Hypersensitivity Reactions

History –

1893 - Emil von Behring

- – Working with diphtheria toxin noted that animals would suffer enhanced responses and even death following a second dose of toxin too small to injure normal untreated animals
- Described this phenomenon as “hypersensitivity”

1902 - Charles Richet and Paul Portier

- Set sail on the yacht of the Prince of Monacco to study the effects of marine toxins in mammals.
- Attempted to protect dogs from the effects of toxins by innoculating them at low doses.
- Re-exposure to innocuous doses resulted in a rapid shock and suffocation
- Coined the term “Ana-phylaxis” to emphasize its antithesis to the familiar “prophylaxis”.

1903 - Maurice Arthus

- Described a stereotypical response in rabbits following repeated intra-dermal injection of protein antigens
- The response, characterized by local erythema, induration, hemorrhage and necrosis became known as the “Arthus Reaction”

1906 - Clemens von Piquet and Bela Schick

- Coined the term “serum sickness” to describe strange systemic symptoms suffered by some patients weeks after receiving diphtheria or tetanus anti-toxin horse serum.
- Postulated for the first time that these hypersensitivity reactions might be the product of immune response.
- Named these responses “allergic” from the Greek *allos ergos*, altered reactivity.

Introduction –

Hypersensitivity reaction is defined as a state of altered reactivity in which the body reacts with an exaggerated immune response to what is perceived as a foreign substance. A pre-requisite for hypersensitivity to occur is a previous/prior exposure to the perceived allergen.

Immune response is a double edged sword… under normal circumstances it helps to fight of allergens, but when the immune response goes overboard, it can be fatal as in the cases of hypersensitivities.

Gell and Coombs classification of hypersensitivity

Type	Mechanism	Examples
I	IgE	Anaphylaxis, asthma, hay fever, eczema, food allergies
II	Cytotoxic Ab	HTR by ABO incompatibility, HDN by Rh incompatibility
III	Immune complexes	Arthus phenomenon, serum sickness, rheumatoid arthritis
IV	Cell-mediated	Koch's phenomenon, contact dermatitis

Depending upon the rapidity and duration of the immune response, two distinct forms of hypersensitivity are recognized:

Immediate type

- Immune response mediated by humoral antibodies.
- Three types – type I, II and III.

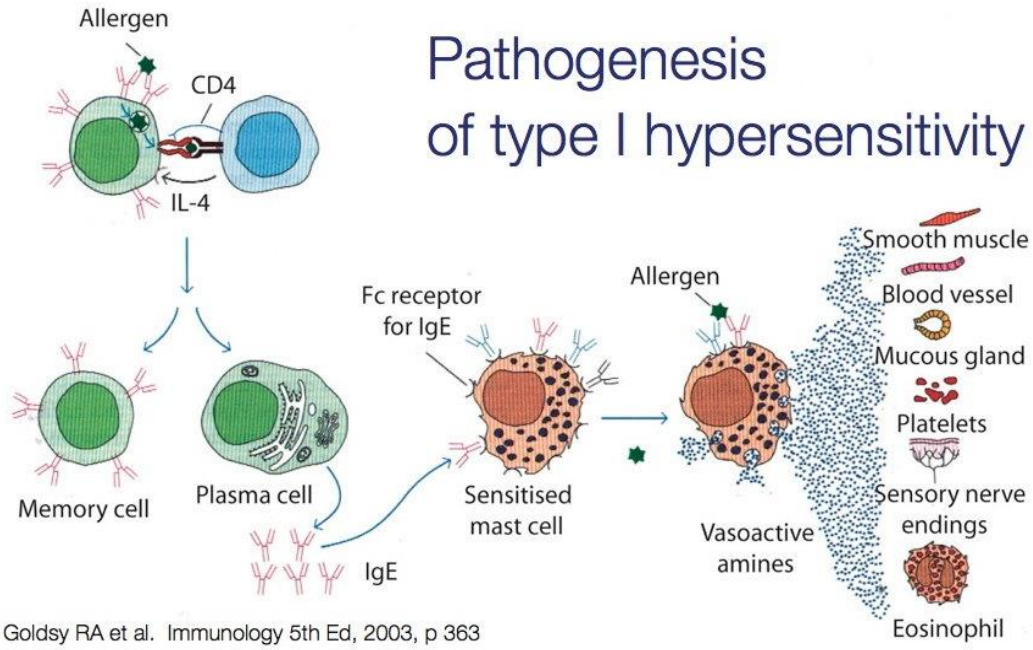
Delayed type

- Slower onset : 24 – 48 hours
- Prolonged effect
- Mediated by cellular response – type IV reaction

