BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024,
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Programme: M.Sc., Biomedical Science

Course Code: BM35C6
Course Title: Immunology

Unit-IV

Immune response to infectious agents & Hypersensitivity reactions

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Unit IV:

Immune response to infectious agents & hypersensitivity reactions. Overview on immunity to intracellular and extracellular pathogens-Bystander damage caused by the immune response to infection- evasion of immune responses by various infectious agents. Overview on hypersensitivity reactions – Gell and Coombs classification, IgE-mediated (Type I), antibody- mediated (Type II), immune complex- mediated (Type III) (Glomerulonephritis, extrinsic allergic alveolitis, serum sickness) and TDTH-mediated (Type IV) hypersensitivity

PRESENTATION: 3

HYPERSENSITIVITY AND ITS TYPES

DEFINITION OF HYPERSENSITIVITY:

In 1906, Von Picquet coined term the hypersensitivity.

Hyper means increased sensitivity means susceptibility or response.

Hypersensitivity refers to excessive, undesirable reactions produced by the normal immune system.

The reactions lead to damage and sometimes fatal to the body.

Where:

Any part of our body, commonly skin, gastrointestinal tract, respiratory tract and blood vessels.

Why:

Hypersensitivity may occur due to various reasons like genetic and environmental factors.

Common triggers: allergens like dust, foods and pollution etc..

Types of hypersensitivity:

The hypersensitivity reactions are distinguished on the basis of time taken to develop effector molecules during the course reaction.

Immediate hypersensitivity

delayed hypersensitivity.

Immediate hypersensitivity:

It also known as type 1 hypersensitivity reactions and involve immunoglobulin E (IgE) mediated release of antibodies against the soluble antigen.

These reactions can cause nausea, vomiting, abdominal pain and diarrhea. Serum sickness, auto- immune disease are different types of immediate hypersensitivity.

- **Delayed hypersensitivity:**

It is also known as type 4 hypersensitivity reactions and involve T- cell mediated reactions. The most common manifestation is a delayed skin eruption, 1-3 days exposure to the allergen. Contact dermatitis, tuberculin reaction are types of delayed hypersensitivity.

P.G.H. Cell and R.R.A. Combs revised the classification of hypersensitivity reactions based on the mechanisms of pathogenesis into five types:

TYPE 1={IgE mediated} hypersensitivity
TYPE 2={cytotoxic} hypersensitivity
TYPE 3={immune complex mediated} hypersensitivity
TYPE 4={delayed or cell mediated} hypersensitivity
TYPE 5={stimulatory}hypersensitivity.

Antibody mediated- type 1, 2, 3
Cell mediated - type 4

TYPE 4 HYPERSENSITIVITY:

Type 4 hypersensitivity is often called delayed type hypersensitivity as the reaction takes two to three days to develop.

Unlike the other types, it is not antibody mediated but rather is a type of cell – mediated response.

HOW?

* Initially APCs presents antigens(like haptens) to T cells.
* T cells are sensitized for the antigens.
* When the antigen re- enters, T cells activated and release cytokines.
* Particularly, interferon- gamma(INF-gamma) and tumor necrosis factor- alpha(TNF-alpha).
* These cytokines activate macrophage.
* Macrophage attack antigen and release more inflammatory mediators.
* It causing inflammation, tissue damage and formation of granulomas.

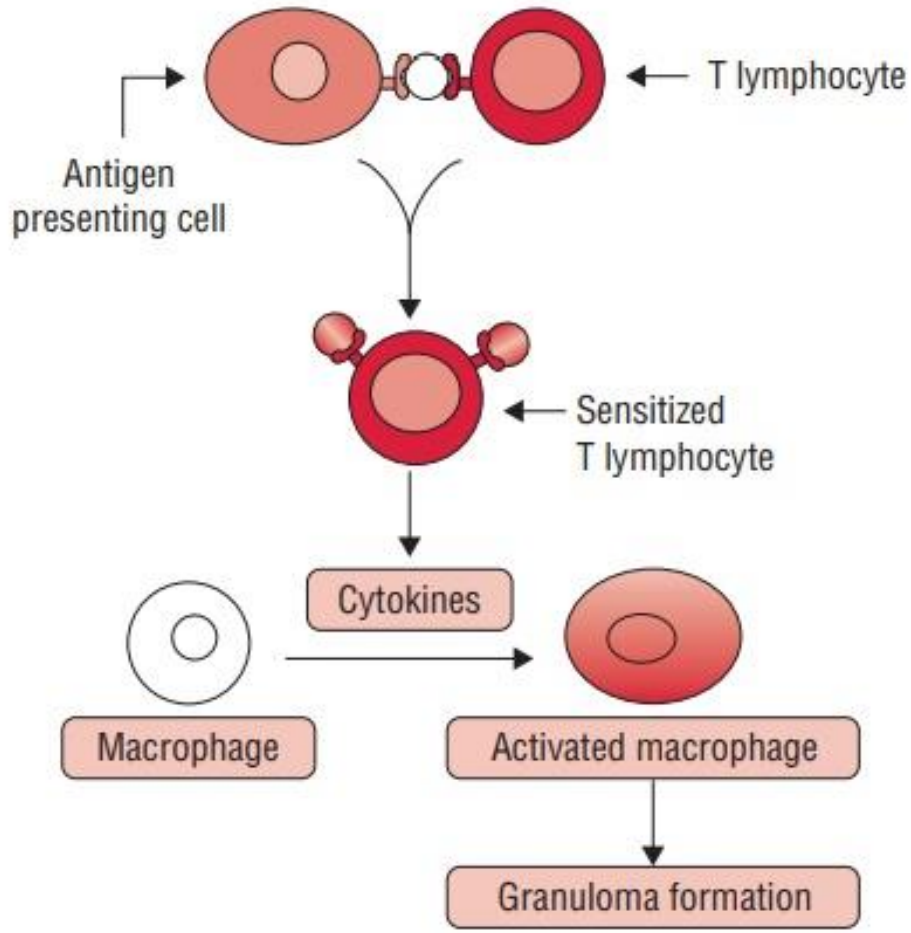


FIG. 19-4. A schematic diagram showing type IV hypersensitivity reaction.

PATHOLOGY OF TYPE 4 HYPERSENITIVITY:

Type 4 hypersensitivity is involved in the pathogenesis of many autoimmune and infectious disease (tuberculosis, blastomycosis etc….) and granulomas due to infections and foreign antigens.

There are three variants of delayed hypersensitivity as listed below;

contact{48 to 72 hours}

Tuberculin{48 to 72 hours}

Granulomatous{21 to 28 days}.

CONTACT DERMATITIS:

It is usually caused by haptens that combine with proteins in the skin of some people to produce immune response.

Reactions to cosmetics, and metals in jewelry (especially nickel) are familiar example of these allergies.

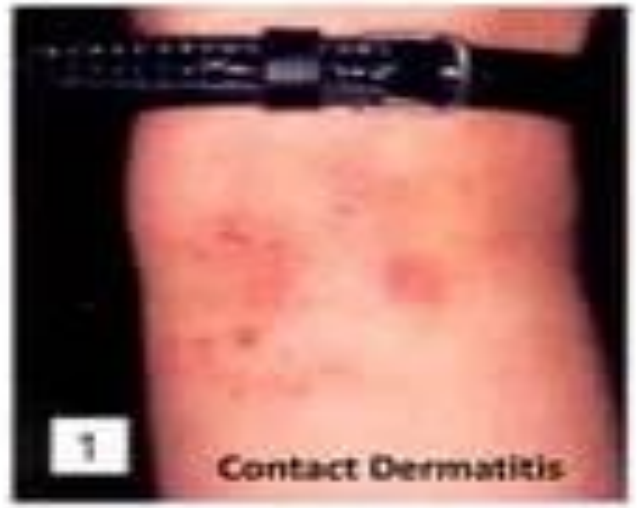
TUBERCULIN:

The test involves injecting a purified protein derivative (PPD SOLUTION) of the tuberculosis bacillus into the skin.

The reaction is measured by measuring the diameter of the raised, hardened area that forms at the injection site.

GRANULOMA:

This reactions that occurs when the body is exposed to an antigen, and it’s characterized by the accumulation of immune cells are called granulomas. Granulomas play a major role in tissue damage caused by infections from slow growing organism like tuberculosis.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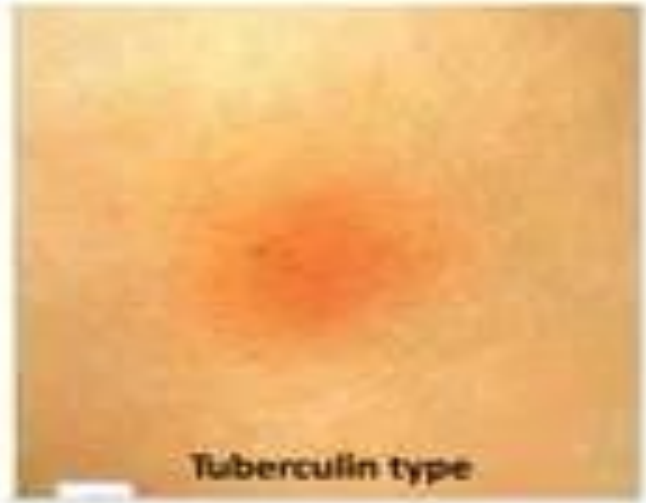
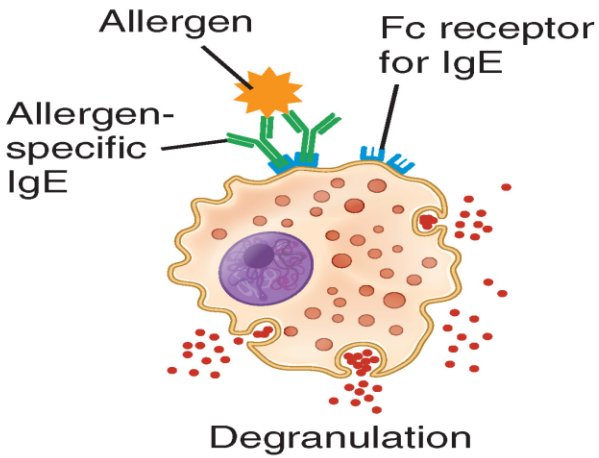
Contact Dermatitis


Tuberculin type

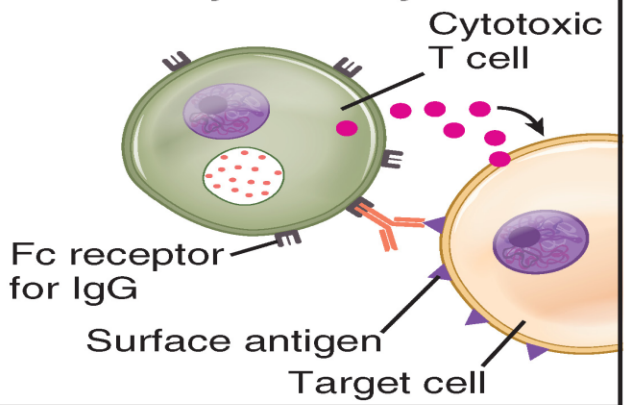

E
G
N
M
Granuloma (TB)

TYPE	REACTION TIME	CLINICAL APPEARANCE	ANTIGEN AND SITE
Contact	48-72 hour	eczema	Epidermal(organic chemicals, heavy metals, etc.....)
Tuberculin	48-72 hour	Local induration	Intradermal(tuberculin etc.....)
Granuloma	21-28 days	hardening	Persistent antigen or foreign body presence (tuberculosis, etc....).

