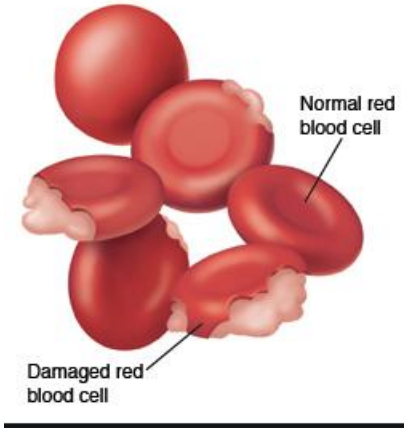
Cytotoxic reactions includes:

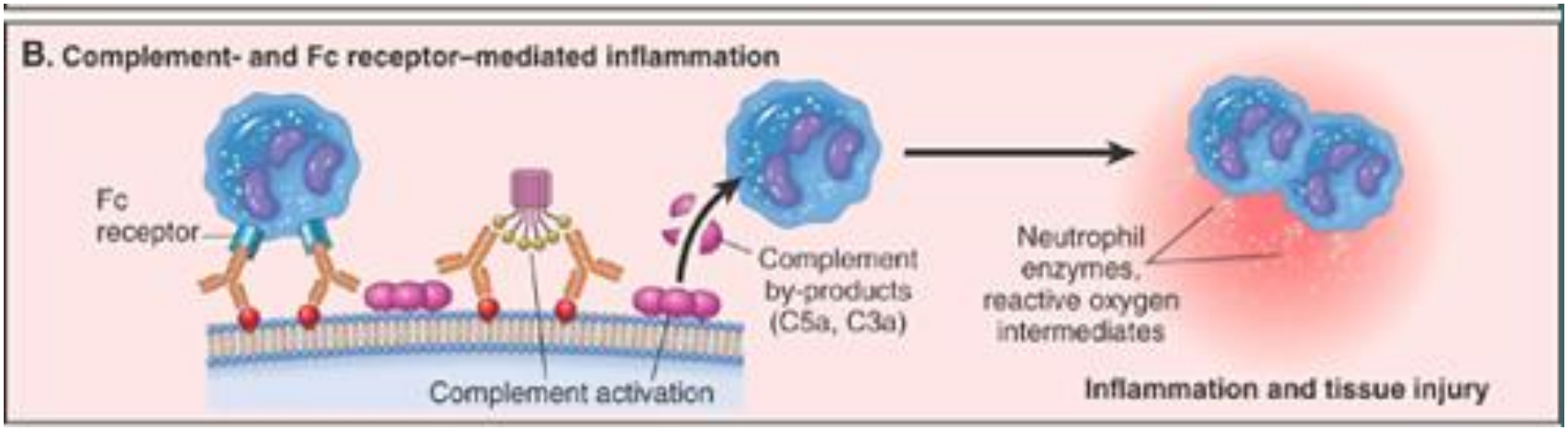
- ❖ Complement-mediated
- ❖ Opsonization & Phagocytosis
- ❖ Antibody-mediated cellular dysfunction



Complement-mediated

- Ab reacts with cell surface Ag leading to fixation of the complement system and then cell lysis.
- Red blood cells are the most common cells damaged by this mechanism
- Ex: **Hemolytic Anemia** .