Type I Hypersensitivity Reactions: Anaphylactic and Atopic reactions -

Type I Hypersensitivity is an allergic reaction provoked by re-exposure to a specific type of antigen referred to as an allergen. Exposure may be by ingestion, inhalation, injection, or direct contact. The difference between a normal immune response and a type I hypersensitive response is that plasma cells secrete IgE. This class of antibodies binds to Fc receptors on the surface of tissue mast cells and blood basophils. The mechanism of reaction involves preferential production of IgE, in response to certain antigens (**allergens).**

IgE has very high affinity for its receptor on mast cells and basophils. A subsequent re-exposure to the same allergen cross links the cell-bound IgE and triggers the release of various pharmacologically active substances. Mast cell degranulation is preceded by increased Ca++ influx, which is a crucial process; ionophores which increase cytoplasmic Ca++ also promote degranulation, whereas, agents which deplete cytoplasmic Ca++ suppress degranulation.



Degranulation results in the release of pharmacologically active substances k/a *anaphylactic mediators* –

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)

Clinically Anaphylaxis may be of two types –

Systemic Anaphylaxis –

- Administration of antisera
- Administration of drugs
- Stings of wasps and bees

Clinical features include – itching, erythema, contraction of respiratory bronchioles, diarrhoea, pulmonary edema, pulmonary haemorrhage, shock & death.

Local Anaphylaxis –

- Hay fever (allergic rhinitis)
- Bronchial asthma
- Food allergies
- Cutaneous anaphylaxis
- Angioedema

Local anaphylaxis is common affecting 10% of the population. 50% of these reactions are familial with a genetic predisposition – *Atopic reactions.*

Management –

Assessment –

Withdraw the offending agent (eg, stop drug infusion). Check the airway and secure if needed. Patients with respiratory compromise may need to be intubated. If laryngeal edema causes oral intubation to be difficult, a tracheostomy must be performed. Assess the level of consciousness and vital signs.

Treatment

- *Administer epinephrine immediately*.
- Start intravenous fluids; these should be administered rapidly and as blood pressure and overall fluid status warrant.

- Consider other vasopressors (eg, dopamine) if hypotension does not respond to the above measures. Norepinephrine may be used if dopamine is not effective. Patients with beta-adrenergic blockade may be particularly difficult to treat. They have both chronotropic and inotropic cardiac suppression. Glucagon has positive inotropic and chronotropic effects and is the drug of choice in these cases. Atropine can also be used but will only be effective in treating bradycardia.

- H1- and H2-receptor blockers can be helpful in alleviating hypotension, pruritus, urticaria, rhinorrhea, and other symptoms. Use albuterol nebulizers if needed to relieve the broncho-spasm.

- Administer a corticosteroid, which is believed to help prevent or control the late-phase reaction. Transfer the patient to the hospital for further observation and care. Late phase reactions can occur 4-6 hours after the initial reaction and can be as severe as or worse than the original reaction. In some cases, late phase reactions can occur up to 36 hours later. Education of the patient and observation is, therefore, important.

Prevention –

- Avoid the triggering allergen as much as possible.

- Patients should be given a prescription for at least 2 auto-injectable epinephrine doses and instructed in their proper use. Importantly, patients must carry them at all times. Patients can also be instructed to carry both an H1 and an H2 antihistamine with them.

- Patients must wear a Medic Alert type of bracelet to alert emergency responders to the possibility of anaphylaxis. Patients should be taught what measures to take in case of a

future anaphylactic reaction, ie, immediately administer epinephrine and take the antihistamine, call emergency services, or go to the nearest emergency department (even if feeling better after the epinephrine).

Medications –

- Epinephrine - Should be administered immediately for anaphylaxis/anaphylactic shock. Multiple preparations allow for delivery SC, IM, or IV. Doses can be repeated q5min prn to maintain blood pressure.
- Bronchodilators (Sympathomimetic) - Inhaled bronchodilators are beta-agonists that come in short- and long-acting forms. Short-acting bronchodilators are used to treat acute bronchospasm. Can also be used prophylactically; *Salmetrol*, *Albuterol*, *formetrol.*
- Corticosteroids - Immunosuppressing agents and, thus, can decrease inflammation. Have particular efficacy in skin eruptions and bronchospasm. Role in anaphylactic shock is limited, although believed to help prevent delayed type of anaphylaxis.
- Histamine1-receptor antagonists (antihistamines)
- Type 1 histamine-receptor blockers act to block action of histamine on H1 receptor after its release from mast cells and basophils. Most effective when used prophylactically; Diphenhydramine – Benadryl, Dihydrex inj (available OTC). Azelastine (Astelin) - delivered via the intranasal route. Cetrizine - Selectively inhibits histamine H1 receptor sites in blood vessels, GI tract, and respiratory tract, which in turn inhibits physiologic effects that histamine normally induces at H1 receptor sites. Once-daily dosing is convenient. Leukotriene inhibitors and immunomodulatory drugs may also be used.

