Hypersensitivity Reaction

-Hypersensitivity refers normal but uncontrolled immune response to the Ags that can produce (inflammation, cell destruction , tissue injury and sometimes fatal) produced by the normal immune system.

-Unusual reaction such as allergic or hypersensitive reaction follows the second exposure to the antigen

-Antigens that trigger allergic reactions are called **allergens.**

(low-molecular-weight substances can enter the body by being inhaled, eaten, or administered as drugs).

Hypersensitivity Reaction

By
Dr. Raghed M. Jassem

Pathogenic mechanisms

*** First exposure to allergen**

Allergen stimulates formation of antibody (IgE type)

IgE fixes, by its Fc portion to it`s receptor (Fcε; CD23) on mast cells and basophiles

*** Second exposure to the same allergen**

binding of allergen to IgE molecules fixed to mast cells leading to activation and degranulation of mast cells and release of mediators

- **Three classes of mediators derived from mast cells:**

1) **Preformed mediators stored in granules (histamine)**
Increases vascular permeability; promotes contraction of smooth muscle

2) **Newly sensitized mediators:**

- **leukotrienes :-** Alter bronchial smooth muscle and enhance effects of histamine on target organs.

- **Prostaglandins:-** Affect smooth muscle tone and vascular permeability

- **Platelets activating factor:-** Enhances the release of histamine and serotonin from platelets

3) **Cytokines produced by activated mast cells & basophiles**
e.g. TNF, IL-3, IL-4, IL-5 IL-13, chemokines

* **These mediators cause:** increase smooth muscle contraction, mucous secretion and bronchial spasm, vasodilatation, increase vascular permeability and edema.

Types of hypersensitivity :-

There are four types of hypersensitivity reactions based on the mechanisms involved and time taken for the reaction :

Type I , Type II, Type III, Type IV

* Types I, II and III are antibody mediated

* Type IV is cell mediated

Type I: Immediate hypersensitivity

-It can range from life threatening anaphylactic reaction to milder manifestations associated with food allergies hypersensitivity.

- **(Anaphylactic reaction (Anaphylaxis)**:- systemic form of type I hypersensitivity an inflammatory reactions produced by an Ag combining with IgE bound to a mast cell :-

1. The offending antigen attaches to the IgE antibody fixed to the surface membrane of mast cells and basophils. Cross-linking between Ag & IgE molecules is necessary to release mediator from mast cells.

2. Activated mast cells and basophils release various mediators.

3. The effects of mediator: produce vascular changes and activation of platelets, eosinophils , neutrophils, and the coagulation cascade