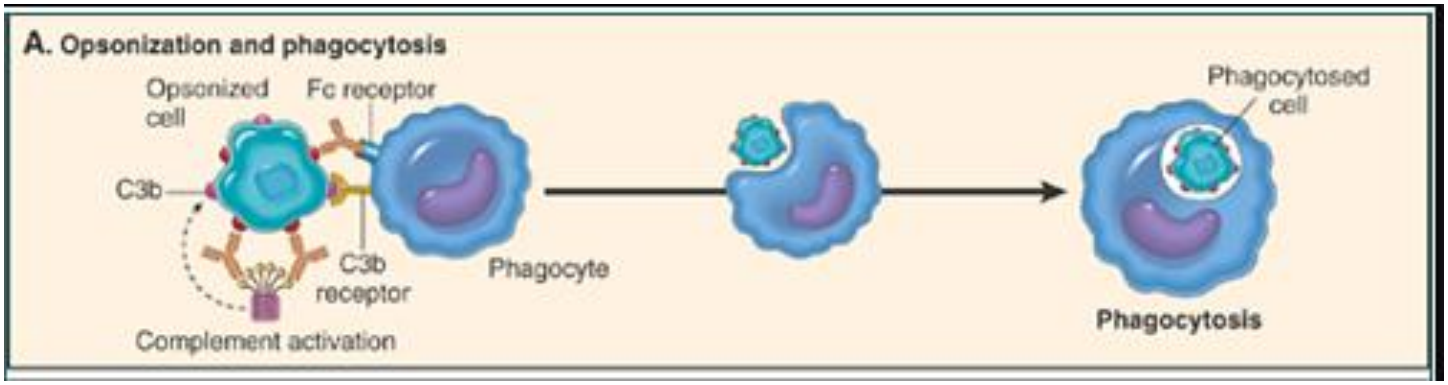




Opsonization & Phagocytosis:

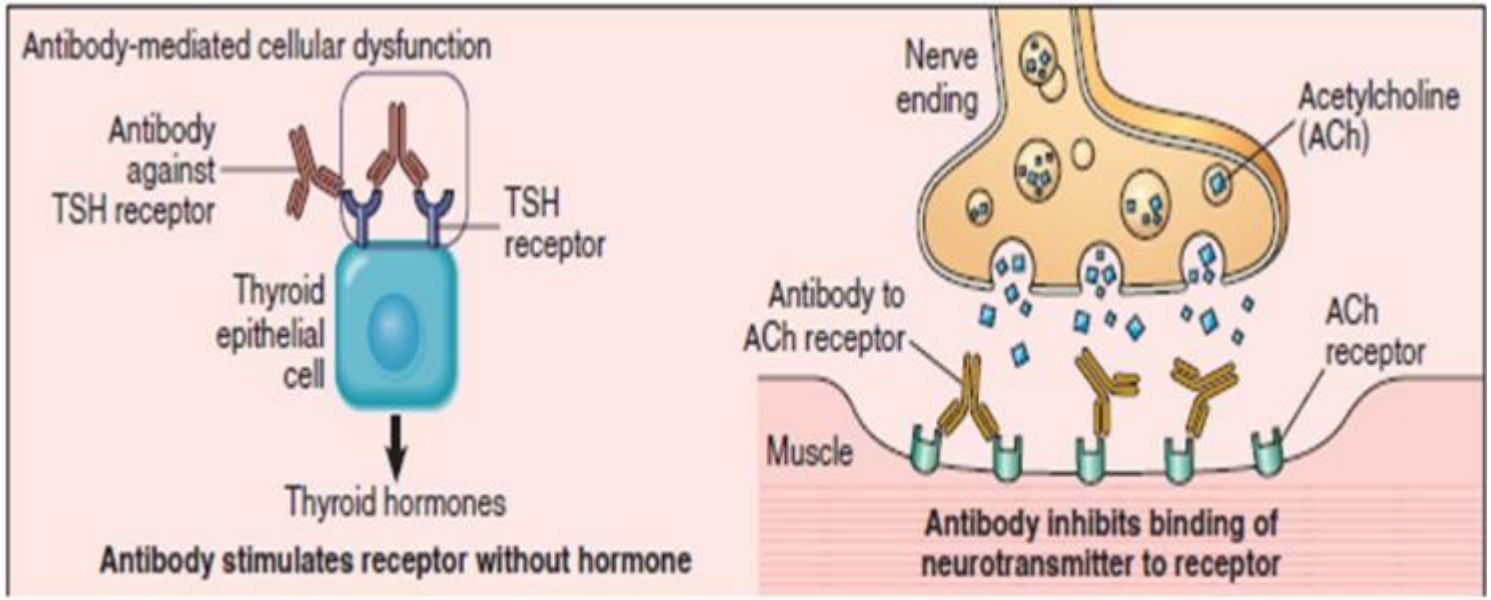
Macrophages, neutrophils, NK cells cause lysis of target cell coated by IgG

- Poststreptococcal rheumatic fever: molecular mimicry: **Antibodies** produced against *S. pyogenes* **cross-react** with various tissue
- Ex. heart, joints – inflammation
- Oncocerca worm infection may lead to blindness because of the cross-reaction of Ab produced against pathogens and proteins of the retina.



