UNIVERSITATEA DE STAT DE MEDICINĂ ȘI FARMACIE
"NICOLAE TESTEMIȚANU" DIN REPUBLICA MOLDOVA

Diseases of Immune System

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"Double – edge sword" of immune response

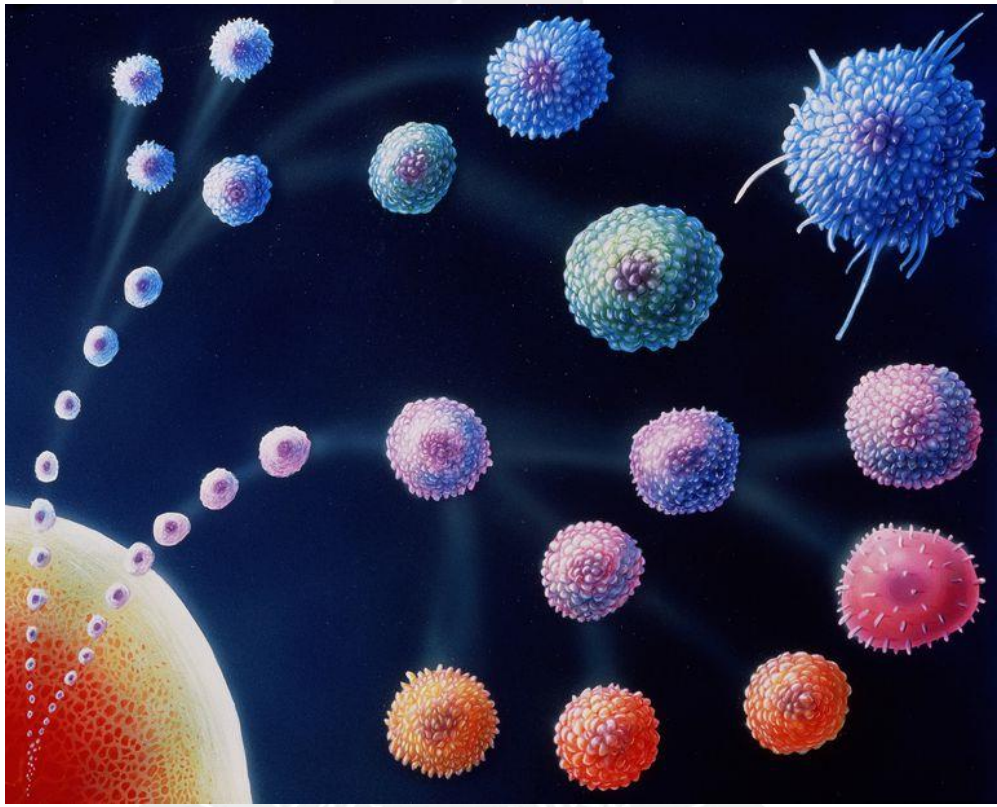
- **Immunity system normally defends us against infectious**

- **A hyperactive immune system may cause diseases that can be sometimes fatal**

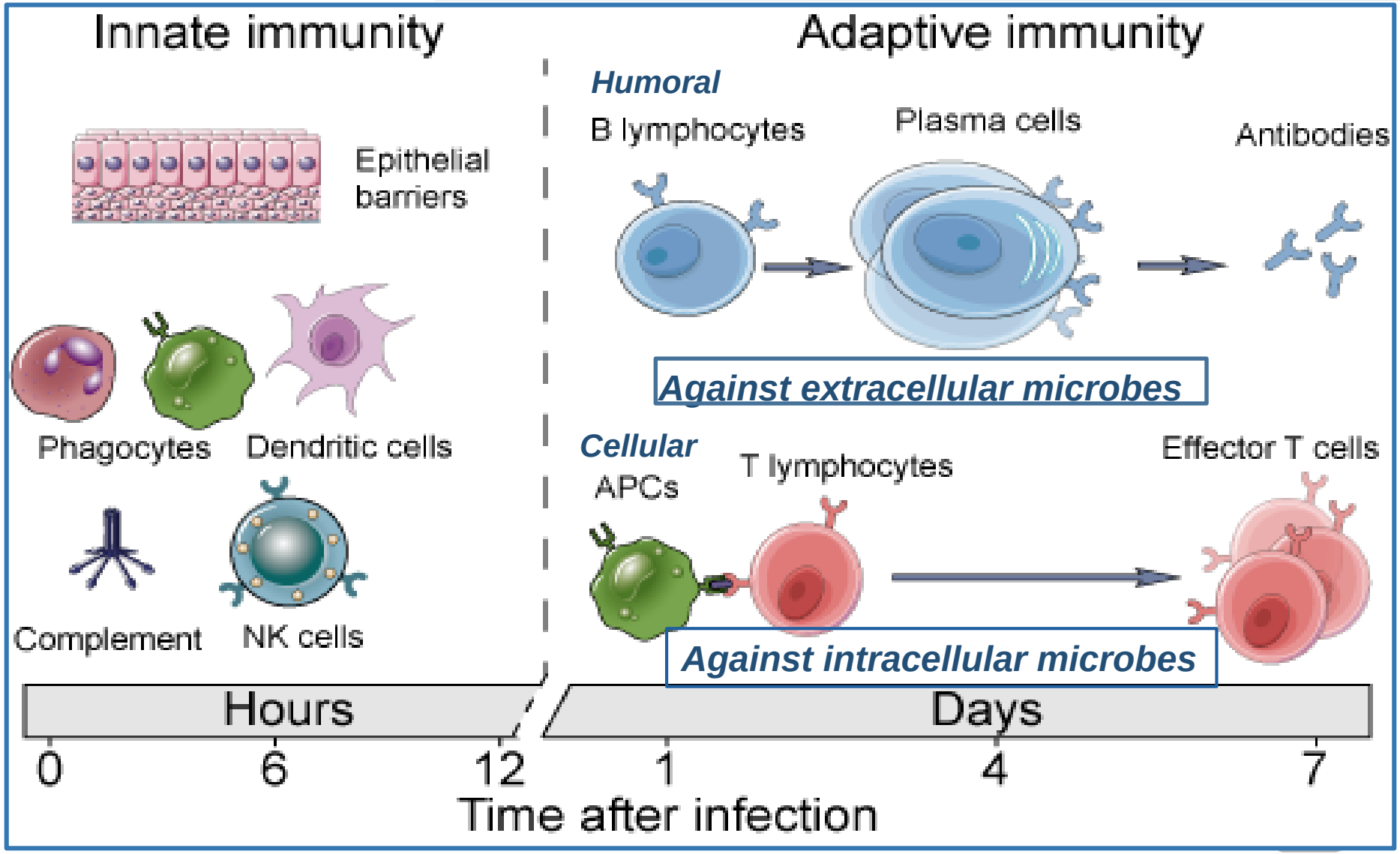
(allergy = hypersensitivity)

The normal immune response

- ***The immunity system is vital for survival, because our environment is teeming with potentially deadly microbes and the immunity system protects us from infectious pathogens.***

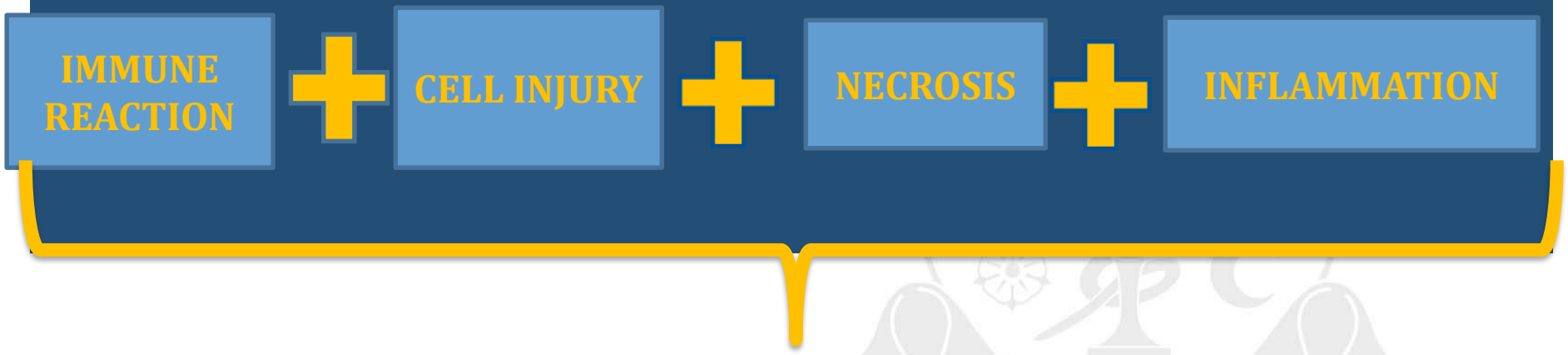


Immune system



Allergy (hypersensibility) **represents exaggerated and qualitatively modified sensibility and reactivity of the body, in response to antigenic and hapten substances, developed on the basis of immunological reactions associated with**

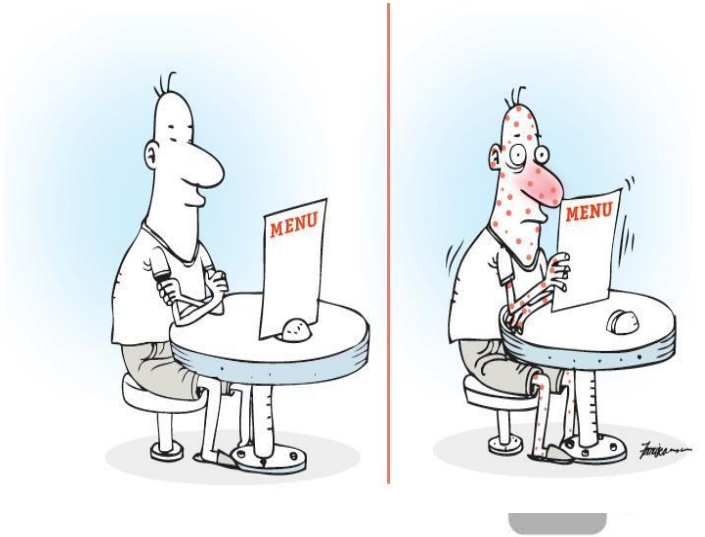
cellular injuries, inflammation and necrosis



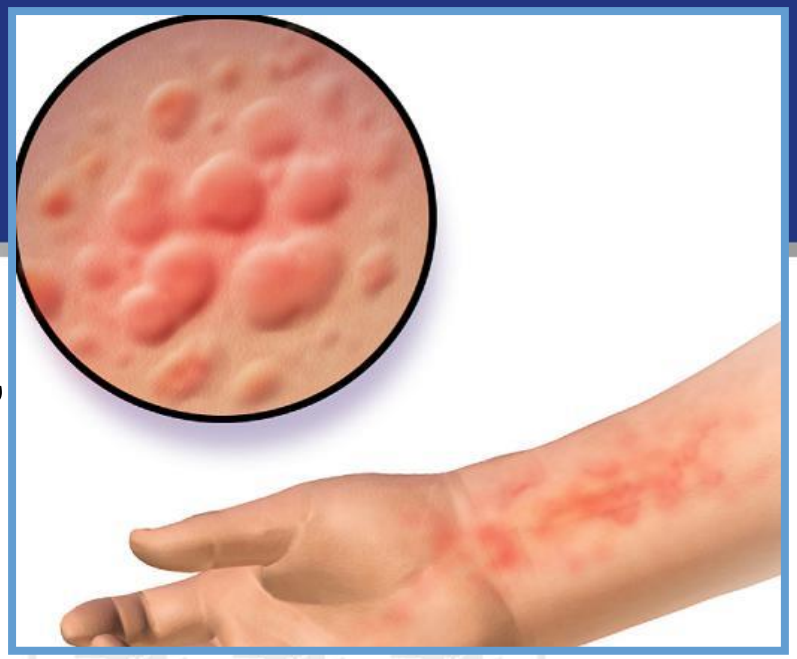
A L L E R G Y

Etiology of allergy. Types of allergens according to the way of entrance

- **Substances of antigenic and hapten nature, that trigger allergic reactions, are called *allergens*.**
- ***Inhaled allergens*, or *respiratory allergens* (solid aerosols, perfumes etc.) penetrate via the airways and cause, especially, allergic diseases of the respiratory system (rhinitis, bronchial asthma etc.);**
- ***Alimentary allergens* – components of alimentary products, penetrating via enteral way, producing first of all allergic reactions of the GIT, but by protruding the natural barriers they can reach the internal medium and thus affect other organs;**



- ***Contact allergens*** **– pass through the skin and mucosa, and produce local allergic reactions;**
- ***Iatrogenic, parenteral, injected allergens –*** **substances administrated directly into the internal medium by subcutaneous, intramuscularly, intravenous route with therapeutic or prophylactic goal.**



Etiology of allergy. Types of allergens according to their origin

ALLERGEN

EXOGENOUS

- House-keeping allergens
- Industrial allergens
- Drugs
- Vegetal allergens
- Infectious allergens
- Parasite allergens

ENDOGENOUS auto-allergens

Native natural allergens – represent normal components of the body, toward which the organism didn't produce immune tolerance during ontogenesis;

Acquired non-infectious antigens, normal body structures which were denaturized by physical, chemical factors or combined with other exogenous substances;

Acquired infectious allergens – natural antigens proper for the body, associated with microorganisms, microbial toxins etc.

