HYPERSENSITVITY REACTIONS

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What is HYPERSENSITIVITY ?

- It is an excessive immune response which leads to undesirable changes in the body i.e. tissue or organ damage / tissue dysfunction
- Hypersensitivity is an inappropriate immune response that may develop in the humoral or cell-mediated responses to either exogenous or endogenous Ag, causing tissue damaging reactions, & resulting disease is called as hypersensitivity disease.
- Was first termed as '*anaphylaxis'*
- It can be systematic, which often leads to shock and can be fatal, or localized, which is seen in various topic reactions

- They are best classified on the basis of immunological mechanism initiating the disease, 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)

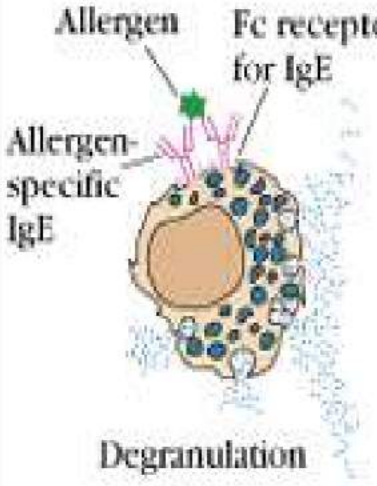
Types of hypersensitivity reaction

TYPE I : IgE MEDIATED

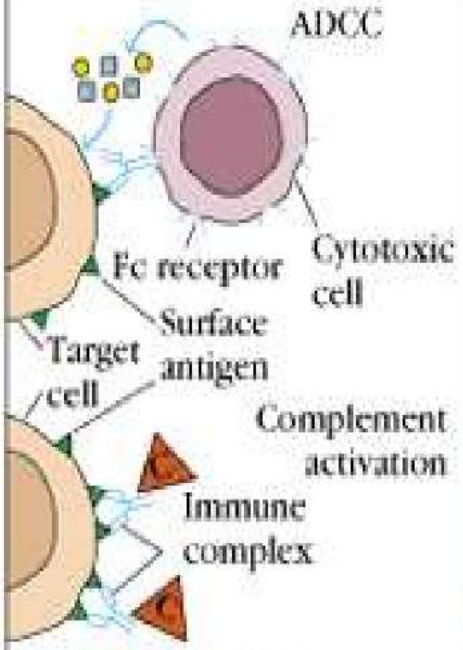
TYPE II :ANTIBODY MEDIATED

TYPE III : IMMUNE COMPLEX MEDIATED

TYPE IV : DELAYED TYPE HYPERSENSITIVITY



Type I



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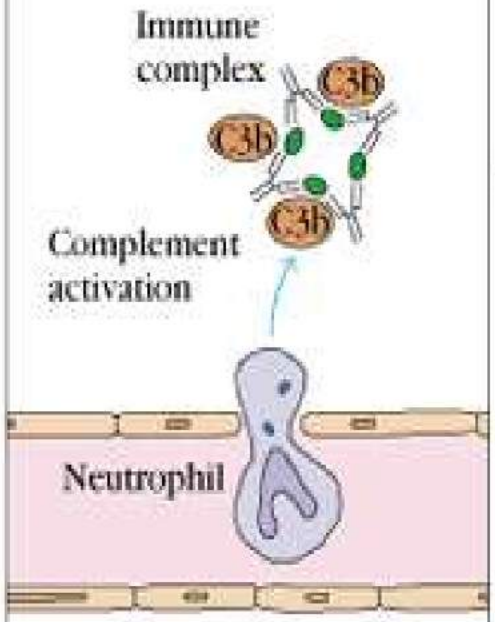
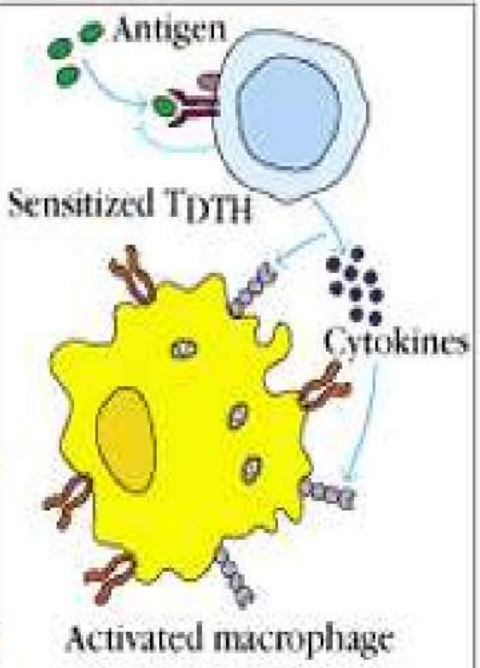