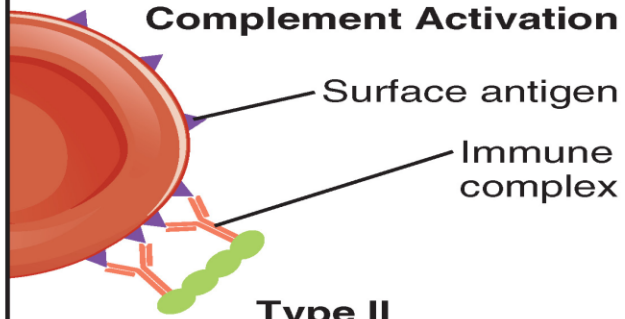


Type I

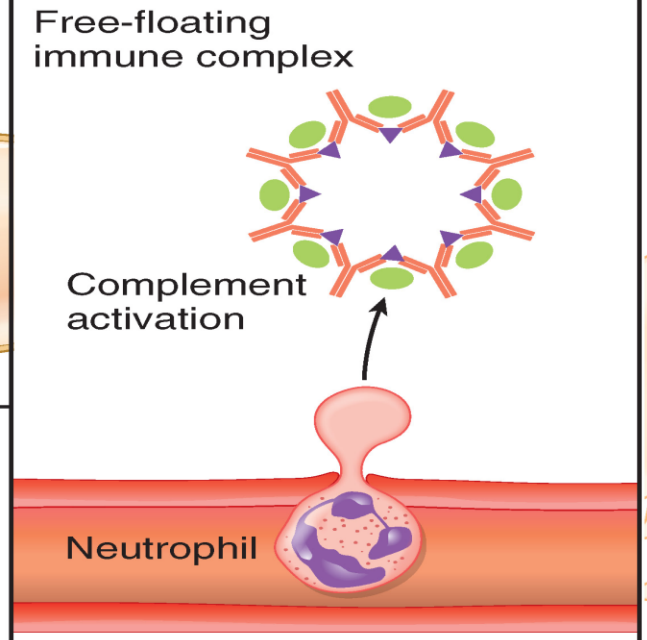
Antibody-Dependent Cellular Cytotoxicity



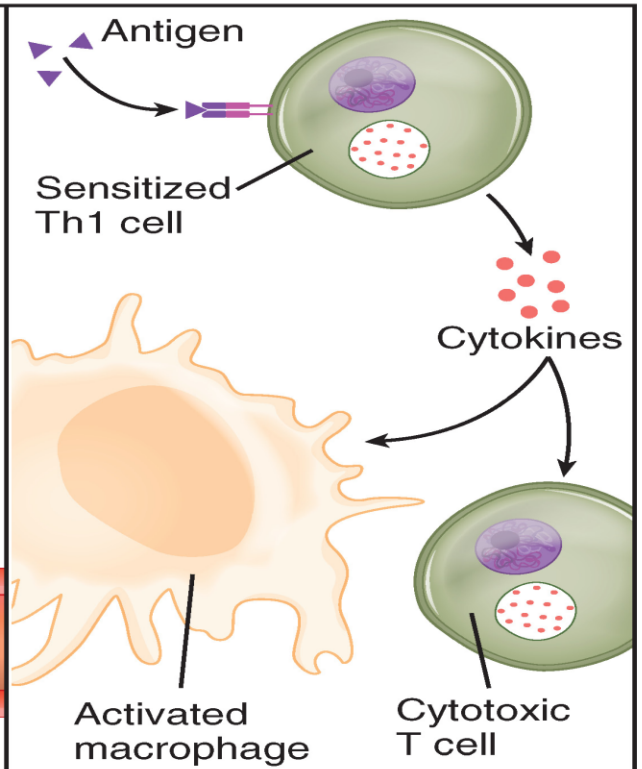
Complement Activation



Type II



Type III



Type IV

IgE-Mediated Hypersensitivity	**IgG-Mediated Cytotoxic Hypersensitivity**	**Immune Complex-Mediated Hypersensitivity**	**Cell-Mediated Hypersensitivity**
IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.	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)	Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site	Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site
Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema	Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis	Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis

IMMEDIATE (TYPE I) HYPERSENSITIVITY

- *Rapid immunologic reaction occurring within minutes after the combination of an antigen with* ***antibody bound to mast cells*** *in individuals previously sensitized to the antigen.*
- These reactions are often called ***allergy.***
- *Take form like:* ***1*****-localized cutaneous swellings (skin allergy)**

  2-nasal and conjunctival discharge (allergic rhinitis and conjunctivitis)

  3-hay fever, bronchial asthma, or allergic gastroenteritis (food allergy).

TWO WELL-DEFINED PHASES

1. First (**vasodilation, vascular leakage, and depending on the location, smooth muscle spasm or glandular secretions).** These changes usually become evident **within 5 to 30 minutes** after exposure to an allergen and tend to subside in 60 minutes.
2. 2 to 24 hours later without additional exposure to antigen and may last for several days. This late-phase reaction is characterized by: **infiltration of tissues with eosinophils, neutrophils, basophils, monocytes, and CD4+ T cells as well as tissue destruction, typically in the form of mucosal epithelial cell damage.**

TABLE 15-5 Penicillin-induced hypersensitive reactions

Type of reaction	Antibody or lymphocytes induced	Clinical manifestations
I	IgE	Urticaria, systemic anaphylaxis
II	IgM, IgG	Hemolytic anemia
III	IgG	Serum sickness, glomerulonephritis
IV	T_H1 cells	Contact dermatitis

COMMON ALLERGY ASSOCIATED WITH HYPERSENSITIVITY TYPE 1

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

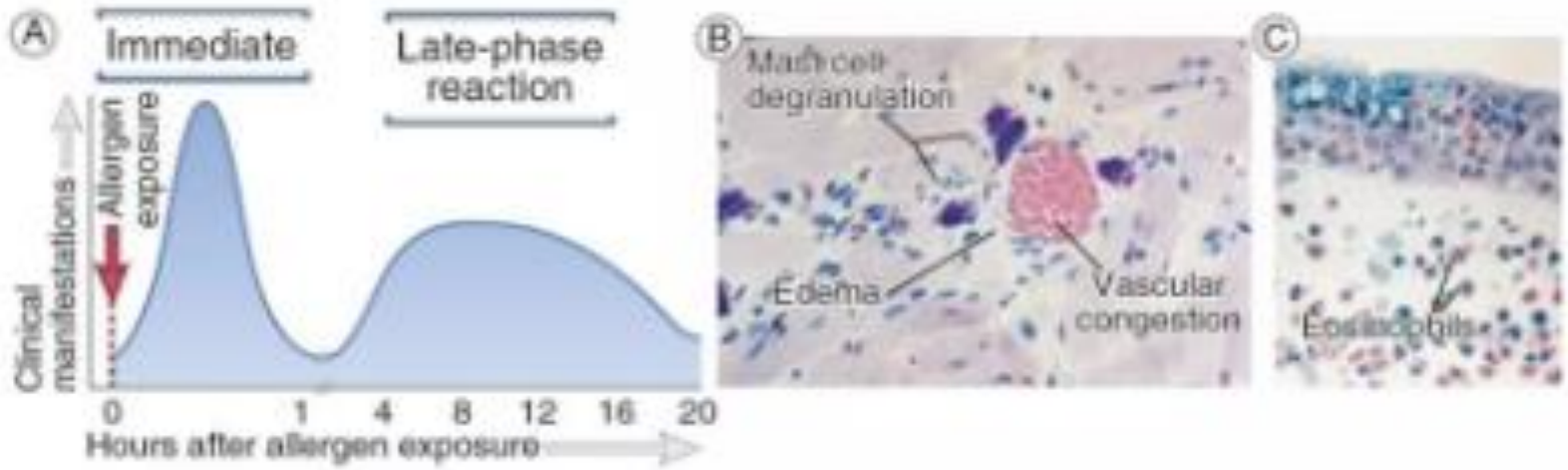
Insect products
- Bee venom
- Wasp venom
- Ant venom
- Cockroach calyx
- Dust mites

Mold spores

Animal hair and dander

Latex

Stages of immediate hypersensitivity reactions



TYPE I HYPERSENSITIVITY DIAGNOSIS:

- History
- Skin prick test – (+) wheal & flare
- CBC(complete blood count) showing eosinophilia
- RAST (Radioallergosorbent assay)

ACTION OF MAST CELL MEDIATORS IN IMMEDIATE (TYPE I) HYPERSENSITIVITY

Action	Mediators
Vasodilation, increased vascular permeability	Histamine PAF(Platelet activating factor) Leukotrienes Neutral proteases that activate complement and kinins Prostaglandin
Smooth muscle spasm	Leukotrienes Histamine Prostaglandins PAF(platelet-activating factor)
Cellular infiltration	Cytokines (e.g., chemokines, TNF) Leukotriene Eosinophil and neutrophil chemotactic factors