Antibody-mediated cellular dysfunction

- In some cases Ab is directed against cell surface receptor <u>impairing the function</u> but not cause cell injury
- MYASTHENIA GRAVIS:
- Ab reacts with ACh receptors on the motor endplate.



Graves disease **Myasthenia gravis**

TYPE III Hypersensitivity

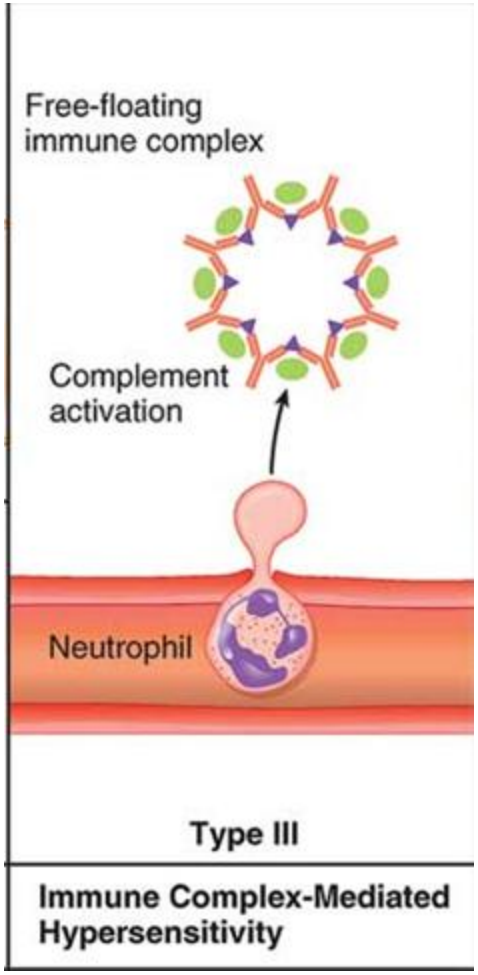
- This type is mediated by **Ag-Ab complexes** which initiate an **inflammatory reaction** in the tissue.

- **IgM** and **IgG** antibodies specific for **soluble antigens** in the **blood** form complexes with the antigens, and the immune complexes may deposit in blood vessel walls in various tissues, causing inflammation, thrombosis, and tissue injury.

- There are 2 patterns of immune-complex mediated injury:

❖ **Systemic Disease** (serum sickness, SLE)