Type II: Cytotoxic Reactions –

These are defined as those reactions which cause injury to the cell by combining humoral antibodies with cell surface antigens, blood cells being affected more commonly. Three types of mechanisms are involved –

a. Cytotoxic antibodies to blood cells

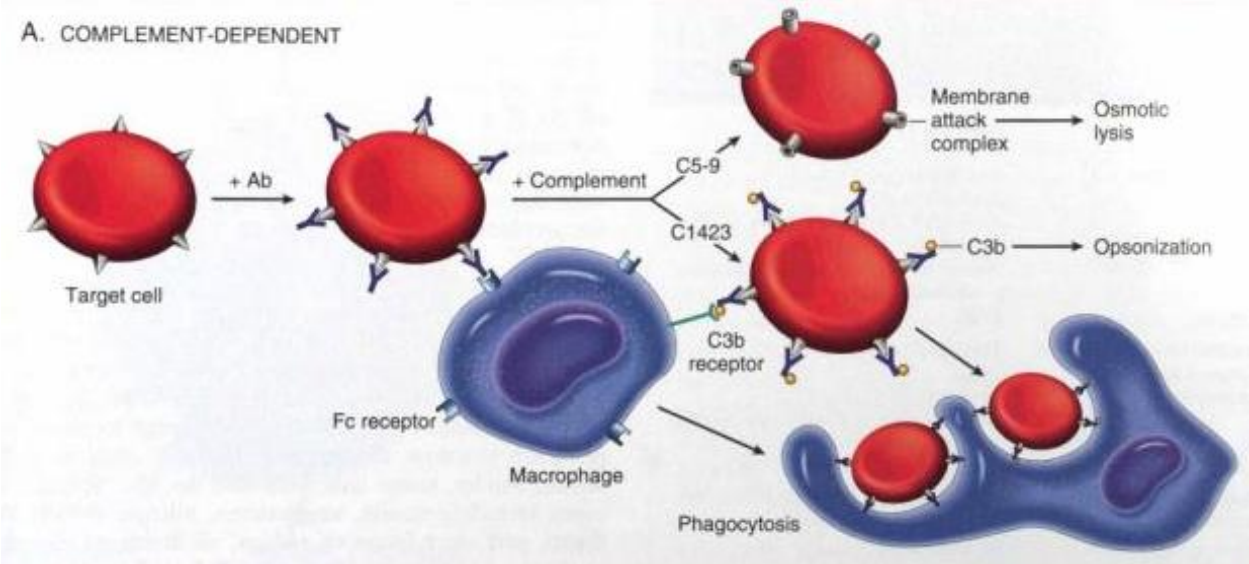
b. Cytotoxic antibodies to tissue components