SYSTEMIC ANAPHYLAXIS

- **Characterized by :**

1-Vascular shock,

2-Edema,

3-Difficulty in breathing

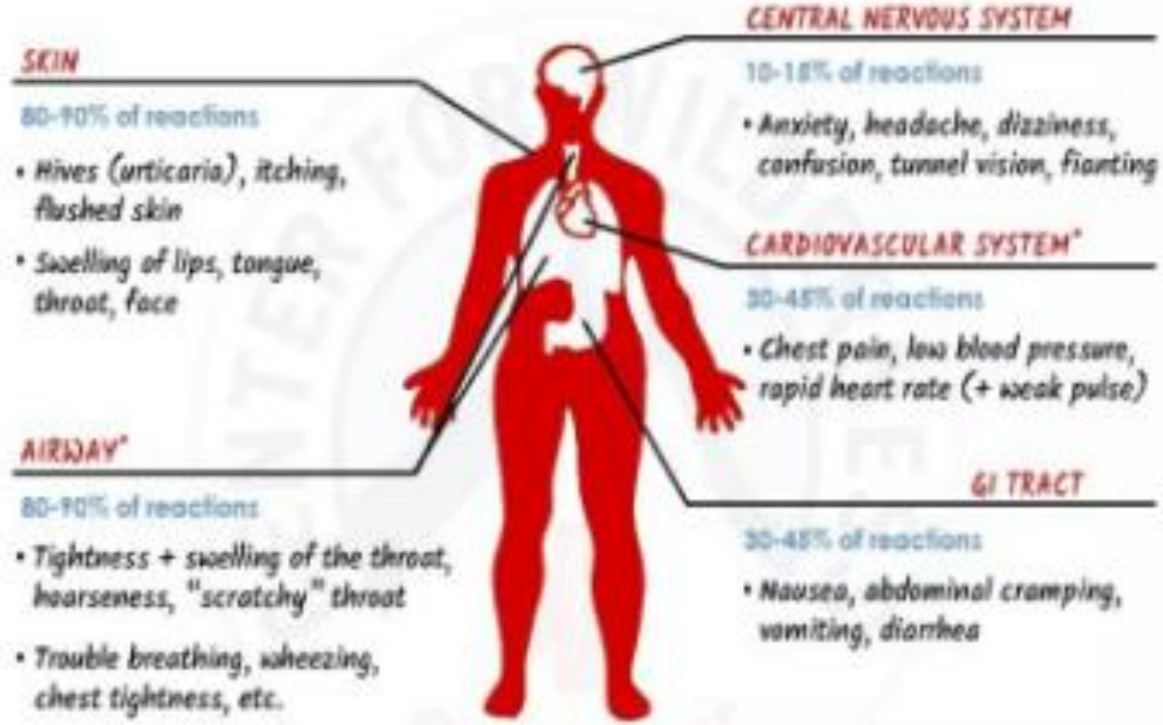
It may occur in:

A) At hospital settings after administration of (such as the antibiotic penicillin) **foreign proteins, hormones, enzymes, polysaccharides, and drugs**

B) In the community setting following exposure **to food allergens** (e.g. peanuts, shellfish) or insect toxins (e.g. those in bee venom).

Symptoms: itching, hives, and skin erythema appear, followed shortly thereafter by a striking contraction of respiratory bronchioles and respiratory distress. **(Vomiting, abdominal cramps, diarrhea, and laryngeal obstruction follow, and the patient may go into shock and even die within the hour).**

Signs of Anaphylaxis



*Potentially Life-Threatening Symptoms

TYPE I HYPERSENSITIVITY TREATMENT:

- Anti-histamine – acts on first phase only
- Corticosteroids – late phase reaction
- Desensitization – to induce tolerance; no IgE production ⟶ deplete already bound IgE

HYPERSENSITIVITY REACTION

TYPE II

TYPE II HYPERSENSITIVITY

- Type II hypersensitivity reaction, also known as cytotoxic reaction
- Ig G (or) Ig M antibodies bind to the antigens on the surface of the cells.
- The antibodies bound cells are marked for destruction.
- They bind to Fc receptors of phagocytes.

  (or)
- Destroy the cells by complement system / NK cells.

MECHANISM OF TYPE II HYPERSENSITIVITY REACTION

BY THREE MECHANISMS

→ Complement mediated lysis of cell

→ Antibody dependent cell mediated cytotoxicity (ADCC)

→ Opsonisation

COMPLEMENT-MEDIATED LYSIS OF CELL

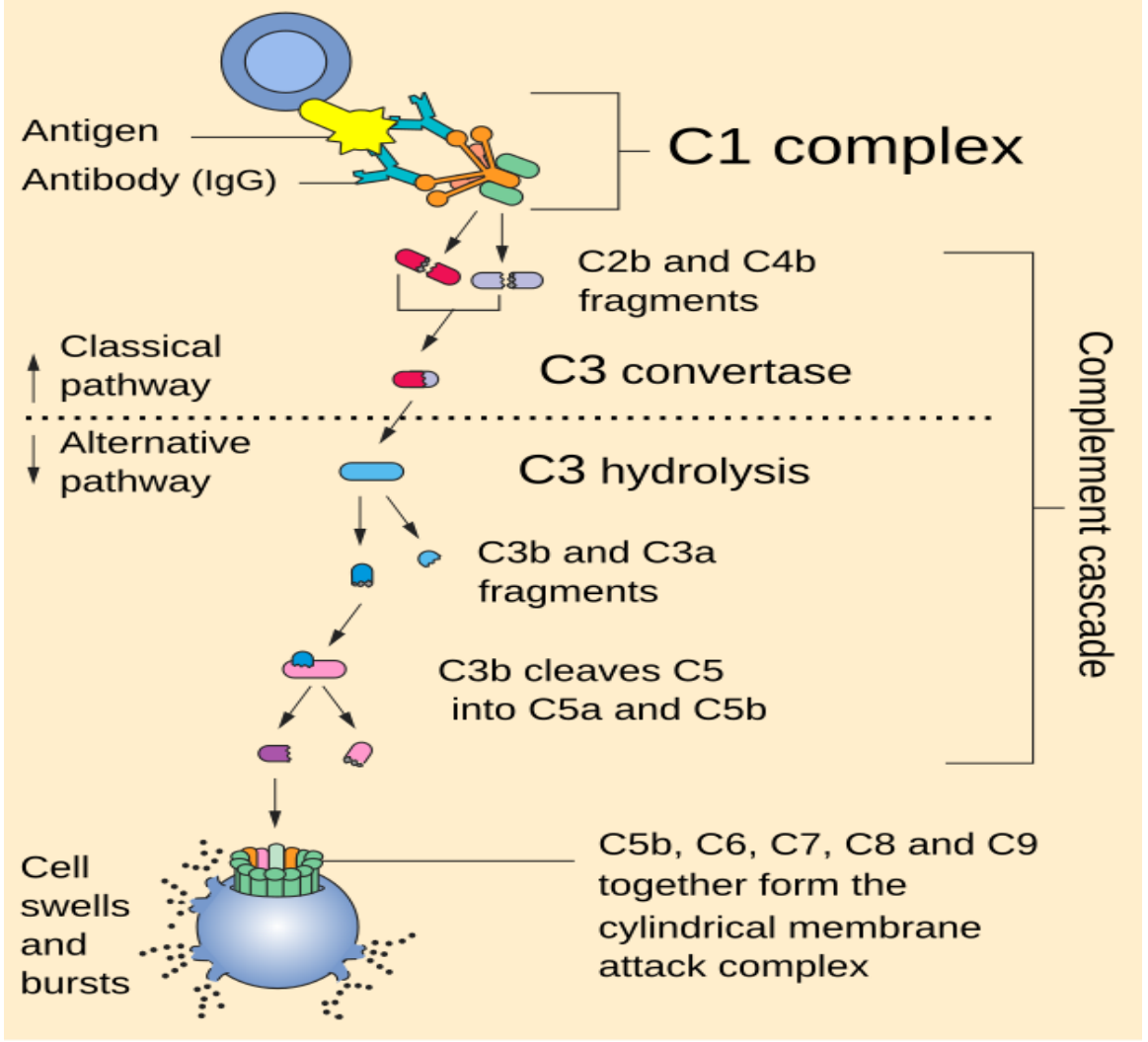
Complement mediated lysis is a process where the immune system destroys pathogens or infected cells. This involves the activation of the complement system, a group of proteins in the blood.

1. Activation: the complement system is activated via the classical, lectin, or alternative pathways.

2. C3 convertase formation: These pathways lead to the formation of C3 convertase, which splits C3 protein into C3a and C3b.