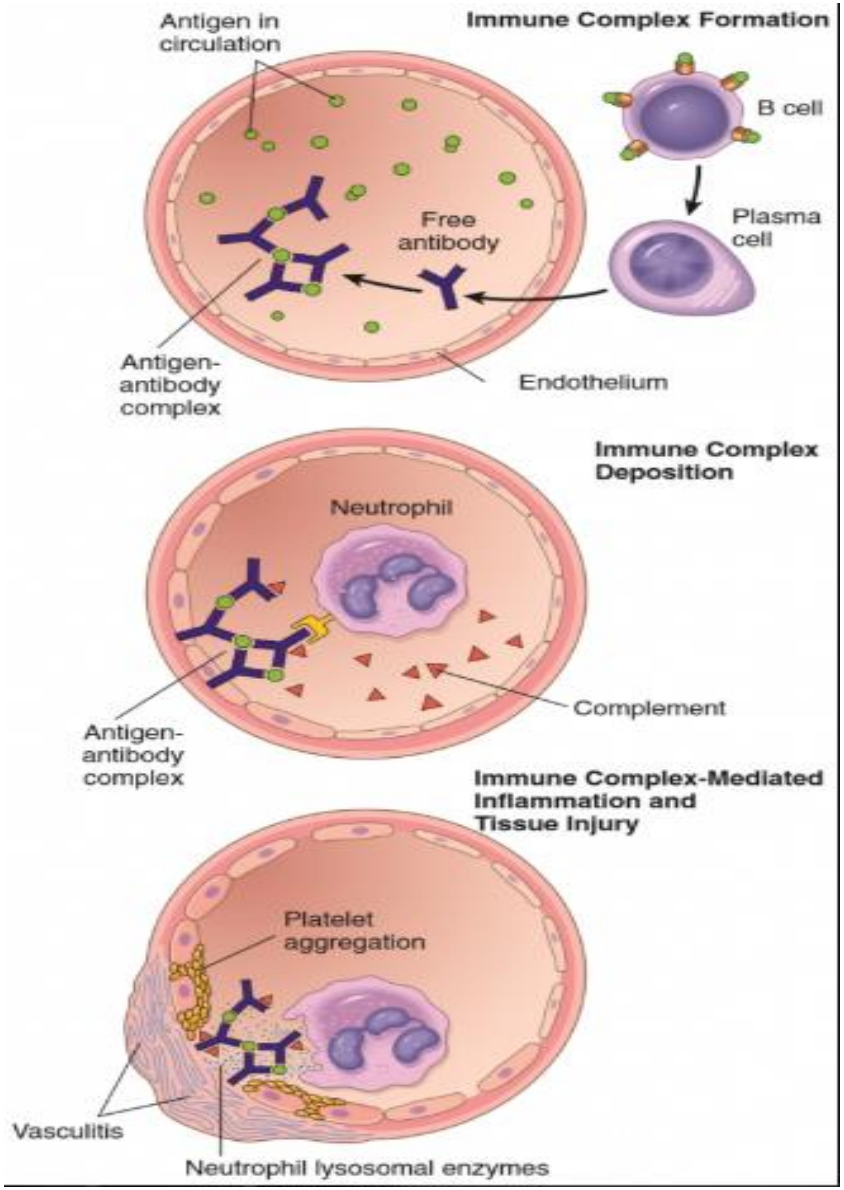
❖ **Local Disease** (Arthus reaction)



SYSTEMIC DISEASE (serum sickness, SLE)

- This is because of a large excess of Ab and immune complexes are deposited at the site of injury especially within the vessel wall ---
- Necrotizing vasculitides
- Neutrophils accumulation

- Example:
- Serum sickness
- Systemic lupus erythematosus (SLE)



LOCAL DISEASE (Arthus reaction)