Type III



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 HYPERSENSITIVITY

- Also called as *Anaphylactic Type Hypersensitivity, Immediate Hypersensitivity, Allergy and Anaphylaxis*
- Rapidly occurring reaction.
- It follows interaction of allergen with IgE antibody previously bound to the surface of the mast cells or basophil in a sensitized host
- May be local or may end in fatal systemic disorder (anaphylaxis)

First exposure of the host to Ag

Induction CD4+T-cells of Th2 type

Secrete cytokines (IL-4,IL-5)

Cause IgE prod by B Cells

IgE+Fc receptors on mast cells & basophil

Re-exposure results in cross linking of IgE on mast cell surface

Release of mediators from mast cells

Initial response

Acts as Growth Factors for Mast Cells

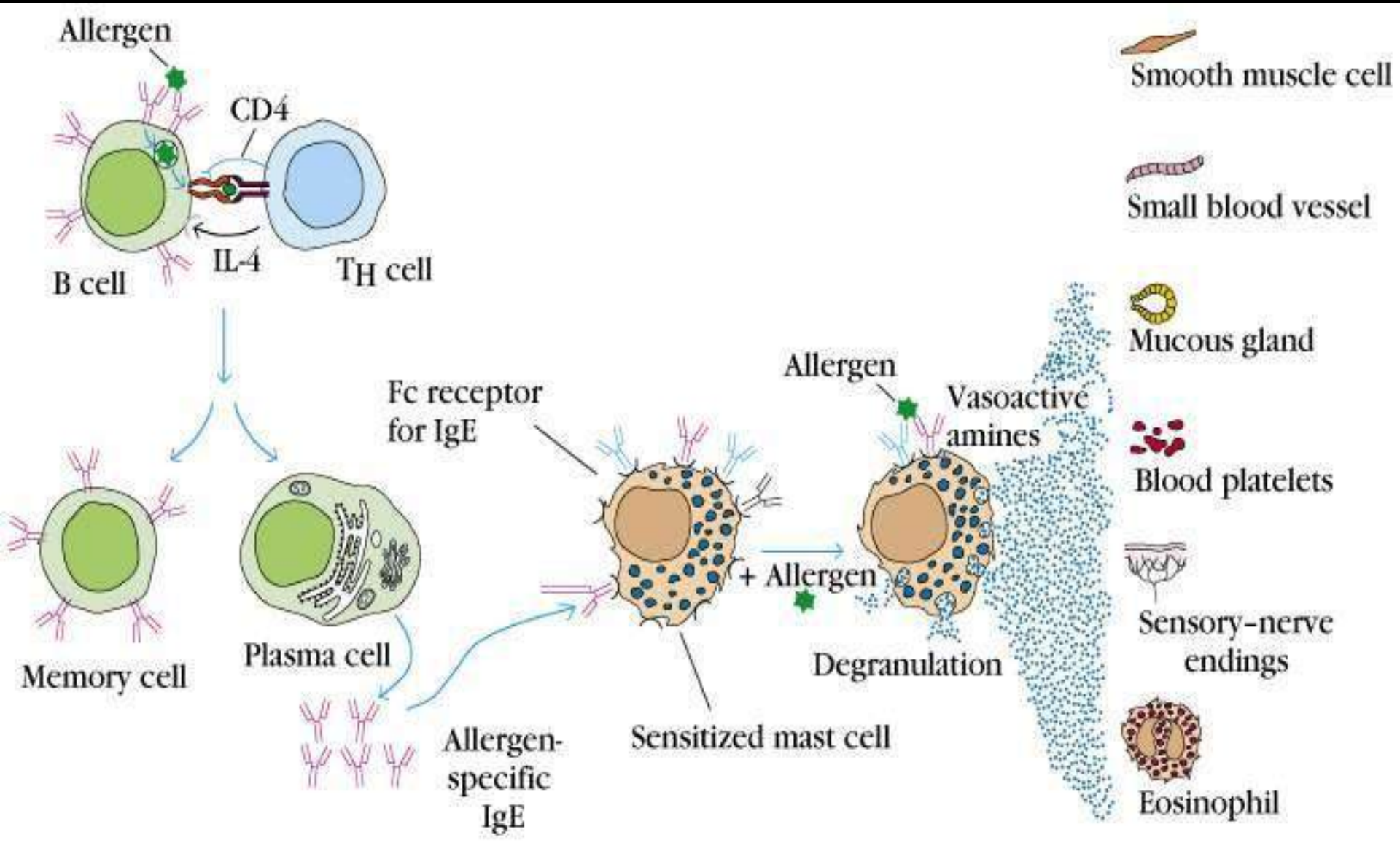
secrete IL-3,IL-4

recruit & activate eosinophils

release of granules

Late-phase reaction

Type I: IgE-Mediated Hypersensitivity



Clinical Manifestation

- May occur as-
  - a) Local reaction
  - b) Systemic disorder

a) **Local reaction:**

- ✓ Ag confined to a particular site, e.g-skin,GI tract or lung
- ✓ Symptoms:
  - Urticaria, diarrhoea, bronchoconstriction

b) **Systemic disorder**

- ✓ Parenteral administration of protein Ag (such as bee venom) or drugs (penicillin)
- ✓ **Symptoms:**
  - ✓ Within minutes pruritis, Urticaria, skin erythema, pulmonary bronchoconstriction, hypersecretion of mucus, vomiting, diarrhoea