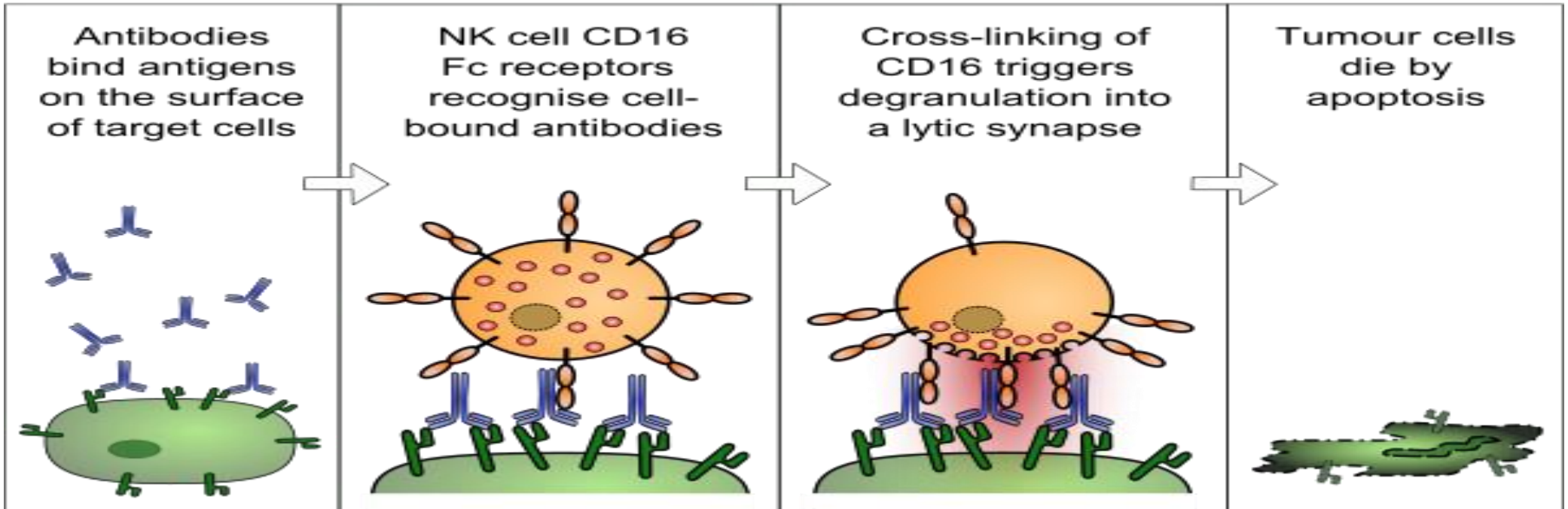
3. Membrane Attack Complex (CAM): C5b forms a complex with other complement proteins (C6, C7, C8, C9), creating the MAC, which forms pores in the target cell membrane.

4. Cell Lysis: The pores disrupt the cell membrane, causing the cell to burst and die.



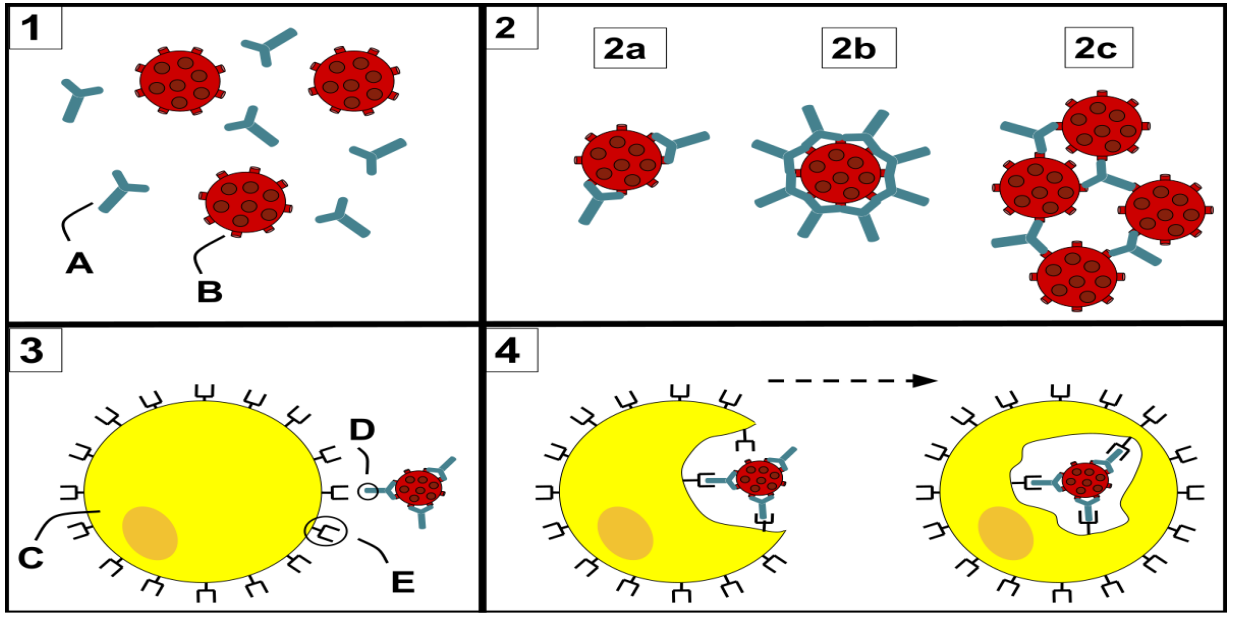
ANTIBODY DEPENDENT CELL MEDIATED CYTOTOXICITY (ADCC)

1. **ANTIBODY BINDING :** Antibodies attach to antigens on the target cell.
2. **EFFECTOR CELL RECOGNITION :** Immune cells like NK cells recognize the bound antibodies.
3. **EFFECTOR CELL ACTIVATION :** These immune cells are activated and release toxic molecules.
4. **CELL DESTRUCTION :** The toxic molecules kill the target cell.



OPSONIZATION

1. **OPSONIN BINDING :** Opsonins, such as antibodies, bind to the surface of the pathogen. This makes the detect the opsonins attached to the pathogen.
2. **RECOGNITION BY PHAGOCYES :** Immune cells like macrophages or neutrophils have receptors that detect the opsonins attached to the pathogen.
3. **PHAGOCYTOSIS :** Once recognized, the phagocytes engulf and digest the pathogen, effectively removing it from the body.

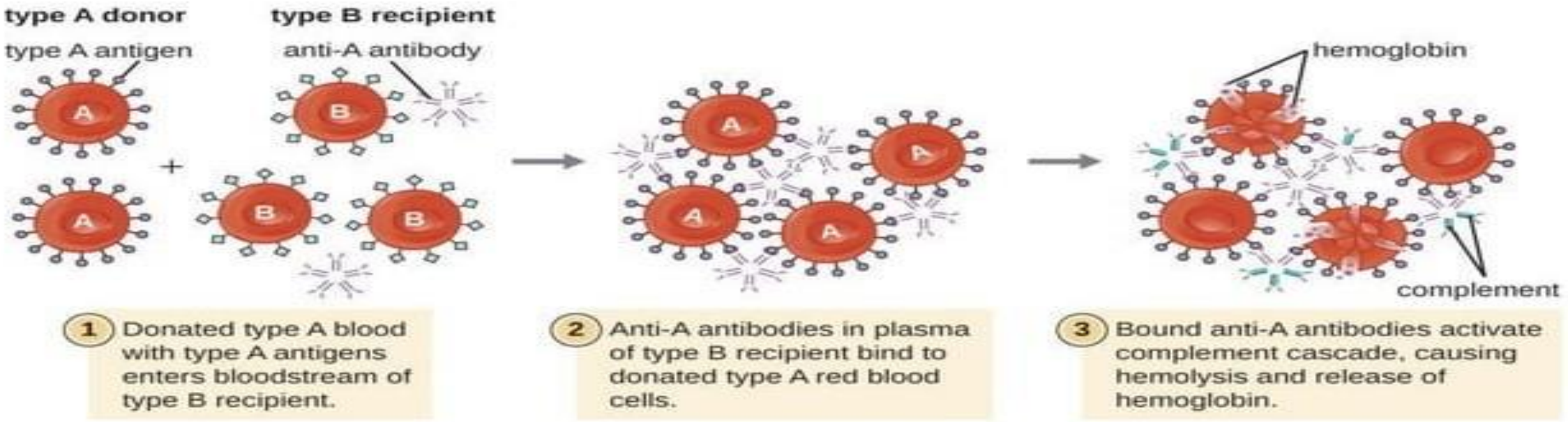


Some example of type II hypersensitivity

- Transfusion reactions
- Hemolytic disease of the newborn
- Autoimmune hemolytic anemia, agranulocytosis, and thrombocytopenia
- Specific drug reactions
- Myasthenia gravis, graves disease, and other autoimmune disorders

TRANSFUSION REACTIONS

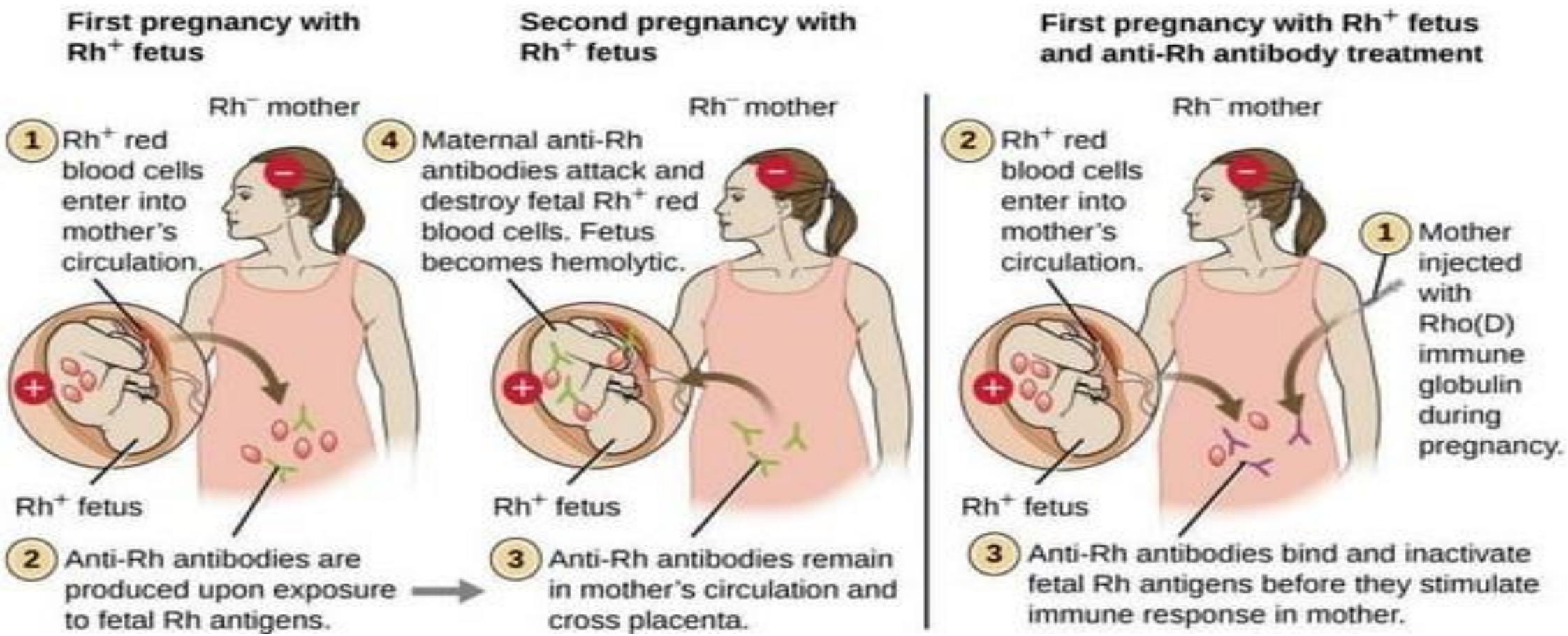
A large number of proteins and glycoproteins are present on the surface of RBCs, of which A, B, and O antigens are of particular importance. Antibodies to these antigens are called isohemagglutinins and are of IgM class. When transfusion with mismatched blood occurs, a transfusion reaction takes place due to the destruction of the donor RBCs through the isohemagglutinins against the foreign antigen.