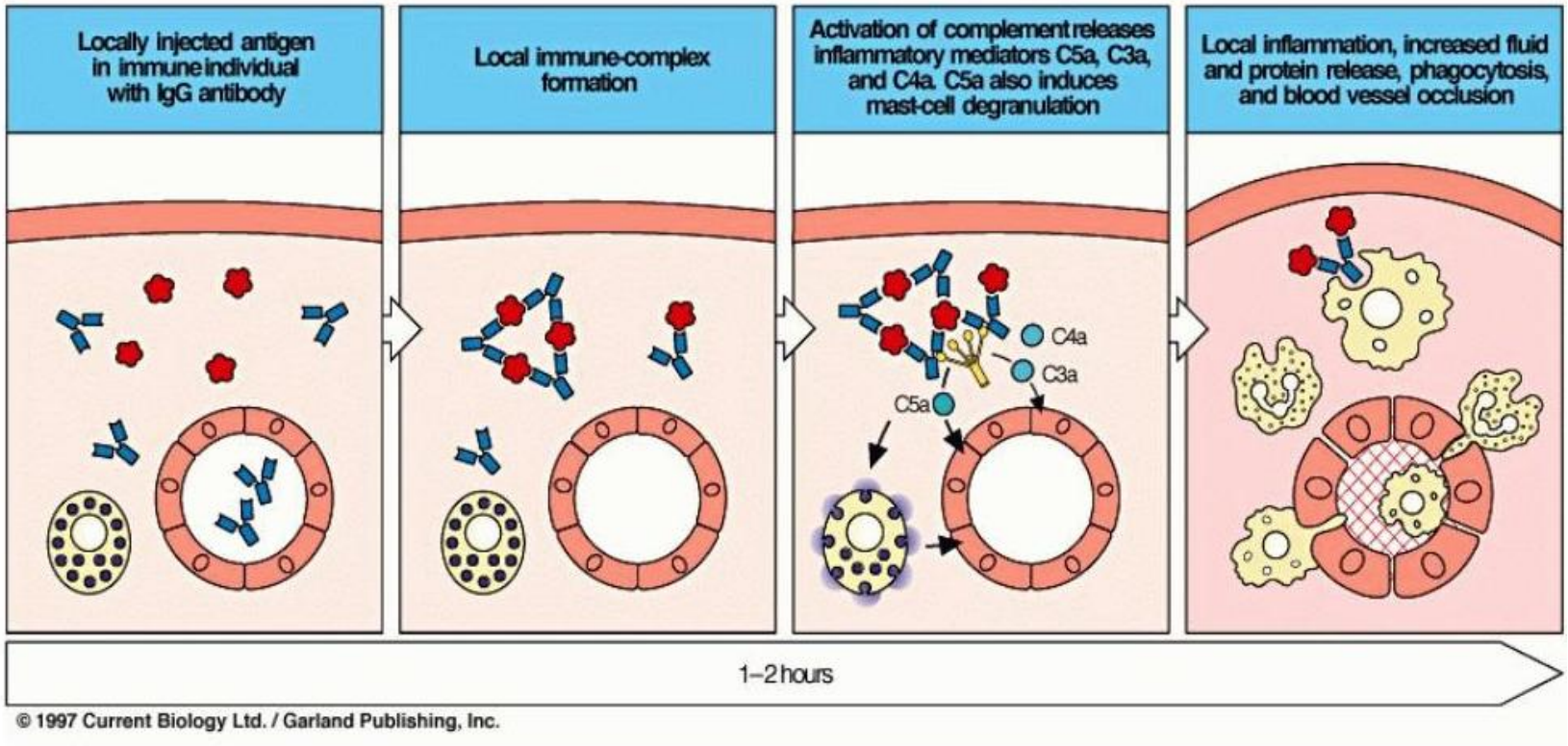
- **Arthus reaction:** intraductal injection of antigens to a personalized person may lead to local intradermal **Ab–Ag complex formation** and local vasculitis, redness, swelling.

- **Example:** Repeated (booster) vaccination with diphtheria or tetanus rarely leads to local vasculitis.

Poststreptococcal acute glomerulonephritis:

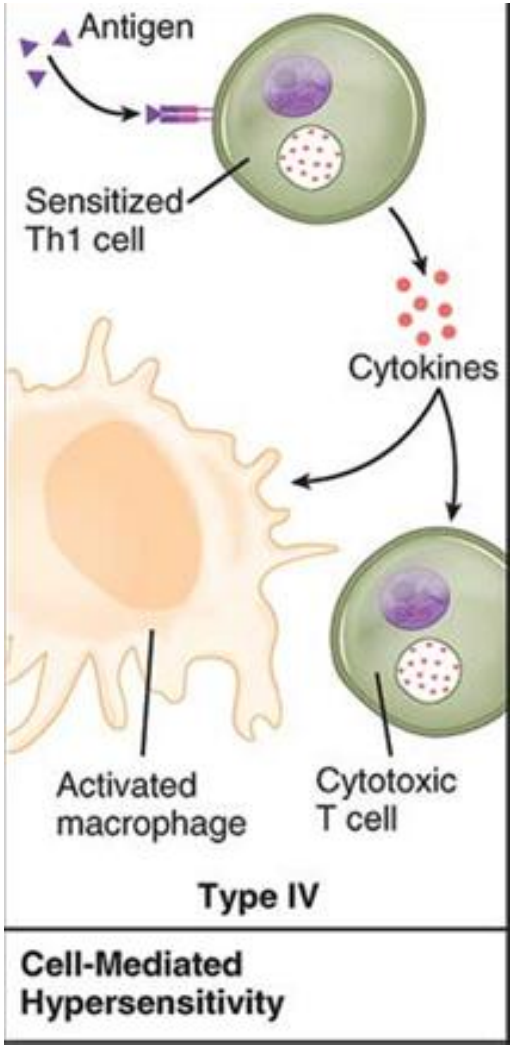
- Ab-Ag complexes deposit in glomeruli HBV infection
- HBsAg-Ab complexes may HBV also cause acute glomerulonephritis

Arthus Reaction



TYPE IV Hypersensitivity

- Type IV hypersensitivity reaction is also known as **delayed type hypersensitivity (DTH).**
- **Cell-mediated** reactions initiated by **T-cells** & mediated by **effector T-cells** and **macrophages**.
- This response involves the interaction of antigens & surface of T- lymphocytes.
- In these disorders, tissue injury may be due to T lymphocytes that induce inflammation or directly kill target cells.