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)

TABLE 16-1 COMMON ALLERGENS ASSOCIATED WITH TYPE I HYPERSENSITIVITY

Proteins
- Foreign serum
- Vaccines

Plant pollens
- Rye grass
- Ragweed
- Timothy grass
- Birch trees

Drugs
- Penicillin
- Sulfonamides
- Local anesthetics
- Salicylates

Foods
- Nuts
- Seafood
- Eggs
- Peas, beans
- Milk

Insect products
- Bee venom
- Wasp venom
- Ant venom
- Cockroach calyx
- Dust mites

Mold spores

Animal hair and dander

Type II-Antibody-Mediated Cytotoxic Hypersensitivity

- Involves the antibody mediated destruction of cells
- The reaction occurs in three different antibody-dependent mechanism
  - Complement dependent reaction
  - Antibody dependent cell-mediated cytotoxicity(ADCC)
  - Anti receptor antibody

a) Complement Dependent Reaction

Antibody binds to

↓

Antigen on target cell surface

↓

Leads to fixation complement to the cell surface

↓

Lysis (osmoticlysis) through membrane attack complex

↓

cell coated with Ab & complement fragments (opsonized) are phagocytosed by macrophage

b) Antibody –dependent cell mediated cytotoxicity(ADCC)

Antibody (IgG)

Target cell

IgG coated target cells are killed by cells
that bear Fc receptors for IgG, such as natural killer cell

c) Antibody –mediated cellular dysfunction

Acetylcholine
(in motor end plate in myasthenia gravis)

