University of Basrah, Medical College – Microbiology Department

Microbiology/ 3rd Year M.B.CH.B. Students

Part V: Basic & Clinical Immunology (17 hours)

Lecture 12

Duration: 1 hour

Hypersensitivity (Part II)

Assist. Prof. Dr. Nibras Saleam Al-Ammar

Reference: Roitt's Essential Immunology 13th Edition, Part 2, Chapter 14, Page 405.

For more detailed instruction, any question, cases need help please post to the group of session.

Key definitions

Frustrated phagocytosis: occurs when phagocytic cells exposed to an opsonized surface & spread as if trying to engulf it, allowing for the observation of phagocytic spreading & the biochemical events that directly precede it.

Choroid plexus: network of capillaries in the walls of the ventricles in the brain.

Farmer's lung: hypersensitivity pneumonitis, immunologically mediated inflammatory disease of the lung involving the terminal airways. It is associated with intense or repeated exposure to inhaled biologic dusts.

Elephantiasis: also known as lymphatic filariasis. Living *Wuchereria bancrofti* are relatively harmless, but the dead parasite found in lymphatic vessels initiates an inflammatory reaction though to be responsible for the obstruction of lymph flow.

Tuberculin: an extract of *Mycobacterium tuberculosis* bacteria.

Epithelioid cell: macrophage that differentiate to morphologically resembles epithelial cells.

Giant cell: large number of macrophages fuse to form multinucleated macrophages referred to as giant cells.

Chronic granuloma: combination of cell types (epithelioid cells, giant cells) with proliferating lymphocytes &fibroblasts associated with areas of fibrosis & necrosis.

Non-immunological granuloma: granuloma arises from persistence of indigestible Ag-Ab complexes or inorganic materials within macrophages. It can be distinguished by the absence of lymphocytes.

TSH: thyroid-stimulating hormone.

Receptor agonist: binding to the receptor and activating it to produce its biological response.

In Graves' disease, auto-Ab bind to TSH receptor leading to excessive stimulation of the cell to produce thyroid hormone.

Learning objectives (LO.s)

Type III hypersensitivity-immune complex-mediated	LO.1
Mechanisms leading to acute inflammatory reactions	LO.2
Factors influence the tendency of immune complexes to develop disease	LO.3
The important role of RBCs in clearance of immune complexes	LO.4
Locally formed immune complexes	LO.5
Circulating immune complexes (systemic)	LO.6
Example of immune complex Hypersensitivity caused by viral infection	LO.7
Type IV hypersensitivity: Cell-mediated (delayed-type)	LO.8
Hypersensitivity Type V: Stimulatory hypersensitivity	LO.9
Innate hypersensitivity reactions	LO.10