According to their chemical composition allergens can be divided in:

- simple proteins
- nucleoproteins
- polysaccharides
- lipopolysaccharide

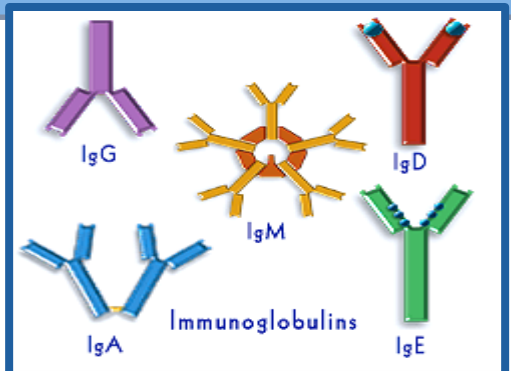
simple organic substances

- anorganic substances
- chemical elements

Immediate hypersensibility

Allergic reactions, which have on the basis humoral immune reactions

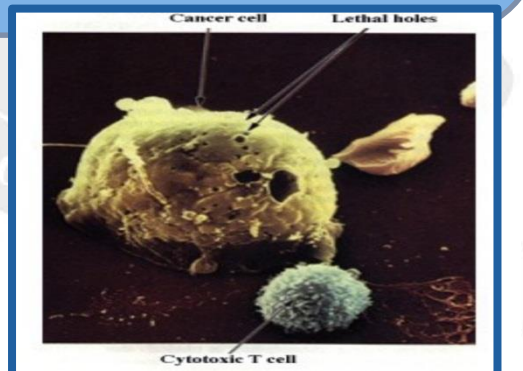
Type I, II and III allergic reaction



Delayed hypersensibility

Allergic reactions which have on the basis cellular immune reactions

Type IV allergic reaction



Types of allergic reaction / hypersensitivity

	Type I	Type II	Type III	Type IV
Immune system involvement	IgE	IgG or IgM	IgG and IgM	T cells
Examples of reactions	**Contact urticaria** (bee sting reaction), local and systemic **anaphylaxis**, seasonal hay fever, food allergies and drug allergies.	Red blood cells destruction after transfusion of mismatched blood type.	Rheumatoid arthritis, systemic lupus erythematosus.	**Allergic contact dermatitis**, type I diabetes mellitus, multiple sclerosis.
	Seconds to minutes	***Minutes to hours***	***Several hours***	***Several days***

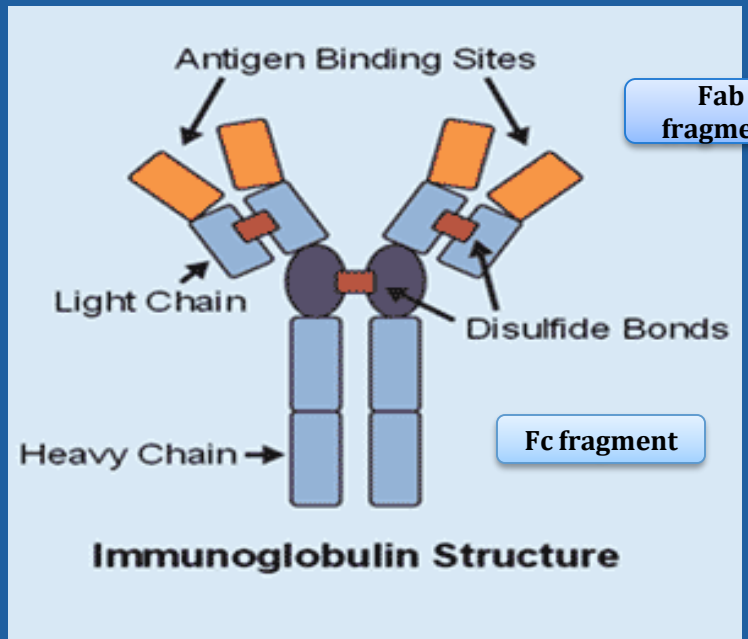
General pathogenesis of immediate hypersensitivity - I, II, III allergic reactions (which develop on the basis of humoral immune reactions)

I. Immunologic stage (stage of sensibilization);

II. Pathochemical stage, (release of biological active substances);

III. Pathophysiologic stage

(clinical manifestations).



I. Immunologic stage sensitization

Increased body sensibility to allergen with formation of sensitized immune cells or immunoglobulins.

ACTIVE

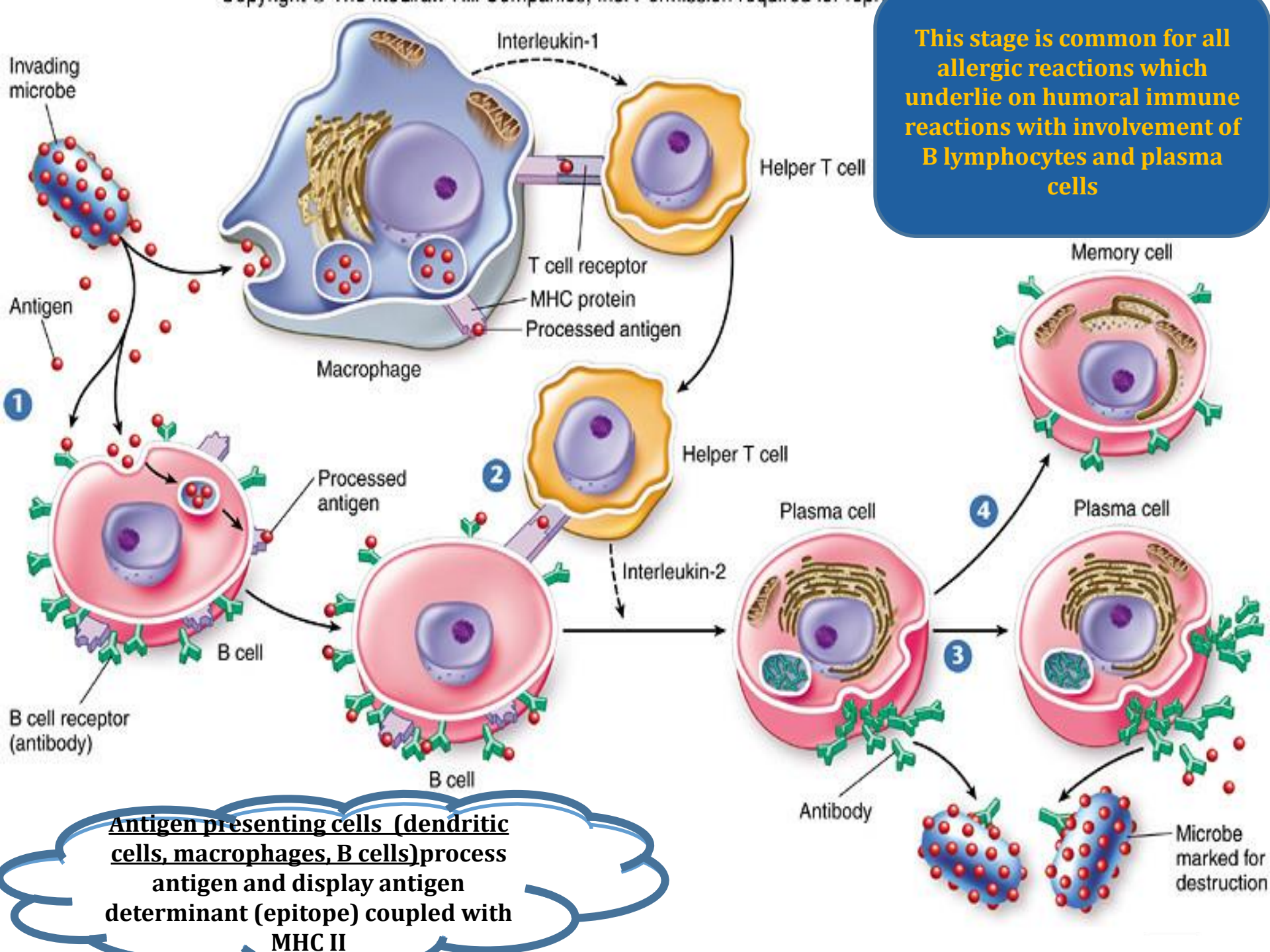
Sensitization occurred at the allergen administration

- The first signs of sensitization (specific antibodies) occur over **4-5 days** after inoculation of antigens.
- Peak sensitization occurs at **12th - 14th day**.
- Maximum duration of sensitization is due to immunological memory and can be lifelong.

PASSIVE

Sensitization achieved by transfer of immunoglobulins from actively sensitized animal to non-sensitized animals (not contacted with relevant allergen)

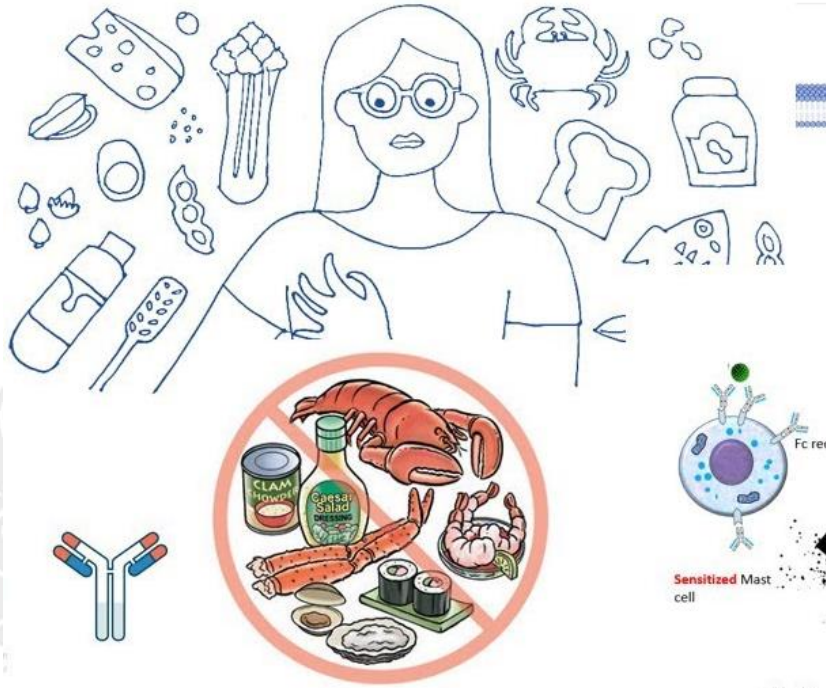
- Occurs over 2-4 hours after the transfer of Ig (time necessary to their fixation on mast cells);
- Lasts up to 2-4 months (the time of transferred-IgE catabolism),
- Does not reappear (lack of immunological memory).


This stage is common for all allergic reactions which underlie on humoral immune reactions with involvement of B lymphocytes and plasma cells
Invading microbe
Interleukin-1
Helper T cell
T cell receptor
MHC protein
Processed antigen
Antigen
Macrophage
Memory cell
1
Processed antigen
2
Helper T cell
Plasma cell
4
Plasma cell
Interleukin-2
B cell
3
B cell receptor (antibody)
B cell
Antibody
Microbe marked for destruction
Antigen presenting cells (dendritic cells, macrophages, B cells)process antigen and display antigen determinant (epitope) coupled with MHC II

Immediate hypersensitivity (type I)

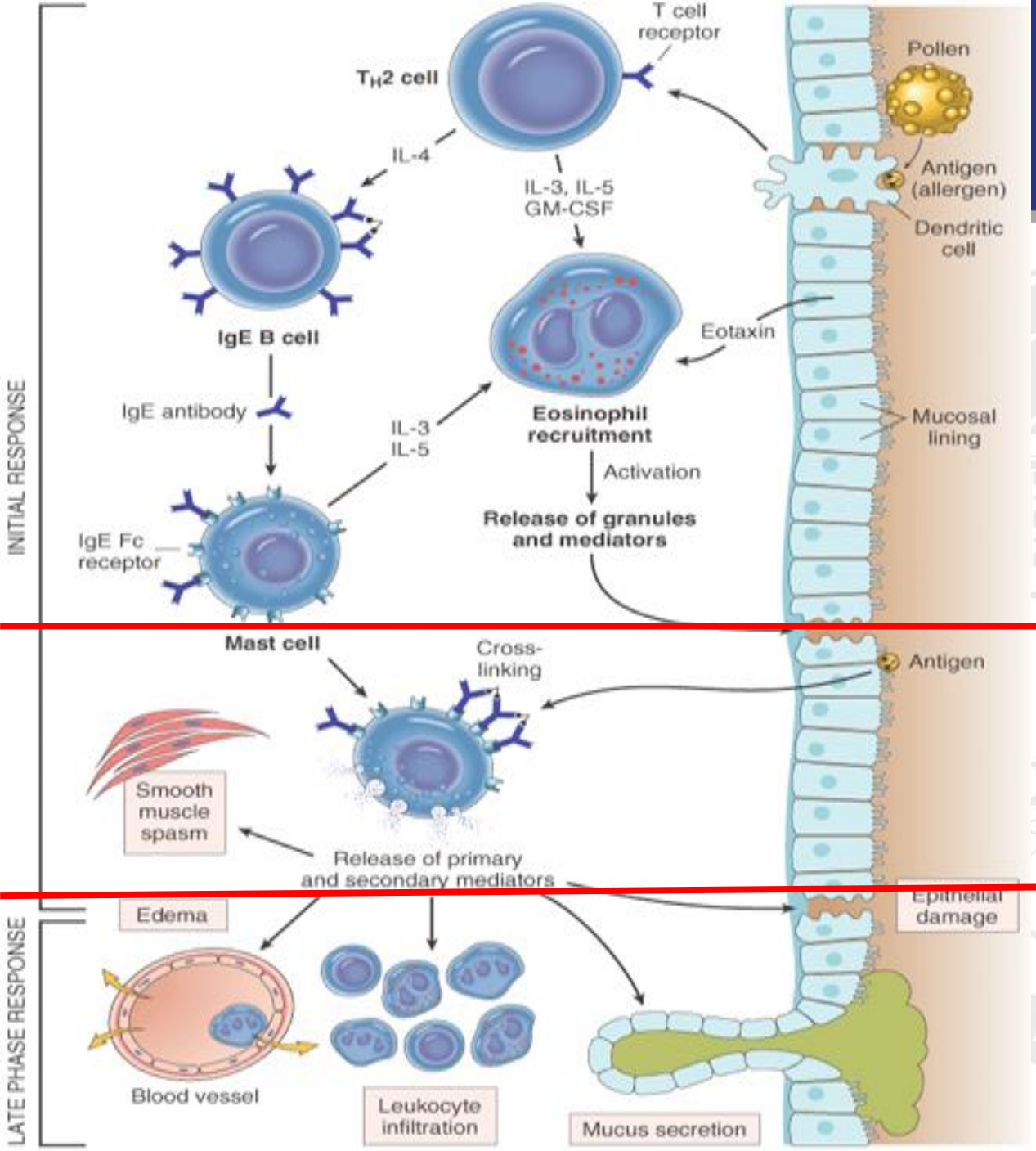
- *Rapid immunologic reaction occurring in a previously sensitized individual that is triggered by the binding of an antigen to IgE antibody on the surface of mast cells, that release mediators and pro-inflammatory cytokines acting on vessels and smooth muscle with subsequent consequenses.*