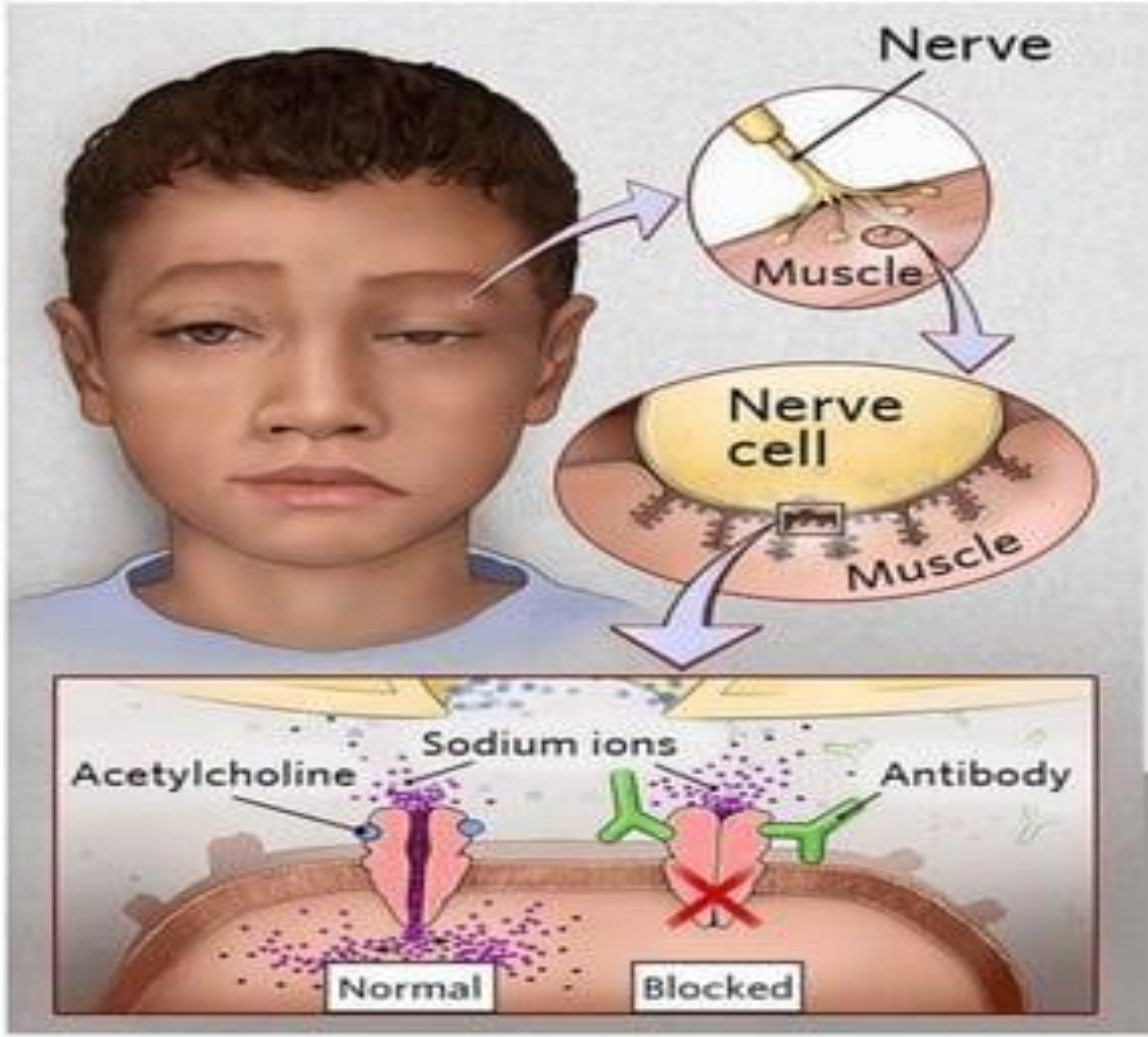
HEMOLYTIC DISEASE OF THE NEW BORN

Hemolytic disease of the newborn (HDN) is a condition where the immune system of a pregnant mother attacks the red blood cells on her unborn baby. This usually occurs when the mother blood type is Rh-negative and the baby blood type is Rh-positive.

1. **CAUSES :** If the mother is Rh-negative and the baby inherits Rh-positive blood from the father, the mother immune system may produce antibodies against the baby red blood cells.
2. **ANTIBODY ATTACK :** These antibodies cross the placenta and destroy the baby red blood cells, leading to hemolysis (breakdown of red blood cell).
3. **EFFECTS :** The destruction of red blood cells can cause anemia, jaundice, and in severe cases, heart failure in the baby.
4. **PREVENTION :** Rh-negative mothers can be given Rh immunoglobulin (Rhlg) during pregnancy to prevent the development of these antibodies.


First pregnancy with Rh+ fetus
Rh− mother
1 Rh+ red blood cells enter into mother's circulation.
Rh+ fetus
2 Anti-Rh antibodies are produced upon exposure to fetal Rh antigens.
Second pregnancy with Rh+ fetus
Rh− mother
4 Maternal anti-Rh antibodies attack and destroy fetal Rh+ red blood cells. Fetus becomes hemolytic.
Rh+ fetus
3 Anti-Rh antibodies remain in mother's circulation and cross placenta.
First pregnancy with Rh+ fetus and anti-Rh antibody treatment
Rh− mother
2 Rh+ red blood cells enter into mother's circulation.
1 Mother injected with Rho(D) immune globulin during pregnancy.
Rh+ fetus
3 Anti-Rh antibodies bind and inactivate fetal Rh antigens before they stimulate immune response in mother.

Myasthenia gravis



Myasthenia Gravis

Disease of Neuromuscular Junction

Features

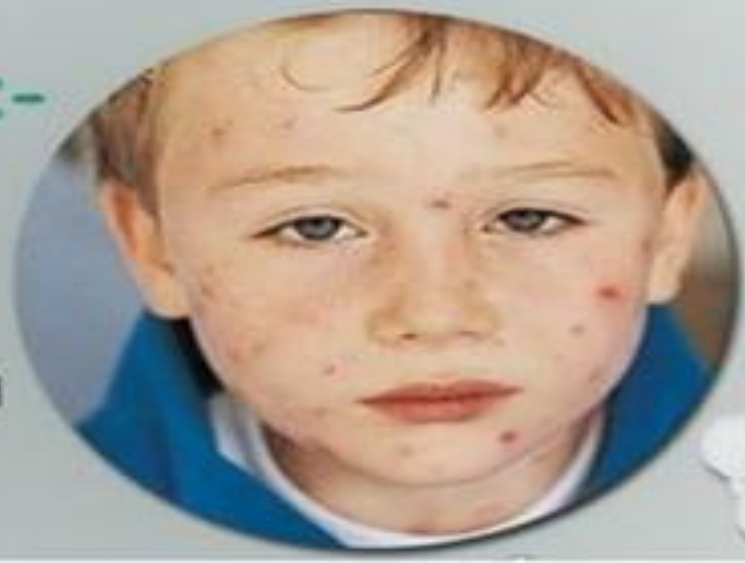
(1) Drooping of eyelids
(2) Weakness in arms legs
(3) Change of Voice
(4) Swalllowing Difficulty

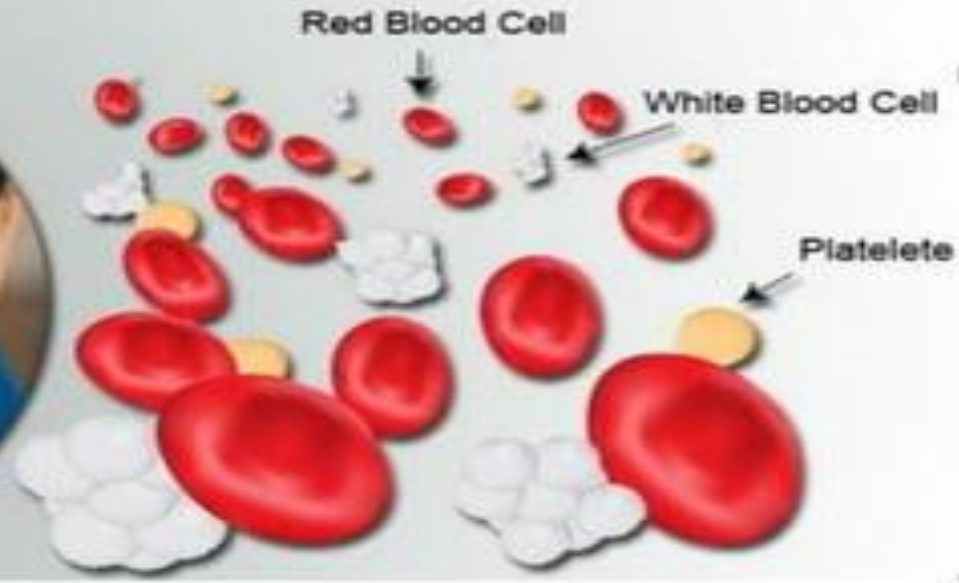
Thrombocytopenia

Immune thrombocytopenia Purpora or ITP is a blood disorder with a low blood platelet count.ITP is an autoimmune disorder where your immune system attacks your platelets.