LO.1

Type III hypersensitivity-immune complex-mediated

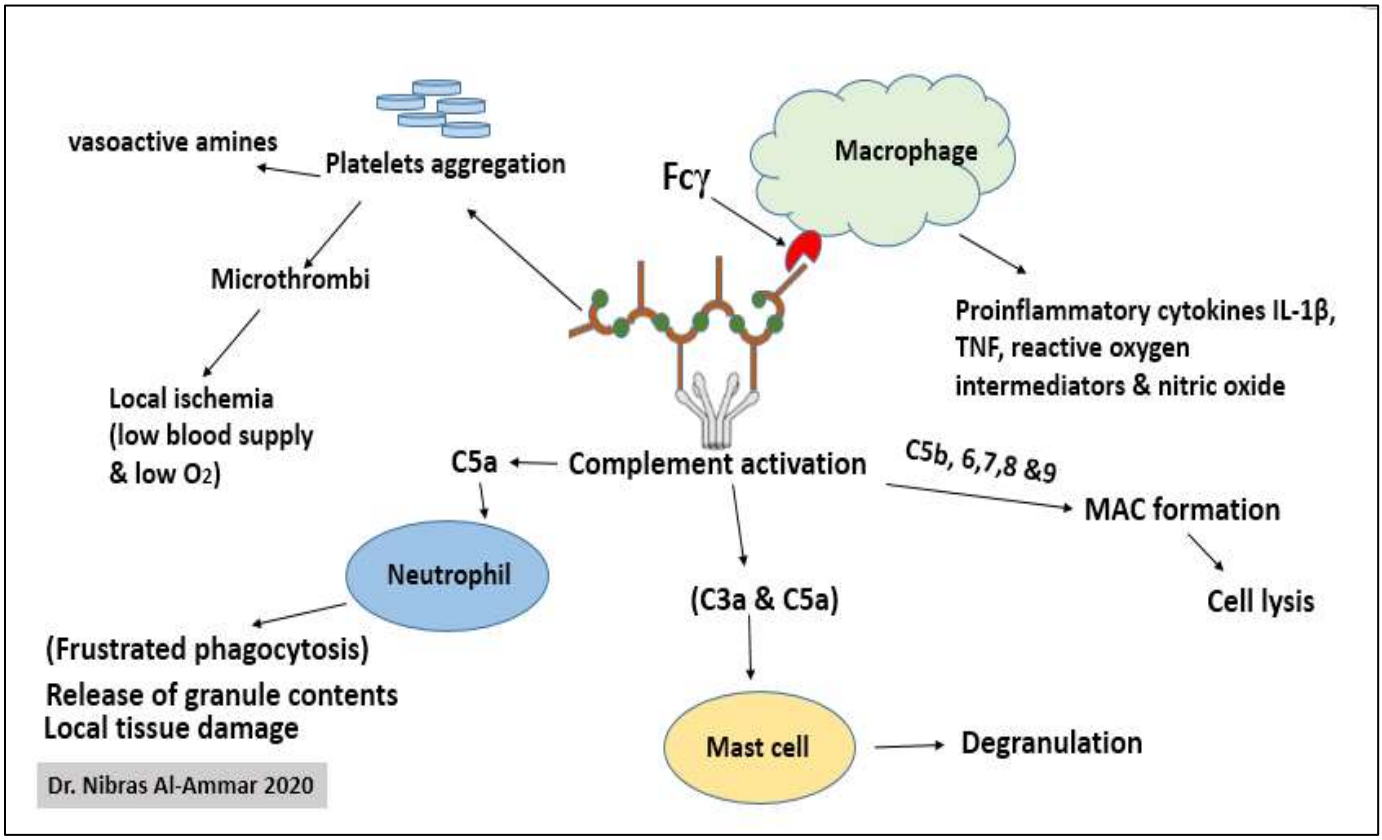
The body may be exposed to excessive amounts of Ag over a period of time as a result of:

1. **Persistent infections**
2. **Autoimmunity of self-components**
3. **Repeated contact with environmental agents**

Ag & Ab complexes within the body may give rise to acute inflammatory reactions through a variety of mechanisms.

LO.2

Mechanisms leading to acute inflammatory reactions



LO.3

Factors influence the tendency of immune complexes to develop disease

Size of the immune complexes: very large complexes, or complexes with many free IgG Fc regions (Ab excess) are rapidly removed from circulation by macrophages in spleen & liver, therefore usually harmless.

The most pathogenic immune complexes are small or intermediate in size and found during (Ag excess). They are cleared less effectively by phagocytes, therefore circulate longer.

- **Charge of the complex.**

The valiancy of Ag.

The avidity of Ab.

The hemodynamics of a given vascular bed. Localization in kidney & joints explained by; the high hemodynamic pressures associated with the filtration function of the glomerulus.

LO.4

The important role of RBCs in clearance of immune complexes

Covalent attachment of C3b to the immune complexes prevents Fc-Fc interactions required to form large insoluble aggregates, and these small complexes bind to CR1 complement receptors on RBC and transported to fixed macrophages in the liver & spleen where they safely destroyed.

If there are defects in this process (deficiencies in classical pathway components, or perhaps if the system is overloaded, then widespread disease involving deposition of these complexes in (kidneys, joints, skin and choroid plexus) may results.

LO.5

Locally formed immune complexes

- The Arthus reaction

Maurice Arthus found that injection of soluble Ag intradermal in hyperimmunized rabbits with high levels of precipitating Ab produced an erythematous & edematous reaction reaching a peak (3-8 h) and then usually resolved.

The lesion characterized by intense infiltration neutrophils. Injected Ag precipitates with Ab too fast for the classical complement system to prevent it; subsequently, the complex is able to bind complement.

Using fluorescent reagents to demonstrate Ag, Igs, & complement components in this lesion.