- ***systemic** – followed by injection of an antigen (bee sting, peanut allergens)*
- ***local** – depending on portal of entry of the allergen (skin allergy, hives, allergic rhinitis, conjunctivitis, hay fever, bronchial asthma or allergic gastroenteritis – in food allergy)*



Type I hypersensitivity

Fixed Ab +free Ag

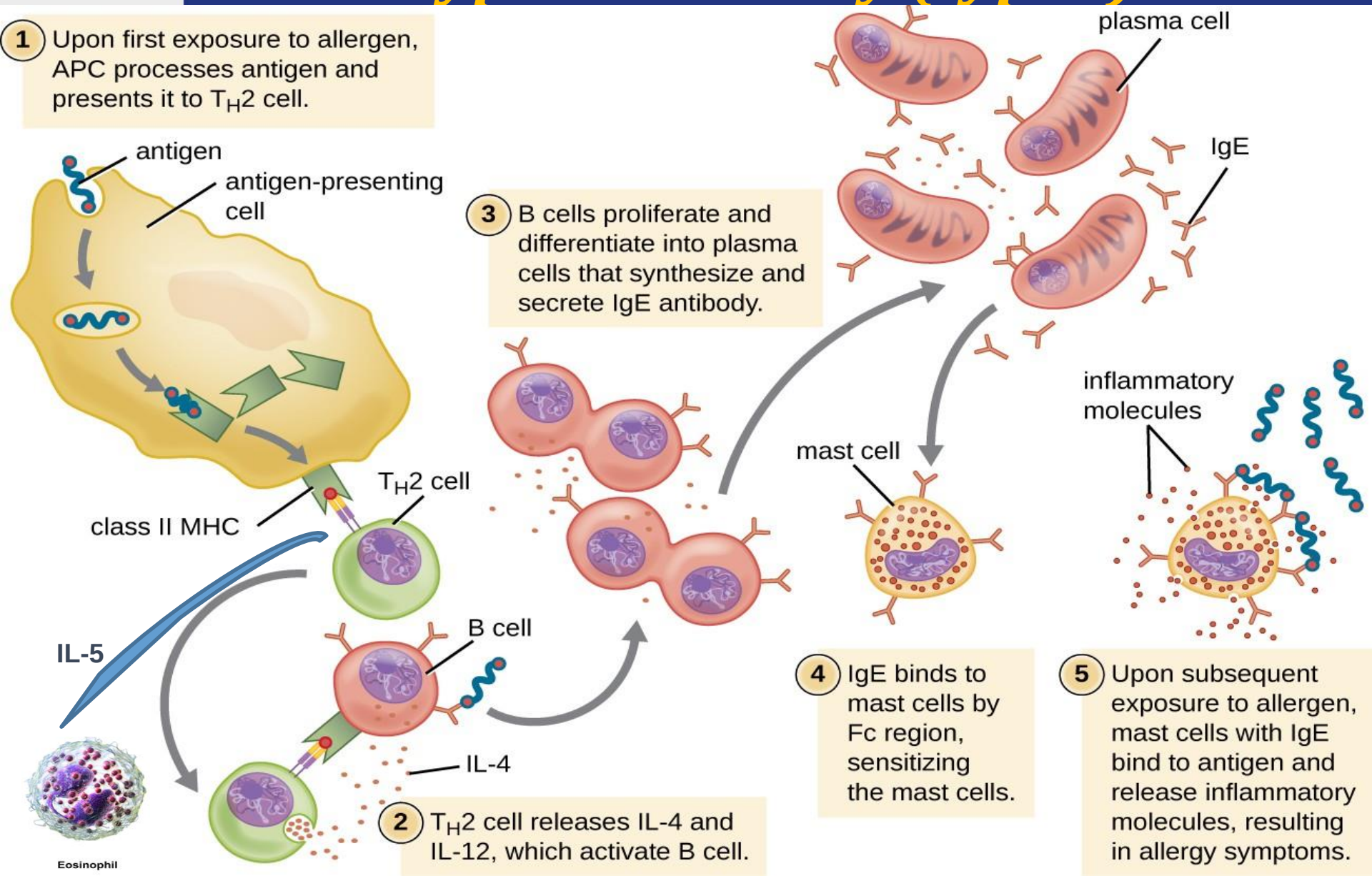


Immunological phase

Pathochemical phase

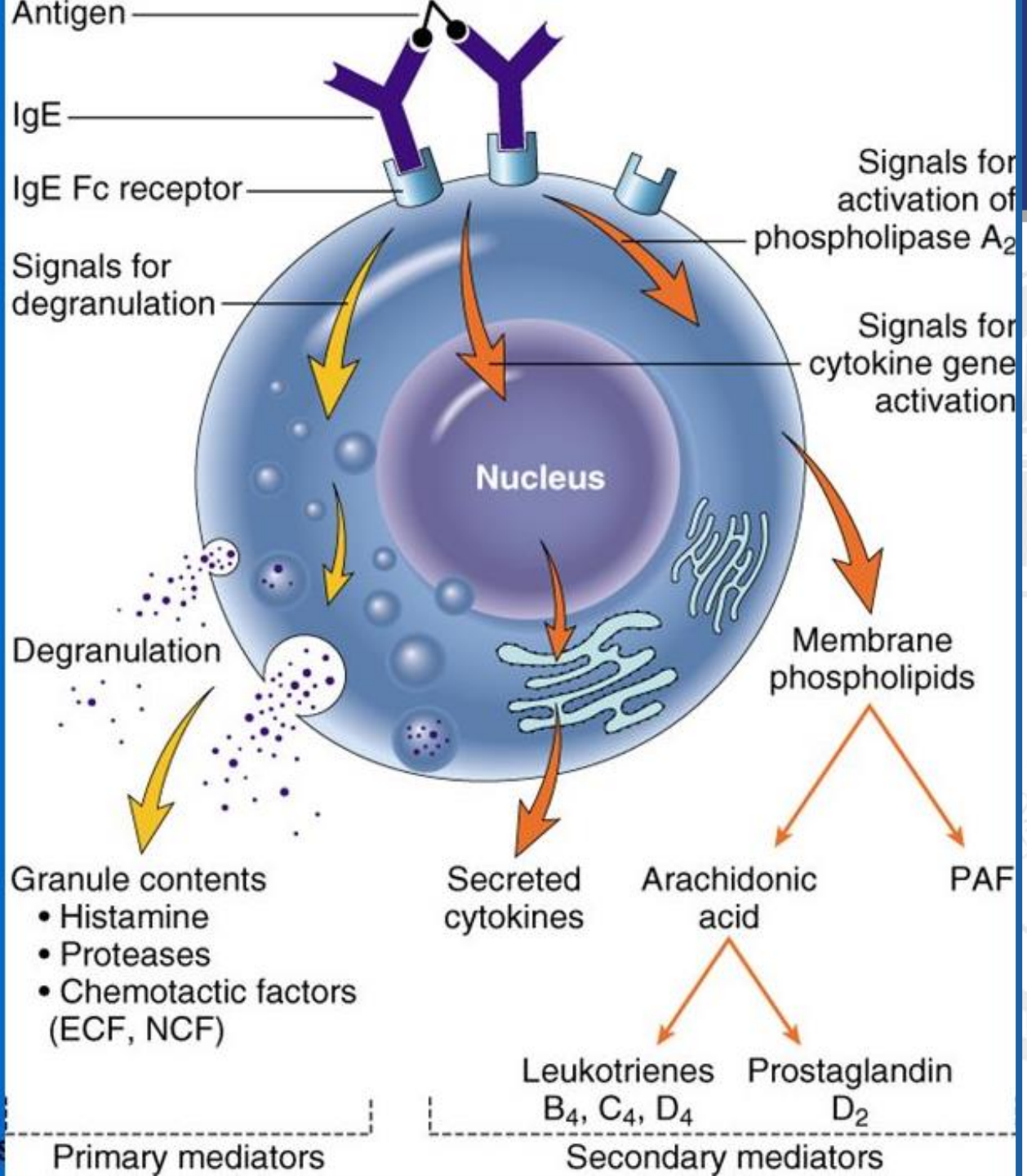
Pathophysiological stage

Immunological stage - immediate hypersensitivity (type I)



Pathochemical stage

1. **Preformed mediators (vasoactive amines, enzymes)**
2. **Lipid mediators (leukotriens, prostaglandins, platelet-activating factor)**
3. **Cytokines and chemokines (TNF-α, IL-1)**



Pathophysiological stage

Immediate reaction (histamine, prostaglandin, and leukotrienes):

- Vasodilation
- Vascular leakage (edema)
- Smooth muscle spasm

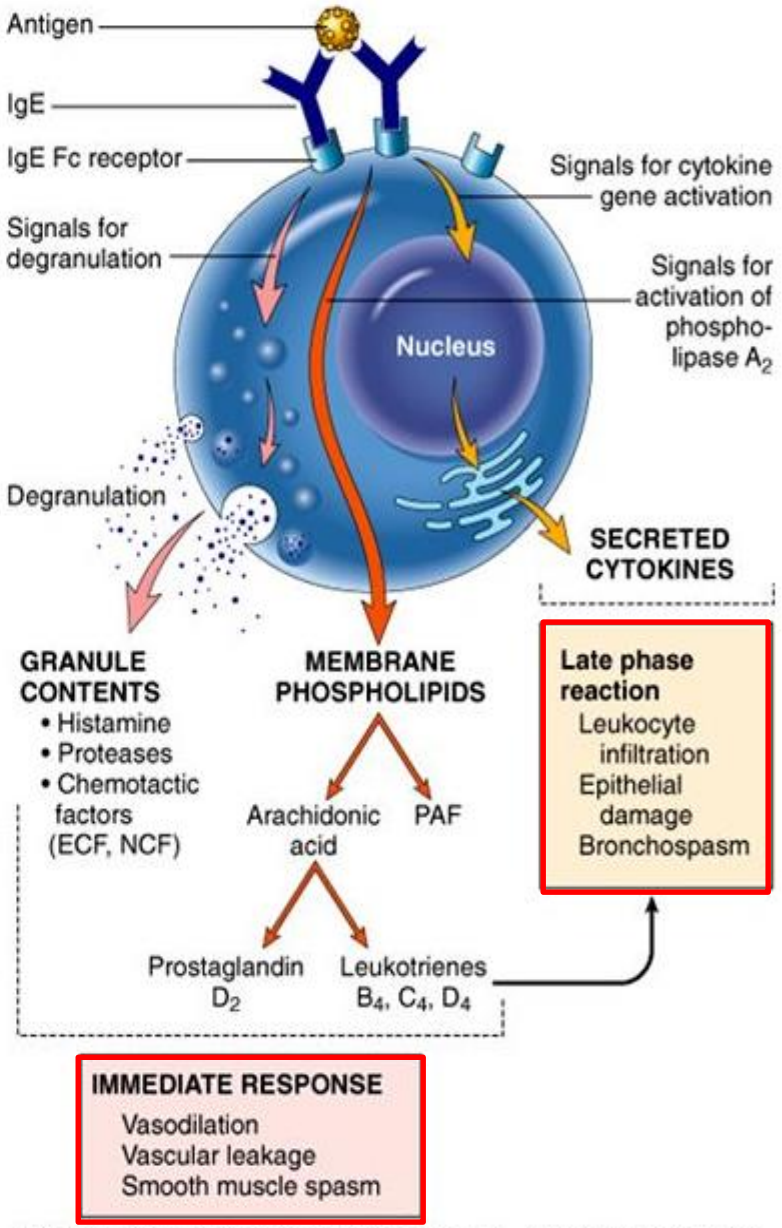
(5-30 min) subside in 60 min

Late-phase reaction (leukotrienes and other cytokines):

