Hypersensitivity Reactions

Roshina Rabail

Hypersensitivity reactions

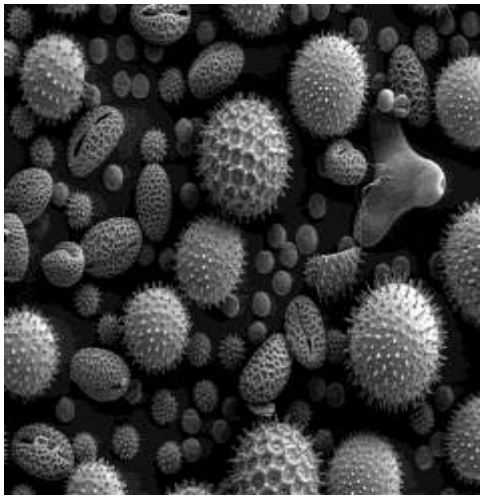
- The immune system is an integral part of human protection against disease, but the normally protective immune mechanisms can sometimes cause detrimental reactions in the host.
- Such reactions are known as hypersensitivity reactions/Allergy, and the study of these is termed immunopathology.

Hypersensitivity

- Hypersensitivity refers to the undesirable or abnormal, sometimes fatal immune reactions produced by the normal immune system. Results from:
  - repeated exposure to an antigen/allergen
  - response of adaptive immune system to self antigens (Auto immune diseases)

An **allergen** is a substance that triggers an allergic reaction in people who are

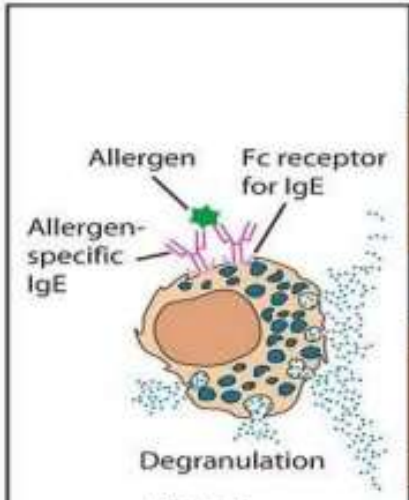
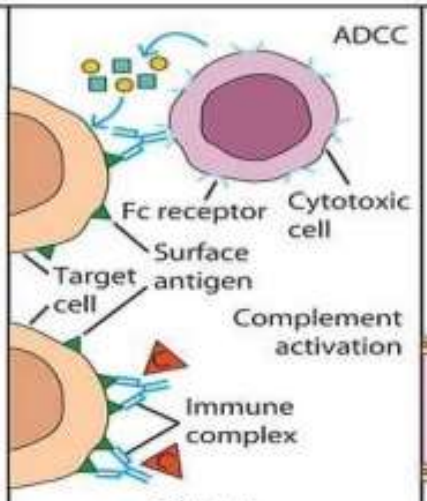
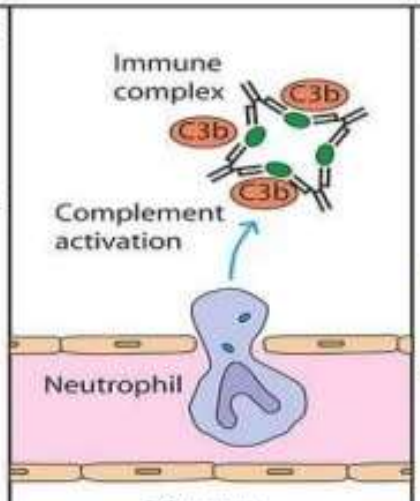
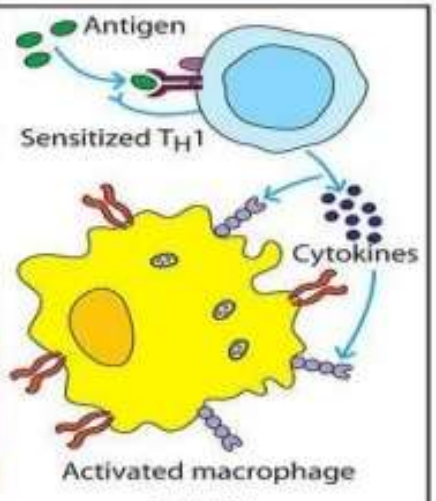
sensitive to that substance.