- In most of these diseases, the major mechanism involves the activation of CD4+ helper T cells, which secrete cytokines that promote inflammation and activate leukocytes, mainly neutrophils and macrophages.

- CTLs contribute to tissue injury in some diseases.

- **Sensitized lymphocytes** can produce **cytokines**, which are biologically active substances that affect the **functions** of **other cells**.

- This type of reaction takes **48-72 hours**, or longer, after contact with the antigen to fully develop & mediated by **T-cells**.

There are 2 types that involve **CD4/8+T Cells**.

1. Acute (within 2-3 days)
2. Chronic (> 1 week)

Acute type (within 2-3 days)

Tuberculin test, contact dermatitis:

- Mediated by CD4+ T helper cells cd4+ cells recognize Ag (tuberculin), this leads to the formation of sensitized cd4+ cells.
- Upon cutaneous injection into previously sensitized individual sensitized cd4+cells become activated and secrete cytokines.

Tuberculin/Mantoux test:

- Intradermal injection of tuberculin = purified tuberculoprotein leads to swelling after 48- 72 h if the patient has been exposed to *Mycobacterium tuberculosis* previously.

Delayed-type hypersensitivity (DTH)
(e.g. tuberculin skin test)

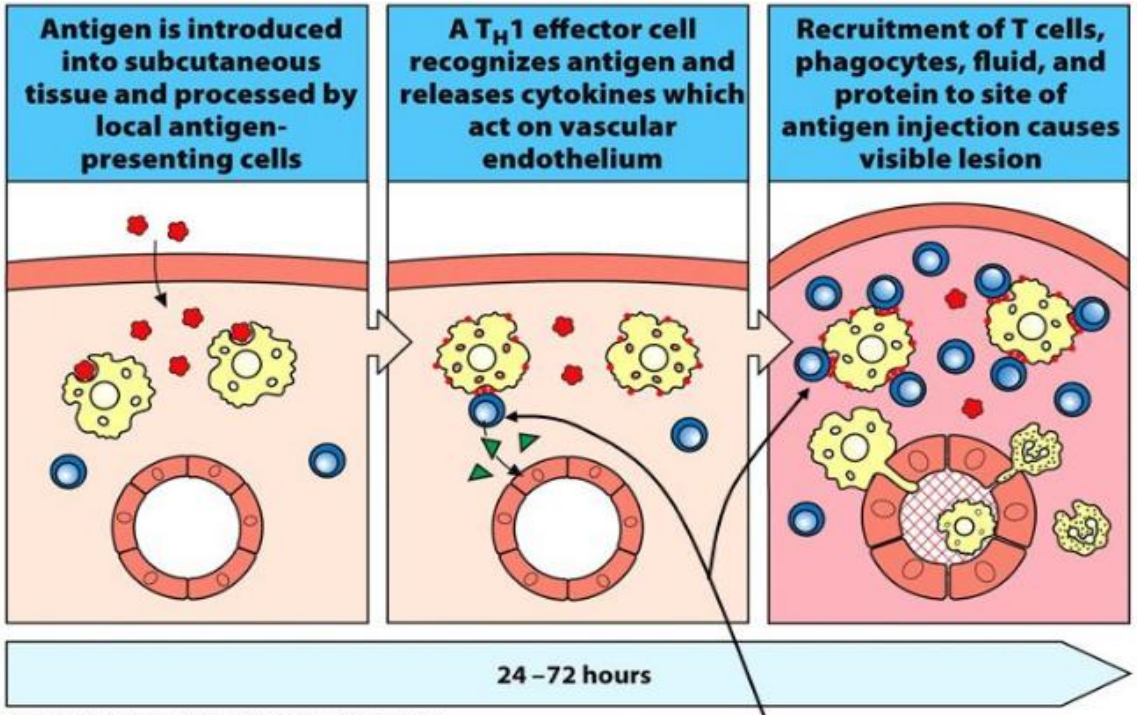


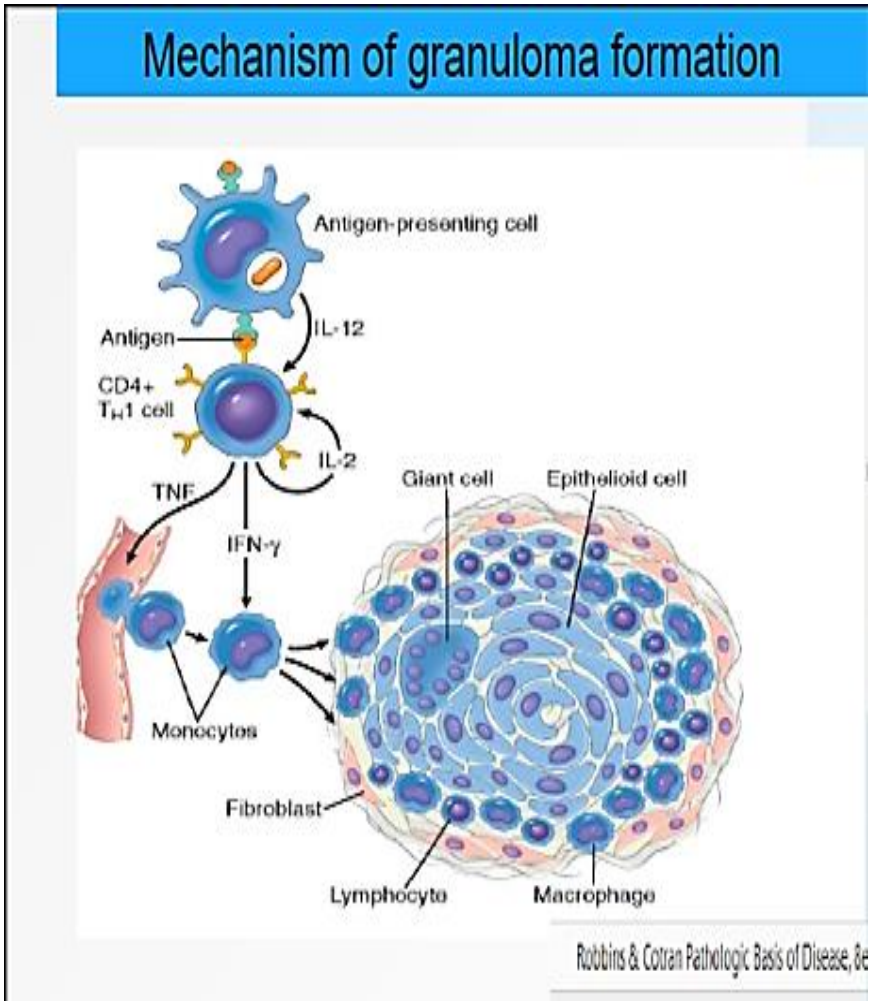
Figure 12.36 The Immune System, 3ed. (© Garland Science 2009)

T_H1 from a previous immunization (memory)

Chronic type (> 1 week)

Granuloma formation, graft rejection:

- Mediated by CD8+ cytotoxic T cell.
- Lymphocytes surrounding epitheloid cells lead to the formation of granuloma.



Summary of Hypersensitivity types:

	Descriptive name	Timing	Mechanism	Examples
I	IgE-mediated Hypersensitivity	<30min	Ag induces cross-linking of IgE bound to mast cells with release of vasoactive mediators	Hay fever, eczema
II	Ab-mediated cytotoxic hypersensitivity	5-8h	Ab directed to cell surface Ag mediates destruction by ADCC or complement	Blood transfusion reactions Rhesus reaction
III	Immune-complex mediated hypersensitivity	2-8h	Ag-IgG/M complexes induce mast cell degranulation via FcgRIII	Arthus reaction Serum sickness
IV	Cell-mediated	1-3 days	T_H1 cells release cytokines that recruit and activate macrophages	Contact dermatitis Tubercular lesions