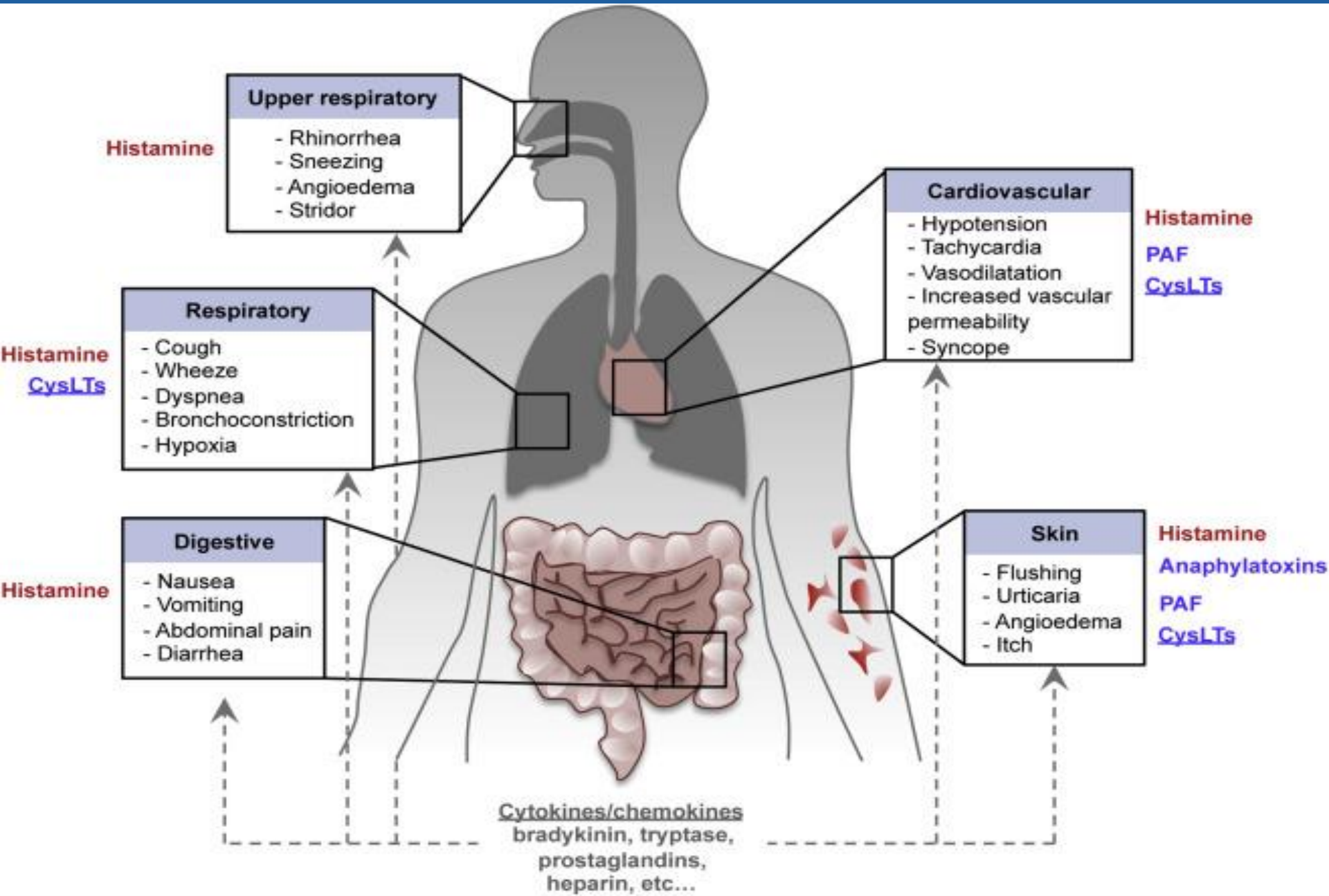
- Leukocyte infiltration (particularly neutrophils and eosinophils)
- Epithelial damage
- Bronchospasm

2 – 8 Hr later without additional exposure to Ag

*Clinical manifestations may be **local** or **systemic** and may range from **mild** (sinusitis) to **severe** (anaphylactic shock). Also, may be acute or **CHRONIC** (e.g. asthma)*



Anaphylactic shock



Emergency treatment of anaphylactic shock

Anaphylactic reaction?

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Airway, Breathing, Circulation, Disability, Exposure

↓

Diagnosis - look for:

- Acute onset of illness
- Life-threatening Airway and/or Breathing and/or Circulation problems [1]
- And usually skin changes

↓

- **Call for help**
- Lie patient flat
- Raise patient's legs

↓

Adrenaline [2]

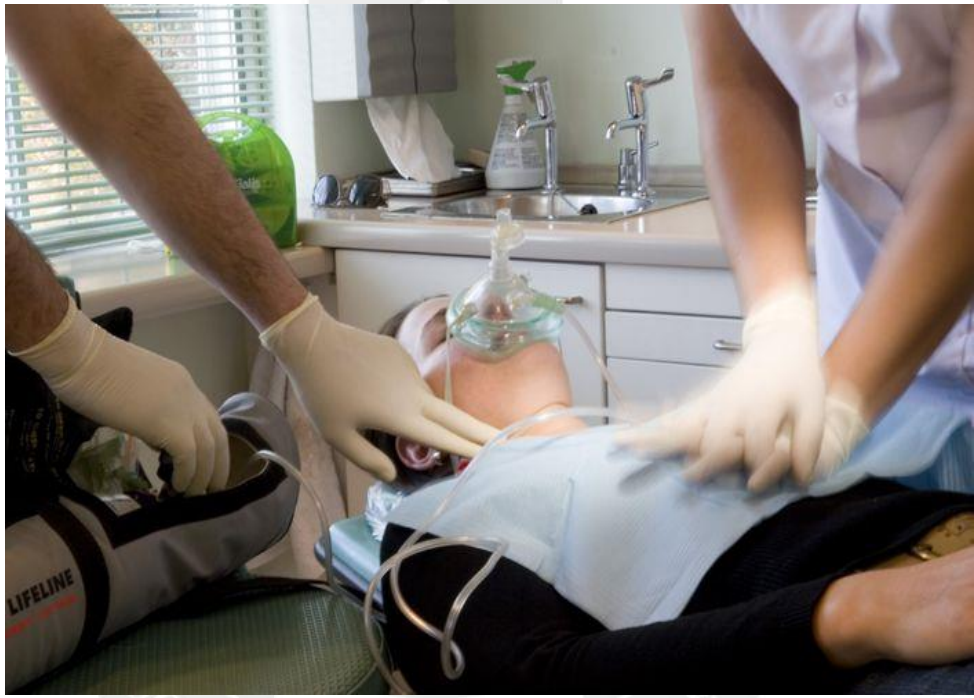
↓

When skills and equipment available:

- Establish airway
- High flow oxygen
- IV fluid challenge [3]
- Chlorphenamine [4]
- Hydrocortisone [5]

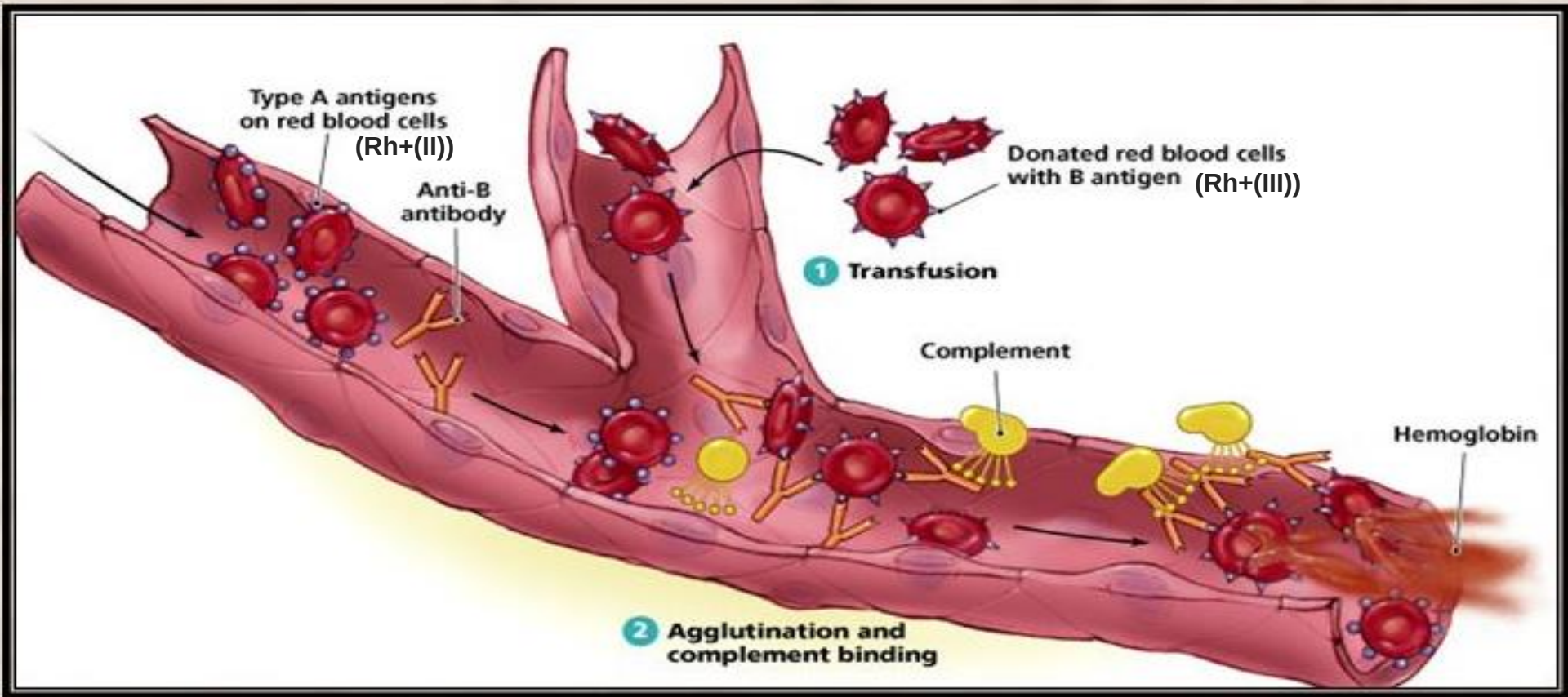
Monitor:

- Pulse oximetry
- ECG
- Blood pressure

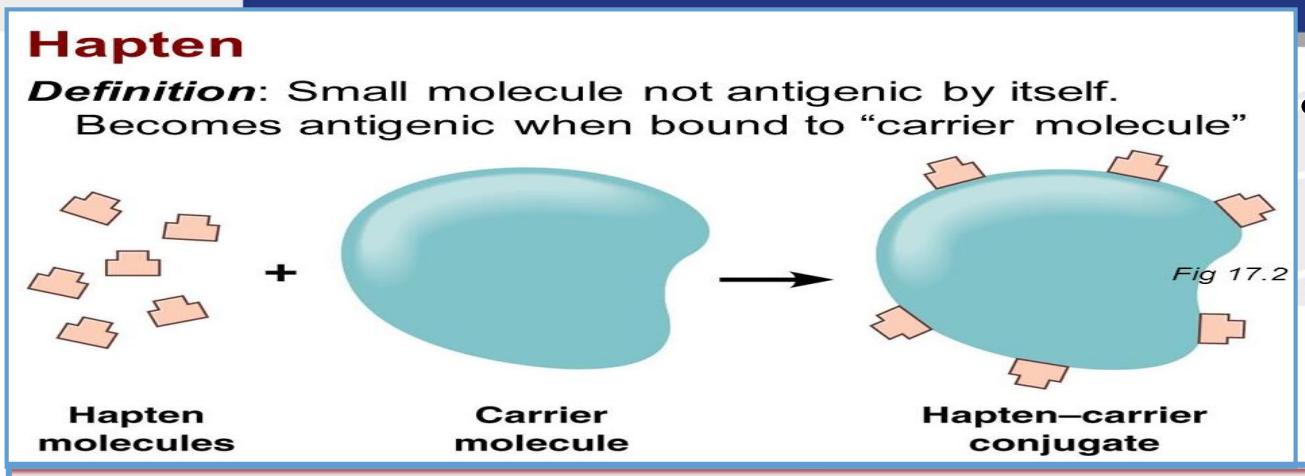


Antibody-Mediated (Type II) Hypersensitivity

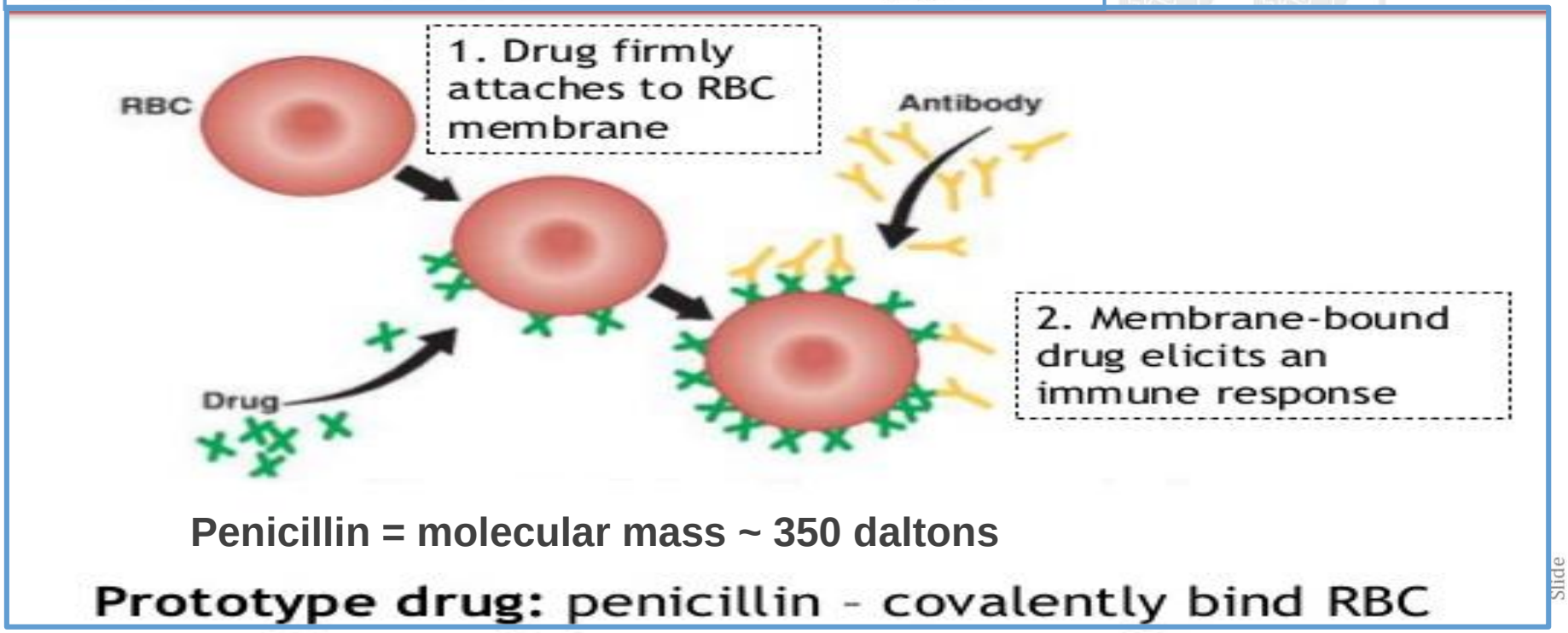
- ***Antibodies (IgG and IgM) that react with antigens present on cell surfaces or in the extracellular matrix cause disease by destroying these cells, triggering inflammation or interfering with normal functions. (free Ab + fixed Ag)***



