جامعة آشور
Ashur University

Ashur university college of medicine
2025-2026

Subject: Immune Disturbances

Title: Hypersensitivity reactions Type IV

Grade (Level): Three (3)

Speaker: Assistant Lecturer Abdullah Al-Sabti, MSc, Clinical Immunology

Objectives

By the end of this topic, students should be able to:

1. **Describe the basic principles** of Type IV (delayed) hypersensitivity.
2. **Explain how cell-mediated immunity** causes delayed hypersensitivity reactions.
3. **Describe the mechanism by which cytotoxic T lymphocytes (CTLs)** kill target cells.
4. **Identify and explain clinical examples** of delayed-type hypersensitivity reactions.
5. **Explain how penicillin can induce hypersensitivity reactions**.

Type IV Hypersensitivity (Cell-Mediated / Delayed-Type Hypersensitivity*)

➢ **Also known as:**

•Delayed-type hypersensitivity (DTH)

•T cell–mediated hypersensitivity

➢ **Target:**

•**Intracellular pathogens** (e.g., Mycobacterium tuberculosis, Leishmania, viruses)

•Contact allergens or haptens (e.g., poison ivy, nickel, topical drugs)

•Autoantigens (e.g., pancreatic beta cells, thyroid cells, myelin)

➢ **Mediators:**