Types of Hypersensitivity Reactions

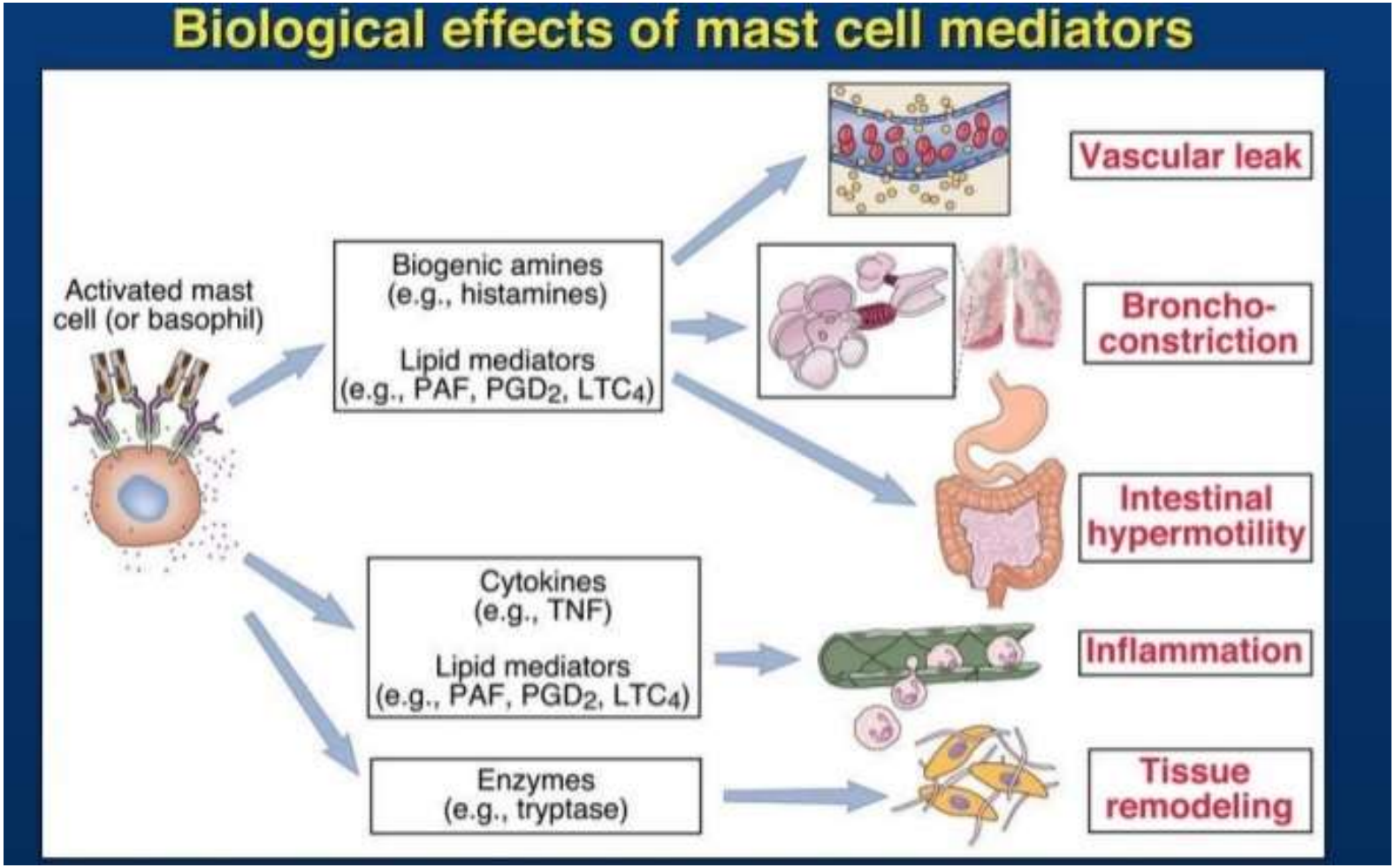
- Hypersensitivity reactions can be divided into four types: based on the mechanisms involved and time taken for the reaction. (by R. Coombs and P. Gell)
  1. (type I) Immediate hypersensitivity
  2. (type II) Antibody-mediated hypersensitivity
  3. (type III) Immune complex-mediated hypersensitivity
  4. (type IV) Cell-mediated hypersensitivity
- Type V: (Autoimmune disease, receptor mediated) This is an additional type that is sometimes (often in Britain) used as a distinction from Type 2.

Hypersensitivity Reactions

 **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_H1 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 Hypersensitivity

- Type I hypersensitivity is also known as immediate or anaphylactic hypersensitivity
- Commonly called Allergy
- Occurs within minutes to the exposure to antigen
- mediated by IgE (rarely by IgG4)
- IgE produced by plasma cells in response to T cells by antigens
- IgE binds to mast cell or basophil causing them to result in degranulation and release several mediators:
  - Histamine: Increase permeability, mucous secretion and smooth muscle contraction
  - Prostaglandins: Contraction of smooth muscles
  - Leukotrienes: Bronchial spasms
- Further reaction is amplified by platelets, neutrophils and eosinophils