Type II hypersensitivity (drug reaction)



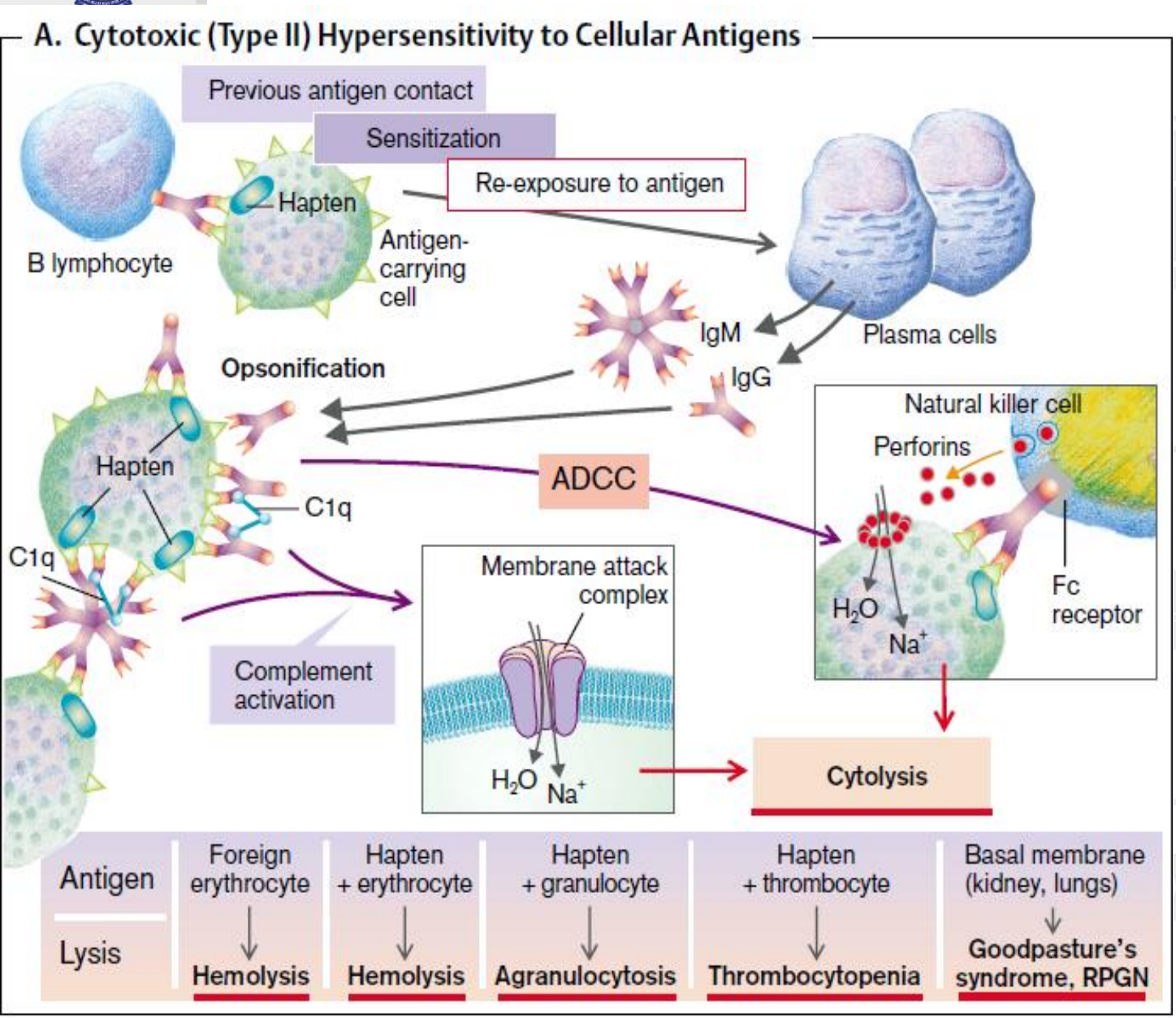
- **Haptene= small molecules with molecular mass <10000 daltons**



Penicillin = molecular mass ~ 350 daltons

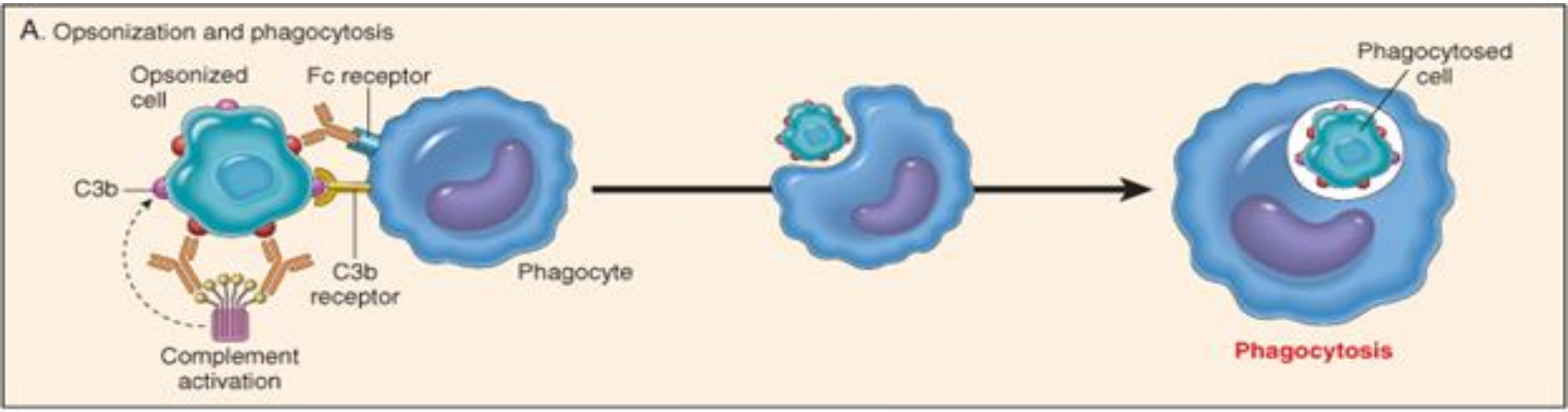
Prototype drug: penicillin - covalently bind RBC

Pathogenesis of type II hypersensitivity

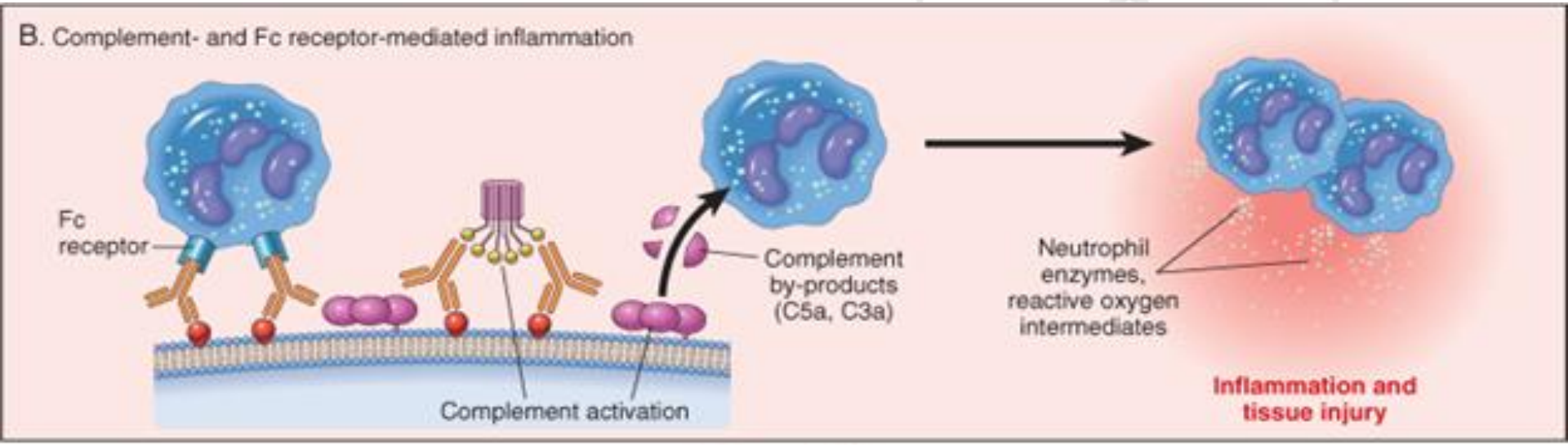


1. *Activation of complement cascade:*
   - *Opsonization and phagocytosis*
   - *Formation of MAC (membrane attack complex)*
   - *Complement and Fc receptor mediated inflammation*
2. *ADCC (antibody dependent cellular cytotoxicity*
3. *Antibody-mediated cellular dysfunction*

