Immunopathology

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Immunopathology

Disorder of Immune system:

1. Hypersensitivity reaction
2. Autoimmunity
3. Immunodeficiency states
4. Amyloidosis

Immunology

Definition:

The branch of medical science that deals with immunity

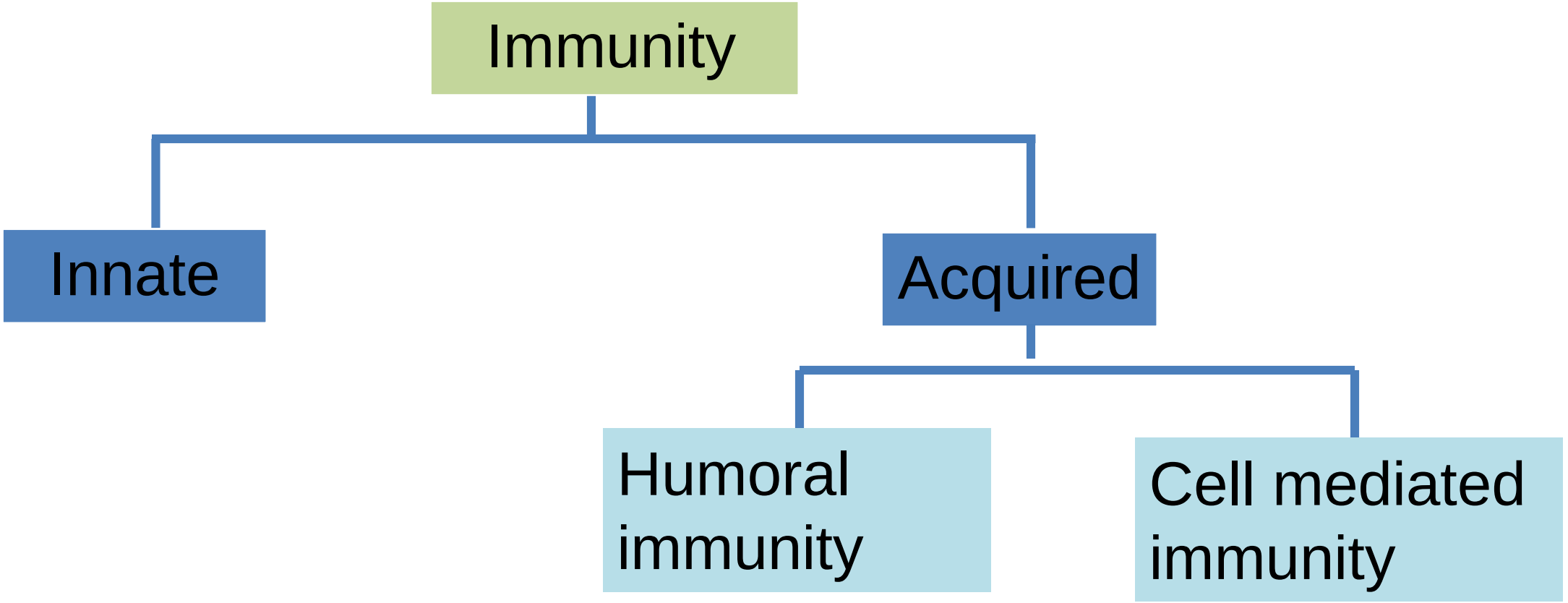
Immunity:

Protection from infectious pathogen.

Innate immunity *is* the resistance of the body against antigen that exists prior to exposure to the antigen (i.e. it is inborn). It is non-specific.

Acquired immunity is the resistance of the body against antigen that occurs after exposure to an antigen. It is specific.

Classification of immunity



Innate Immunity:

It acts as a first line and 2nd line defense

Components:

Anatomical Barrier: Skin, Mucous membrane GIT and Respiratory tract.

Mechanical: Cilia, Sneezing, Cough

Biological: Complement system

Blood cells- Phagocytosis (by macrophage, Neutrophil)

Natural killer cell. mast cell, C reactive protein.

Acquired Immunity:

- 3rd line of defense
- It develops throughout life
- Needs exposure to foreign substance
- Efficient and selective
- Has memory

Active immunity- It is that type of adaptive immunity, where resistance is induced after contact with foreign antigens, eg. Microbes.

Passive immunity- It is that type of adaptive immunity, where the preformed antibody is introduced into a host to produce specific immunity.

Difference between Active and Passive Immunity

Active	Passive
Active participation of host	Not so
Develops after a considerable latent period	Starts immediately
Long lasting	Short lasting
No risk of hypersensitivity	Risk of hypersensitivity

Lymphocytes

Lymphocytes constitute 20-40% cells of WBC of blood

Can be divided in to three major type

- B-lymphocytes
- T-lymphocytes
- Natural killer cells

Cells of immune system

Immunity	Cells	Secreted molecules
Innate	Neutrophils Eosinophils Macrophages NK cells	Complement Cytokines
Acquired	B lymphocytes T lymphocytes All the cells of innate immunity	Antibodies Complement Cytokines

List key facts about T lymphocytes

- T lymphocytes are typically found in the following locations:
  - Paracortical areas of lymph nodes
  - Periarteriolar sheaths of the spleen
  - Thymus
  - Bone marrow and peripheral blood

- T lymphocytes account for 60% to 70% of circulating lymphocytes in the blood.

There is functional diversity of T-cell populations:

CD4+ helper/inducer cells constitute approximately 60% of mature T lymphocytes, and

CD8+ suppressor/cytotoxic cells constitute approximately 30% of mature T lymphocytes.

Furthermore, CD4+ cells differ in their ability to secrete cytokines:

TH1 subset secretes IL-2 and IFN-γ,

TH2 secretes IL-4 and IL-5

List key features of B lymphocytes:

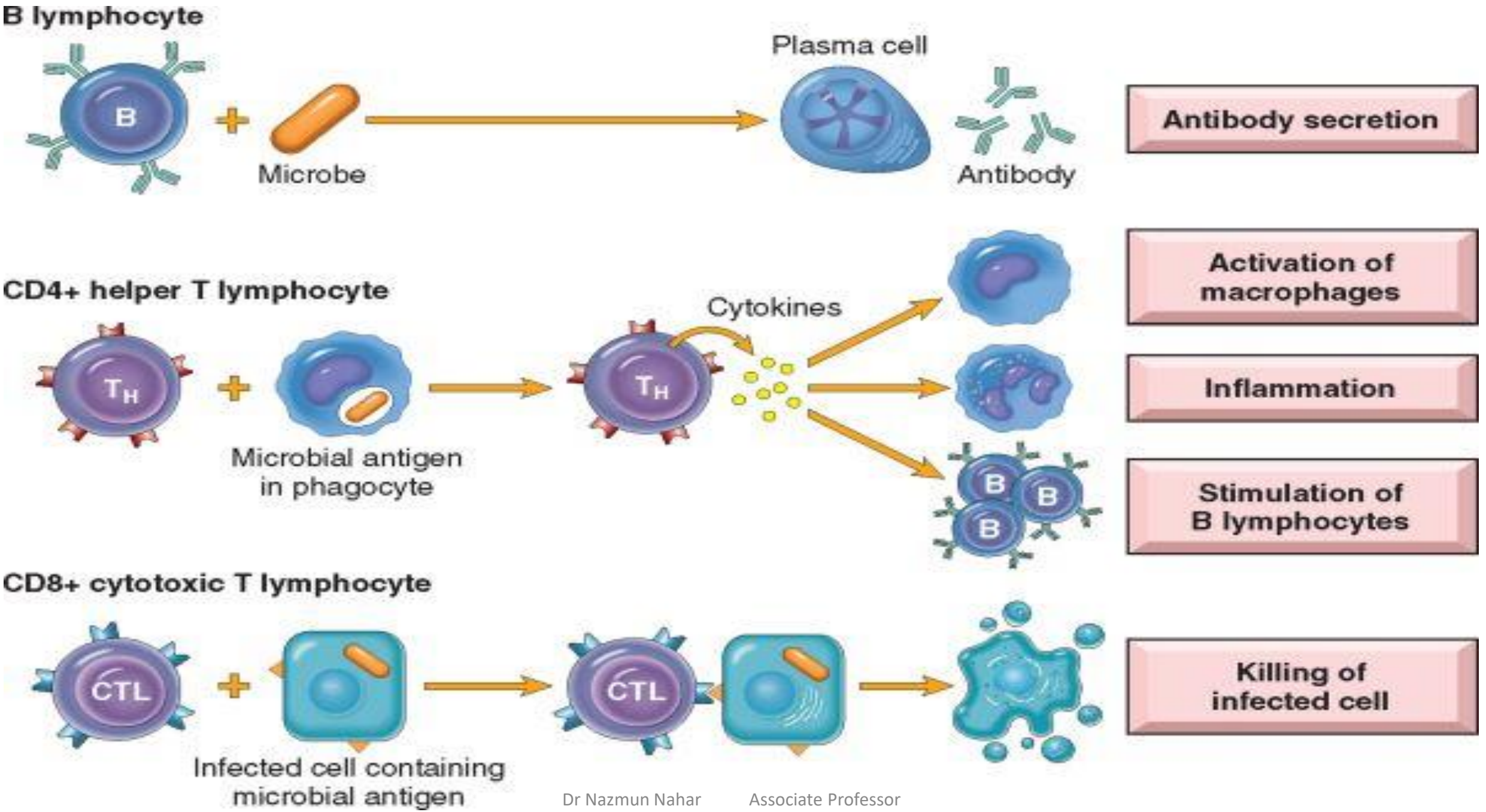
- B lymphocytes are typically found in the following locations:
  - Superficial cortex of lymph nodes
  - Germinal centers and mantle zone of stimulated lymph nodes
  - Follicles of the white pulp of the spleen
  - Mucosa-associated lymphoid system (MALT) in intestines and the respiratory tract
  - Bone marrow and peripheral blood

B lymphocytes contd.

- B lymphocytes constitute 10% to 20% of circulating lymphocytes in the blood.
- On antigenic stimulation, B cells form plasma cells that secrete antigen-specific immunoglobulins.

List key features of natural killer (NK) cells.

- NK cells are large granular lymphocytes
- constitute approximately 10% to 15% of circulating lymphocytes.
- They can kill a variety of virus-infected cells and some tumor cells without prior sensitization (i.e., “natural” killer).


B lymphocyte
B
Microbe
Plasma cell
Antibody
Antibody secretion
CD4+ helper T lymphocyte
TH
Microbial antigen
in phagocyte
Cytokines
TH
Activation of
macrophages
Inflammation
B
B
B
Stimulation of
B lymphocytes
CD8+ cytotoxic T lymphocyte
CTL
Infected cell containing
microbial antigen
CTL
Killing of
infected cell

IMMUNOLOGIC TOIERANCE

It is the phenomenon of unresponsiveness to an antigen induced by exposure of lymphocytes to that antigen.

Two types

1. Central tolerance
2. Peripheral tolerance

IMMUNOLOGIC TOIERANCE Contd.

Central tolerance

- Immature self reactive T and B lymphocyte recognize self antigens during their maturation, thymus for T cell and bone marrow for B cell.

Peripheral tolerance

Mature lymphocytes that recognize self antigen in peripheral tissues become functionally inactive or suppressed by regulatory T-lymphocytes or die by apoptosis

IMMUNOLOGIC TOIERANCE Contd.

Mechanisms of Peripheral tolerance :

1. **Anergy :** lymphocytes that recognize self antigens may be rendered functionally unresponsive ,a phenomenon called anergy.
2. **Suppression by regulatory T cell :** Prevent immune reactions against self antigen.
3. **Deletion by apoptosis.**

AUTOIMMUNITY

A combination of the inheritance of susceptibility genes, which may contribute to the breakdown of self tolerance, and environmental triggers, such as infection and tissue damage, which promote the activation self reactive lymphocytes.

Pathogenesis of Autoimmunity:

1. **Susceptibility genes**
   Interfere →Self tolerance .

2. **Environmental triggers .** e.g,; infection, tissue injury, inflammation.

   → Promote self reactive activation of lymphocyte → enter into tissue → causes tissue damage.

Autoimmune Disease

- Rheumatoid arthritis
- Type 1 diabetes
- Multiple sclerosis
- Systemic lupus erythematous
- Ankylosing spondylitis
- Celiac diseases

Autoimmune Disease Contd.

- Autoimmune hemolytic anaemia
- Autoimmune thrombocytopenia
- Autoimmune atrophic gastritis of pernicious
- anaemia.
- Myasthenia gravis
- Graves disease

Antibody:

Antibodies are plasma proteins which are produced in response to antigens with which it reacts specifically.

Immunoglobulin

Structurally similar to antibody but may or may not be endowed with antibody activity.

Hypersensitivity:

In appropriate or excessive immune response to an antigenic stimulus in a pre-sensitized host leading to Tissue damage

Adverse clinical reaction to antigen.

Classification: Coombs and Gel classification

a. Type I - Anaphylactic hypersensitivity
b. Type II - Cyto-toxic hypersensitivity
c. Type III - Immune complex mediated hypersensitivity
d. Type IV - Delayed or cell mediated hypersensitivity

Type-I or Immediate hypersensitivity :

Type-I hypersensitivity is a rapid immunologic reaction occurring in a previously sensitized individual that is triggered by the binding of an antigen to IgE antibody on the surface of mast cells.

In immediate hypersensitivity the injury is caused by

TH2 cells,
IgE antibodies, and
mast cells and other leukocytes.