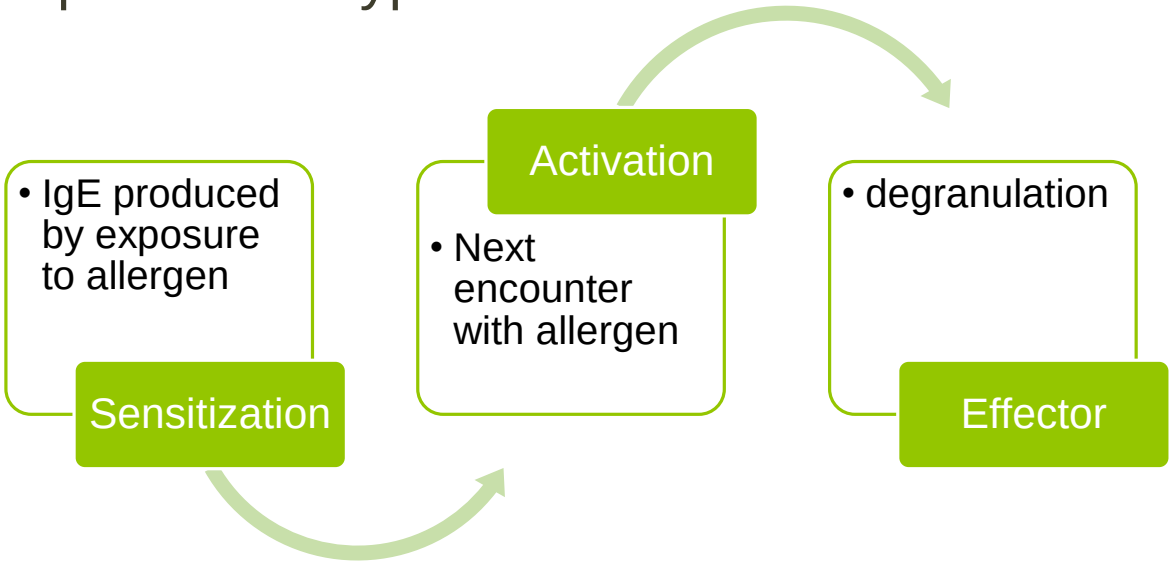

Biological effects of mast cell mediators
Activated mast cell (or basophil)
Biogenic amines (e.g., histamines)
Lipid mediators (e.g., PAF, PGD2, LTC4)
Cytokines (e.g., TNF)
Lipid mediators (e.g., PAF, PGD2, LTC4)
Enzymes (e.g., tryptase)
Vascular leak
Broncho-constriction
Intestinal hypermotility
Inflammation
Tissue remodeling

Type I Hypersensitivity

- Mast cells are triggered by some other stimuli such as:
  - exercise, emotional stress, chemicals, anaphylotoxins (*e.g.*, C4a, C3a, C5a, *etc.*).
- Anaphylactic Shock: Massive Drop in Blood Pressure, can be fatal in minutes
- Cytokines that contribute to HS I are: IL-4,IL-5,IL-6, TNF-α
- The reaction may involve
  - skin (urticaria and eczema),
  - eyes (conjunctivitis),
  - nasopharynx (rhinorrhea, rhinitis),
  - bronchopulmonary tissues (asthma)
  - gastrointestinal tract (gastroenteritis).

Type I Hypersensitivity

- Antigens that stimulate Type I HS are called Allergens
  - Examples are: House dust, pollens, cosmetics, Insects, Clothing, Drugs etc.
- Atopic people tend to mount IgE responces
- Three phases of Type I HS are:



Anaphylactic shock

- Anaphylaxis is a severe, whole-body allergic reaction to a chemicals that has become an allergen.
- This reaction is quick and involves the whole body.
- Tissues in different parts of the body release histamine and other substances.
- This causes the airways to tighten and leads to other symptoms.
- Anaphylaxis can occur in response to any allergen. Common causes include:
  - - Drug allergies
  - - Food allergies
  - - Insect bites/stings
- Anaphylaxis is life-threatening and can occur at any time.
- Risks include a history of any type of allergic reaction.

Anaphylactic shock

- Anaphylactoid reaction:
  - Some drugs (morphine, x-ray dye, Aspirin and others) may cause an anaphylactic-like reaction when people are first exposed to them.
  - These reactions are not the same as the immune system response that occurs with "true" anaphylaxis. However, the symptoms, risk for complications, and treatment are the same for both types of reactions.
- Symptoms:
  - develop rapidly, often within seconds or minutes. They may include the following:
    - Abdominal pain or cramping
    - Abnormal breathing sounds, wheezing, Difficulty breathing
    - Anxiety, Palpitations
    - Cough
    - Difficulty swallowing
    - Fainting, light-headedness, dizziness, Confusion
    - Skin redness, Hives, itchiness
    - Nasal congestion
    - Nausea, vomiting, Diarrhoea
    - Slurred speech

Type I HS Reactions

Localized Anaphylaxis

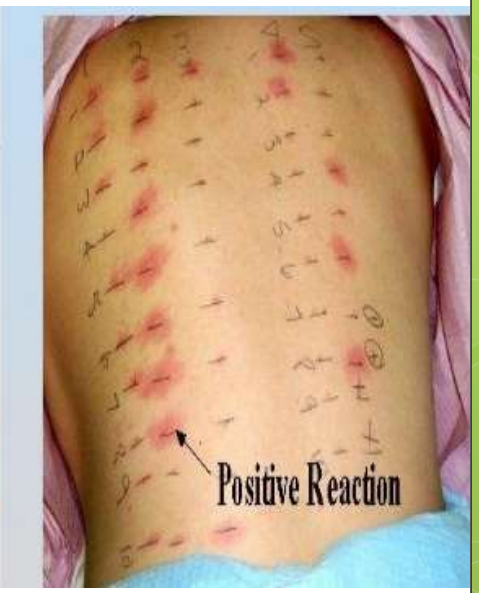
- Cutaneous anphylaxix
- Allergic rhinitis
- Food allergies
- Dermatitis
- Asthma