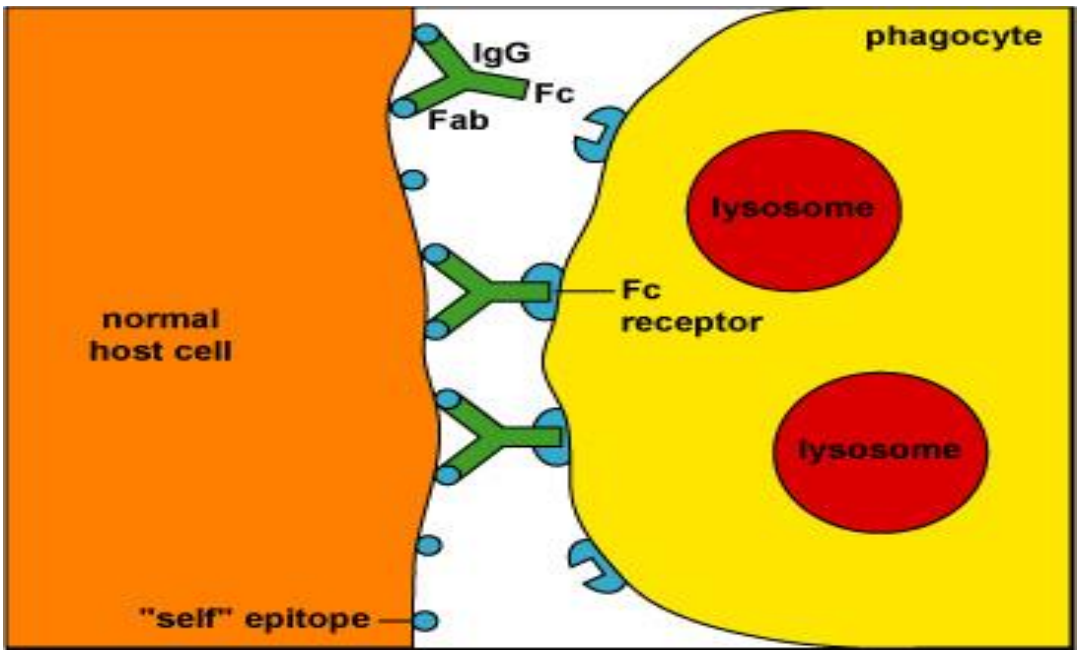
c. Antibody-dependent cell mediated cytotoxicity (ADCC)

Either IgG or IgM is made against normal self antigens as a result of a failure in immune tolerance or a foreign antigen resembling some molecule on the surface of host cells enters the body and IgG or IgM made against that antigen then cross reacts with the host cell surface.

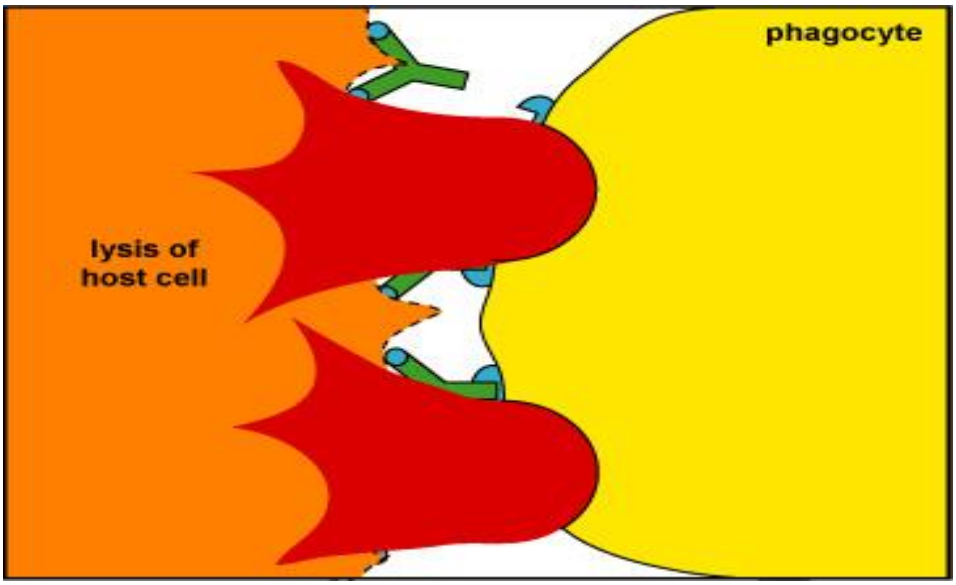
Cytotoxic antibodies to blood cells –

- Involves the direct cytolysis of blood cells by combining the cell surface antigen with IgG or IgM antibodies. Complement system is activated resulting in cell membrane injury. Cell surface is made susceptible to phagocytosis by *opsonization.* Examples –
  - Autoimmune hemolytic anaemia
  - Transfusion reactions due to ABO incompatibility
  - Erythroblastosis Foetalis
  - ITP

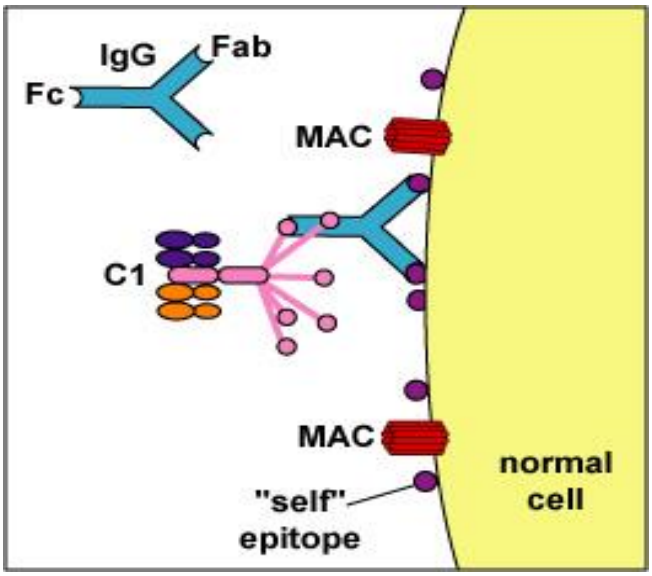




Opsonization during Type II hypersensitivity - (Step 1)