Allergens: Drugs: penicillin

Serum injection : anti-diphtheritic or anti-tetanic serum

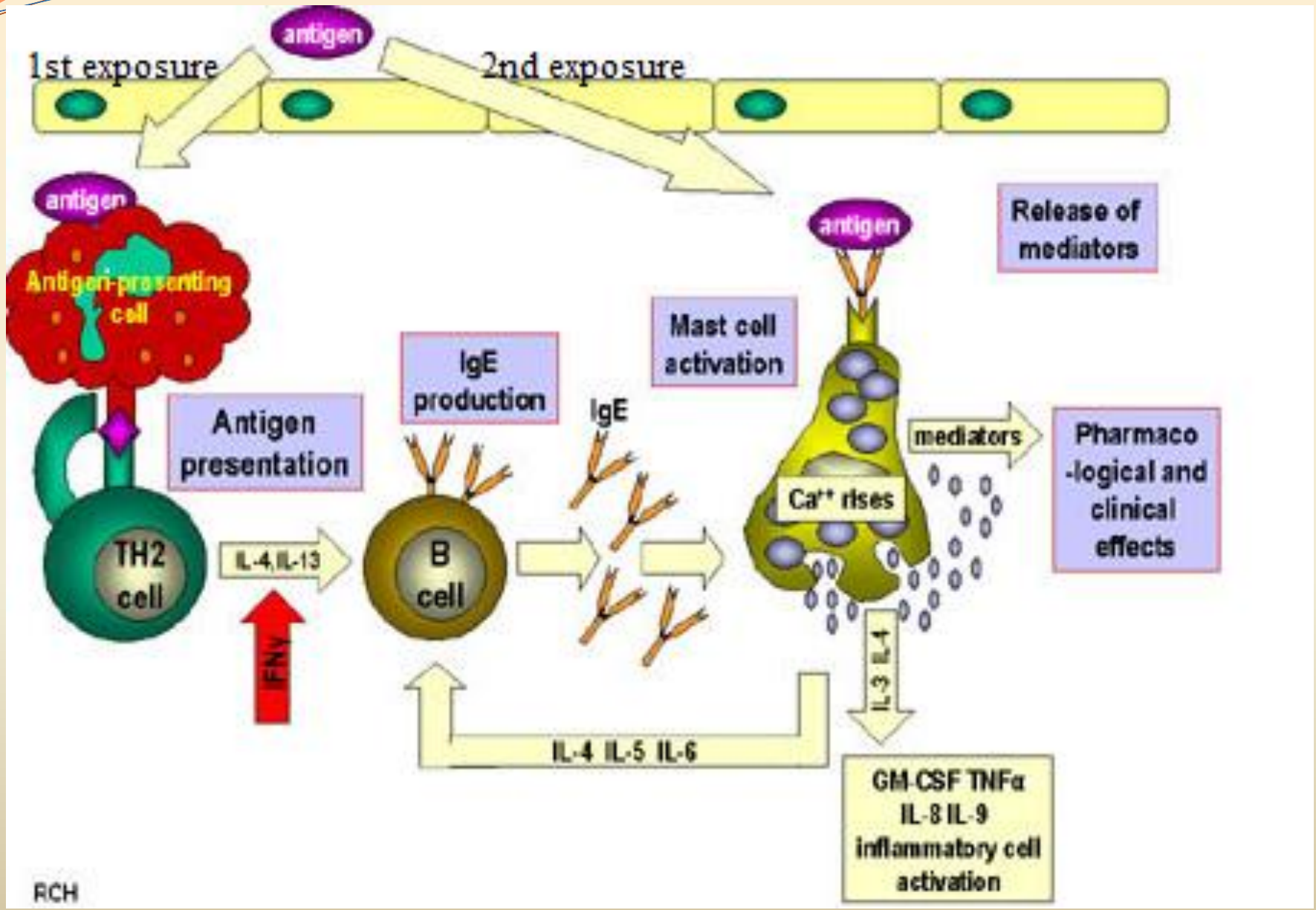
* **Clinical picture:**

Shock due to sudden decrease of blood pressure, respiratory distress due to bronchospasm, cyanosis, edema, urticaria

- **Treatment:** corticosteroids injection & antihistamines. Also adrenaline can be lifesaving in anaphylaxis.

-The reaction usually takes 15 - 30 minutes from the time of exposure to the antigen, although sometimes it may have a delayed onset (10 - 12 hours).

- It is believed that physical allergies (e.g., to heat, cold, ultraviolet light) cause a physiochemical derangement of proteins or polysaccharides of the skin and transform them into **autoantigens** responsible for the allergic reaction.


antigen
1st exposure
2nd exposure
antigen
Antigen-presenting cell
Antigen presentation
TH2 cell
IL-4,IL-13
IFNγ
IgE production
B cell
IgE
Mast cell activation
antigen
Release of mediators
Ca++ rises
mediators
Pharmaco -logical and clinical effects
IL-3 IL-4
IL-4 IL-5 IL-6
GM-CSF TNFα IL-8 IL-9 inflammatory cell activation
RCH

- **Atopic reaction** :- it is a local atopic allergies (localized reaction) occurs as an immediate response to mediators released from mast cell degranulation which may involve

- skin (urticaria and eczema)
- eyes (conjunctivitis)
- nasopharynx (rhinitis)
- bronchopulmonary tissues (asthma)
- gastrointestinal tract (gastroenteritis) or food allergy.

- Localized reactions are severe but rarely fatal

- Skin reactions are characterized be the appearance of redness and itching at the site of the introduction of the allergen.