Symptoms :-

- Excessive bruising.
- Blood in vomit, stool, or urine.
- Heavy menstrual period
- Nosebleed





An example of a cytotoxic reaction is **thrombocytopenia.**
In this disease, antibody molecules are elicited by certain drug molecules. The antibodies unite with antigens on the surface of thrombocytes (platelets), and with complement activation, the thrombocytes are destroyed. The result is an impaired blood-clotting mechanism.

HYPERSENSITIVITY REACTION TYPE 3

What is a hypersensitivity reaction?

- Our immune system plays a crucial role in protecting our body against pathogens, but sometimes there is an exaggerated response. This exaggerated response is triggered by the interaction of the immune system with an antigen (allergen) and is referred to as hypersensitivity.
- Where?
- Any part of our body commonly skin, GI tract, respiratory tract and Blood vessels.
- Why?
- Hypersensitivity reaction may occur due to various reasons like genetic and environmental factors.
- Common triggers: allergens like pollen, dust, mites, Foods etc….

HISTORY

- Maurice Arthus
- Discovered the Arthus reaction in 1903. Arthus observed that rabbits injected with horse serum repeatedly developed a local reaction, including edema, erythema, and induration.
- Gel and Coombs defined type III hypersensitivity reactions as those involving soluble immune complexes.

TYPE 3 –IMMUNE COMPLEX MEDIATED HYPERSENSITIVITY REACTION

- Hypersensitivity reaction Produced by the antigen-antibodies complex Is called immune complex.
- They can precipitate in various tissues such as skin, joints, vessels, or glomeruli and trigger the classical complement pathway.
- Complement activation leads to the recruitment of inflammatory cells (monocytes and neutrophils) that release lysosomal enzymes and free radicals at the site of immune complexes, causing tissue damage.
- The most common diseases involving a type III hypersensitivity reaction are serum sickness, post-streptococcal glomerulonephritis, systemic lupus erythematosus, farmers' lung (hypersensitivity pneumonitis), and rheumatoid arthritis.

Mechanism of Type III (Immune Complex) Hypersensitivity

- In type III hypersensitivity, antibodies bind to antigens to form immune complexes in the circulation. These complexes travel through the blood-stream and get deposited in various susceptible tissues.
- There are two major forms of immune complex-mediated hypersensitivity.

Localized type 3 reaction or Arthu's Reaction:

- The immune complexes are formed locally that is directly in the tissues mostly seen in the skin and pulmonary diseases resulting from inhaled antigens.
- Microscopic examination of tissue reveals neutrophil adhering to the vascular endothelium and migrating into the tissues at the site of immune complexes deposition.
- Eg: Arthus reaction and hypersensitive pneumonitis

Generalized Type 3 Reaction

- When large amounts of antigen enter the bloodstream and bind to an antibody, circulating immune complexes can form. If antigens in excess, small complexes form because these are not easily cleared by the phagocytic cells, they can cause tissue damaging type reactions at various sites.
- Eg: serum sickness and Glomerulonephritis

What is an Arthus reaction?

An Arthus reaction refers to an acute, localized inflammatory response that typically occurs after vaccination. It is classified as a type III hypersensitivity reaction, which is when antigen-antibody clusters, also known as immune complexes, are formed due to an abnormal immune system response. The reaction usually presents at the site of injection after a vaccination (e.g., tetanus-diphtheria booster). In some rare instances, an Arthus reaction may result from multiple, repeated insect bites.

Symptoms

- Most individuals present with redness, swelling, and pain. It can also subsequently lead to induration (i.e., hardening of the area due to increased fibrous tissue) localized to the affected area.

HYPERSENSITIVITY PNEUMONITIS

- Hypersensitivity pneumonitis is a rare immune system disorder that affects your lungs. This disease is also called bird fancier’s lung, extrinsic allergic alveolitis, farmer’s lung, hot tub lung, or humidifier lung.
- Hypersensitivity pneumonitis can happen when you repeatedly breathe in bacteria , mold, or chemicals in your environment that cause inflammation in your lungs.

Symptoms:

- Shortness of breath
- Cough
- Abnormal sounds when you breathe (called rales)
- Flu-like illness
- Condition
- Chest pain

Bagassosis

The fungi Thermoactinomyces saccharic and T. vulgaris thrive in pressings from saccharis. Subjects working in sugarcane mills may inhale dust from molding hot sugarcane bagasse and develop type III (Arthus reaction) hypersensitivity. The condition is expressed as a hypersensitivity pneumonitis

Farmer’s lung

This is another instance of hypersensitivity pneumonitis. Farmer’s lung is caused by Actinomycetes (or other organic dusts), which thrive in moldy hay. Subjects working in such environments may develop antibodies to the mold spores. Subsequent inhalation of dust containing spores may induce hypersensitivity pneumonitis characterized by nausea, chills, fever, coughing, tachycardia, dyspnea, and cyanosis. Treatment would include standard antiallergic regimens such as those consisting of cromolyn sodium and corticosteroids.

Humidifier lung

This condition, also known as air-conditioner lung, is common among workers involved with refrigeration and air-conditioning equipment. The hypersensitivity is due to the various species of the fungi Micropolyspora and Thermoactinomyces.

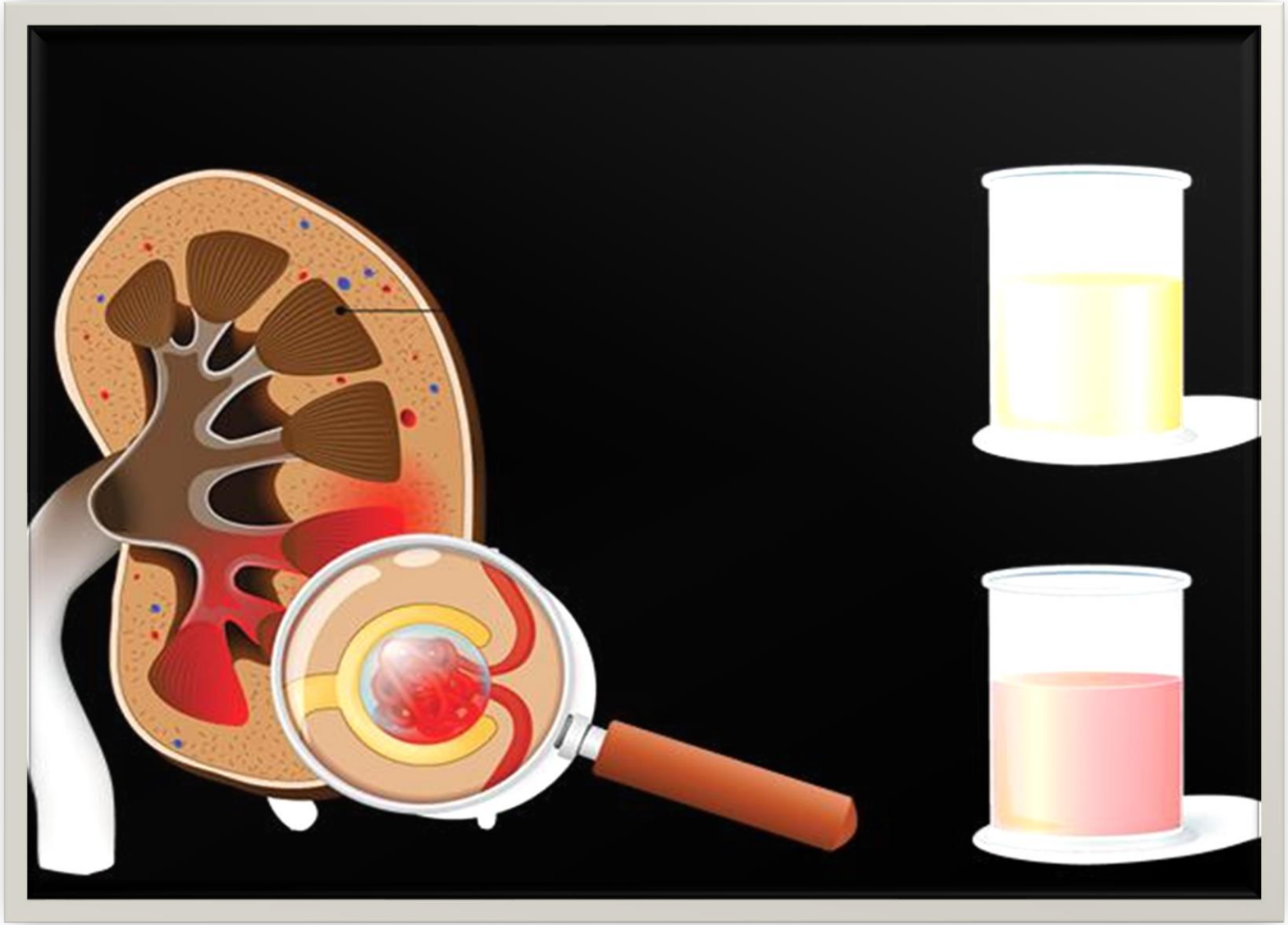
Bird fancier’s lung

Known variously as bird breeder’s lung, pigeon breeder’s lung, or hen worker’s lung, this form of hypersensitivity pneumonitis is due to antigens in bird droppings.

GLOMERULONEPHRITIS

- Glomerulonephritis is a type of inflammation that can occur in the kidneys as a result of a type III hypersensitivity reaction.
- They can be due to genetic errors, autoimmunity, microbes or abnormal immunoglobulins, like modified IgA or paraproteins.
- Immune complex−mediated glomerulonephritis that is induced by infection may involve an antecedent infection, such as streptococcal pharyngitis or pyoderma preceding acute poststreptococcal glomerulonephritis.
- An assessment of kidney function, amount of proteinuria and hematuria are crucial elements to evaluate, when glomerulonephritis is suspected.

GLOMERULONEPHRITIS



SERUM SICKNESS

- Generalized Type 3 reaction were often observed after the administration of antitoxins containing foreign serum, such as horse anti- tetanus or anti- diphtheria serum.
- In such cases, the recipient of a foreign antiserum develops antibody specific for the foreign serum proteins these antibodies then form circulating immune complex with foreign serum antigens.
- Typically within days or weeks after exposure to foreign serum antigens, an individual begins to manifest a combination of symptoms that are called serum sickness.
- What are the symptoms?
- Fever
- Weakness
- Generalized vasculitis (rashes)with edema and erythema.