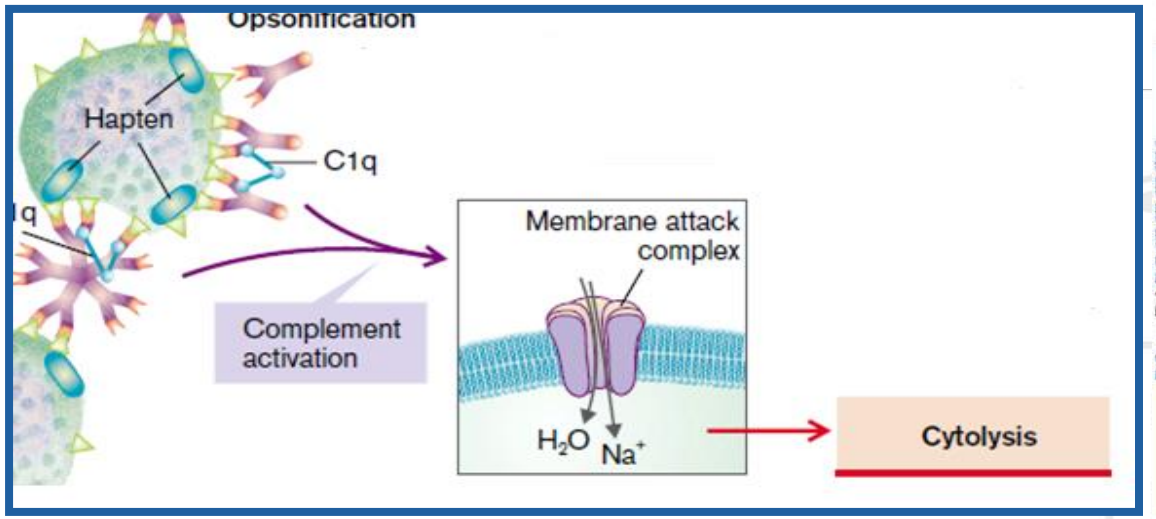
Opsonization and phagocytosis

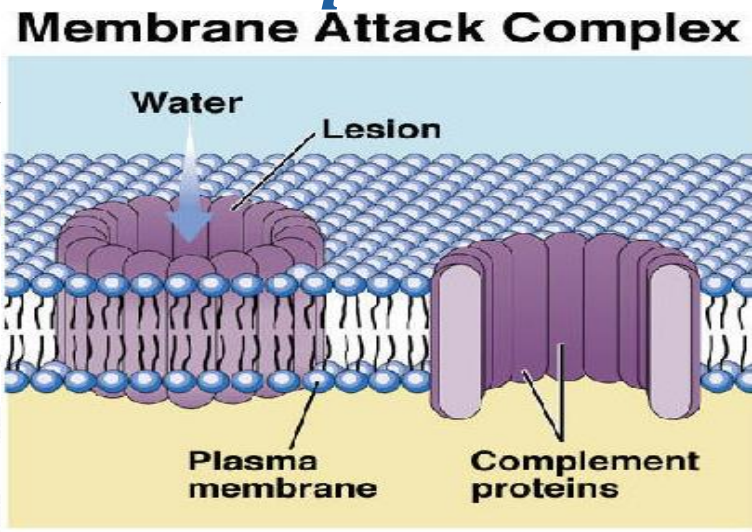


Complement and Fc receptor – mediated inflammation

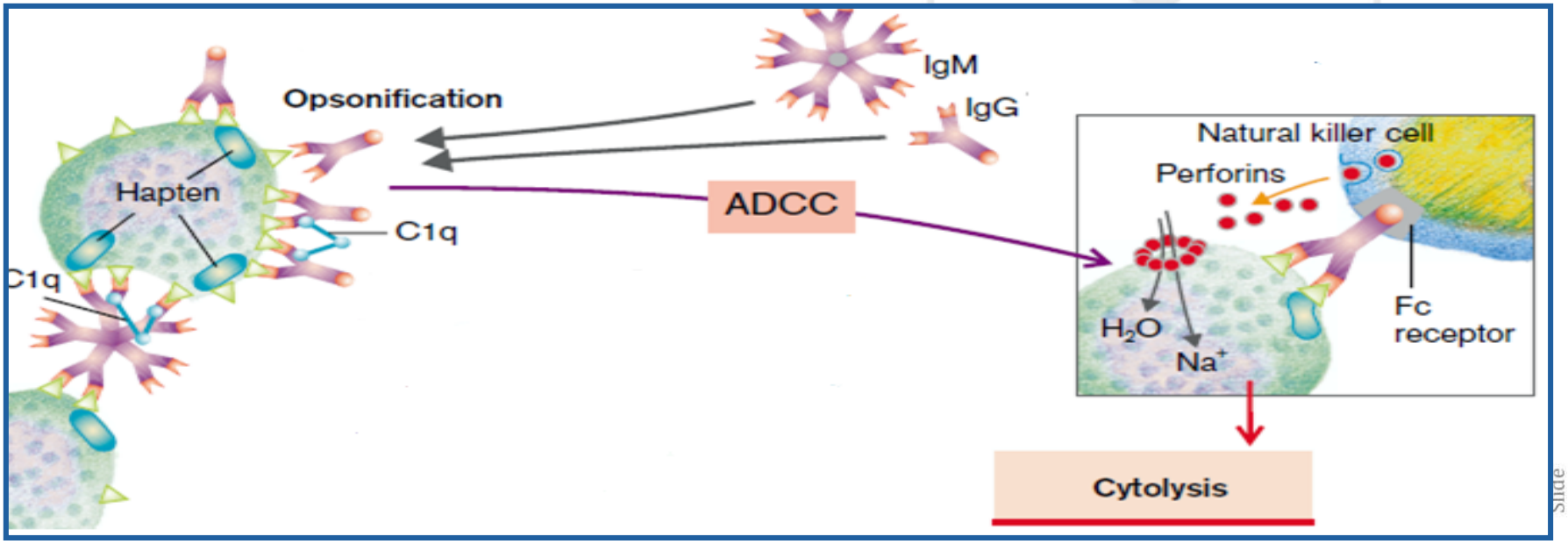


Formation of membrane attack complex

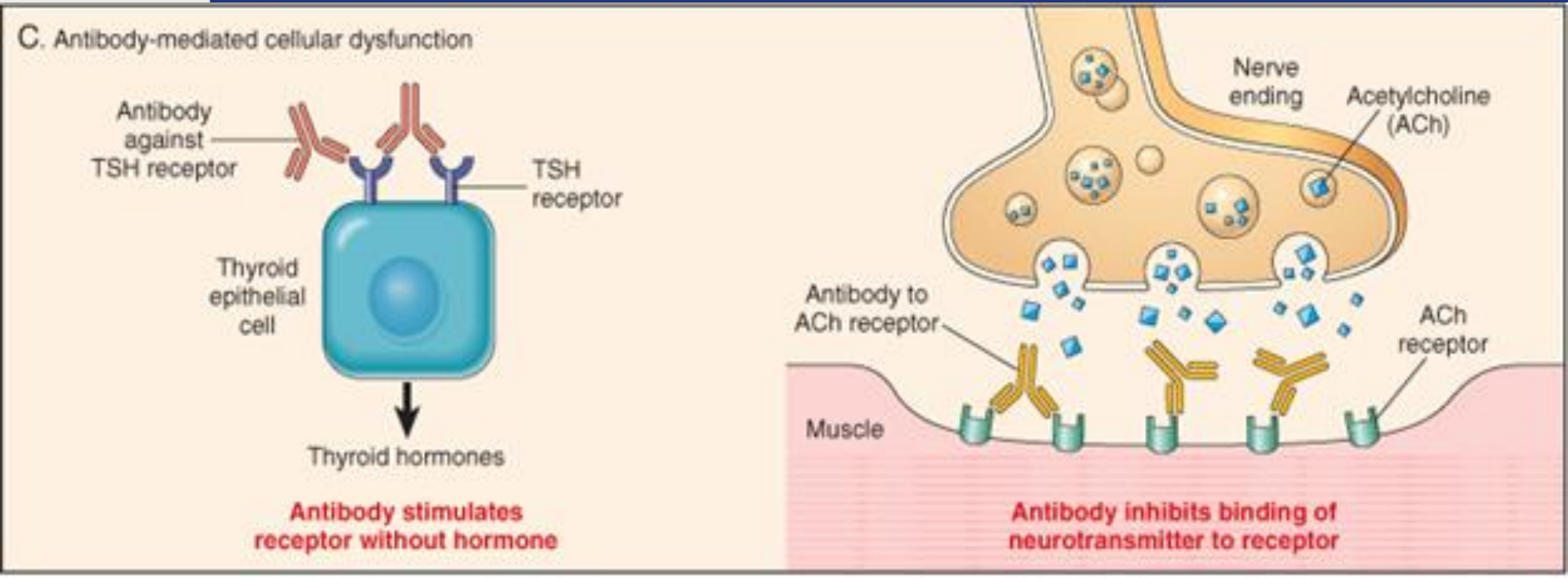




Antibody – dependent cellular citotoxicity (ADCC)



Antibody – mediated cellular dysfunction



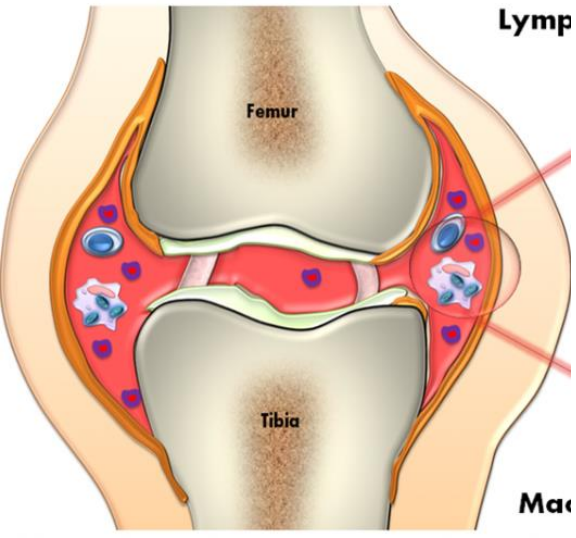
Graves disease (hyperthyroidism)

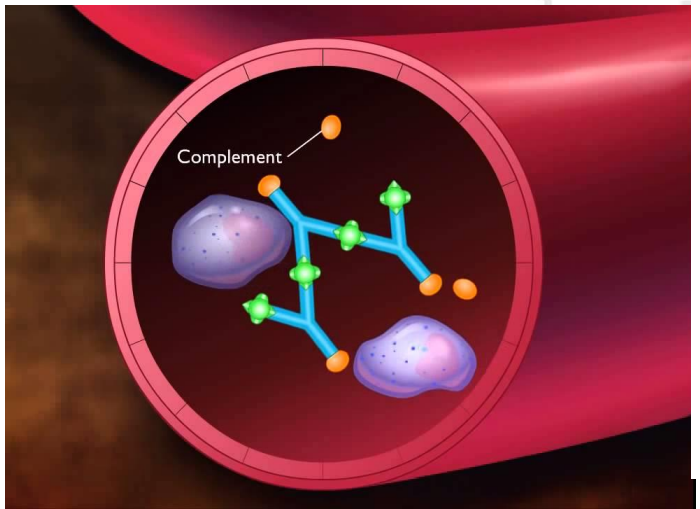
Myasthenia gravis

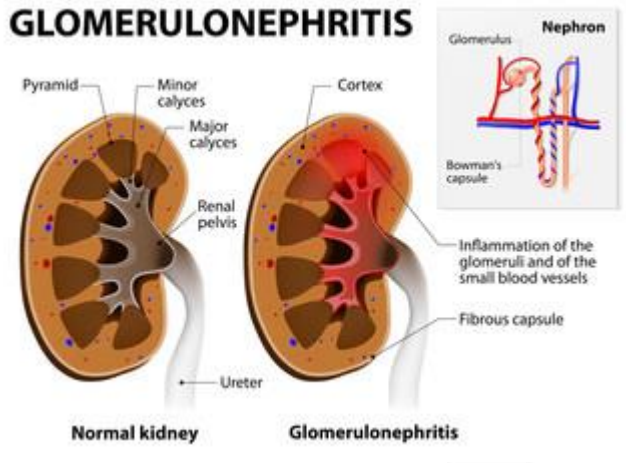
Antibodies are directed against receptors and impair or dysregulate function without causing cell injury or inflammation

Immune Complex–Mediated (Type III) Hypersensitivity (Ag free + Ab free)

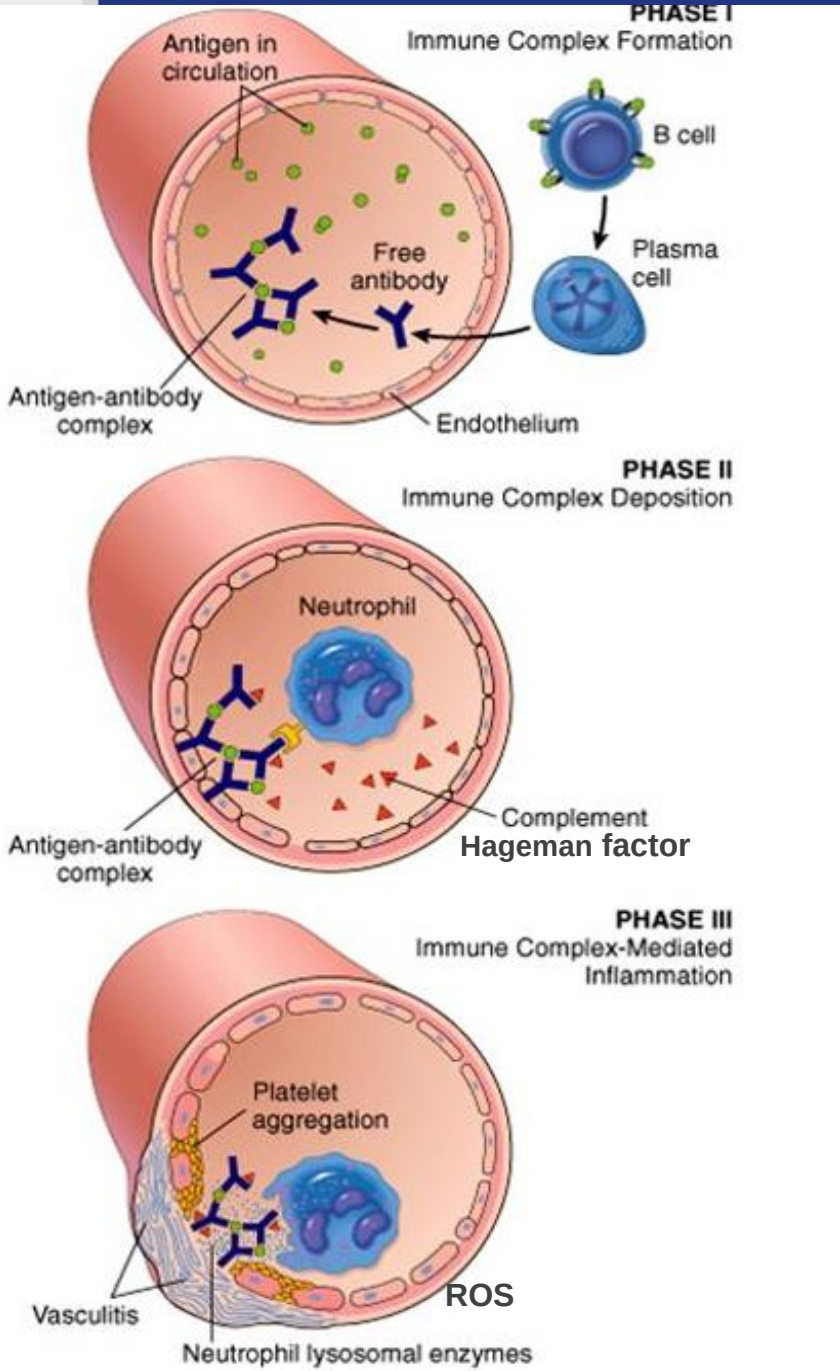
- IgG and IgM antibodies bind antigens usually in the circulation, and the antigen-antibody complexes deposit in tissues and induce inflammation. The leukocytes that are recruited (neutrophils and monocytes) produce tissue damage by release of lysosomal enzymes and generation of toxic free radicals.
- Immune complexes typically deposit in vessel walls.
- Immune complex–mediated diseases tend be systemic, but often preferentially involve the *kidney* (glomerulonephritis*), joints* (arthritis), and *small blood vessels* (vasculitis), all of which are common sites of immune complex deposition







Pathogenesis of type III allergic reaction



- Formation of immune complexes (Ag + Ab) ~ a week
- Deposition of immune complexes: pathogenic – excess antigen, medium to small size complexes that are broken down slowly
- Inflammation and tissue damage