The most important type of allergen are :-

- Inhalants: dust, mite feces, tree or pollens, mould spore.
- Ingestants : milk, egg, fish, chocolate and wheat
- Contacts : wool, nylon, animal fur

This phenomenon can be diagnosis by making of skin test to identify an allergy or confirm sensitivity to a specific antigen.

* There is a strong familial predisposing to atopic allergy

Type II: Cytotoxic hypersensitivity(Ab dependent):-

The immune response will be produced when the initiated antibodies bind to antigens on the patient's own cell surfaces.

- This antigen may be normally endogenous (part of cell membrane or circulating antigen) or exogenous chemical (hapten) that attaches to cell membrane.

Ex :- Drug-induced hemolytic anemia, ,immune hemolytic anemia in a new borne and thrombocytopenia .

•The reaction time is minutes to hours

•It is type of autoimmune disease

How it develops ???

The antibodies produced by the immune response bind to antigens on the patients own cell surfaces.

These cells will be acting as antigen-presenting cells. This causes a B cell response (produced Abs) against the foreign antigen.

An example of type II hypersensitivity is the reaction to penicillin wherein the drug can bind to red blood cells, causing them to be recognized as different; B cell proliferation will take place and antibodies to the drug are produced. IgG and IgM antibodies bind to these antigens to form complexes that cause activated :-