LO.5

Variants of Arthus-type reaction

Reactions:

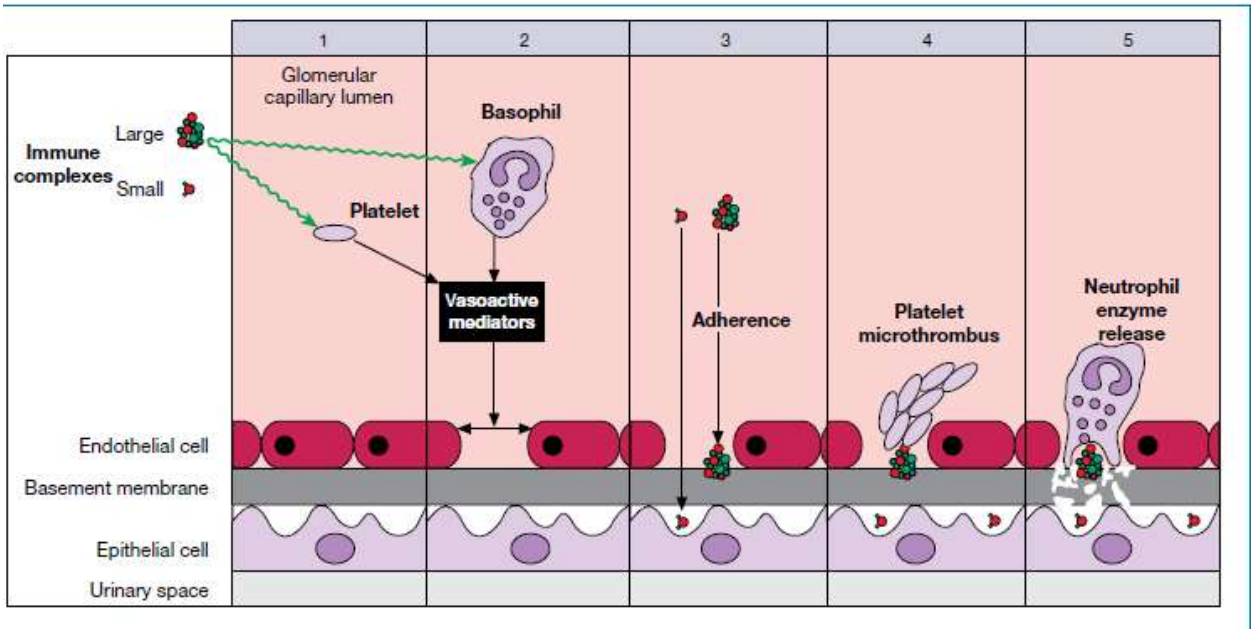
- **to inhaled Ags (Farmer's lung).**
- **to resident infections (elephantiasis).**
- **to released microbial Ags in the skin of lepromatous leprosy (after treatment with chemotherapy).**
- **in syphilis patients receiving penicillin.**
- **In rheumatoid arthritis, where complexes formed locally in the joint due to (production of self-associating IgG anti-IgG by synovial plasma cells).**

LO.6

Circulating immune complexes (systemic)

Example of disease resulting from circulating immune complexes:

- **Immune complex glomerulonephritis (small complexes reach the epithelial side, whereas larger complexes retained in or on the endothelial side of the glomerular basement membrane.**



LO.7

Example of immune complex Hypersensitivity caused by viral infection

The dengue hemorrhagic fever & dengue shock syndrome

Occur during a second infection with dengue virus

[As far as there are five types of virus, Abs that have been produced to one type during the 1st infection may not neutralize a second strain but facilitate its entry into and replication within monocytes & macrophages by attachment of immune complexes to Fc receptors].

LO.8

Type IV hypersensitivity: Cell-mediated (delayed-type)

The best-known example is:

The Mantoux reaction

- Obtained by injection of tuberculin into the skin of an individual in whom previous infection with mycobacterium had induced a state of cell-mediated immunity (CMI).