Opsonization during Type II hypersensitivity - Phagocytes binding to the Fc portion of the IgG and discharge their lysosomes causing cell lysis (Step 2)



Membrane attack complex lysis during type II hypersensitivity - IgG or IgM reacts with epitopes on the host cell membrane and activates the classical complement pathway. Membrane attack complex (MAC) then causes lysis of the cell.

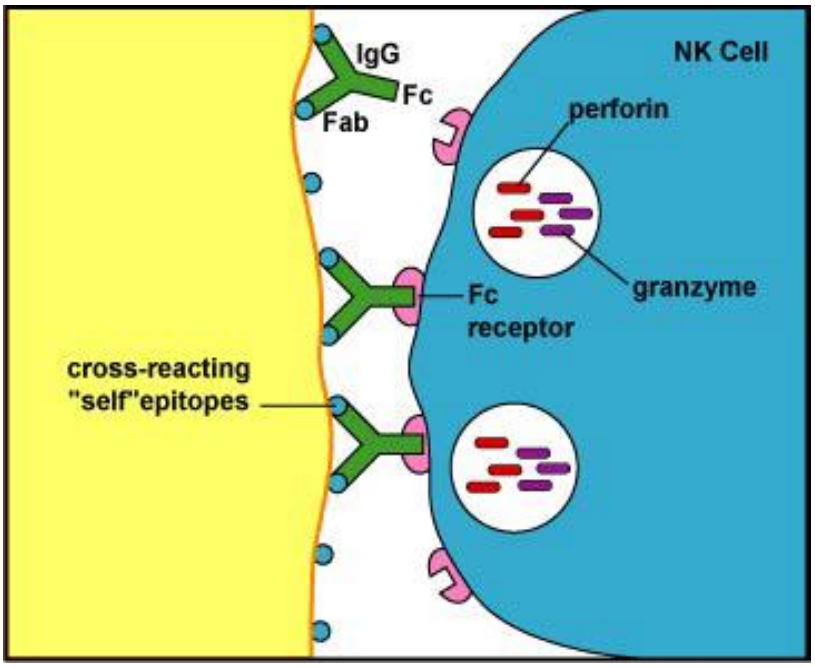
Cytotoxic antibodies to tissue components

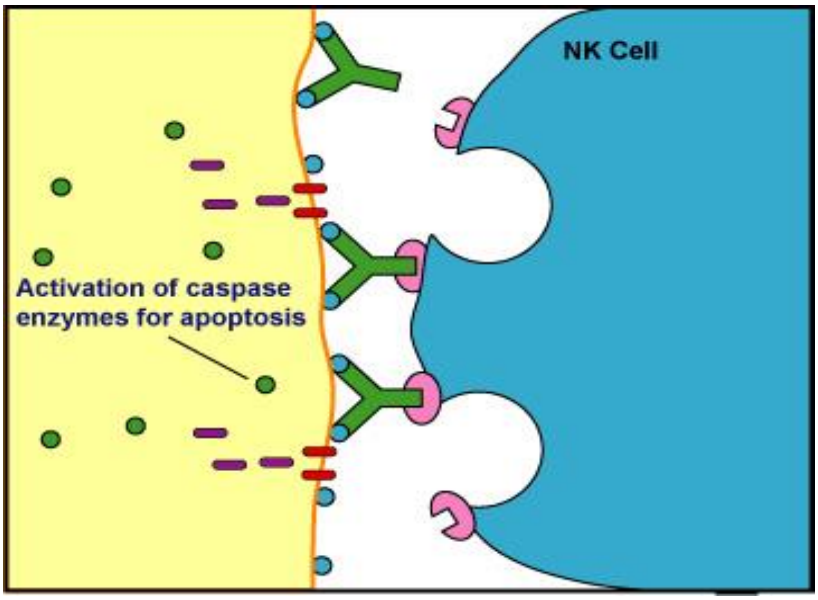
Cellular injury may be brought about y auto-antibodies reacting with some components of tissue cells in certain diseases –

- Grave's disease (primary hyperthyroidism) – thyroid auto-antibody is formed which reacts with the TSH receptor to cause hyperfunction and proliferation.
- Myasthenia Gravis – antibody to Acetylcholine receptor of skeletal muscle is formed which blocks the neuromuscular transmission at the motor end plate, resulting in muscle weakness.