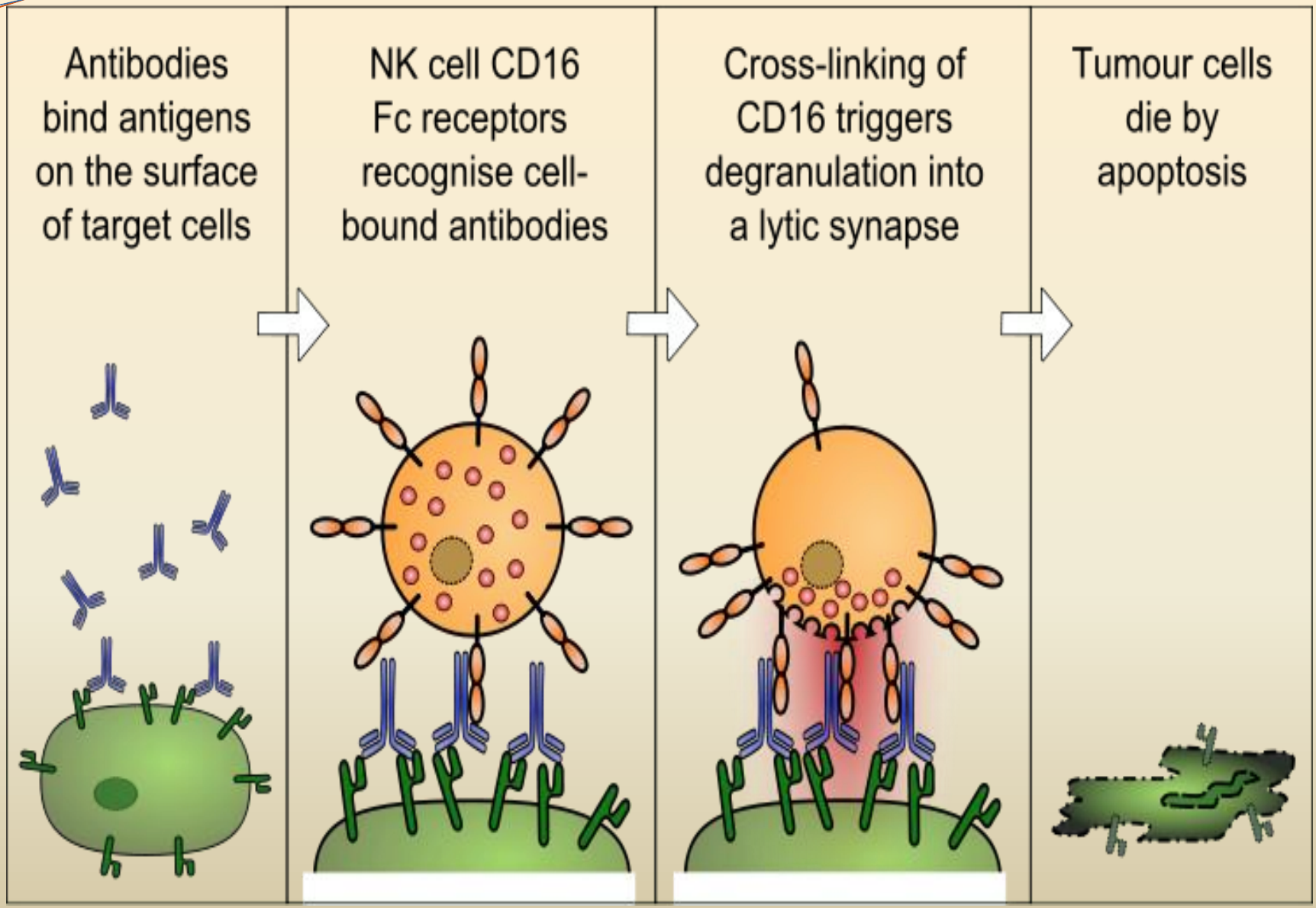
Mechanism of Cytolysis

* Cell lysis due to :

1) **Complement fixation** to (Ab-Ag) complex on cell surface (erythrocytes, leukocytes and platelets) . Activation of complement will lead to cell lysis by (MAC) ex:-acute transfusion reactions

2) **Antibody depended cellular cytotoxicity (ADCC):**

Cells are coated with specific antibodies (e.g. tumor cells, graft cells or infected cells) then the Abs coated cells can be lysis (killed) by cells possess Fc receptors like (NK, macrophages, neutrophils and eosinophils). Once the Fc receptor binds to the Fc region of IgG, the Natural Killer cell releases cytokines such as IFN-γ, and cytotoxic granules containing perforin and granzymes that enter the target cell and promote cell death by triggering apoptosis.


Antibodies bind antigens on the surface of target cells
NK cell CD16 Fc receptors recognise cell-bound antibodies
Cross-linking of CD16 triggers degranulation into a lytic synapse
Tumour cells die by apoptosis

Diagnostic Evaluation. The following procedures are generally used for the prenatal or postnatal diagnostic evaluation of **(Hemolytic Disease of the Fetus and Newborn)** (HDFN):

- ABO blood grouping
- Rh testing
- Screening for irregular antibodies; identification and tittering of any antibodies

Prevention and treatment :-

Checking the donor and recipient and providing immunization to prevent HDFN in new born infants

Type III Hypersensitivity (Immune Complex Mediated Reaction)