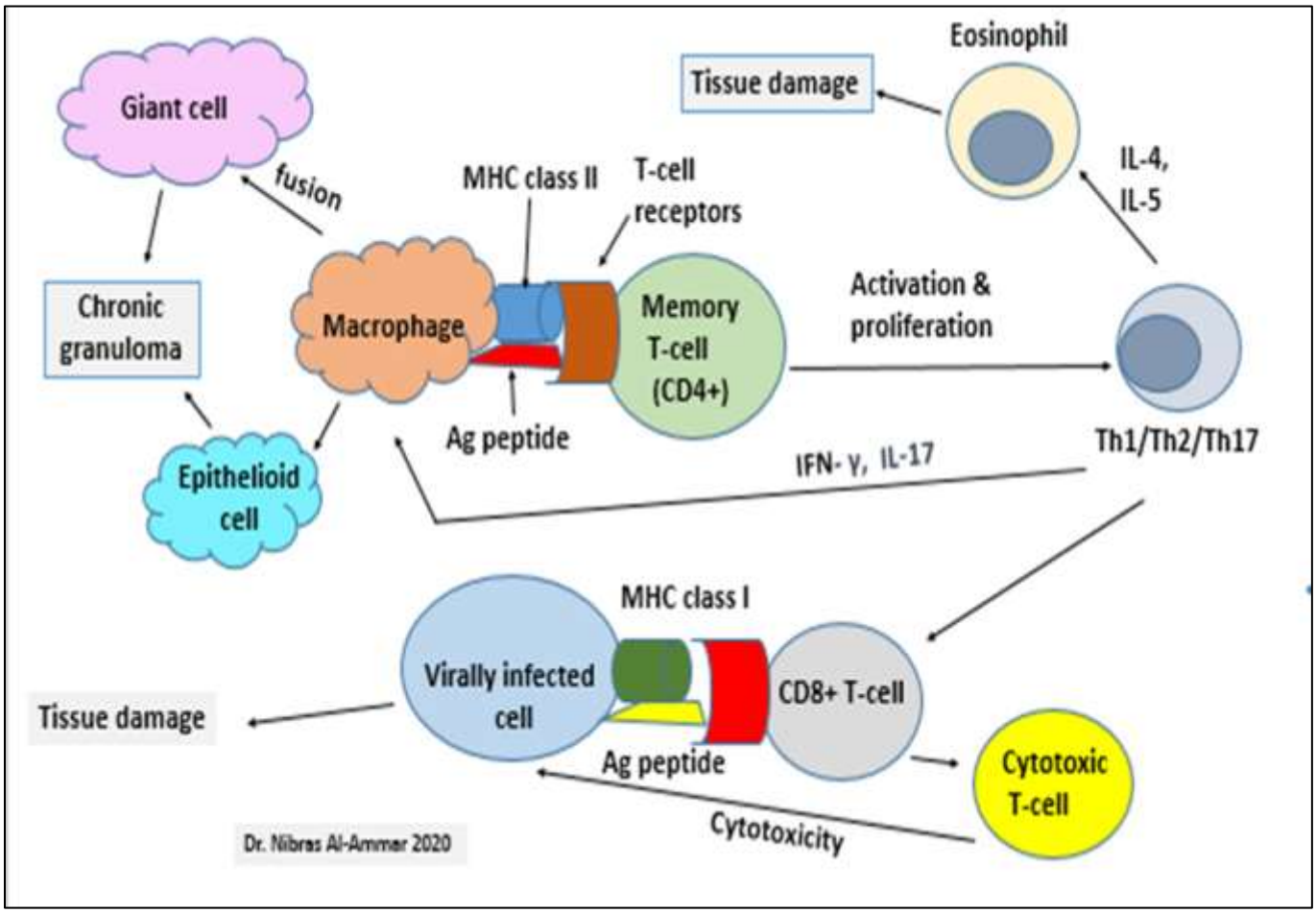
- Characterized by erythema (redness) & induration (hardening of the tissue), which appears only after several hours & reaches a maximum at 24-48 hours, thereafter subsiding.

Histologically:

- **Earliest phase of the reaction seen as a perivascular cuffing of blood vessels with mononuclear cells.**
- **Followed by a more extensive exudation of mono-& polymorphonuclear cells.**
- **Polymorphonuclear cells soon migrate out of the lesion leaving behind mononuclear cell infiltrate consisting of lymphocytes & cells of monocyte-macrophage series.**