- The precise manifestation of serum sickness depends on the quantity of immune complexes formed as well as overall size of the complex, determine the size of their deposition.
- Formation of circulating immune complexes contribute to the pathogenesis of a number of conditions other than serum sickness.

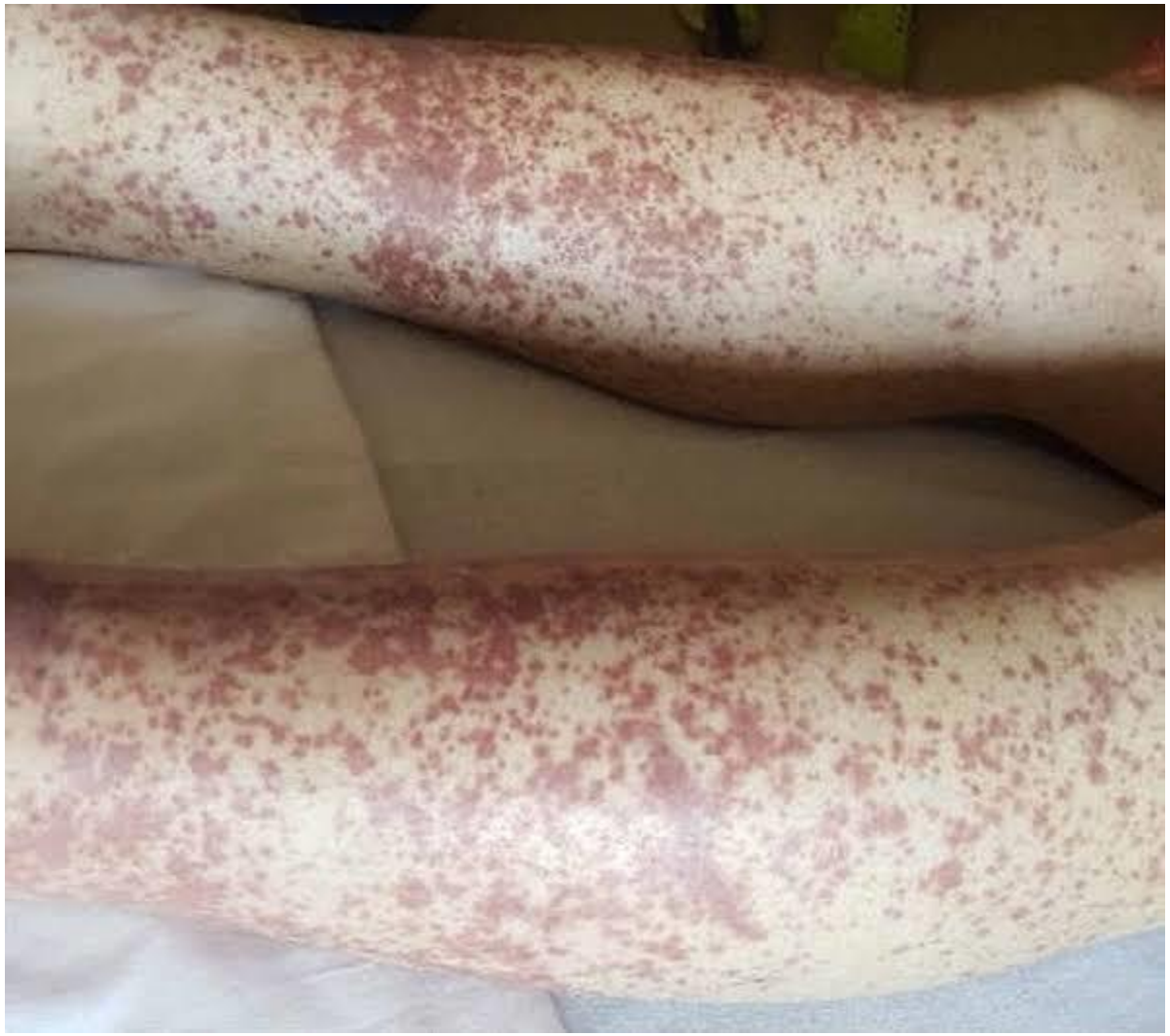
Autoimmune diseases

- Systemic lupus erythematosis
- Rheumatoid arthritis
- Goodpastures syndrome

Drug reactions

- Allergies to penicillin and sufonamides

Systemic lupus erythematosis

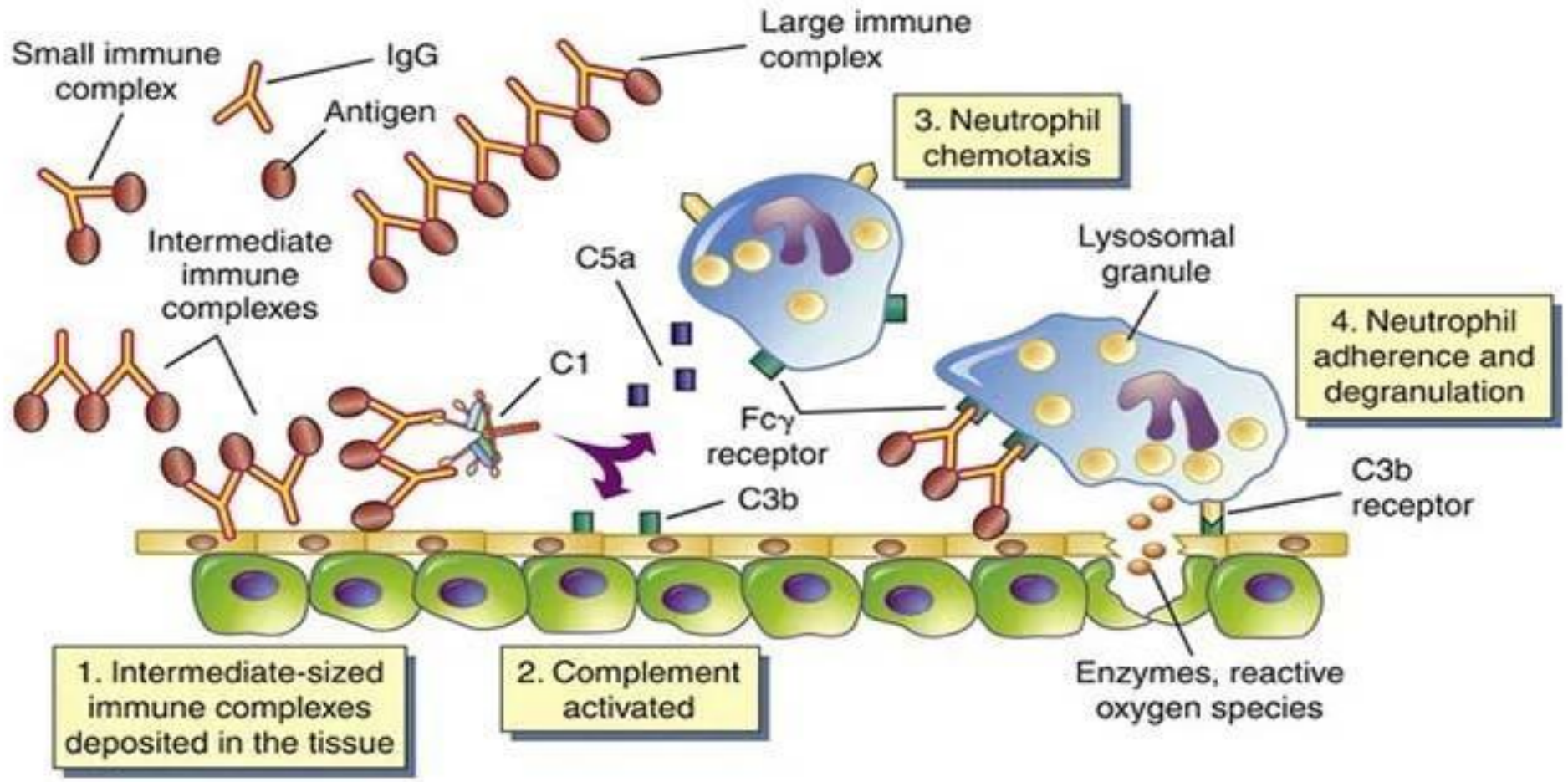


The mechanism of both the types can be summarized as follows:

- Antigen-antibody complexes are formed when antibodies bind to antigens.
- Incase the complex is not cleared by normal process of phagocytosis, the immune complexes persist in the circulation.
- The immune complexes subsequently deposit in tissues.
- The tissue deposited complexes activate the classical complement cascade.
- The complement fragments (e.g. C3a and C5a) that form during complement activation activate a variety of potent mediators of inflammation causing an influx of neutrophils and monocytes to the site of deposition.
- The attracted neutrophils attempt to engulf the immune complexes. Since the complexes are deposited over the tissues, the neutrophils do not succeed.

- Consequently, the neutrophils release a number of substances like prostaglandins, lysosomal enzymes, and free oxygen radicals over the complexes causing damage to the tissues at the site of immune complex deposition.
- Additionally, the binding of the Fc region of antibody in the immune complex may bind to the Fc receptor on platelets causing aggregation, blood clots and blockage of blood vessels leading to hemorrhages at the site.