Table- Mechanisms of Hypersensitivity Reactions

Type	Immune Mechanisms	Histopathologic Lesions	Prototypical Disorders
Immediate (type I) hypersensitivity	Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; later recruitment of inflammatory cells	Vascular dilation, edema, smooth muscle contraction, mucus production, tissue injury, inflammation	Anaphylaxis; allergies; bronchial asthma (atopic forms)

Table- Mechanisms of Hypersensitivity Reactions contd

Type	Immune Mechanisms	Histopathologic Lesions	Prototypical Disorders
Antibody-mediated (type II) hypersensitivity	Production of IgG, IgM → binds to antigen on target cell or tissue → phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes	Phagocytosis and lysis of cells; inflammation; in some diseases, functional derangements without cell or tissue injury	Autoimmune hemolytic anemia; Goodpasture syndrome

Table- Mechanisms of Hypersensitivity Reactions contd

Type	Immune Mechanisms	Histopathologic Lesions	Prototypical Disorders
Immune complex–mediated (type III) hypersensitivity	Deposition of antigen-antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules	Inflammation, necrotizing vasculitis (fibrinoid necrosis)	Systemic lupus erythematosus some forms of glomerulonephritis; serum sickness; Arthus reaction

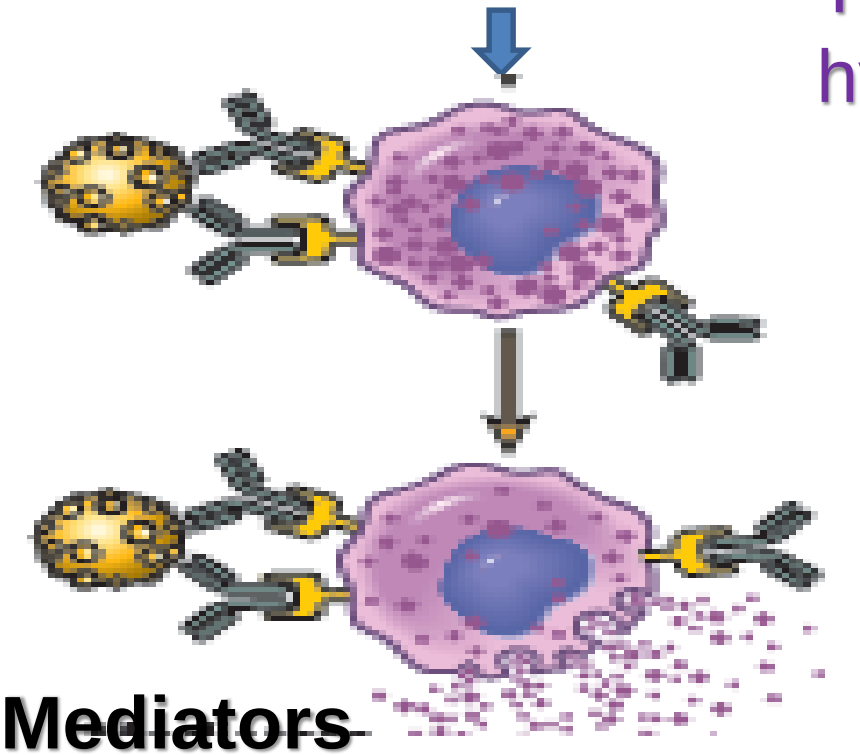
Table- Mechanisms of Hypersensitivity Reactions contd

Type	Immune Mechanisms	Histopathologic Lesions	Prototypical Disorders
Cell-mediated (type IV) hypersensitivity	Activated T lymphocytes → (1) release of cytokines, inflammation and macrophage activation; (2) T cell–mediated cytotoxicity	Perivascular cellular infiltrates; edema; granuloma formation; cell destruction	Contact dermatitis; multiple sclerosis; type 1 diabetes; tuberculosis