•**$CD4^+$ Th1 cells / Th17 cells** → release **lymphokines**

•**$CD8^+$ cytotoxic T lymphocytes (CTLs)** → direct cell killing

•Key lymphokines: **IFN-γ, TNF-α, TNF-β, MIF, MAF, MCAF, IL-2, IL-8**

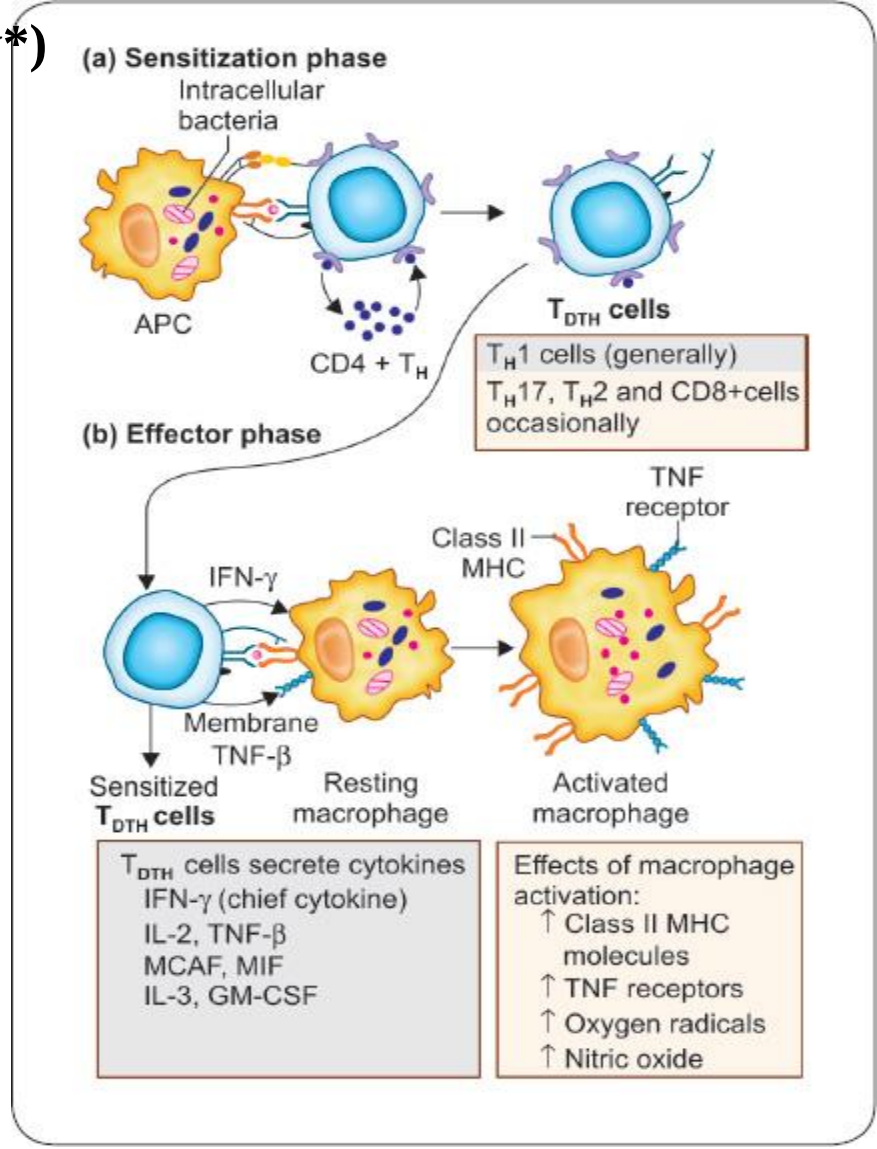
➢ **Onset:**

•Reaction develops **12–72 hours** after antigen exposure (peak at 48–72 hours)

➢ **Affected sites:**

•Skin, lungs, joints, kidneys, and other tissues depending on antigen exposure

•Can cause **localized or systemic tissue damage**



*"The inflammatory response happens when previously sensitized T-lymphocytes (CD4+ or CD8+) recognize and interact with a specific antigen."

Mechanisms of Injury (Immunopathogenesis)

1. $CD4^+$ T-cell (Th1 / Th17) mediated DTH

•Sensitization phase:

- Antigen-presenting cell (APC, e.g., macrophage or Langerhans cell) presents antigen → naïve Th1 cell → formation of **sensitized Th1 (Tdth) cells**

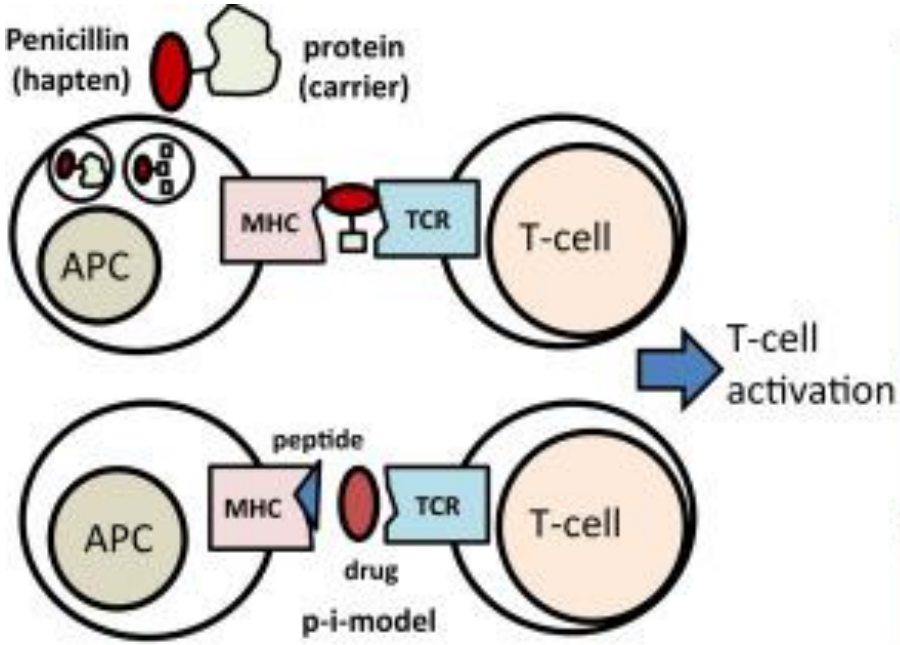
•Effector phase:

- Re-exposure to antigen → **Th1 cells release lymphokines**
- Cytokines **activate macrophages**, which release **reactive oxygen species, nitric oxide, proteases, lysosomal enzymes**
- Result: **tissue inflammation and injury**