Systemic Anaphylaxis

- Anaphylactic Shock
- Mast cells degeneration all over body
- Laryngeal edema
- Bronchial constriction

Laboratory Tests for Type I Hypersensitivity

- CBC
  - Increased WBC – eosinophil count
- Increased serum IgE levels
  - Normal values 39IU/ml
  - Does not determine indicate specific antigen
- Radioallergosorbent Test (RAST)
  - Determines the blood concentration of IgE directed against a specific antigen and thus can determine specific antigen



Treatment of Type I HS

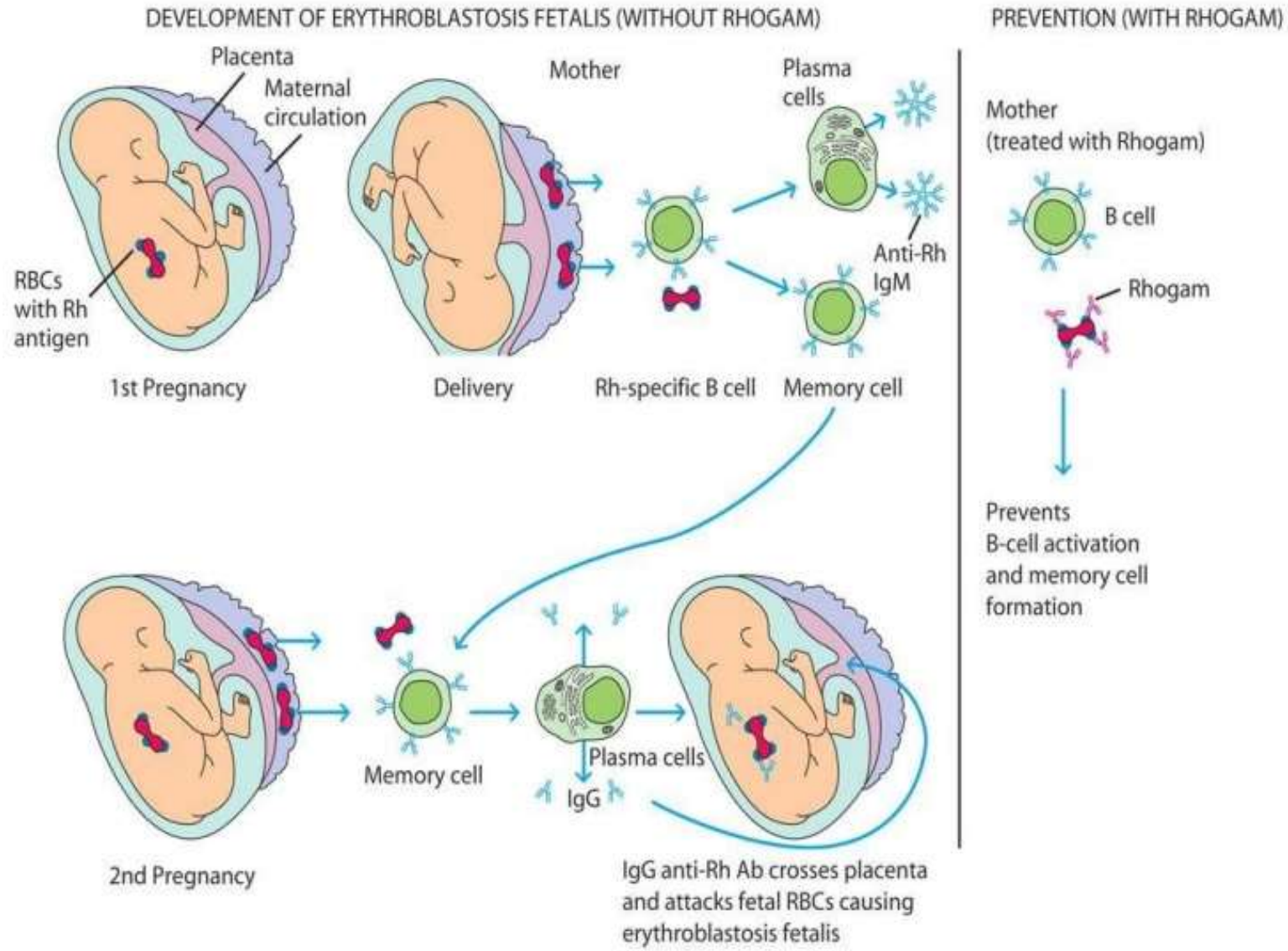
- Avoid Allergens
- Drugs:
  - Anti-histamines: Compete histamine for its receptors
  - Epinephrine : best for anaphylactic shock, (reverse effects of granules) quick but short duration.
  - Cortisone: Blocks histamine synthesis
- Hyposensitization: repeated injections of allergens may shift from IgE to IgG