Type I - hypersensitivity

Repeat exposure to allergen

Activation of mast cell; release of mediators



Mediators

Vasoactive amines, lipid mediators

Cytokines

Immediate hypersensitivity reaction

Late phase reaction

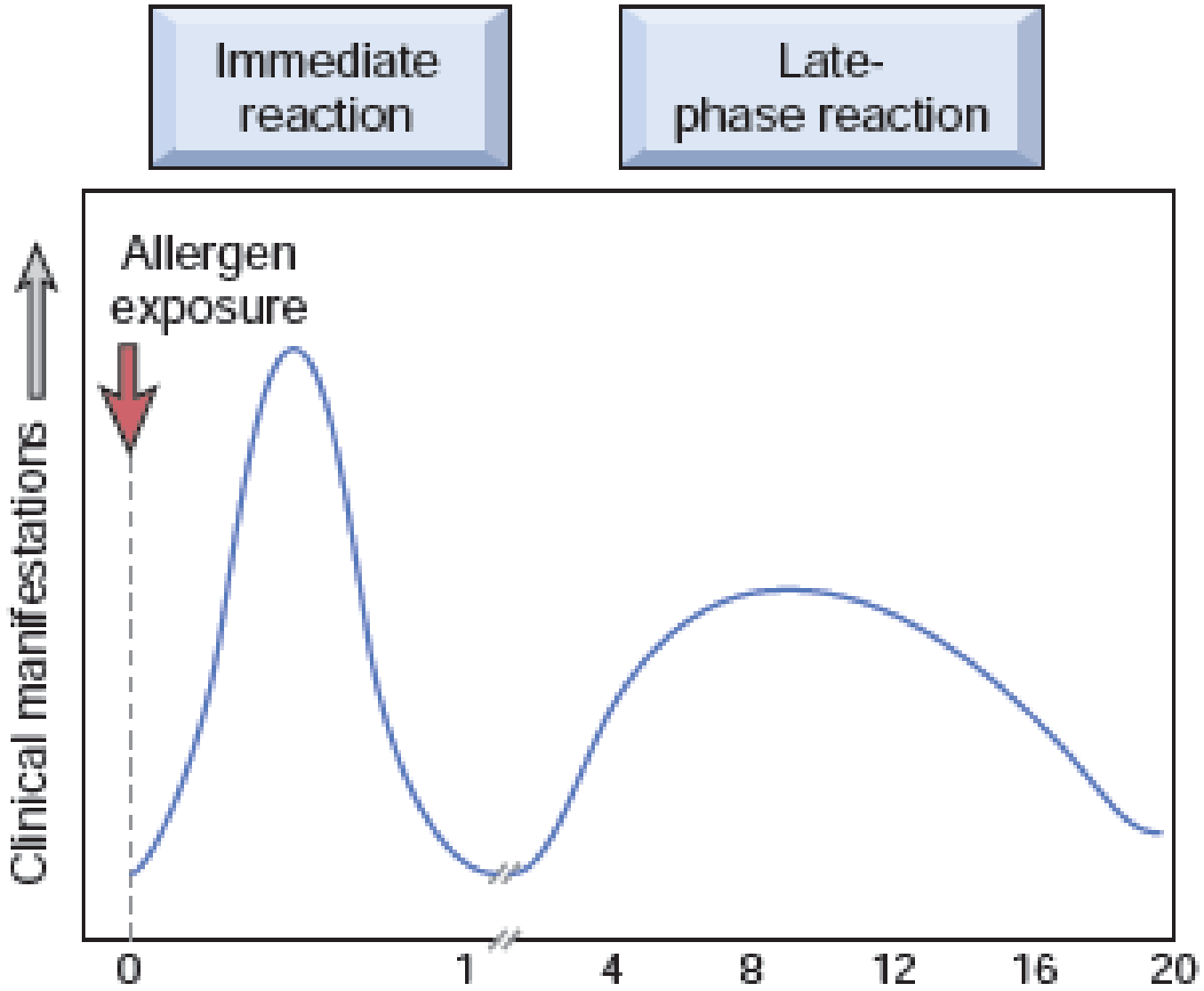
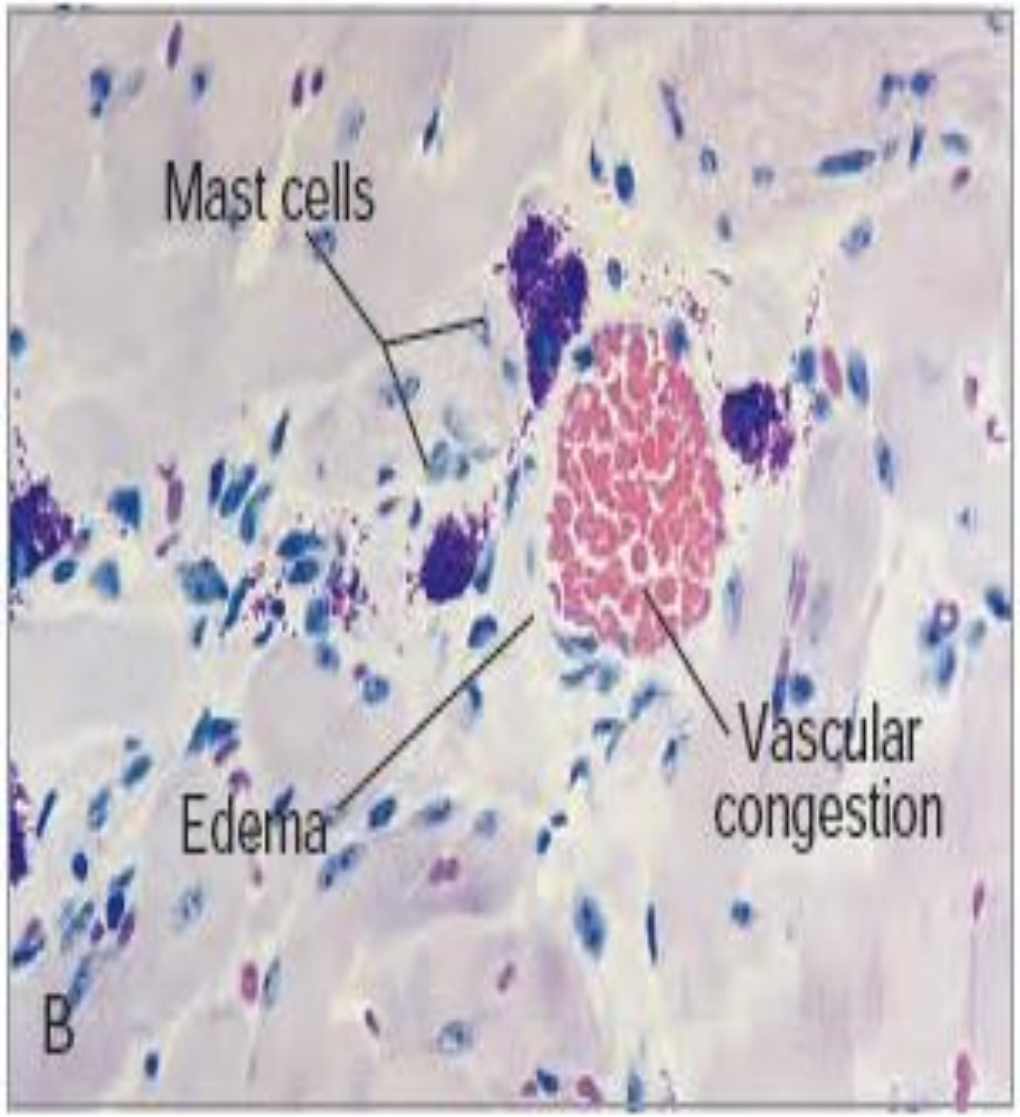
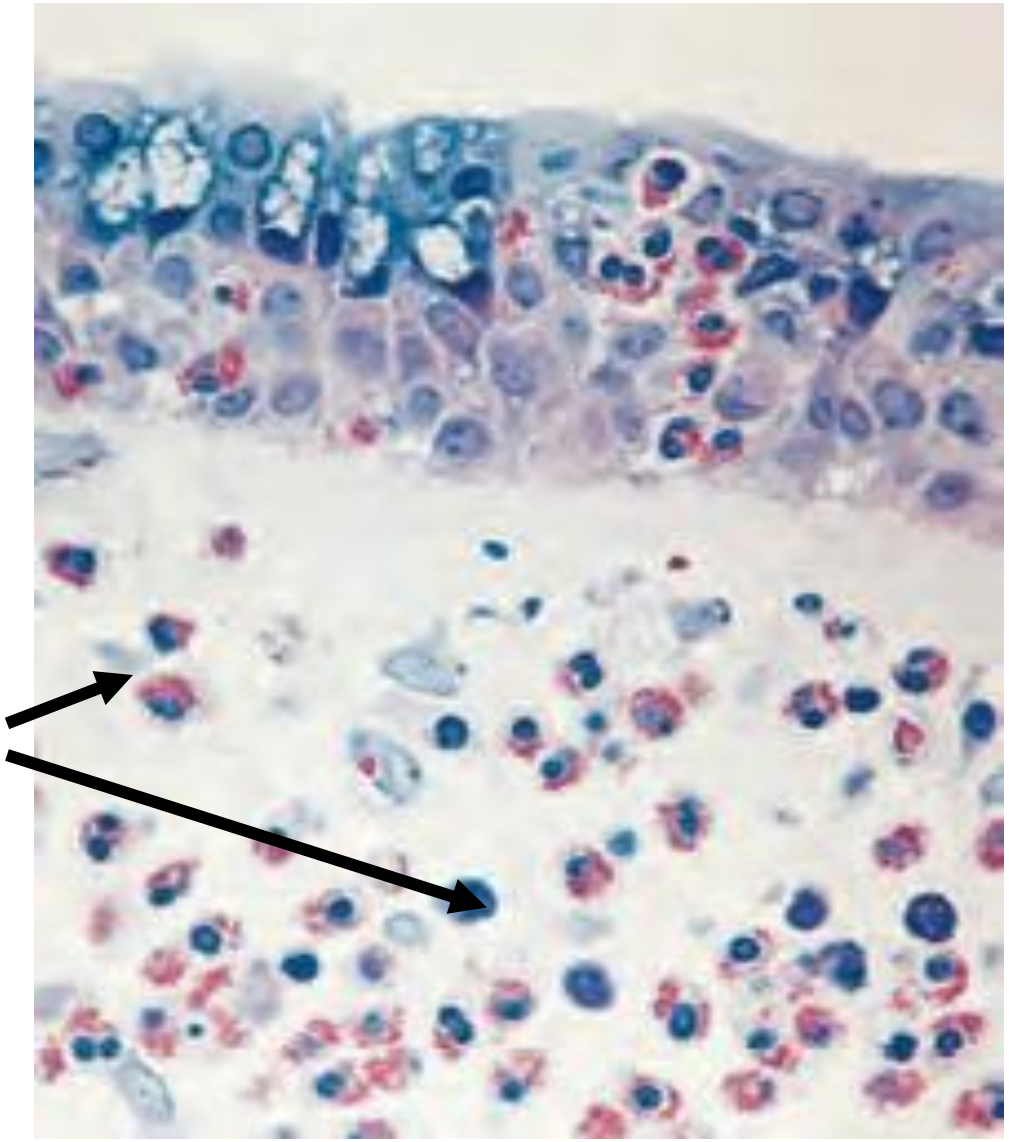