Antibody-dependent cell mediated cytotoxicity (ADCC)

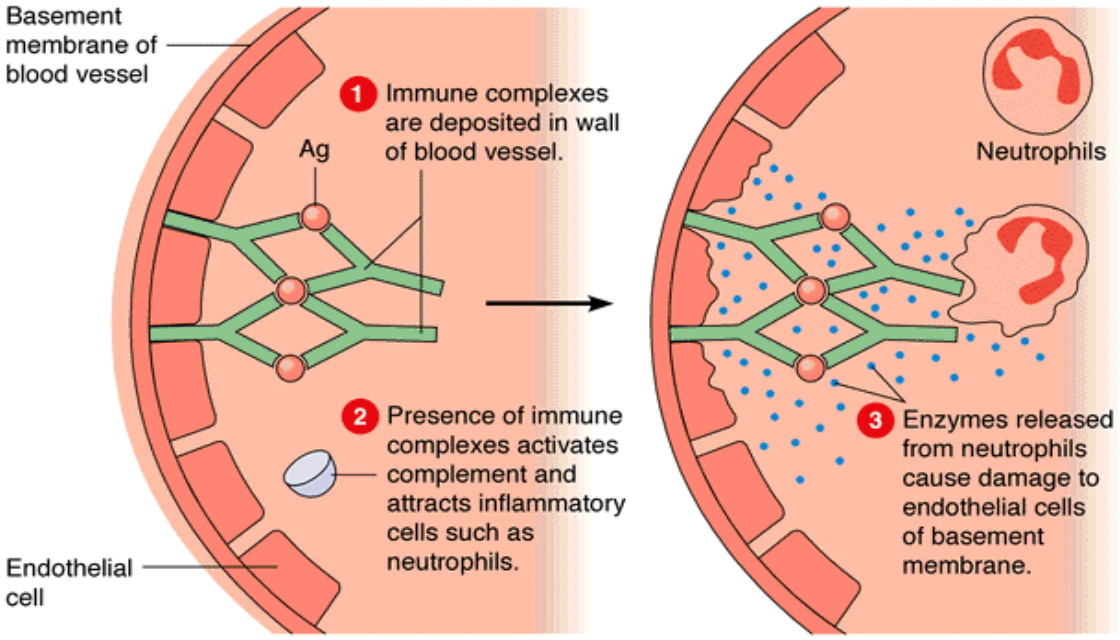
- Mediated by leucocytes like monocytes, neutrophils, eosinophils, and NK cells.
- The cellular injury occurs by lysis of antibody coated target cells through Fc receptors on lecocytes.
- NK cells attach to the Fc portion of the antibodies. The NK cell then release pore-forming proteins called perforins and proteolytic enzymes called granzymes. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation.


IgG
Fc
Fab
NK Cell
perforin
granzyme
Fc
receptor
cross-reacting
"self"epitopes


NK Cell
Activation of caspase
enzymes for apoptosis

Type III Hypersensitivity: Immune complex reactions -

When antibodies (Ig G or Ig M) and antigen coexist immune complexes are formed which have the capacity to activate the complement system. The Immune complexes are removed by reticuloendothelial system. Some immune complexes escape phagocytosis. Immune complexes get deposited in tissues on the basement membrane of blood vessels and cause tissue injury.



Diseases produced by immune complexes are those in which antigens persists without being eliminated as:

a- Repeated exposure to extrinsic antigen,

b- Injection of large amounts of antigens,

c- Persistent infections,

d- Autoimmunity to self components.