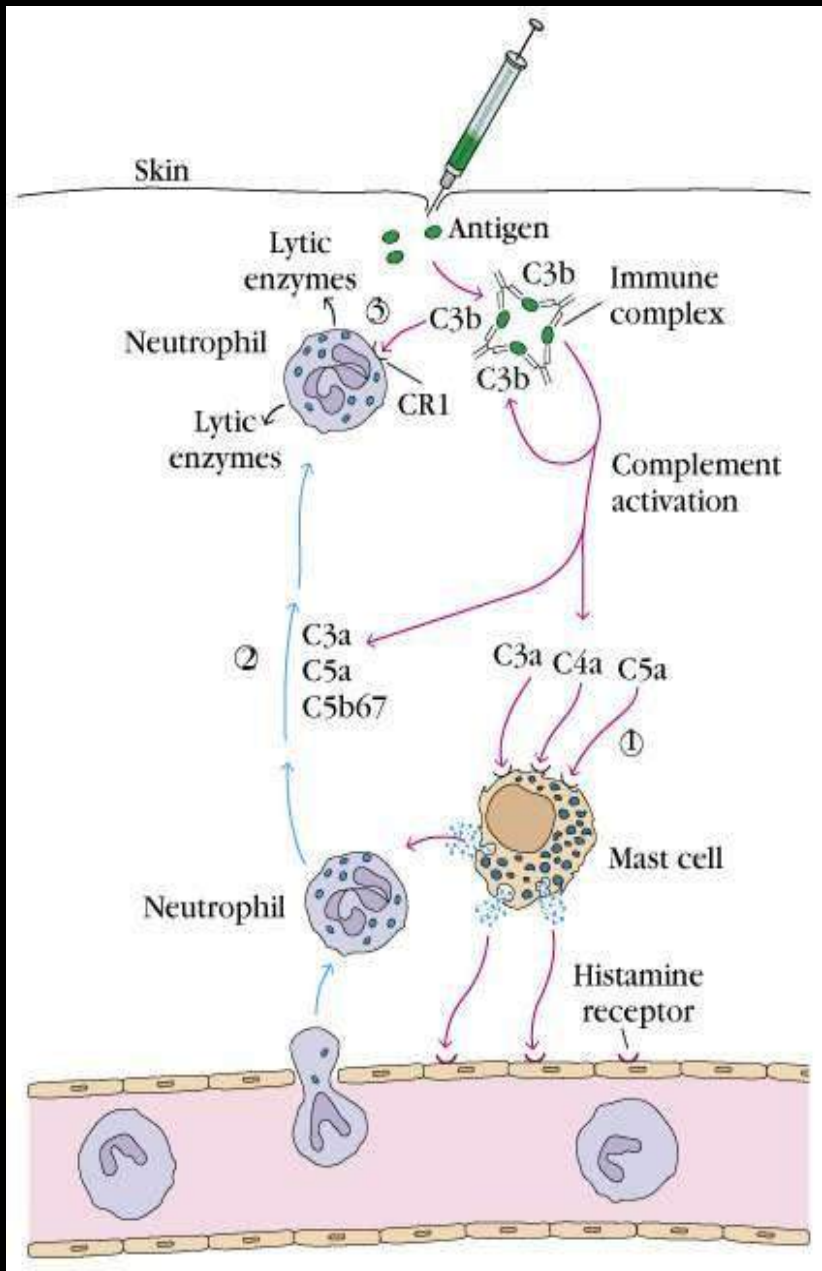
Antibody against acetylcholine receptor

Type III-Immune Complex-Mediated Hypersensitivity

- It is mediated by the deposition of Ag-Ab (immune) complex, followed by complement activation & accumulation of neutrophils.
- 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
  - Systemic reaction when formed in the blood reaction and are deposited in many organs

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
   - Takes few hours, reaches peak 4-10 hours after injection
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 this reaction.
- 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, initiating inflammatory reaction in various sites throughout the body.
- 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

- Also called as cell mediated hypersensitivity or delayed type hypersensitivity
- A hypersensitive response mediated by sensitized T- cells, which release various cytokines
- Generally occurs 2-3 days after T-cells interact with antigen
- An important part of host defense against intracellular parasites and bacteria
- It is of two basic types:
  - Delayed type hypersensitivity, initiated by CD4+T-cell
  - Direct cell cytotoxicity, mediated by CD8+ Cytotoxic T-cell

Delayed type Hypersensitivity

First exposure to Ag

↓

Ag picked up by Ag presenting cell

↓

Presented to CD4+ T-cell

↓

Leads to sensitized CD4+cell of Th1 type

↓

Second exposure intradermal injection

↓

Memory cell(CD4+T-cell)