Type II Hypersensitivity

- Cytotoxic
- IgG or IgM antibody mediated
- Involves complement system, phagocytes and T cells. Which directly damage cell surface
- The reaction time is minutes to hours.
- Examples are:
  - Transfusion reactions: Incompatible donor cells are lysed
  - Haemolytic disease of newborn: Fetal cells are destroyed by maternal anti-Rh antibodies that cross the placenta
  - Autoimmune haemolytic anemia resulted from drugs like Penicillin

Type II Hypersensitivity

- Haemolytic Disease of newborn:
  - Involves Rh blood group system
  - Rh- mom with Rh+ fetus, makes antibodies that enter mom's circulation at birth
  - Next pregnancy: IgG antibodies cross placenta, destroy fetal RBC, leading to jaundice and brain damage.
- Diagnosis:
  - include detection of circulating antibody against the tissues involved
  - the presence of antibody and complement in the lesion (biopsy) by immunofluorescence.
  - The immunofluorescent staining in type II HS is linear
- Prevention:
  - Giving mother RhoGAM right after birth


DEVELOPMENT OF ERYTHROBLASTOSIS FETALIS (WITHOUT RHOGAM)
PREVENTION (WITH RHOGAM)
Placenta
Maternal circulation
RBCs with Rh antigen
1st Pregnancy
Mother
Delivery
Plasma cells
Anti-Rh IgM
Rh-specific B cell
Memory cell
Mother (treated with Rhogam)
B cell
Rhogam
Prevents B-cell activation and memory cell formation
2nd Pregnancy
Memory cell
Plasma cells
IgG
IgG anti-Rh Ab crosses placenta and attacks fetal RBCs causing erythroblastosis fetalis