2. $CD8^+$ CTL-mediated cytotoxicity

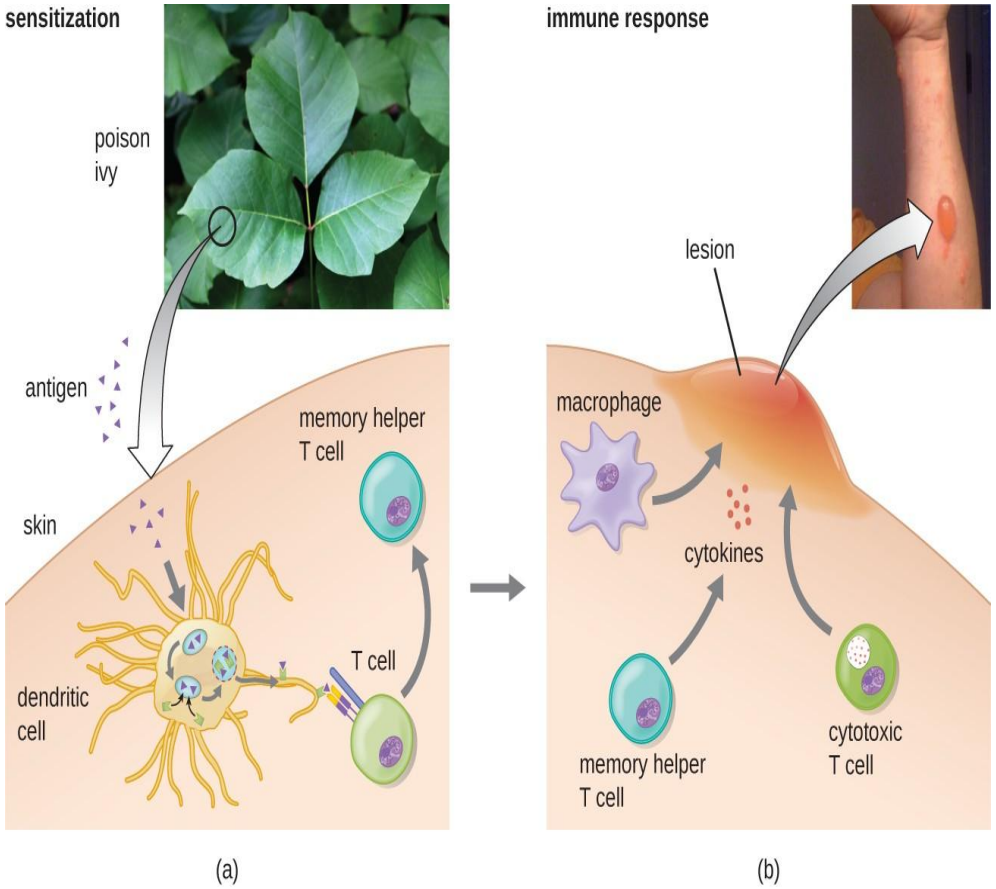
•Steps:

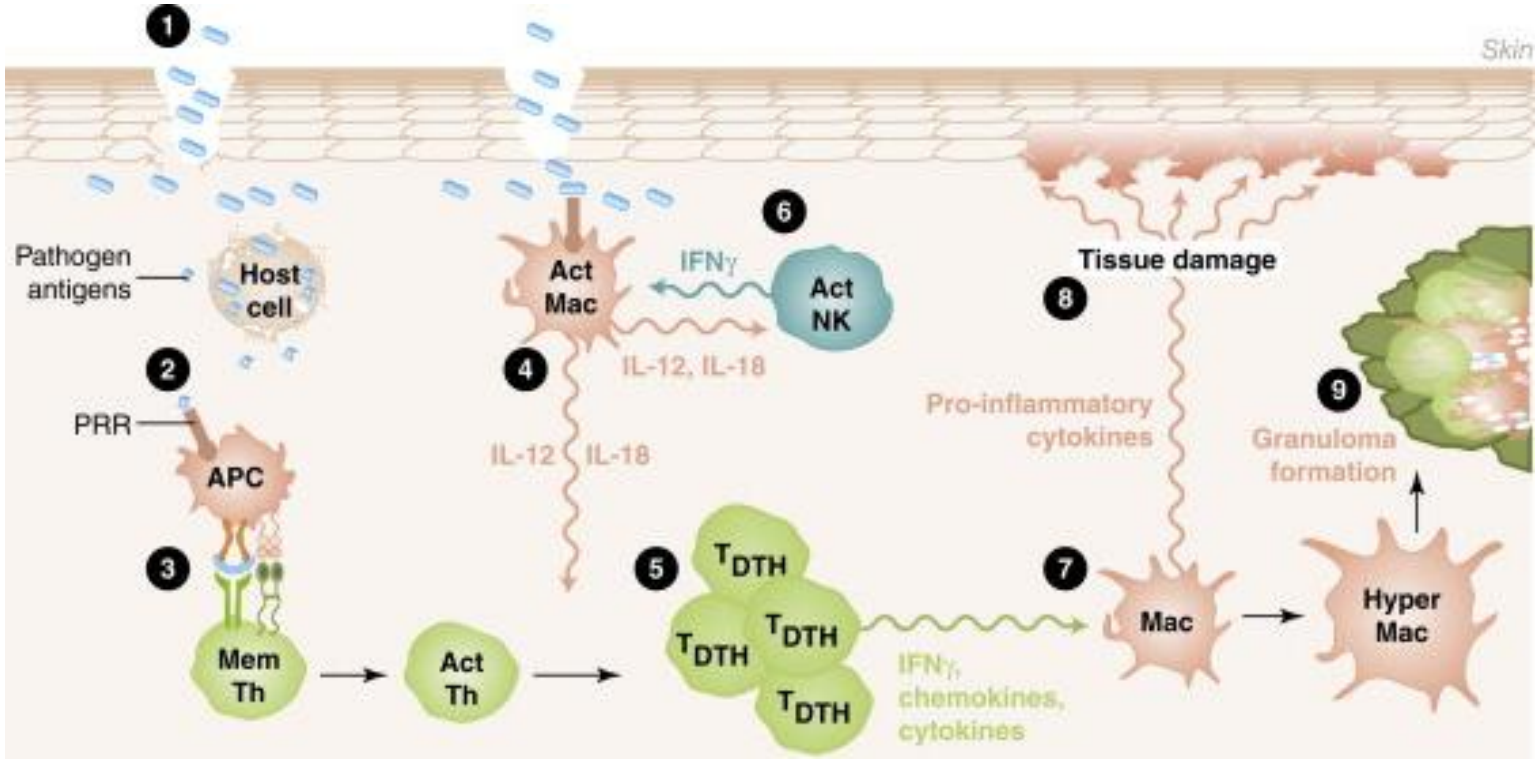
- **Attachment** to target cell
- **Activation** and concentration of cytotoxic granules
- **Exocytosis** of perforin and granzymes → target cell death
- **Detachment** ("hit-and-run" phenomenon)



Results / Tissue Effects

- **Erythema, induration, edema** at antigen site
- **Cellular infiltration** by macrophages and lymphocytes
- **Tissue necrosis** in severe reactions
- **Chronic inflammation** → granuloma formation





Clinical Examples

1. Tuberculin (Mantoux) Test

•**Principle:** Intradermal injection of purified protein derivative (PPD)

•**Positive reaction:** Erythema & induration >10 mm at 48–72 hrs → indicates prior TB exposure or BCG vaccination

•**Negative reaction:** No induration → absence of exposure or anergy (e.g., AIDS, sarcoidosis)

2. Allergic Contact Dermatitis

•**Causes:** Topical drugs (neomycin), metals (nickel, chromate), plant haptens (poison ivy, oak, sumac), preservatives, dyes