Fig- Phases of immediate hypersensitivity reactions

Immediate reaction is characterized by vasodilation, vascular leakage, and depending on the location, smooth muscle spasm or glandular secretions.



Eosinophil



Effects of Type I – hypersensitivity:

Systemic reaction (e.g., by a bee sting),
but can also follow antigen ingestion
(e.g., peanut allergens).

Local reactions –
cutaneous rash or blisters (skin allergy, hives),
allergic rhinitis
and conjunctivitis
bronchial asthma, or
allergic gastroenteritis (food allergy).

Type II hypersensitivity / Cyto-toxic hypersensitivity / Antibody dependent cell mediated cytotoxicity.

Antibodies that react with antigens present on cell surfaces or in the extracellular matrix cause disease by destroying these cells, triggering inflammation, or interfering with normal functions.

Mechanism-

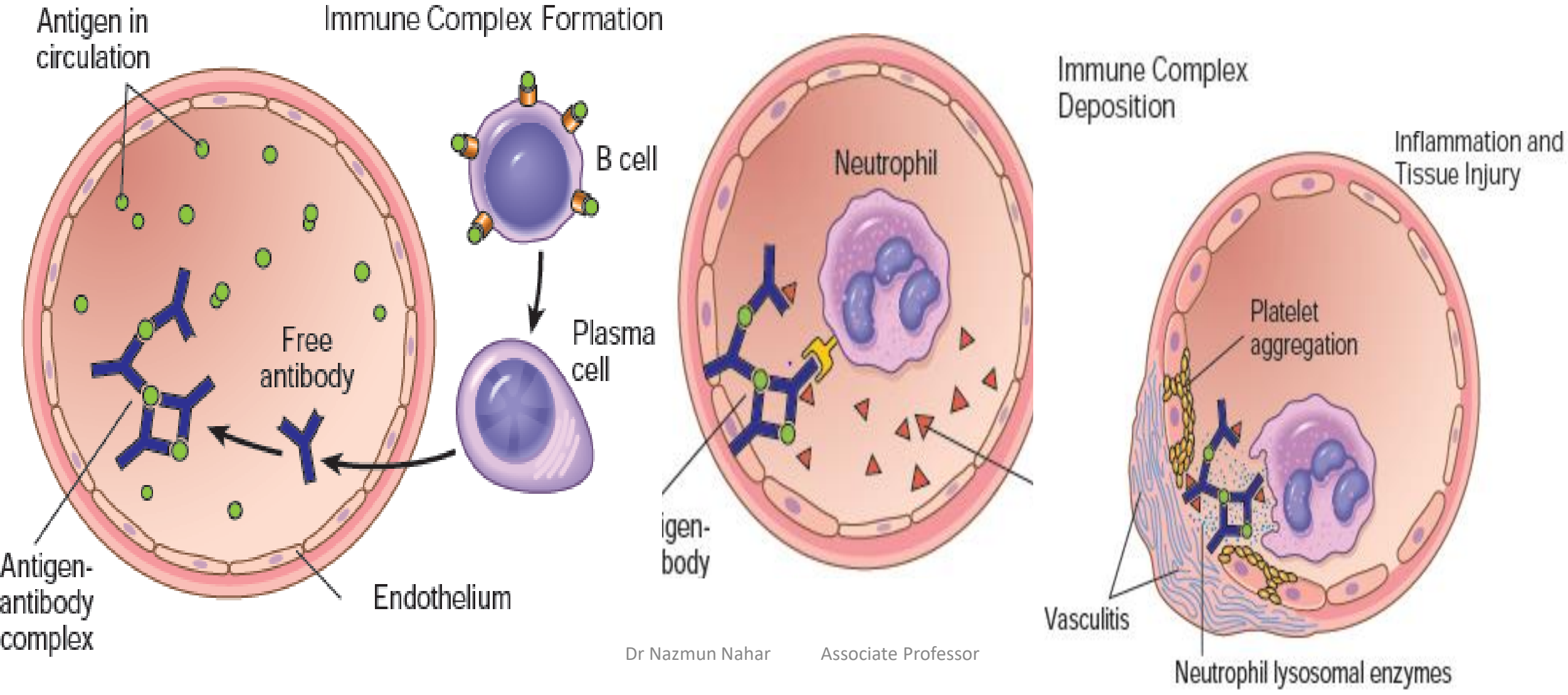
- Complement mediated cell lysis

e.g transfusion reactions,
erythroblastosis fetalis
autoimmune hemolytic anemia,
agranulocytosis, and
thrombocytopenia,

Example of type II hypersensitivity

- Mismatched ABO blood group transfusion
- Rh incompatibility reaction
- Auto-immune hemolytic anaemia
- Drug induced reaction
- Myasthenia gravis
- Graves disease (hyperthyroidism)

Type III- Immune complex mediated hypersensitivity



- Type III hypersensitivity reactions can be generalized.

- When large amount of antigen enter the bloodstream and bind to antibody
- Circulating immune complex is formed.

- Arthus reaction- When immune complex is formed in excess of antibody

  Example- Farmers Lung

- Serum sickness- When immune complex is formed in excess of antigen

  Example- During treatment of tetanus with ATS

The pathogenesis of immune complex disease can be divided into three phases.