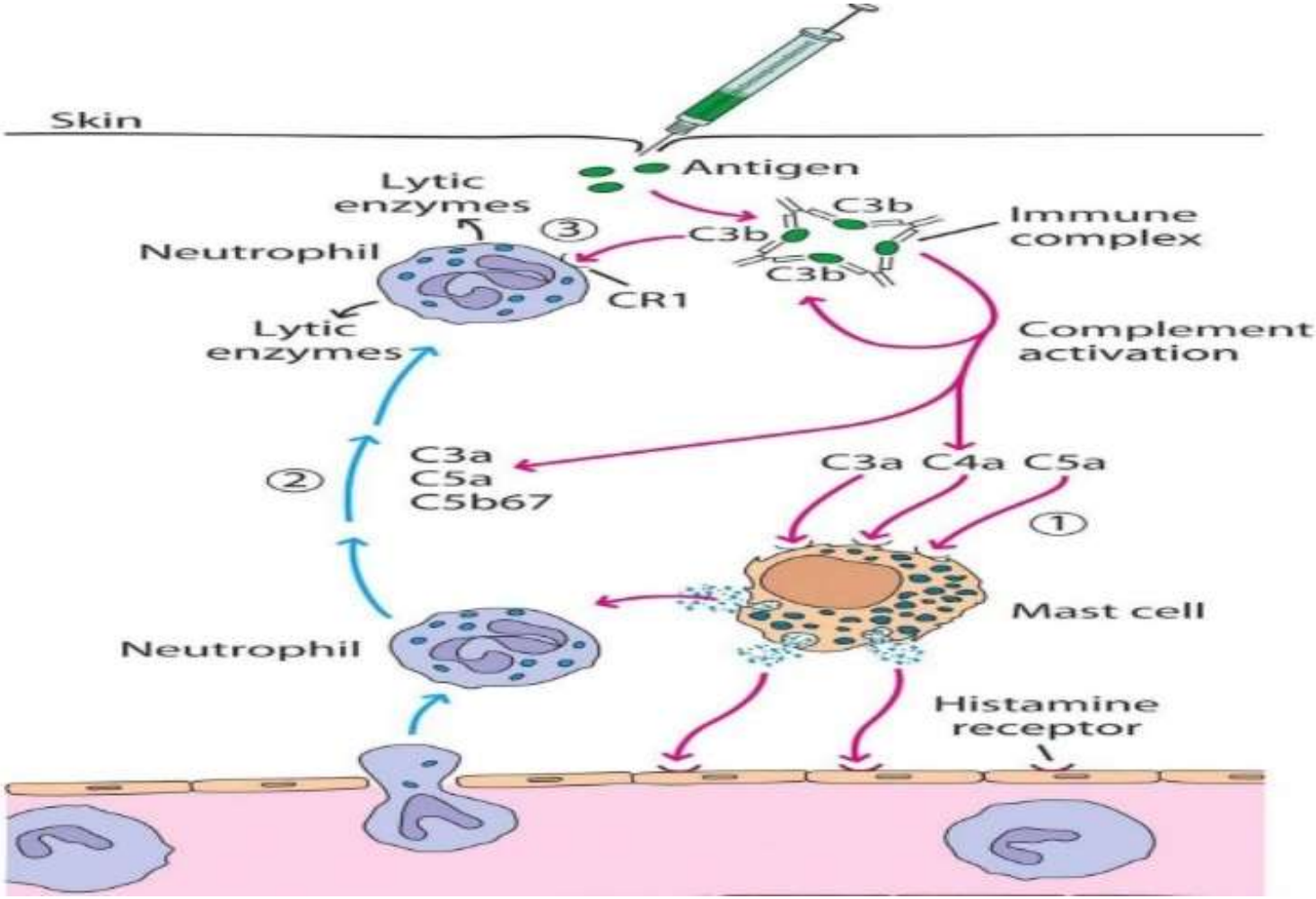
Type III Hypersensitivity Reactions

- Antigen Antibody immune complex hypersensitivity
- 3 - 10 hours after exposure to the antigen
- Mediated by soluble immune complexes, IgG/IgM antibodies and complement (C3a, 4a and 5a)
- Large amounts of Antigen-Antibody complexes are accumulated in blood
- When deposited in organs can cause inflammatory damages like:
  - Rheumatoid arthritis
  - Glomerulonephritis

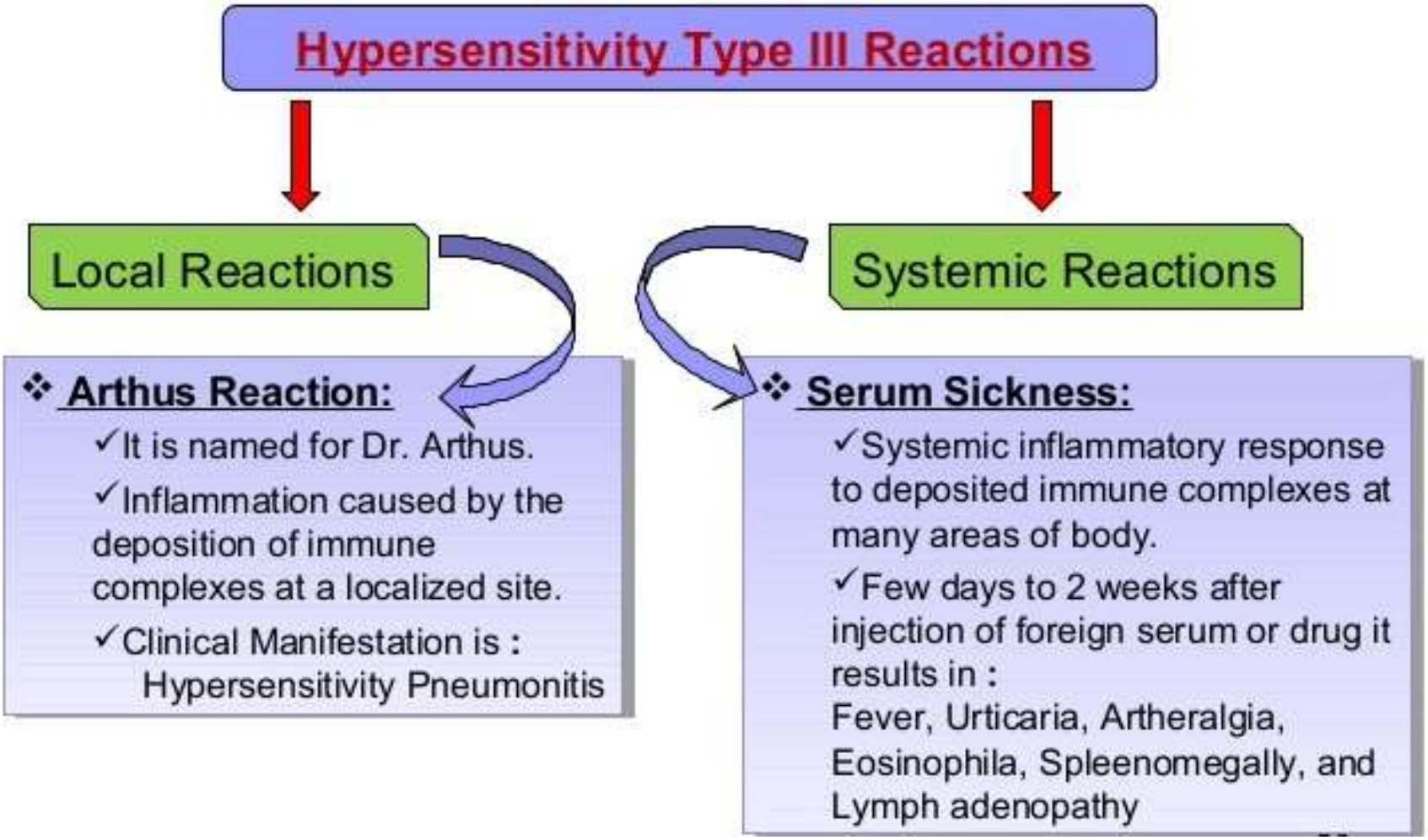
Type III Hypersensitivity Reactions

- The damage is caused by platelets and neutrophils.
- Diagnosis involves examination of tissue biopsies for deposits of immunoglobulin and complement by immunofluorescence microscopy
- The immunofluorescent staining in type III hypersensitivity is granular
- Examples are:
  - Serum Sickness from circulating complexes e.g; Glomerulonephritis, RA, Chronic infections
  - Arthus Reaction from localized complexes e.g insect bite, hypersensitivity pneumonitis