•**Mechanism:** Haptens bind to skin proteins → presented by Langerhans cells → activate Tdth cells → cytokine-mediated inflammation

•**Clinical features:**

- Acute: erythema, edema, vesicles, bullae
- Chronic: scaling, dry eczema

•**Diagnosis:** History, lesion distribution, **patch test** (Ag applied to skin → reaction in 48–72 hrs)

3. Granulomatous Inflammation

•Chronic Th1/macrophage activation → **granuloma formation**

•Seen in **tuberculosis, sarcoidosis**

4. Autoimmune Diseases

•Type 1 diabetes mellitus (beta cell destruction)

•Hashimoto’s thyroiditis

•Multiple sclerosis (myelin destruction)

Other explanation of Clinical example of Delayed-type (Type IV) hypersensitivity

1. Tuberculin skin test (Mantoux test):

- A positive tuberculin test indicates that the person has previously sensitized T-lymphocytes against Mycobacterium tuberculosis.

Principle:

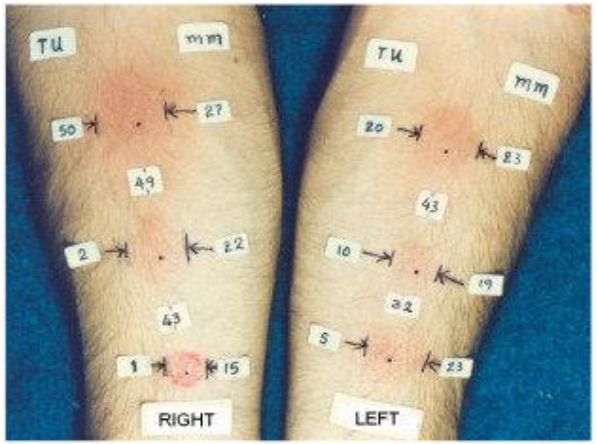
- The test uses PPD (purified protein derivative) obtained from M. tuberculosis.
- PPD is injected intradermally.
- The reaction is delayed, appearing after 48–72 hours.
- A positive result is characterized by erythema and induration with a diameter greater than 10 mm.

Explanation:

- Sensitized Th1 cells recognize the antigen and release cytokines, leading to local inflammation and induration, which is typical of Type IV hypersensitivity.
- Negative Mantoux Test Indicates: No tuberculosis infection and no previous BCG vaccination,

OR

- Anergy (state of immune unresponsiveness) due to: Over whelming or severe infection Immunosuppressive conditions, such as: Sarcoidosis AIDS Hodgkin’s disease
- Positive Mantoux Test Indicates: Active tuberculosis infection Latent (subclinical) TB infection Past history of TB infection Previous BCG vaccination



Other explanation of Allergic Contact Dermatitis (Type IV Hypersensitivity)Cause:

Occurs after skin contact with sensitizing substances (antigens), such as:

Topical drugs: e.g. neomycin

Metals: nickel, chromate (costume jewelry)

Cosmetics

Plants: poison ivy, poison oak, poison sumac(plant oil: urushiol)

Dyes, rubber compounds, preservatives, etc.

Immunological Mechanism:

Most causative substances are small molecules (haptens).

Haptens bind to skin proteins, forming a hapten–protein complex.

This complex is taken up by antigen-presenting cells (Langerhans cells) in the skin.

The antigen is processed and presented with MHC class II molecules.

This leads to activation of sensitized T helper (Tdth) cells.

On re-exposure, activated T cells release cytokines → inflammation and skin damage.

This is a delayed reaction (48–72 hours) → Type IV hypersensitivity.

Immunological Features:

T-cell mediated disease ($CD4^+$ and $CD8^+$ T cells)

Delayed eczematous response occurring 48 hours after exposure

Classified as Type IV (delayed) hypersensitivity

Clinical Features:

Eczematous skin lesions with itching and irritation

Acute phase: Erythema Edema Vesicles Bullae formation

Chronic phase : Scaling Thickened skin

Site of Lesion Helps Diagnosis:

Ear lobes: earrings

Neck: necklace

Wrist: watch, bracelets, bands

Diagnosis:

History of exposure

Distribution of skin lesions

Patch test (in vivo test) :A low dose of suspected antigen is applied to the skin.Test site is examined after 48–72 hours.Development of eczema indicates Type IV hypersensitivity.