LO.8

Cellular basis of type IV hypersensitivity



LO.8

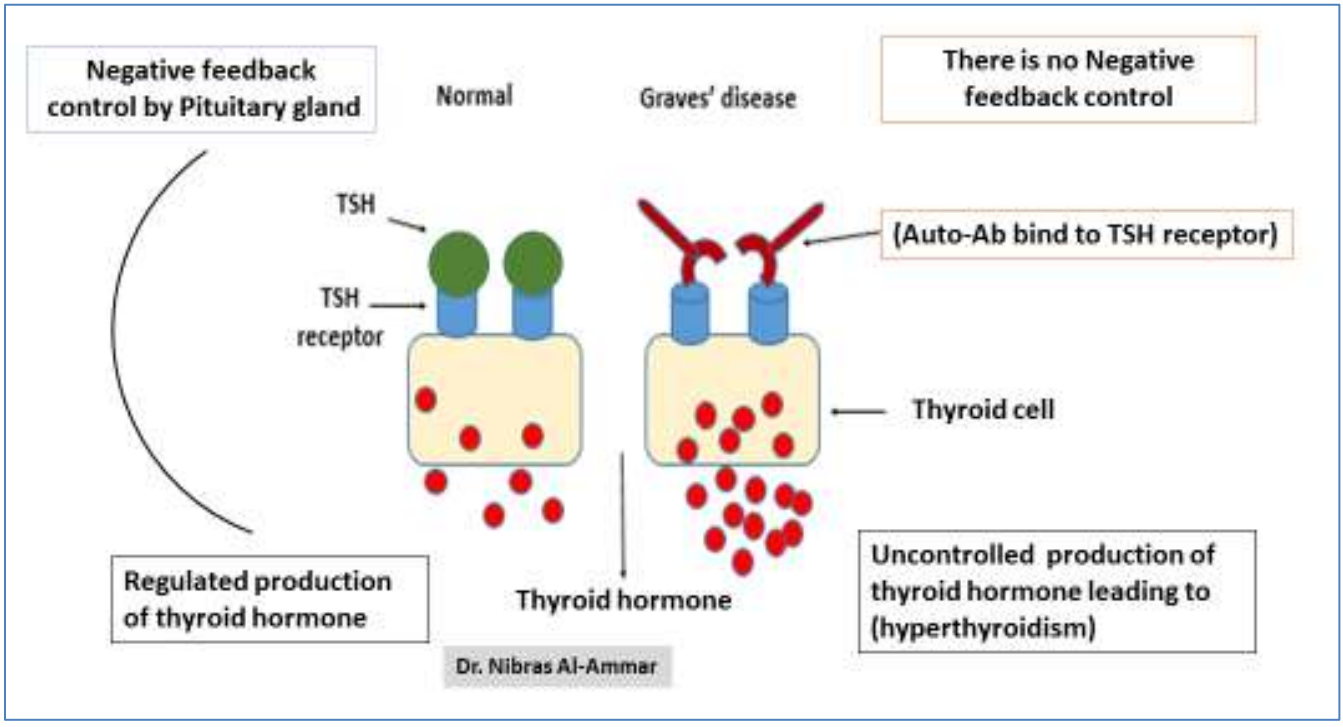
Examples of diseases caused tissue damage by Type IV hypersensitivity:

- **Infections:** Tuberculosis, leprosy, Measles, herpes simplex virus, hepatitis B virus, fungal & parasitic diseases.
- **Inflammatory bowel disease:** Crohn's disease & ulcerative colitis.
- **Sarcoidosis**
- **Contact dermatitis**
- **Psoriasis**

LO.9

Hypersensitivity Type V: Stimulatory hypersensitivity

It is similar to type II hypersensitivity in that it is due to Abs to cell surface Ags, but in this case the Abs do not mediate their effect via cytotoxicity but rather are directed to a cell surface receptor & act as agonist leading to stimulation of the cell. (Ex: Hyperthyroidism in Graves' disease, preeclampsia and hypertension).



LO.10

Innate hypersensitivity reactions

Some infections provoke a toxic shock syndrome involving excessive release of TNF, IL-1β, Il-6 & activation of alternative complement pathway.

- Acute respiratory distress syndrome: associated with Gm-ve bacteria (lipopolysaccharide endotoxin provoking a massive invasion of the lung by neutrophils).

- **Gram +ve bacteria cause release of TNF & macrophage migration inhibitory factor (MIF) through direct action on macrophages & stimulation of selected T-cell families by the enterotoxin super antigens.**
- **Aberration of innate mechanisms may underline idiopathic pulmonary fibrosis.**
- **A role for innate responses has been proposed as a contributory factor to the pathogenesis of Alzheimer's disease.**

☺

Thank You