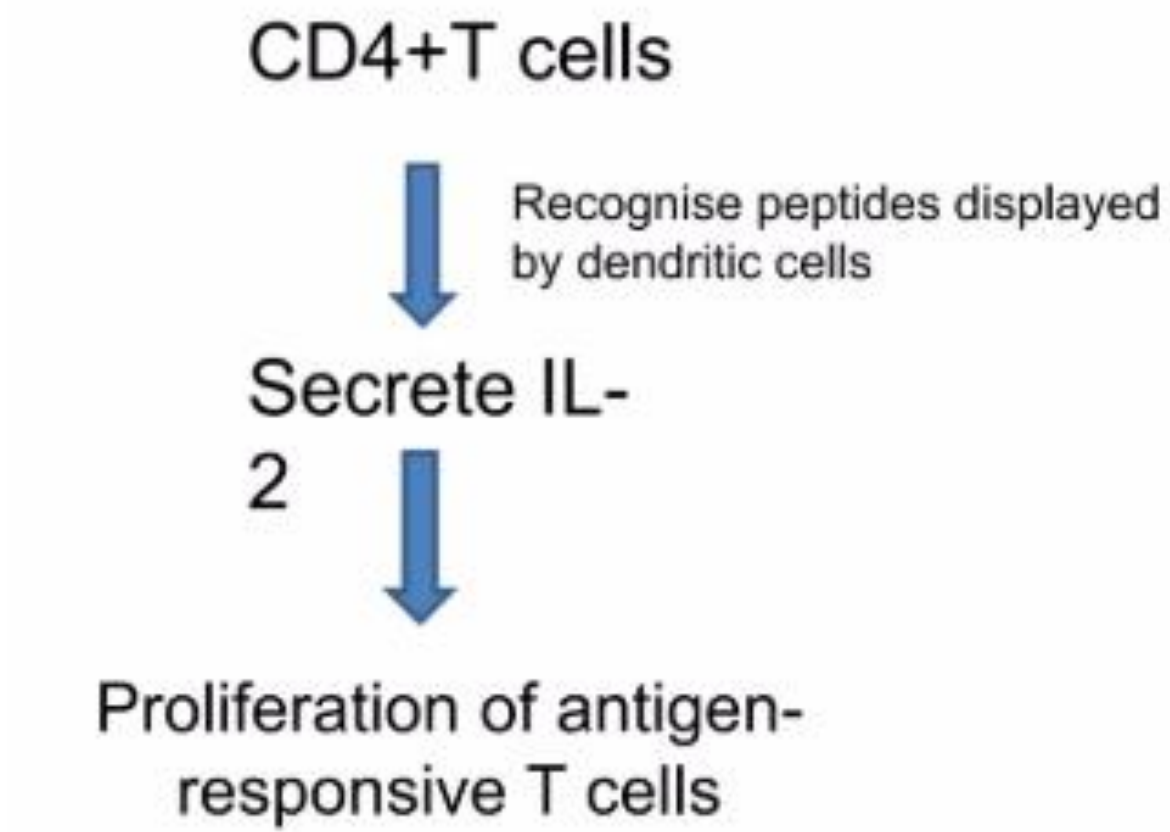
HYPERSENSITIVITY REACTION TYPE 3



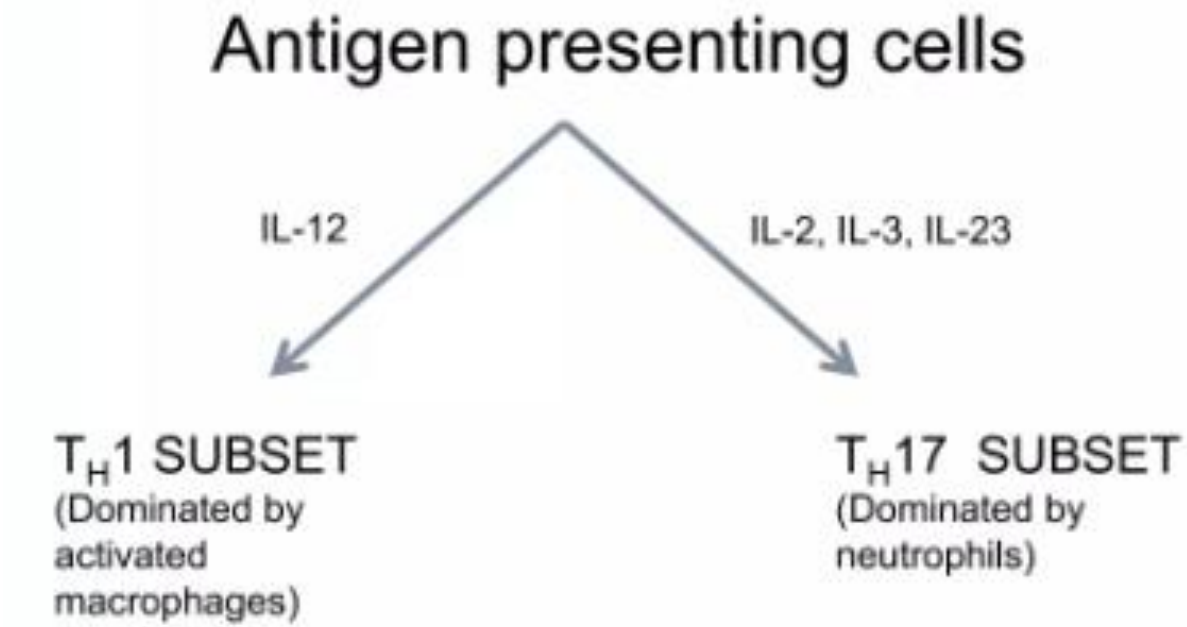
Type IV Hypersensitivity

- Cell-mediated immune disorders
- Caused by:
  - Cytokines produced by CD4+T cells
  - Cell killing by CD8+ T cells

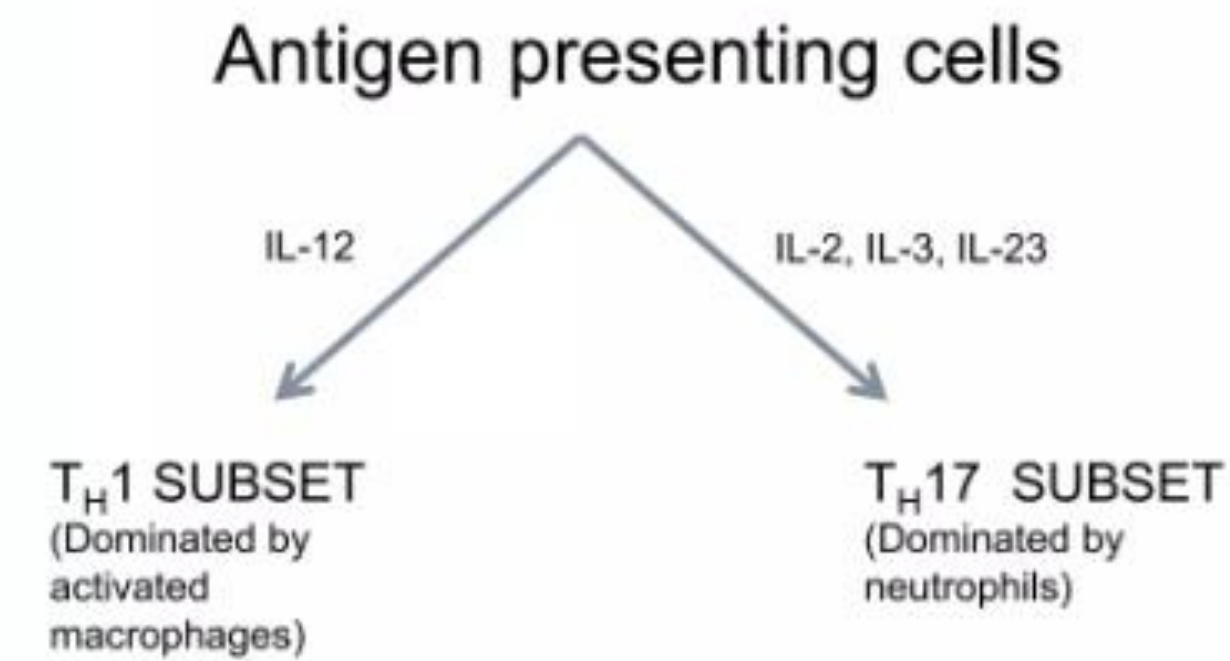
Activation of CD4+T cells

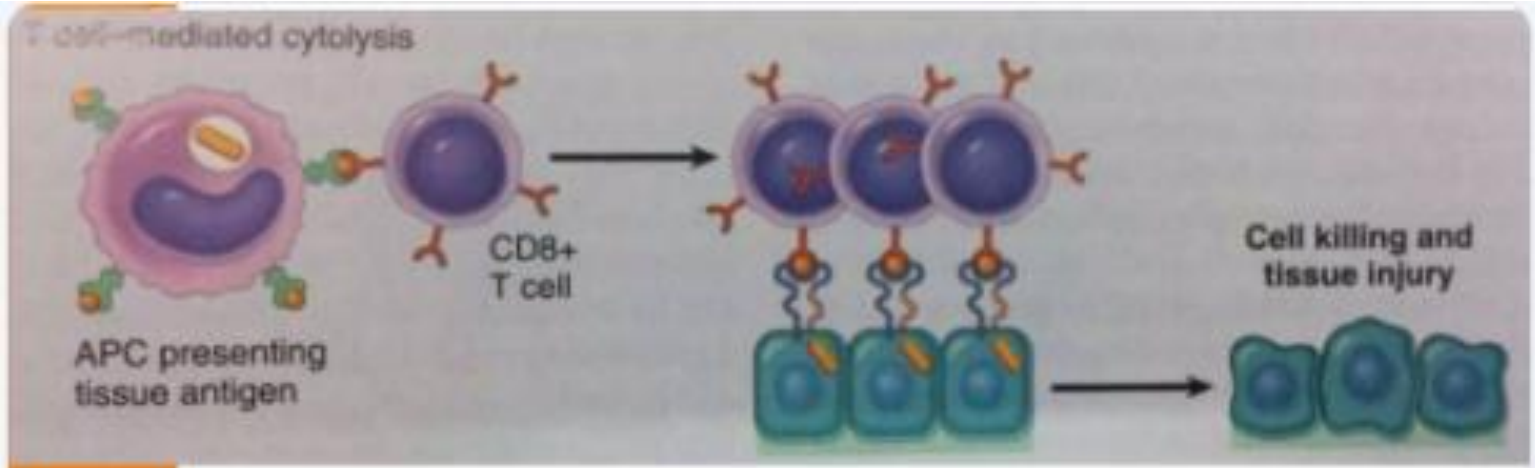


Differentiation of antigen responsive T-cells



Differentiation of antigen responsive T-cells





T-cell mediated killing of targets involves:

- Perforins and granzymes
- Activation of apoptosis.
- Examples: Type 1 Diabetes Mellitus

ACKNOWLEDGEMENT

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