Arthus Reaction



Hypersensitivity Type III Reactions



Examples of Type III HS

Glomerulonephritis

- Immune complexes in the blood are deposited in glomeruli
- Damage to the glomerular cells impedes blood filtration
- Kidney failure and, ultimately, death result

Rheumatoid arthritis

- Immune complexes deposited in the joint
  - Results in release of inflammatory chemicals
  - The joints begin to break down and become distorted
- Trigger not well understood
- Treated with anti-inflammatory drugs

Type IV Hypersensitivity

- Delayed Hypersensitivity
- T Cell mediated cytotoxicity
- Start after hours to days of exposure
- Release of cytokines, NK cells and macrophage activation
- No antibodies involved
- Localized reactions at site of antigen
- Examples are: TB. Leprosy. Poison IVY

Type IV Hypersensitivity

- Sensitization stage:
  - Memory T cells are generated by dendritic cells
- Effector stage:
  - On secondary contact, T memory cells are activated and produce cytokines which cause tissue destruction and inflammation
  - Continued exposure can cause chronic inflammation and result in granuloma formation

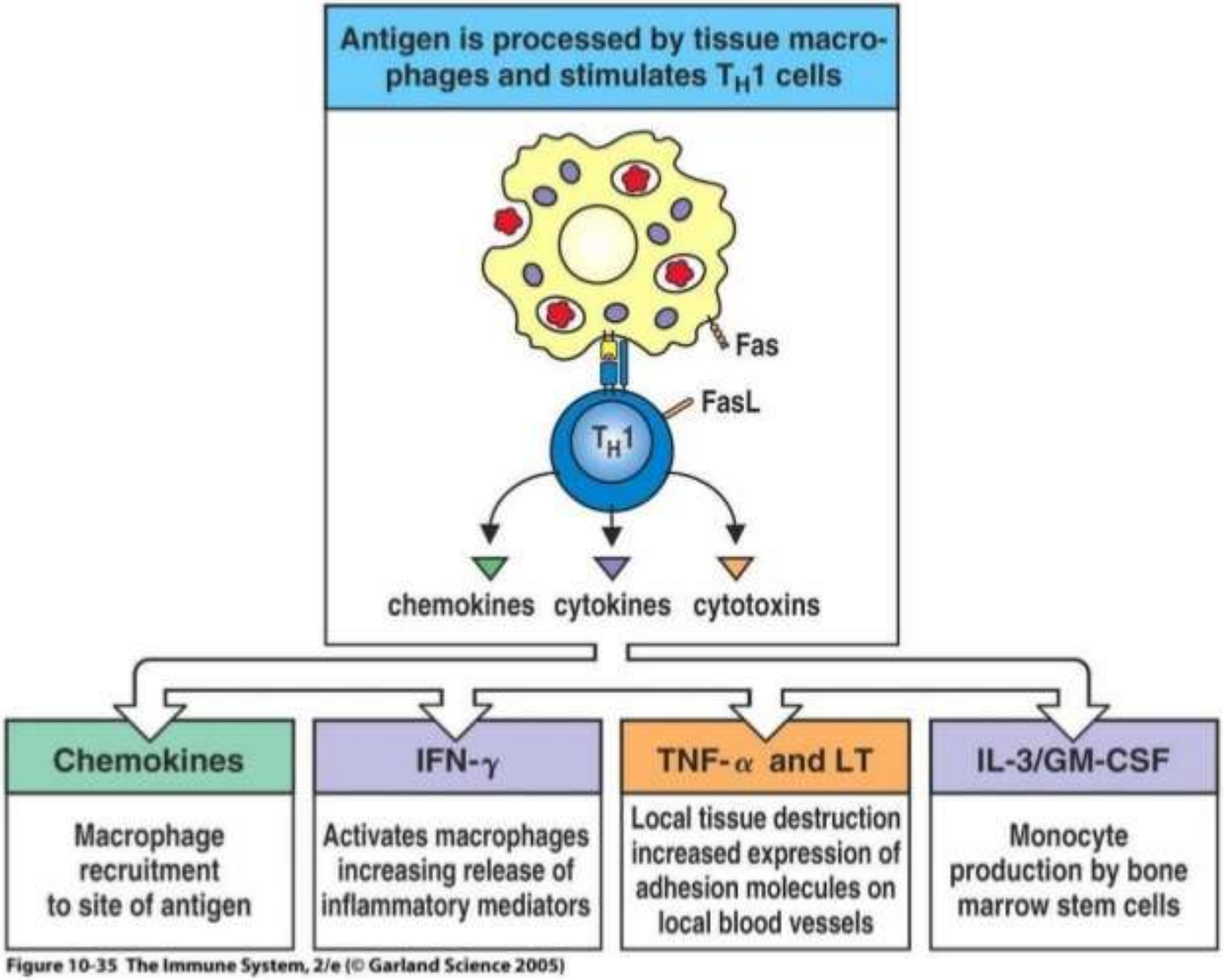
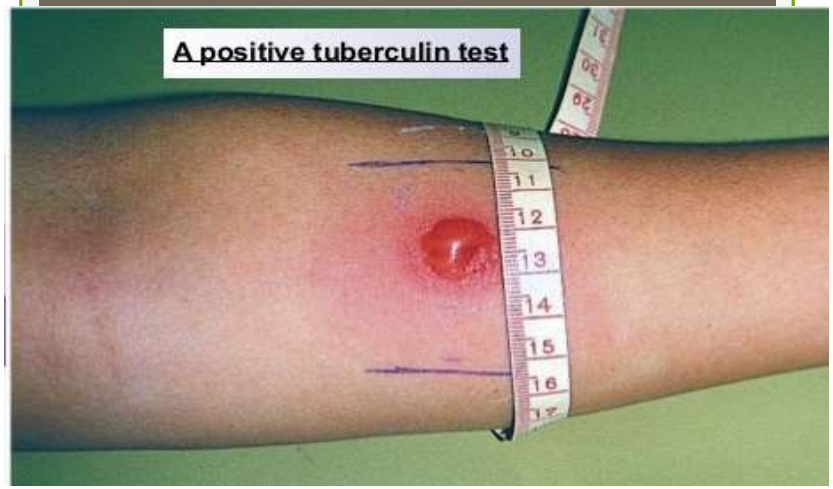
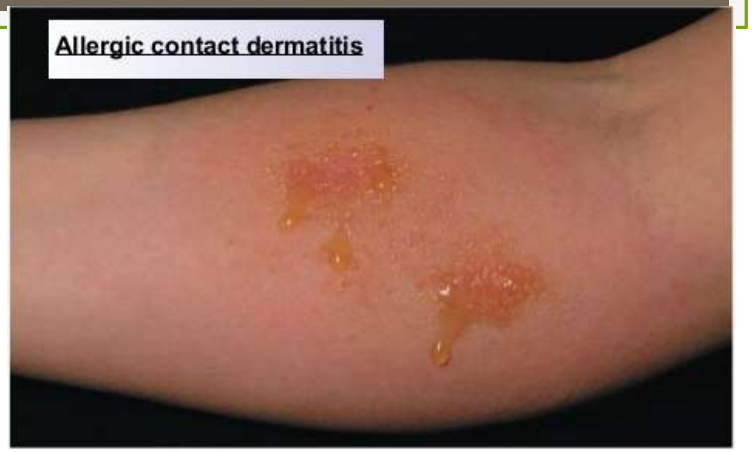