Mediators:

- ✓ complement system (C3a, C3b, C5a, C5b-C9)
- ✓ Hageman factor (Factor XIIa) – clotting system, kinin system, fibrinolytic system
- ✓ Leukocytes – lysosomal enzymes, ROS

General pathogenesis of type IV allergic reactions

(delayed allergic reaction= late hypersensibility)

I. Immunologic stage **(stage of sensibilization);**

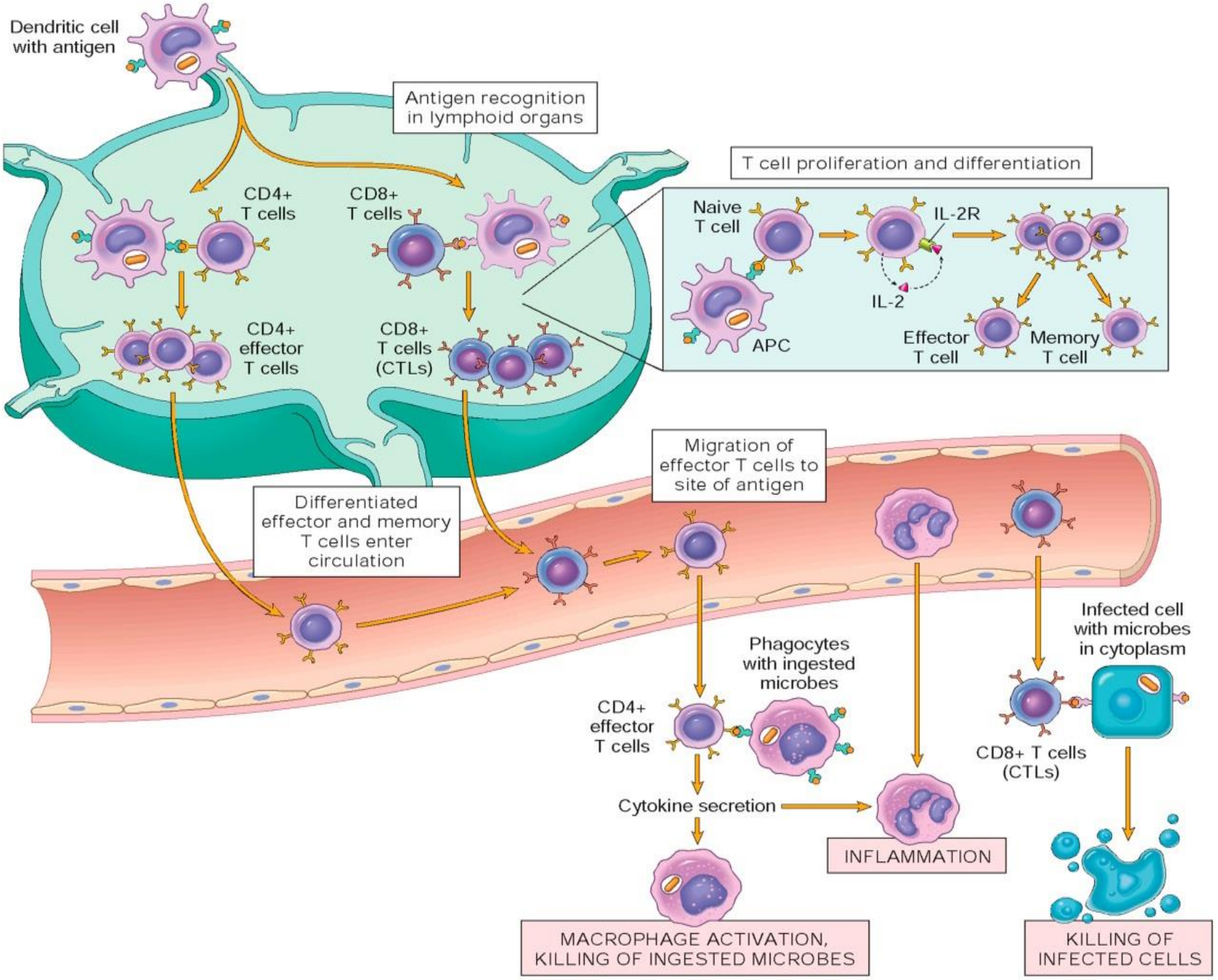
II. Pathochemical stage, **(release of biological active substances);**

III. Pathophysiologic stage **(clinical manifestations).**

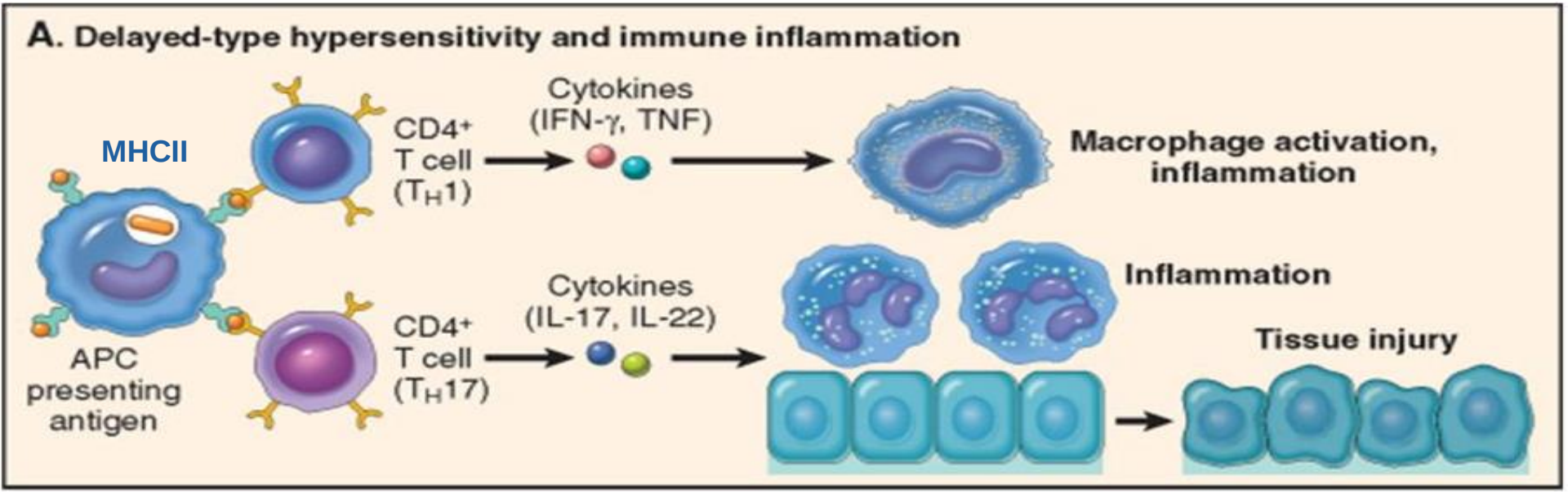
Etiological factors of type IV hypersensitivity

It is triggered mainly:

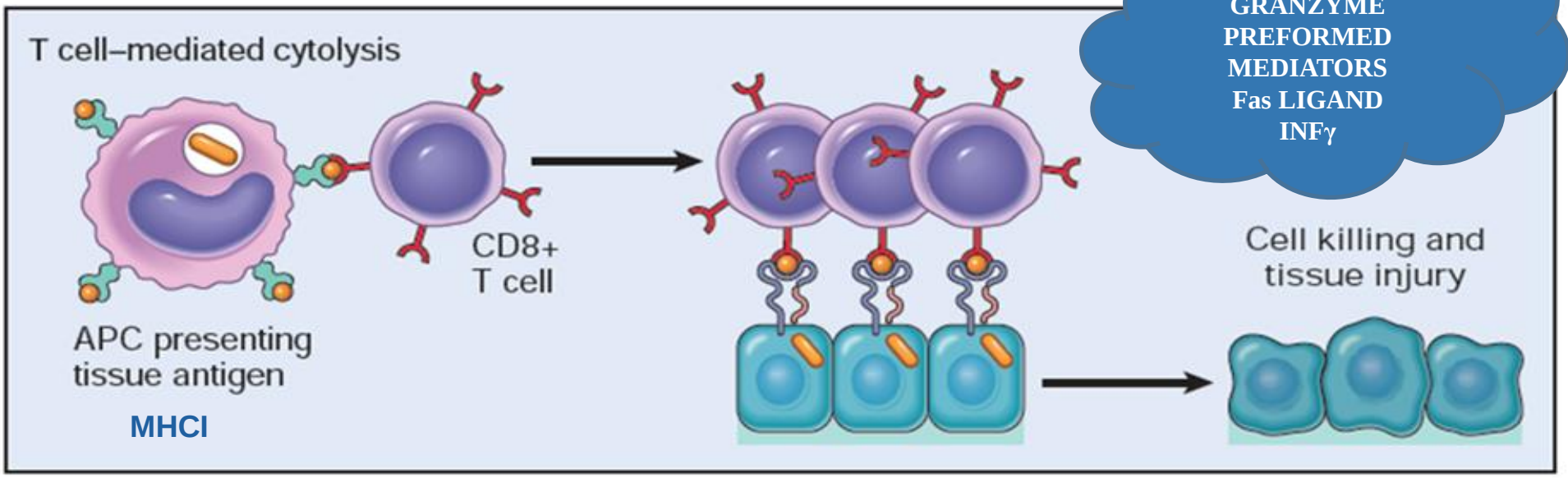
- **by *proteins from pathogens (viruses, tuberculosis,* lepra, leishmaniasis, listeriosis, fungal infections),**
- **other foreign proteins(e.g., the wheat protein gliadin that causes *celiac disease),***
- ***and haptens, for example, drugs,* metals (e.g., nickel), cosmetics, plant constituents**

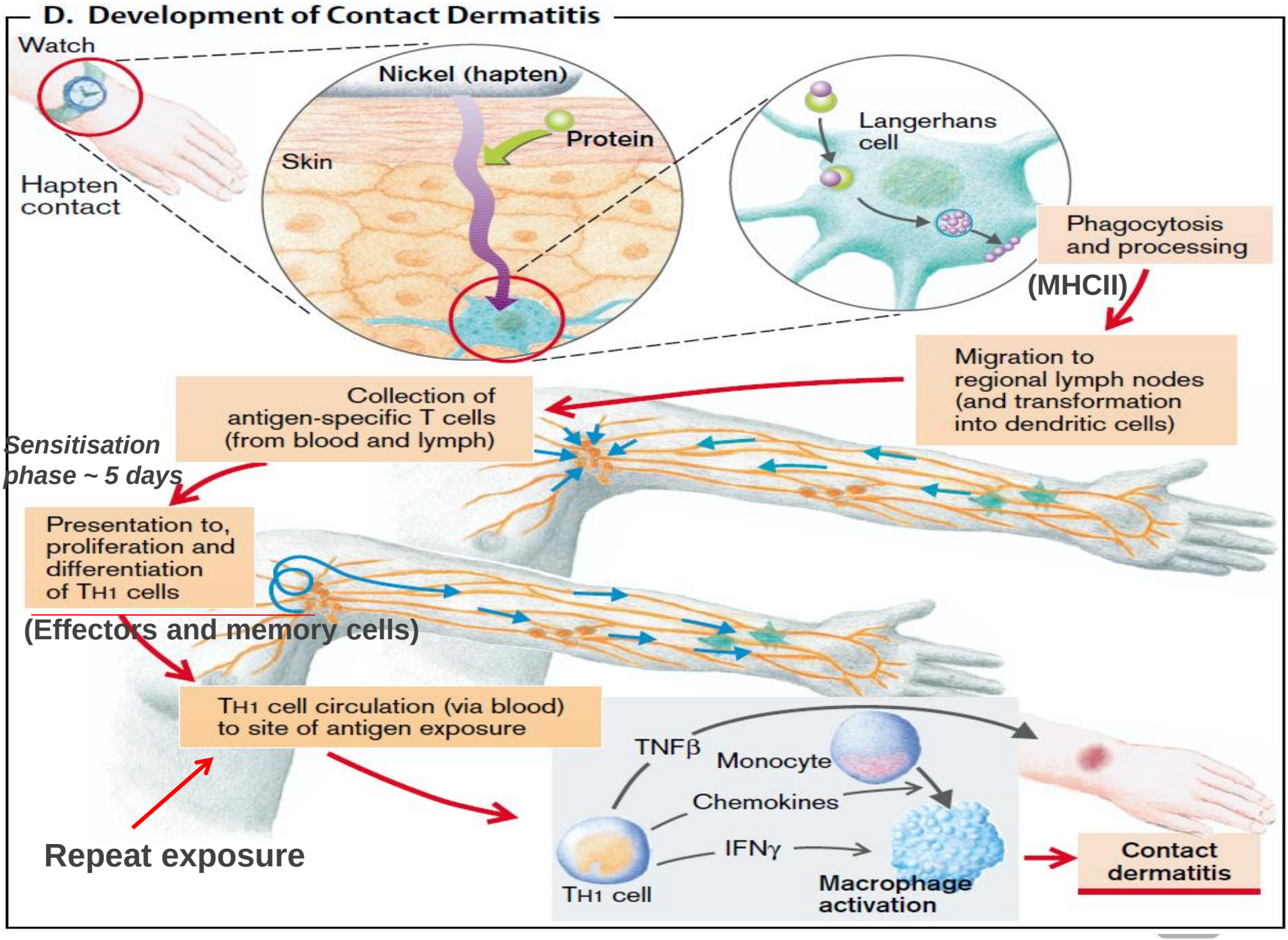

Dendritic cell with antigen
Antigen recognition in lymphoid organs
CD4+ T cells
CD8+ T cells
CD4+ effector T cells
CD8+ T cells (CTLs)
T cell proliferation and differentiation
Naive T cell
APC
IL-2R
IL-2
Effector T cell
Memory T cell
Migration of effector T cells to site of antigen
Differentiated effector and memory T cells enter circulation
Phagocytes with ingested microbes
CD4+ effector T cells
Cytokine secretion
INFLAMMATION
MACROPHAGE ACTIVATION, KILLING OF INGESTED MICROBES
Infected cell with microbes in cytoplasm
CD8+ T cells (CTLs)
KILLING OF INFECTED CELLS