1. **Formation of immune (Antigen- antibody) complexes.**
2. **Deposition of immune complexes.**
3. **Inflammation and tissue injury.**

Sites of deposition:

Renal glomeruli, small blood vessels, Joints, Skin, Heart, Serosal surface

Example of type III hypersensitivity:

A. Autoimmune disease
    1. SLE
    2. Rheumatoid Arthritis
B. Drug reaction
    1. Allergies to penicillin
C. Infectious disease
    1. Post streptococcal glomerulonephritis
    2. Meningitis
    3. Hepatitis
    4. Malaria

Type IV or delayed or cell mediated hypersensitivity

The cell-mediated type of hypersensitivity is caused by

inflammation resulting from cytokines produced by CD4+ T cells and cell killing by CD8+ T cells

Tuberculin type hypersensitivity-

which is produced by the intracutaneous injection of purified protein derivative (PPD, also called tuberculin), a protein-containing antigen of the tubercle bacillus. In a previously sensitized individual, reddening and induration of the site appear in 8 to 12 hours, reach a peak in 24 to 72 hours, and thereafter slowly subside. A positive skin test indicates that the person has been infected.

If the DTH response is absent or impaired, however, T-lymphocytes are unable to localise the invading micro-organism and patients develop invasive, aggressive disseminated disease, such as acute miliary tuberculosis

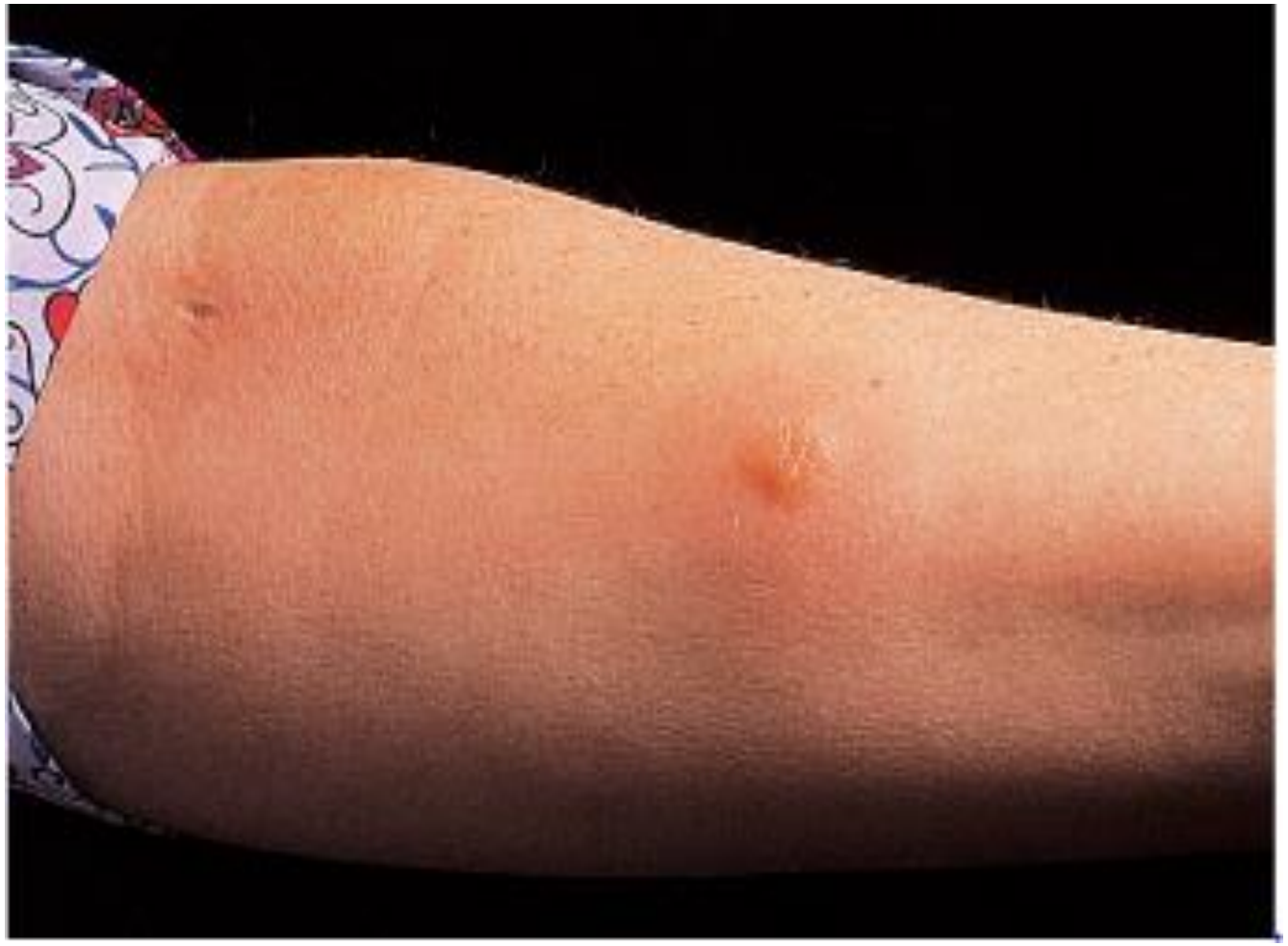


Fig- A positive Mantoux test in a person previously immunised with BCG.

Type IV hypersensitivity contd.

Main immune cells involved	Pathologic feature or clinical feature
CD4 (helper) T cells and macrophage	Granuloma
CD8 (cytotoxic) T cells	Pruritis, vesicular rash (contact dermatitis)

How are granulomas formed?

Granulomas form in response to bacteria and fungi that cannot be readily eliminated (e.g., Mycobacterium tuberculosis) or substances that initiate a cell mediated hypersensitivity.

Macrophages that arrive at the site of injury ingest the noxious material and become activated.

Activated macrophages secrete chemokines to recruit new macrophages and lymphocytes.

How are granulomas formed contd.

With sustained activation, macrophages often undergo a morphologic transformation into epithelioid cells.

A microscopic aggregation of epithelioid cells, usually surrounded by a collar of lymphocytes, is referred to as a granuloma. This pattern of inflammation, called granulomatous inflammation

Under the influence of IFN-γ, some epithelioid cells fuse into multinucleated giant cells.

Morphology of Tuberculous granuloma:

Grossly, granular, cheesy appearance and is therefore called caseous necrosis.

Microscopically, an area of central necrosis surrounded by multiple Langhans-type giant cells, epithelioid cells, and lymphocytes, rim of fibroblasts and connective tissue.