Mechanism of Tissue injury -

Immune complexes trigger inflammatory processes:

activate *release*

1) Immune complexes ⟶ the complement ⟶ anaphylatoxins

stimulate *release*

⟶ degranulation of basophiles and mast cells ⟶ histamine

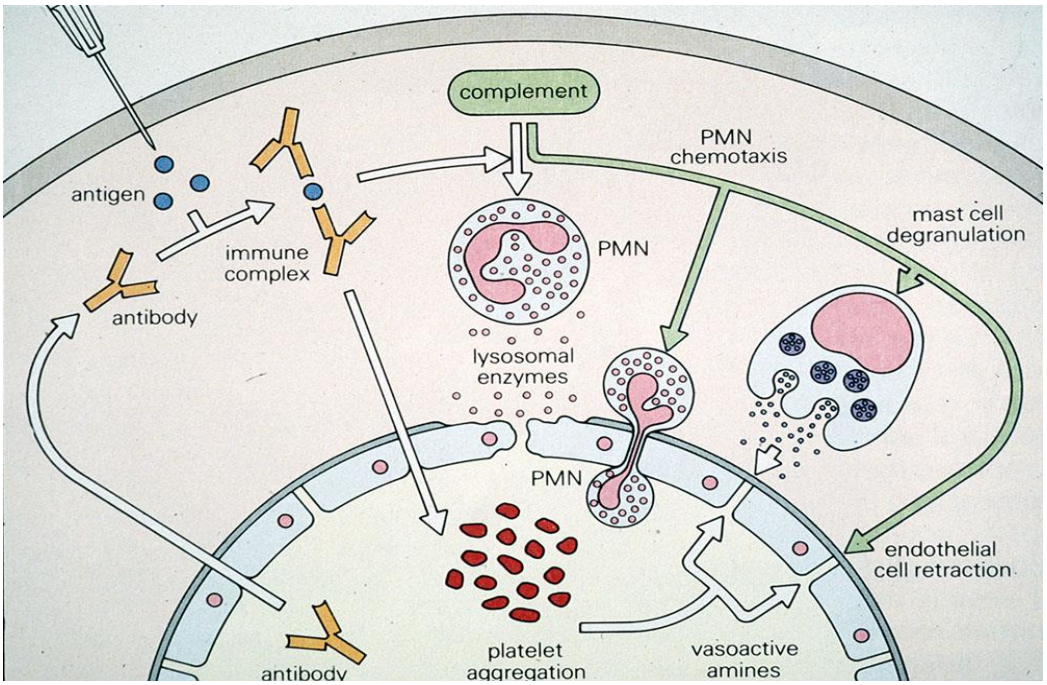
⇧ *vascular permeability and help deposition of immune complexes*

2) Neutrophils are attracted to the site by immune complexes and release lysosomal enzymes which damage tissues and intensify the inflammatory process.

3) Platelet aggregation & hageman factor activation ,initiates formation of microthrombi.

4) Release of C3b ,the opsonin that promotes phagocytosis.

5) Production of chemotactic factors which direct the migration of polymorphonuclear leukocytes & monocytes.


complement
PMN
chemotaxis
antigen
immune
complex
antibody
PMN
mast cell
degranulation
lysosomal
enzymes
PMN
endothelial
cell retraction
antibody
platelet
aggregation
vasoactive
amines

Type IV Hypersensitivity: DTH – Delayed type hypersensitivity –

Delayed hypersensitivity reactions are inflammatory reactions initiated by mononuclear leukocytes. Appears 48-72 hours after antigen exposure. Mediated by T cells and monocytes/macrophages rather than by antibodies.

Delayed hypersensitivity is a major mechanism of defense against various intracellular pathogens, including mycobacteria, fungi, and certain parasites, and it occurs in transplant rejection and tumor immunity. The central role of $CD4^+$ T cells in delayed hypersensitivity is illustrated in patients with AIDS.

If T-cell function is abnormal, the patient presents with opportunistic infections, including infection with mycobacteria, fungi, parasites, and, often, mucocutaneous candidiasis. Undesirable consequences of delayed-type hypersensitivity (DTH) reactions include illness such as contact dermatitis and allograft rejection.

Examples of DTH reactions are contact dermatitis (eg, poison ivy rash), tuberculin skin test reactions, granulomatous inflammation (eg, sarcoidosis, Crohn disease), allograft rejection, graft versus host disease.

Foreign antigen → local immune response

↓

up regulation of endothelial cell adhesion molecules

↓

Accumulation of leucocytes at site

↓

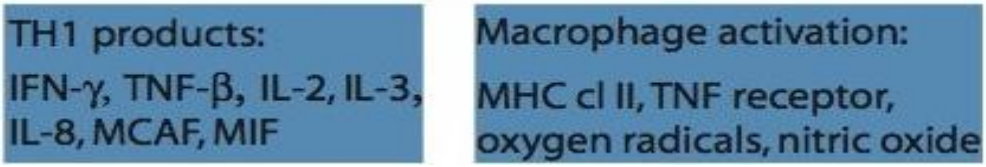
Phagocytosis of antigen + presentation to T-cells and Macrophages via APC (T-cells have specific receptors for the processed antigens)