↓

Activated CD$+T-cell

↓

Secrete Th1 cytokines

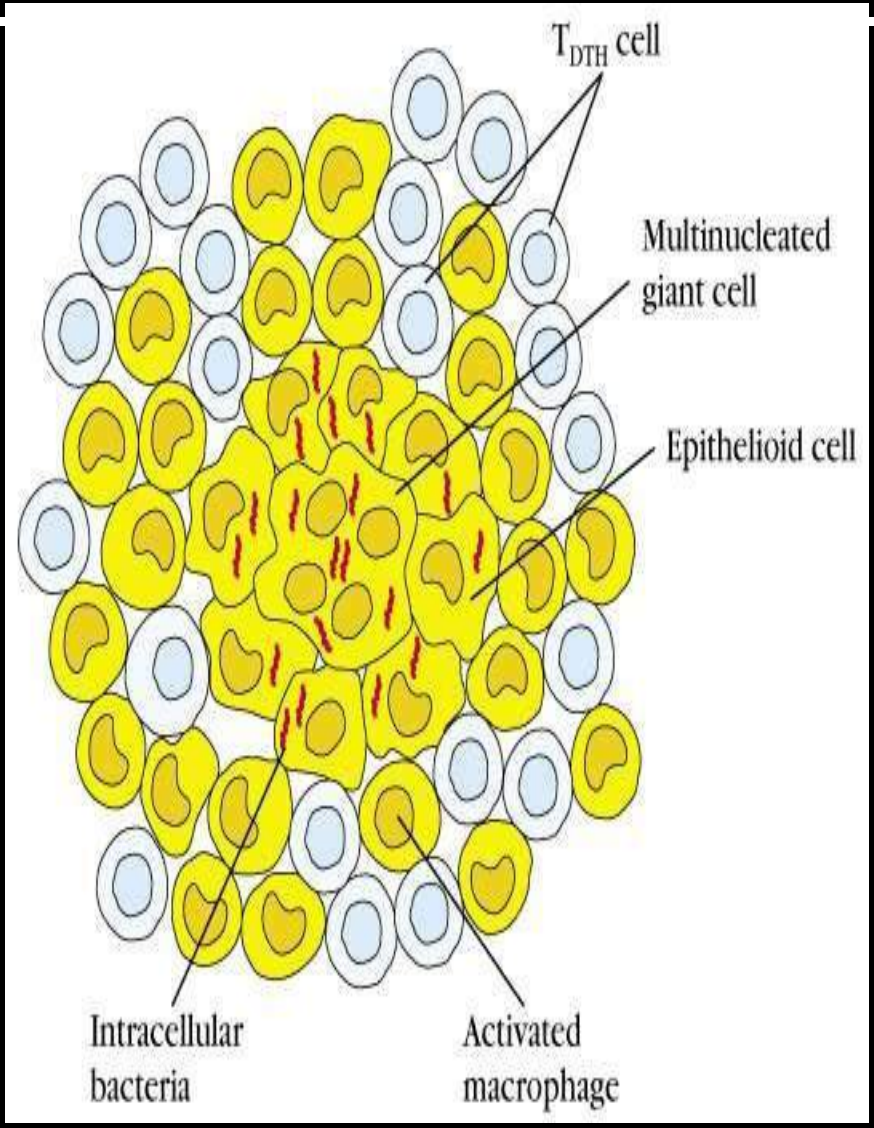
↓

Causes delayed type hypersensitivity

What happens if the DTH response is prolonged?

A granuloma develops…

- Continuous activation of macrophages induces the macrophages to adhere closely to one another, assuming an epithelioid shape and sometimes fusing together to form giant, multinucleated cells.