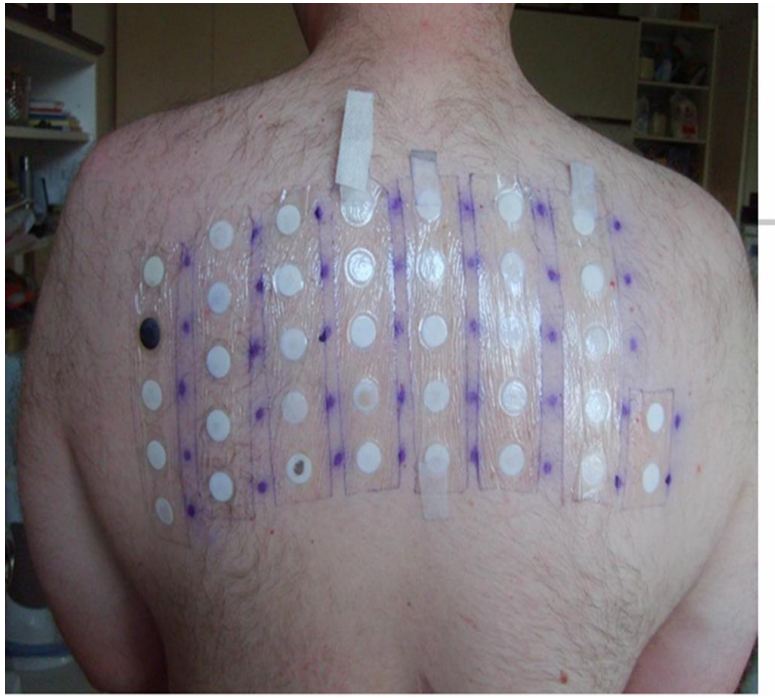
+ Weak Positive Reaction: non-vesicular with erythema, infiltration, possibly papules

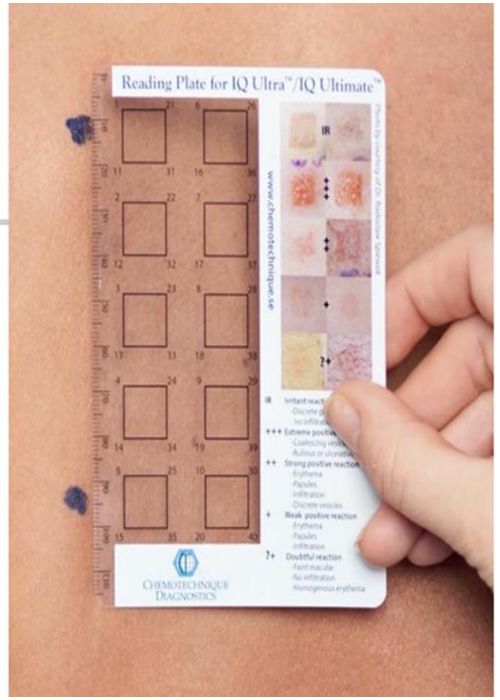
++ Strong Positive Reaction: vesicular, erythema, infiltration, papules

+++ Extreme Positive Reaction: bullous or ulcerative reaction

? Doubtful Reaction: faint macular erythema only

IR Irritant Reaction: Pustules as well as patchy follicular or homogeneous erythema without infiltrations are usually signs of irritation and do not indicate allergy. Itching is a subjective symptom that is expected to accompany a positive reaction.





A 30 year old male develops intense itching, a red and swollen rash, and tiny & very large multiple blisters 48 hours after contact with an ivy plant, the blisters occur in a straight line in the area where the plant brushed along the skin.

Q1) Your provisional diagnosis?