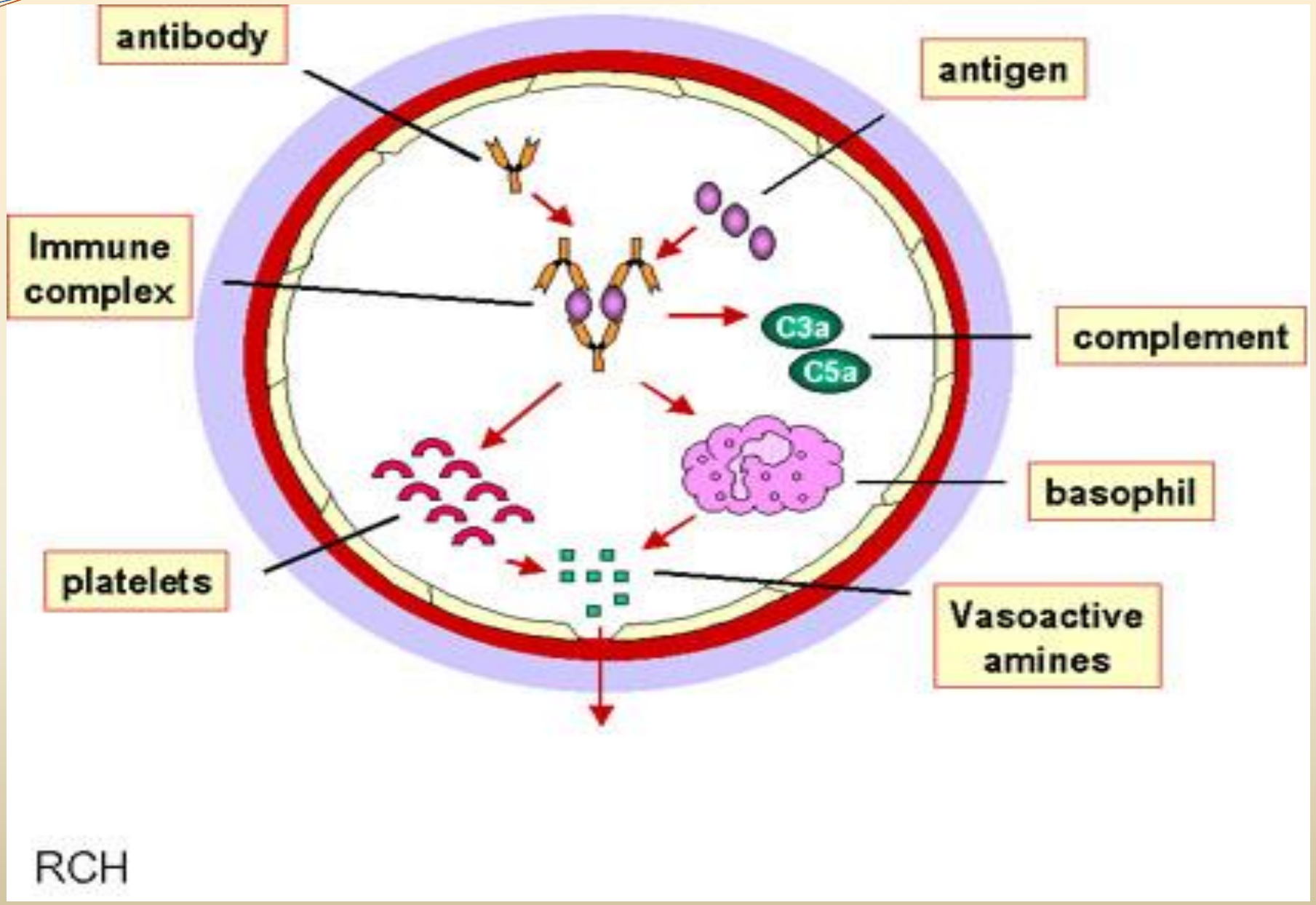
Type III hypersensitivity reactions are caused by the deposition of immune complexes in blood vessel walls and tissues.