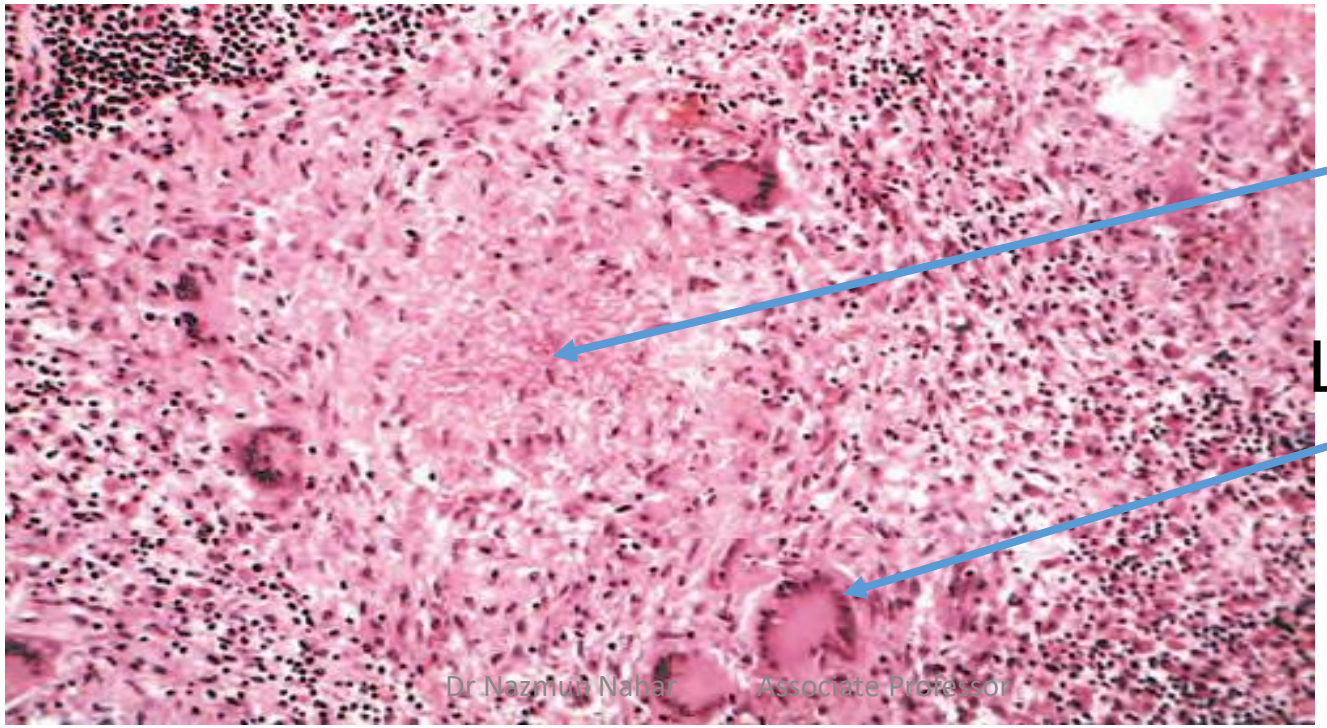


Fig- Tuberculous granuloma

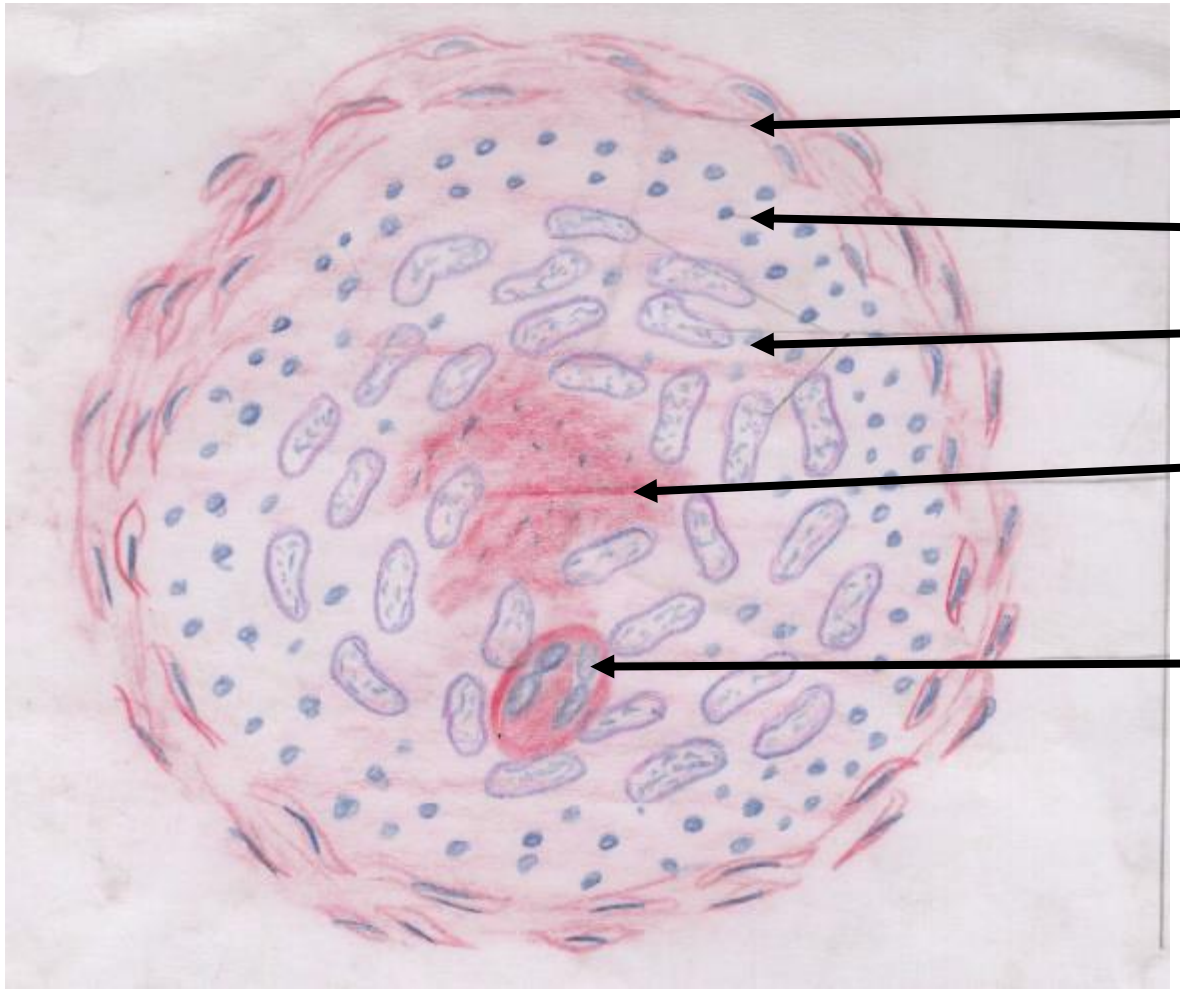
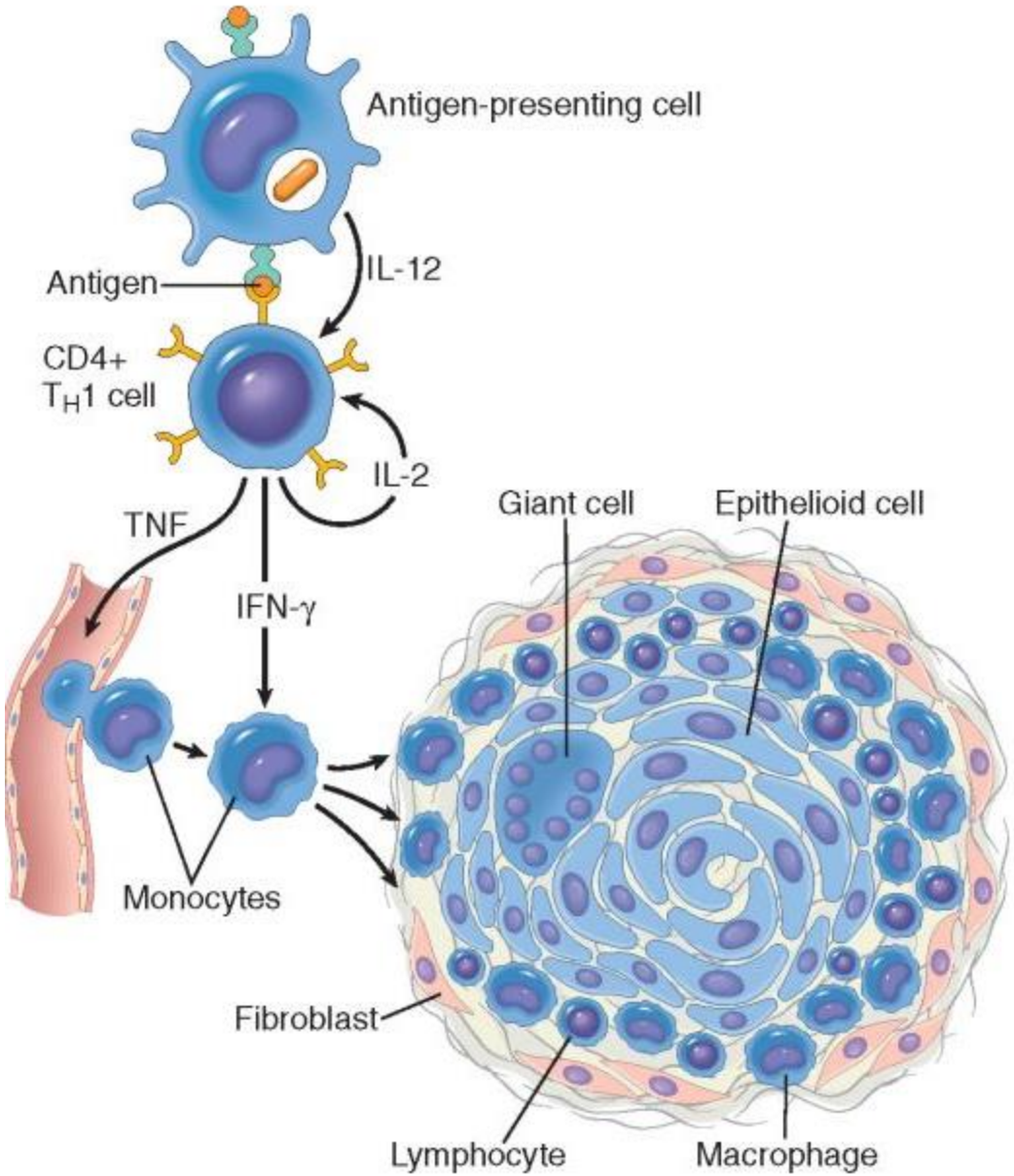