Q2) Give the immune-pathogenesis of that condition.





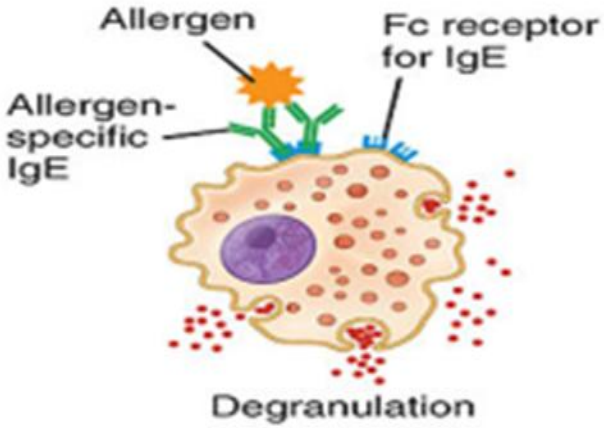
Patient Presentation: A 12-year-old male presents with a history of increased
thirst, frequent urination, unexplained weight loss, and fatigue over the past few weeks. He has also experienced several episodes of bed-wetting, which is unusual for his age.
History: The patient has no significant medical history and comes from a family with a history of autoimmune diseases, including type 1 diabetes in his mother and celiac disease in his aunt.
Examination: Physical examination reveals a young boy who appears thin and tired. His vital signs show a slightly elevated heart rate, and a fingerstick blood glucose test shows a blood sugar level of 320 mg/dL (normal fasting blood glucose is less than 100 mg/dL).
YOUR DIAGNOSIS AND IMMUNEPATHOGENSIS?

Summary

•Type IV hypersensitivity is **T-cell mediated**, **antibody-independent**, and **delayed**
•**Protective role:** Defense against intracellular pathogens
•**Pathological role:** Tissue damage in contact dermatitis, chronic infections, autoimmune diseases
•**Diagnosis:** Skin tests (Mantoux, patch test), clinical history, tissue biopsy in granulomatous disease

Objective	Section / Key Points in Notes
Principles of Type IV H.S.	"Cell Mediated (Delayed) Hypersensitivity"; delayed onset, T-cell mediated, complement/antibody independent
Mechanism of cell-mediated DTH	"Mechanism of delayed type H.S." – Sensitization & Effector phases; macrophage activation; cytokine release
CTL-mediated cytotoxicity	"Mechanism of CTLs (CD8+ T lymphocyte)" – attachment, perforin/granzyme release, detachment
Clinical examples of DTH	"Clinical examples on delayed type H.S." – Tuberculin test, contact dermatitis, granulomatous inflammation, autoimmune diseases
Penicillin-induced H.S.	"Allergic contact dermatitis" – drugs as haptens; T-cell activation → delayed inflammation

Feature	Type I (Immediate)	Type II (Cytotoxic)	Type III (Immune Complex)	Type IV (Delayed, Cell-Mediated)
Mediator	IgE on mast cells/basophils	IgG/IgM vs cell antigens	IgG/IgM-antigen complexes	T cells (CD4+ Th1/Tdth, CD8+ CTLs)
Timing	Minutes	Hours to days	3-8 hours	48-72 hours
Mechanism	Histamine release, anaphylaxis	Complement, phagocytosis/lysis	Complement activation, neutrophils	Cytokines (IFN-γ), macrophage activation, cytotoxicity YouTube
Examples	Anaphylaxis, asthma, hives	Autoimmune hemolytic anemia, Goodpasture	SLE, serum sickness, Arthus	TB skin test, poison ivy, graft rejection
Histology	Eosinophils, edema	Antibody/complement on cells	Neutrophils, vasculitis	Lymphocytes/macrophages, granulomas