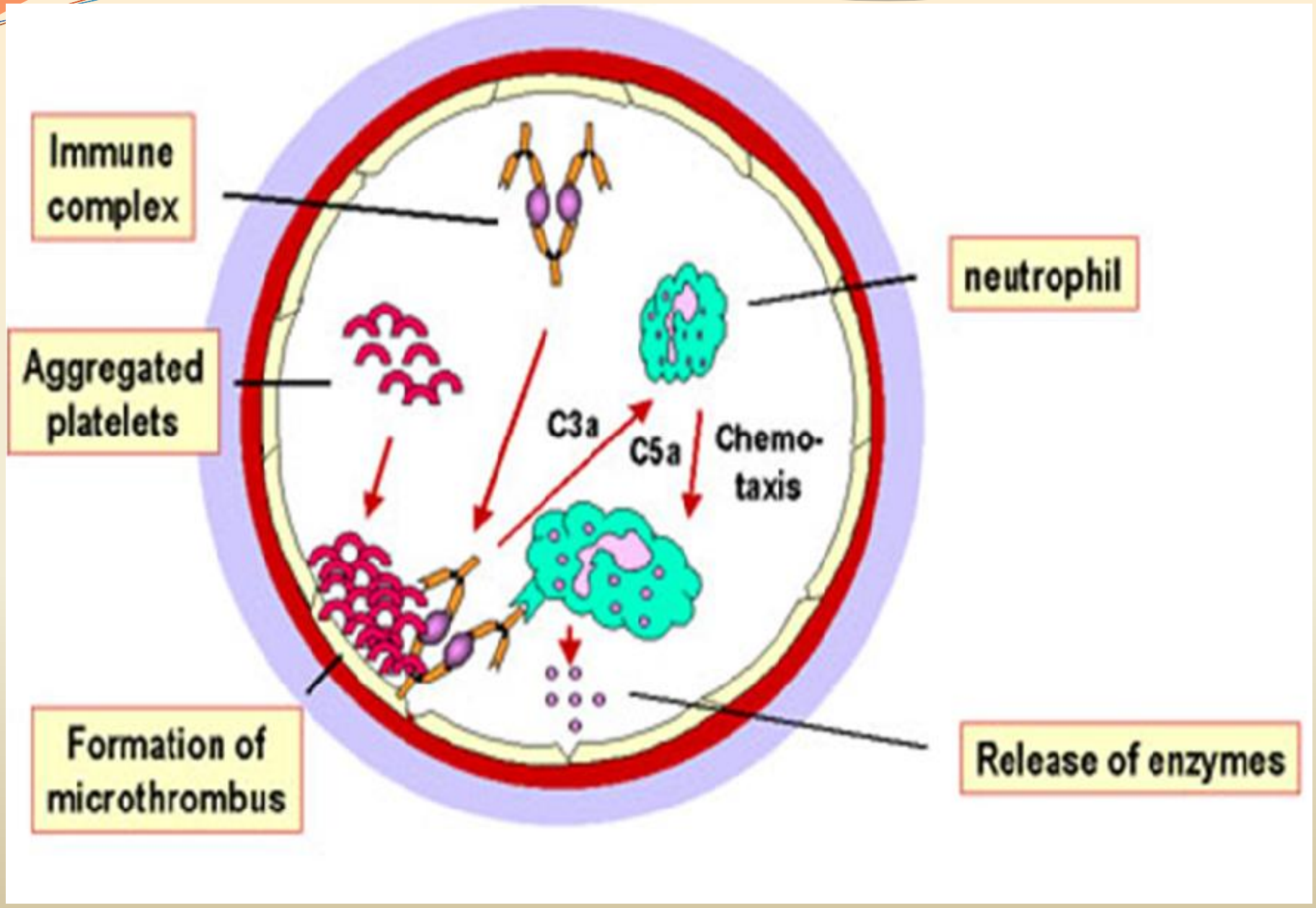
Repeated antigen exposure leads to sensitization individual with the production of specific (IgM & IgG) that will be leading to an insoluble antigen-antibody complex formation (as part of the normal immune response) .During normal condition these complexes are usually cleared by complement system activation or by macrophages and leukocytes attracted . But if these complexes are deposited in tissues so they are caused disease in various situations.

How it develops ???

- Failure of the immune system to clear immune complexes because it present in a soluble form and form small immune complex
- These immune complexes insert themselves into small blood vessels, joints, and glomeruli, causing symptoms.
- Such depositions in tissues induce an inflammatory response, and can cause damage wherever they precipitate. The cause of damage is as a result of the action of cleaved complement anaphylotoxins C3a & (C5a) mediate the induction of granule release from mast cells (histamine can cause urticaria)

- Also cause recruitment of inflammatory cells into the tissue (mainly those with lysosomal action, leading to tissue damage through phagocytosis by PMNs and macrophages)
- The reaction can take hours, days, or even weeks to develop, depending on whether or not there is immunlogic memory of the precipitating antigen.
- ex:- chronic infection such as HBs.


antibody
antigen
Immune complex
C3a
C5a
complement
basophil
platelets
Vasoactive amines
RCH


Immune complex
neutrophil
Aggregated platelets
C3a
C5a
Chemo-taxis
Formation of microthrombus
Release of enzymes

There are two general anatomic sites of antigen-antibody interactions:

1. Antibody can react with soluble antigens in the circulation and form immune complexes & that antigen may be exogenous (chronic bacterial, viral or parasitic infections)

2. Antibody can also react with structural antigens that form part of the cell surface membranes or with fixed intercellular structures such as the basement membranes. The endogenous (non-organ specific autoimmunity: *e.g.*, systemic lupus erythematosus, SLE).

Clinical conditions of Type III Hypersensitivity

-The reaction may be general (*e.g.*, serum sickness)(it is an inflammatory reaction to protein that derived from nonhuman source) (ex:- animal serum or some drug)

-Or may involve individual organs including skin (*e.g.*, systemic lupus erythematosus), kidneys (*e.g.*, lupus nephritis), lungs (*e.g.*, aspergillosis), blood vessels (*e.g.*, polyarteritis), joints (*e.g.*, rheumatoid arthritis) or other organs.