CD4+Tcell – mediated inflammatory reaction



CD8+ T cell –mediated cytotoxicity



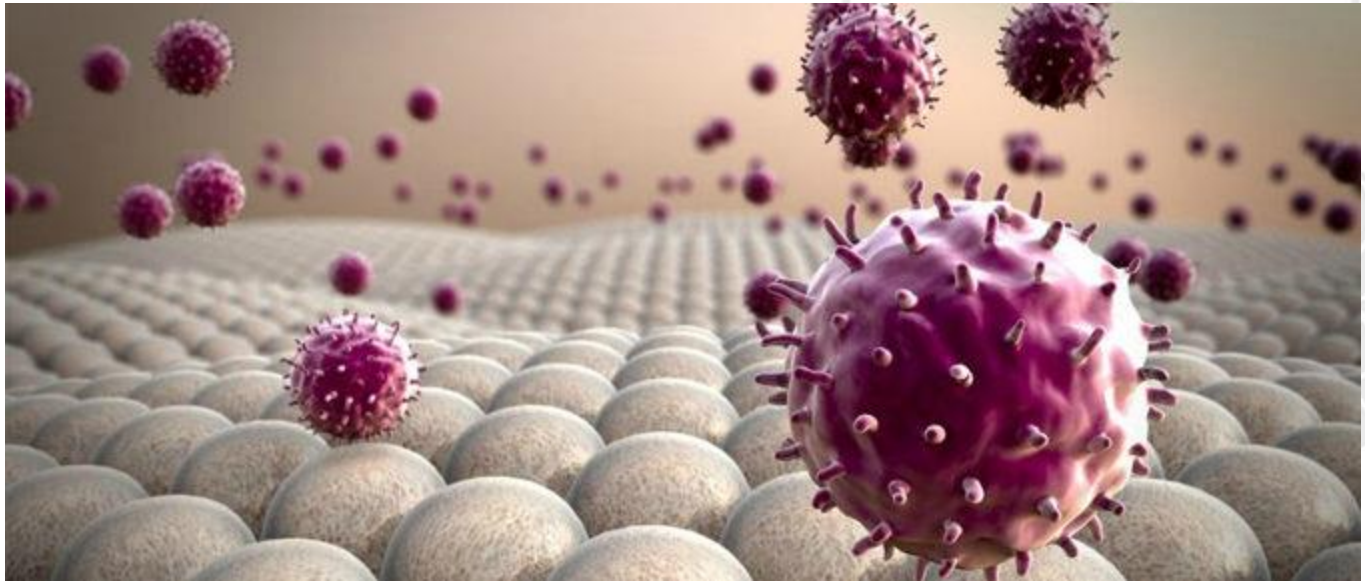

D. Development of Contact Dermatitis
Watch
Hapten contact
Nickel (hapten)
Protein
Skin
Langerhans cell
Phagocytosis and processing
(MHCII)
Migration to regional lymph nodes (and transformation into dendritic cells)
Collection of antigen-specific T cells (from blood and lymph)
Sensitisation phase ~ 5 days
Presentation to, proliferation and differentiation of TH1 cells
(Effectors and memory cells)
TH1 cell circulation (via blood) to site of antigen exposure
Repeat exposure
TNFβ
Monocyte
Chemokines
IFNγ
TH1 cell
Macrophage activation
Contact dermatitis

AUTOIMMUNE DISORDERS

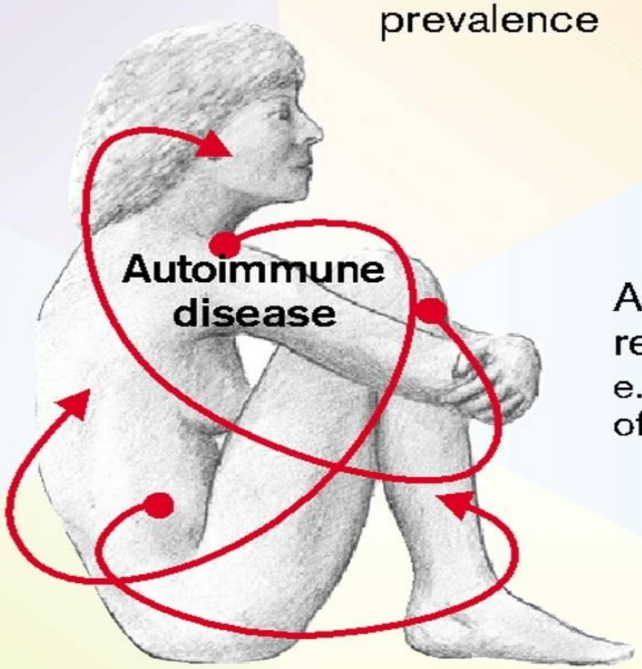
The immune system normally exists in an equilibrium in which lymphocyte activation, which is required for defense against pathogens, is balanced by the mechanisms of tolerance, which prevent reactions against self-antigens.

The underlying cause of autoimmune diseases is the failure of tolerance, which allows responses to develop against self-antigens.

Immune reactions against self-antigens – *autoimmunity* - are an important cause of certain diseases in humans.



A. Causes of Autoimmune Disease



Genetic predisposition, mainly HLA-II genotype

Hormonal influences → Sex prevalence

Estrogens stimulate but androgens suppress immune response

Psychological factors

Altered immune regulation, e.g. altered activity of T-suppressor cells (?)

Breakdown of T-cell anergy (overexpression of co-stimulators)

Infection

Superantigens (staphylococcal, streptococcal endotoxins – not require presentation of Ag to APCs)

Cross-reaction of antiforeign antibodies, e.g. anti-streptococcal antibodies against endocardium and myocardium

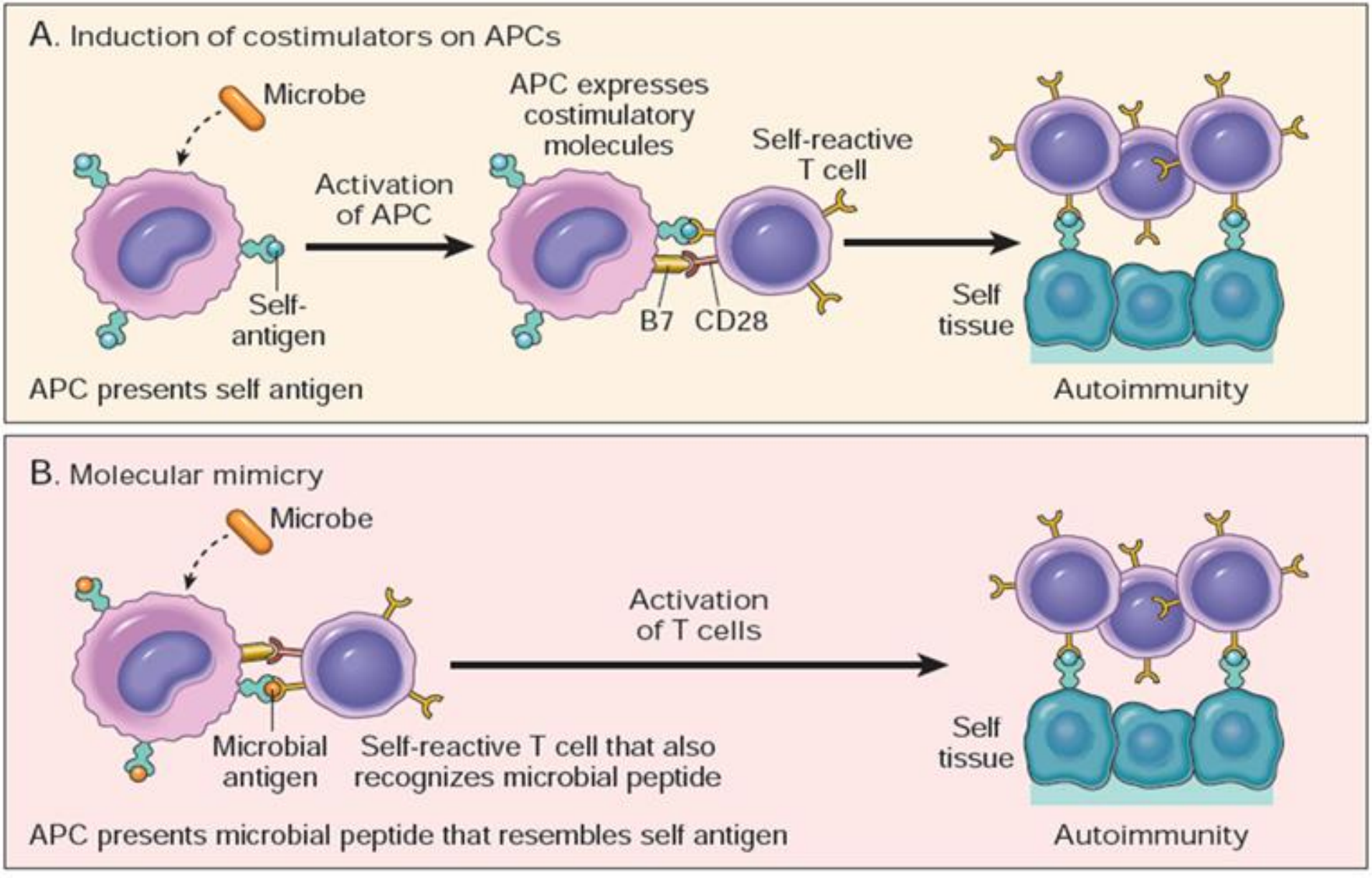
Molecular mimicry

Infection

Cancellation of immunological ignorance of autoantigens from immunologically privileged regions, e.g. eye, brain, uterus, sperm, thyroglobulin

Realise of sequestrated antigens

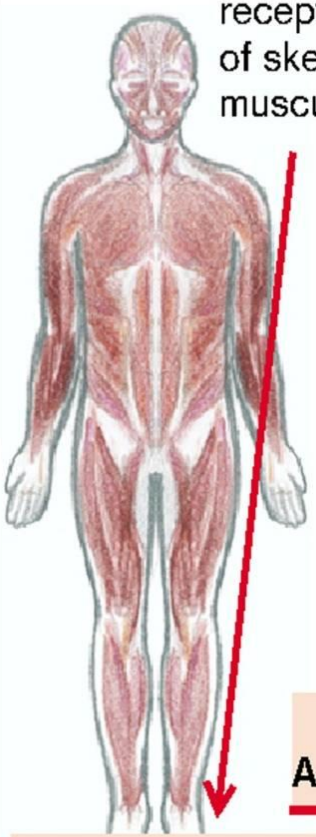
Postulated role of infections in autoimmunity



B. Organ-Specific and Tissue-Specific Autoimmune Diseases

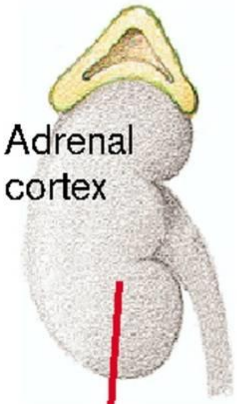
Organ-specific autoantibodies or T cell activation against

Tissue-specific autoantibodies against



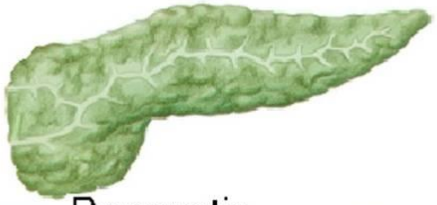
Acetylcholine receptors of skeletal musculature

Myasthenia gravis pseudoparalytica



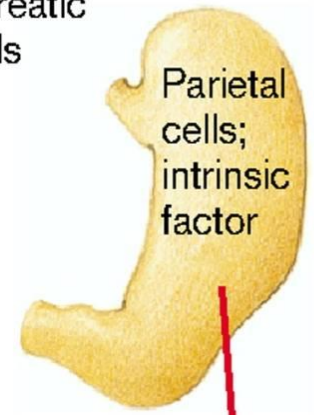
Adrenal cortex

Idiopathic Addison's disease



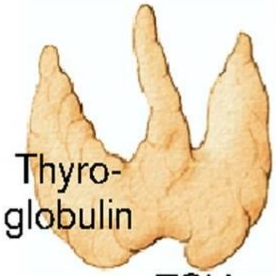
Pancreatic B cells

Diabetes mellitus



Parietal cells; intrinsic factor

Atrophic gastritis, pernicious anemia



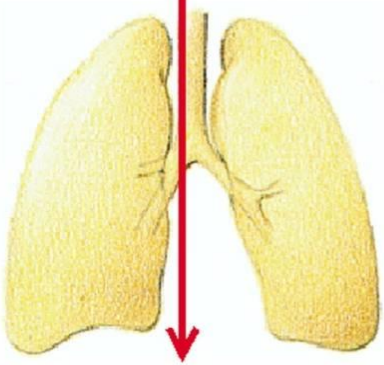
Thyro-globulin

TSH receptor

Hashimoto's thyroiditis

Graves' disease

Basal membranes



Glomerulo-nephritis

Pulmonary bleeding

Goodpasture's syndrome

Thank you !!!