Figure 10-35 The Immune System, 2/e (© Garland Science 2005)



- Tuberculin Skin Test
  - An injection of tuberculin beneath skin
  - Identifies Human being infected with Mycobacterium tuberculosis
  - No response when individual is not infected
  - Red hard swelling in infected individuals



- Contact Dermatitis:
  - Small molecules act as hapten and combine with complex protein in skin
  - Taken up by antigen presenting cells
  - Activate T cells
  - T memory cells are generated
  - Next exposure T memory cells cause Delayed Type Hypersensitivity (DTH)
  - Intense irritating skin rash, fluid filled blisters,

- Graft Rejection:
  - Rejection of tissues or organs transplanted
  - Grafts are perceived as foreign by immune system
  - MHC involved

Table - Comparison of Different Types of hypersensitivity				
Characteristics	Type-I (anaphylactic)	Type-II (cytotoxic)	Type-III (immune complex)	Type-IV (delayed type)
Antibody	IgE	IgG, IgM	IgG, IgM	None
Antigen	Exogenous	Cell surface	Soluble	Tissues and organs
Response time	15-30 minutes	Minutes-hours	3-8 hours	48-72 hours
Appearance	Weal and flare	Lysis and necrosis	Erythema and edema, necrosis	Erythema and induration
Histology	Basophils and eosinophil	Antibody and complement	Complement and neutrophils	Monocytes and lymphocytes
Transferred with	Antibody	Antibody	Antibody	T-cells
Examples	Allergic asthma, hay fever	Erythroblastosis fetalis Goodpasture's nephritis	SLE, farmer's lung disease	Tuberculin test, poison ivy, granuloma

Type V Hypersensitivity

- This is an additional type that is sometimes (often in Britain) used as a distinction from Type 2.
- Instead of binding to cell surface components, the antibodies recognize and bind to the cell surface receptors
- This either prevents the intended ligand binding with the receptor or mimics the effects of the ligand, thus impairing cell signaling.
- Some clinical examples:
  - - Graves' disease
  - - Myasthenia gravis
- The use of Type 5 is rare. These conditions are more frequently classified as Type 2,

Questions