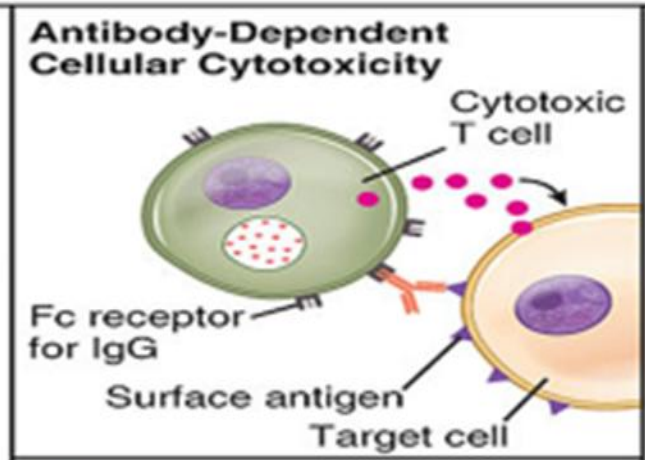


Type I

IgE-Mediated Hypersensitivity

IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.

Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema



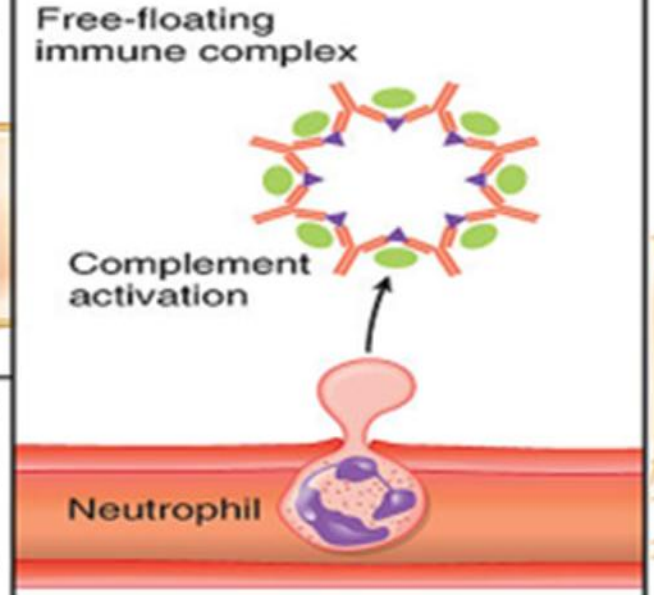


Type II

IgG-Mediated Cytotoxic Hypersensitivity

Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)

Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis

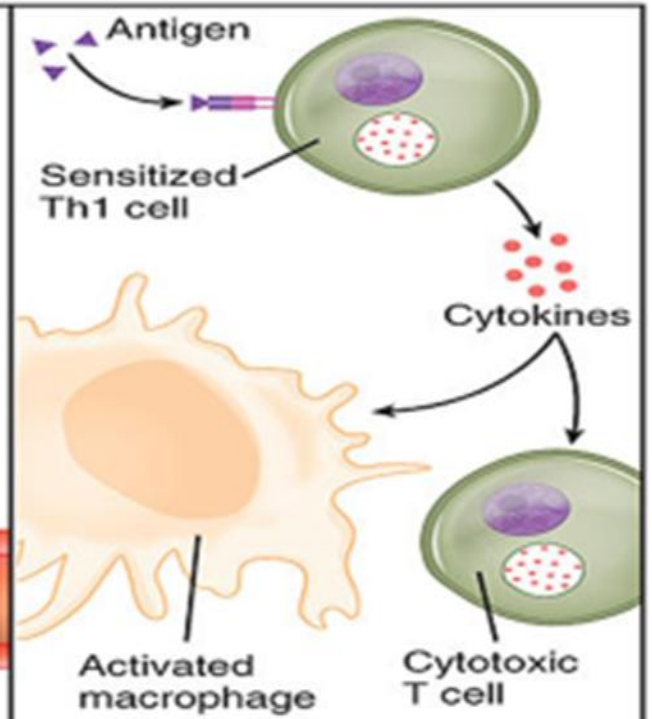


Type III

Immune Complex-Mediated Hypersensitivity

Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site

Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus



Type IV

Cell-Mediated Hypersensitivity

Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site

Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis

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