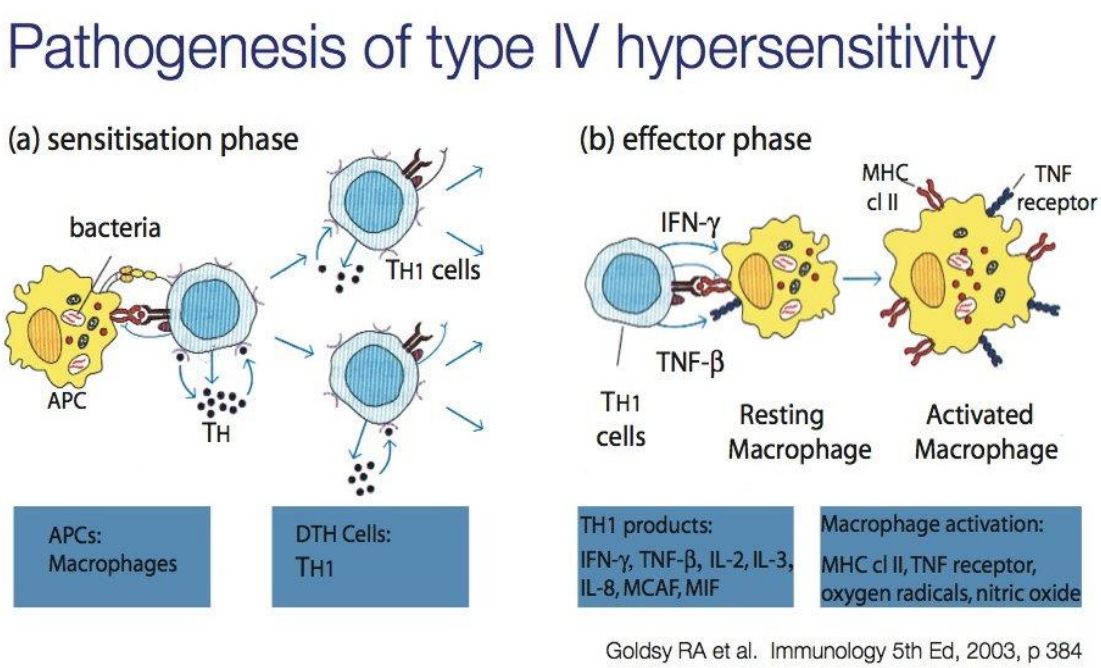
↓

Macrophages and T-cells release chemical mediators

The characteristic histologic appearance of the macrophage–T-cell infiltrate is a granuloma. This type of infiltrate in the tissue is called granulomatous inflammation.

- Mediators released by -:





Clinical presentation –

- *Contact hypersensitivity*: Examination usually reveals edematous and erythematous epidermal tissue with microvesicles. If the offending antigen is from the *Rhus* genus of plants, the involved area usually appears in a linear fashion. If the offending antigen is nickel (eg, jewelry), then the involved area is oriented in a fashion consistent with the area of contact.

- *Tuberculin hypersensitivity reactions*: Approximately 48-72 hours following the intradermal administration of purified *M tuberculosis* protein, patients who have been exposed to *M tuberculosis* develop an area of erythema and induration.

- *Granulomatous hypersensitivity reactions*: The physical examination findings differ depending on the underlying disease. For example, if the patient has active TB, then a chronic cough, malaise, night sweats, weight loss, and pyrexia are present.

Delayed hypersensitivity reactions are normal physiological events. Anything that alters these normal events can lead to multiple opportunistic infections. Immune deficiencies (congenital or acquired) and immunosuppressive agents can alter this normal response.

Treatment –

Medical treatment is specific for the disease entity –

Contact dermatitis: The treatment of contact dermatitis varies depending on the severity of the disease. The best advice is to avoid the offending antigen. Pharmaceutical treatment varies, including over-the-counter corticosteroid preparations, prescription corticosteroid preparations, injectable corticosteroids, oral corticosteroids, and Burow solution.

Tuberculin hypersensitivity skin reactions: Treatment is rarely needed because this response is usually short-lived and self-limited. Topical corticosteroid preparations can be applied as needed. On rare occasions, the reaction to a delayed hypersensitivity skin test may be extreme and result in axillary lymphadenopathy and fever. Such reactions are self-limited and may be treated with an antipyretic medication such as aspirin or ibuprofen.