Diagnosis :- through

1- the present of circulating immune complexes in serum

2- depletion in the level of complement

3-Fluorescent staining of tissue biopsy specimens can be used to observe the deposition of immune complexes in tissues

Type IV: Cell Mediated Delayed Type Hypersensitivity (DTH)

➢It differ from other three types of hypersensitivity in an important points:
1-Is depend on activation of specific effector Th1 cells rather than on Ab
2- It starts after a latent period of several hours and peaks at 48-72 hr

Mechanisms of damage in delayed hypersensitivity :- Group of T cell mediated responses to antigen

- Direct killing of target cells (by CD8+ T cells)

- Indirect via activation of macrophages & CD4+ T cells (Th1)

Helper T (Th1) cells secrete cytokines (IL-2 ,IFN-gamma and TNF alpha/beta, *etc)* cause activation of monocytes and more macrophages, which also cause damage .The delayed hypersensitivity lesions mainly contain monocytes and a few T cells.

.

DTH reactions are initiated when tissue macrophages recognize the presence of danger signals and initiate the inflammatory response. Dendritic cells loaded with antigen migrate to local lymph nodes, where they present antigen to T cells.

Specific T cell clones proliferate in response to antigens and migrate to the site of inflammation. T cells and macrophages stimulate one another through the cytokine network.

Tumor necrosis factor-α (TNF-α) is secreted by macrophages and T cells and stimulates much of the damage in DTH reactions .

Characteristics DTH are involved

- In the pathogenesis of many autoimmune
- DTH is a major mechanism of defense against various intracellular pathogens, including mycobacteria, fungi, and certain parasites
- Rejection of foreign tissue grafts,
- Elimination of tumor cells bearing neoantigens
- Formation of chronic granulomas

DTH can be a physiologic reaction to pathogens that are difficult to clear, such as Mycobacterium tuberculosis. This triggers the most extreme DTH reactions, characterized by granuloma formation, extensive cell death, and appearance of necrosis.

	Hypersensitivity Types and Their Mechanisms			
	Type I	**Type II**	**Type III**	**Type IV**
Immune reactant	IgE	IgG or IgM	IgG and IgM	T cells
Antigen form	Soluble antigen	Cell-bound antigen	Soluble antigen	Soluble or cell-bound antigen
Mechanism of activation	Allergen-specific IgE antibodies bind to mast cells via their Fc receptor. When the specific allergen binds to the IgE, cross-linking of IgE induces degranulation of mast cells.	IgG or IgM antibody binds to cellular antigen, leading to complement activation and cell lysis. IgG can also mediate ADCC with cytotoxic T cells, natural killer cells, macrophages, and neutrophils.	Antigen-antibody complexes are deposited in tissues. Complement activation provides inflammatory mediators and recruits neutrophils. Enzymes released from neutrophils damage tissue.	T_H1 cells secrete cytokines, which activate macrophages and cytotoxic T cells.
Examples of hypersensitivity reactions	Local and systemic anaphylaxis, seasonal hay fever, food allergies, and drug allergies	Red blood cell destruction after transfusion with mismatched blood types or during hemolytic disease of the newborn.	Post-streptococcal glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Contact dermatitis, type I diabetes mellitus, and multiple sclerosis

Tuberculin –Type Hypersensitivity

* When the tested Ag is injected intradermally in sensitized person

* Local indurate area appears injection site (48-72 hs)

* Indurations due to accumulation of: macrophages and lymphocytes

* Similar reactions observed in diseases

e.g. brucellosis and lepromin test in leprosy

Methods of diagnosis

1) History taking for determining the allergen involved

2) Skin tests:

Intradermal injection of different allergens

A wheal and erythema develop at the site of allergen to which the person is allergic

3) Determination of total serum IgE level and specific IgE levels to the different allergens for type I.

4) The presence of antibody and complement in the lesion (biopsy) by immunofluorescence in type II (appear in the linear form) and type III (appear in granular form)