Fig: Tubercular Granuloma


Antigen-presenting cell
IL-12
Antigen
CD4+
T_H1 cell
IL-2
TNF
IFN-γ
Giant cell
Epithelioid cell
Monocytes
Fibroblast
Lymphocyte
Macrophage

The Fate of a granuloma is

1. The caseous material may undergo liquefaction and extend into surrounding soft tissues, discharging contents on the surface. The **cold abscess.**

2. In tuberculosis of tissues like bones, joints, lymph nodes and epididymis, sinuses are formed and the sinus tracts are lined by tuberculous granulation tissue.

The Fate of a granuloma contd.

3. The adjacent granulomas may coalesce together enlarging the lesion which is surrounded by progressive fibrosis.

4. In the granuloma enclosed by fibrous tissue, calcium salts may get deposited in the caseous material. (Dystrophic calcification)

Example of type IV hypersensitivity:

1. Tuberculin test
2. Contact dermatitis

What is amyloid?

- Amyloid is a proteinaceous substance deposited between cells in various tissues and organs in a variety of clinical settings.

- Amorphous, eosinophilic, hyaline extracellular substance is seen under the microscope.
- **Congo red staining is typical.**

What is amyloidosis?

Amyloidosis is a group of diseases characterized by a deposition of amyloid in various organs.

The two main types

Primary amyloidosis- due to excessive production of plasma cell derived immunoglobulin light chain.

Secondary amyloidosis- are sequelae of extensive prolonged inflammatory activity.

Immunodeficiency

- **Failure or deficiency of immune system.**
- **Types of Immunodeficiency:**
  1. Primary (or congenital)
     - Inherited genetic defects in immune cell development or function, or inherited deficiency in a particular immune molecule.
  2. Secondary (or acquired)
     - A loss of previously functional immunity due to secondary causes.

Causes of Primary (or congenital) immunodeficiency

1. Severe combined immunodeficiency diseases

(Deficiency of T cells, B cells Igs)

- Thymic alymphoplasia
- Agammaglobulinaemia
- Wischott-Aldrich syndrome

2. T cells defect

- Digeorge's syndrome

Causes of Primary (or congenital) immunodeficiency Contd.

3. B cells defect – antibody deficiency disease

- Autosomal recessive agammaglobulinaemia
- IgA deficiency

4. Complement deficiency syndrome

5. Disorder of phagocytosis

- MPO deficiency
- Chediak-Higashi syndrome

Causes of secondary (or acquired) immunodeficiency

1. Cancer (immunoproliferative disease)
2. Malnutrition
3. Splenectomy
4. Immunosuppressive therapies
5. Stress/emotions
6. Aging (thymic atrophy)
7. Infection

Acquired Immunodeficiency Syndrome (AIDS)

- Fetal disease caused by the retrovirus human immunodeficiency virus (HIV-1 & 2)
- Basic lesion is suppression of CD_4+ helper T lymphocytes by HIV.
- Mode of transmission
  - Sexual contact
  - Blood transmission
  - Intravenous drug abusers
  - Contaminated needles & syringes
  - Transplacental spread

SAQ of Immunological disorders

1. What is anaphylactic reaction?
2. Give various examples of anaphylactic reactions.
3. Write short note on:
    - MHC.
    - Autoimmune disease.
4. A 30 years old lady presented with diffuse enlargement of thyroid gland. Exophthalmos & high serum free T_3 & T_4 level .
    - What is your diagnosis?
    - What immunological mechanisms contribute to its development?

Thank You