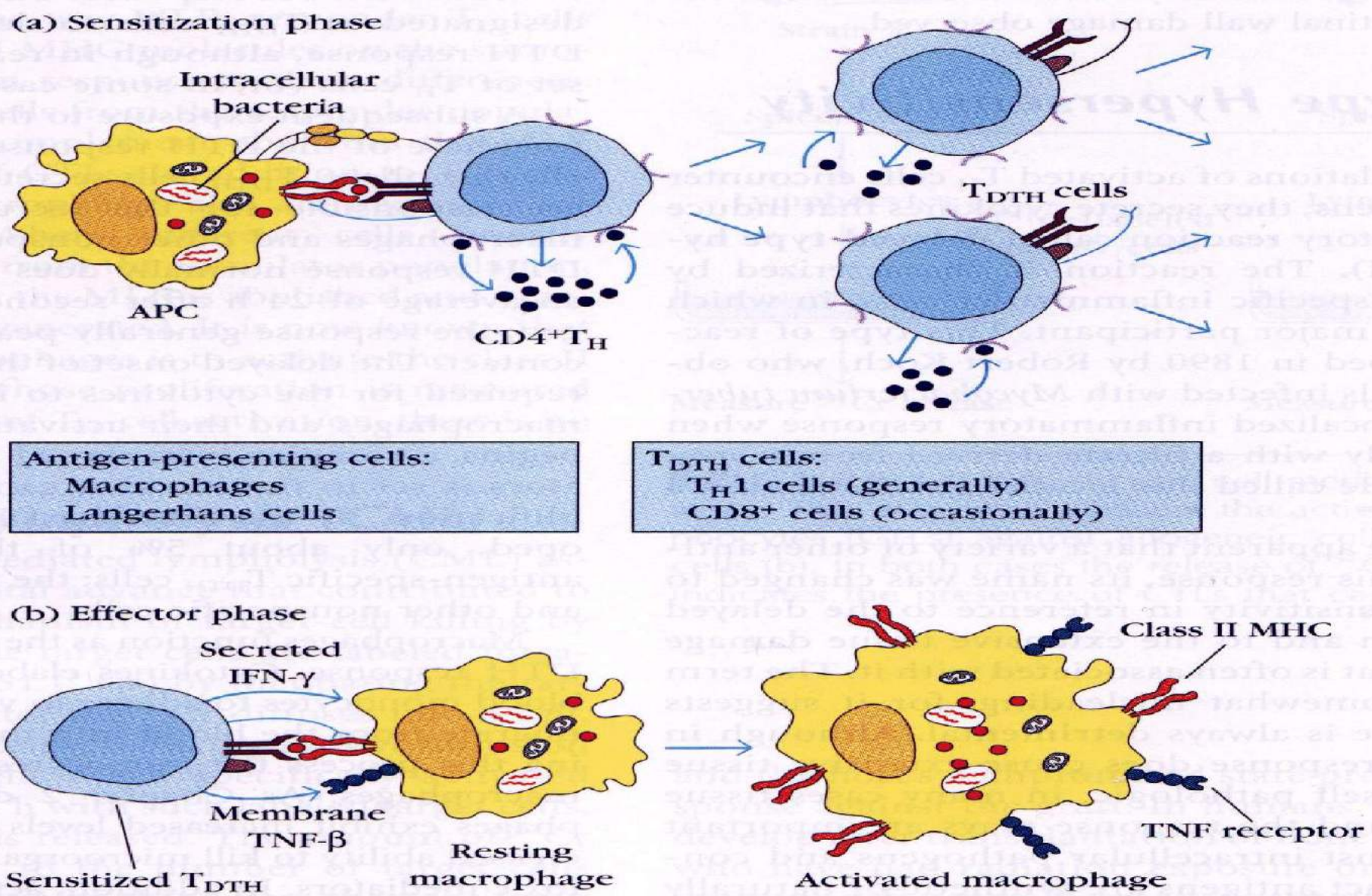
Phases of the DTH Response

- Consists of two phases:
  - Sensitization phase
  - Effecter Phase

1. 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

2. Effecter phase:

- occurs upon subsequent exposure to the Ag
- What happens during this phase?
  - ✓ T_{DTH} cells secrete a variety of cytokines and chemokines, which recruit and activate macrophages
  - ✓ Macrophage activation promotes phagocytic activity and increased concentration of lytic enzymes for more effective killing
  - ✓ Activated macrophages are also more effective in presenting Ag and function as the primary effector cell.


(a) Sensitization phase
Intracellular bacteria
APC
CD4+TH
TDTH cells
Antigen-presenting cells:
Macrophages
Langerhans cells
TDTH cells:
TH1 cells (generally)
CD8+ cells (occasionally)
(b) Effector phase
Secreted IFN-γ
Membrane TNF-β
Sensitized TDTH
Resting macrophage
Class II MHC
TNF receptor
Activated macrophage
TDTH secretions:
Cytokines: IFN-γ, TNF-β, IL-2, IL-3, GM-CSF
Chemokines: IL-8, MCAF, MIF
Effects of macrophage activation:
↑ Class II MHC molecules
↑ TNF receptors
↑ Oxygen radicals
↑ Nitric oxide

Protective Role of DTH Response

- Defence against intracellular pathogens, transplant rejection, tumour immunity.
- Cells harboring intracellular pathogens are rapidly destroyed by lytic enzymes released by activated macrophages

Detrimental Effects of DTH Response

- The initial response of the DTH is nonspecific and often results in significant damage to healthy tissue
- In some cases, a DTH response can cause such extensive tissue damage that the response itself is pathogenic
- Example: *Mycobacterium tuberculosis* – an accumulation of activated macrophages whose lysosomal enzymes destroy healthy lung tissue
- In this case, tissue damage far outweighs any beneficial effects.

How Important is the DTH Response?

- The AIDS virus illustrates the **vitally** important role of the DTH response in protecting against various intracellular pathogens.
- The disease cause severe depletion of CD4+ T cells, which results in a loss of the DTH response.
- AIDS patients develop life-threatening infections from intracellular pathogens that normally would not occur in individuals with intact DTH responses.

References:

- Textbook of Veterinary General Pathology by J. L. Vegad
- Textbook of Veterinary Pathology by Ganti A. Shastri


Thank You!