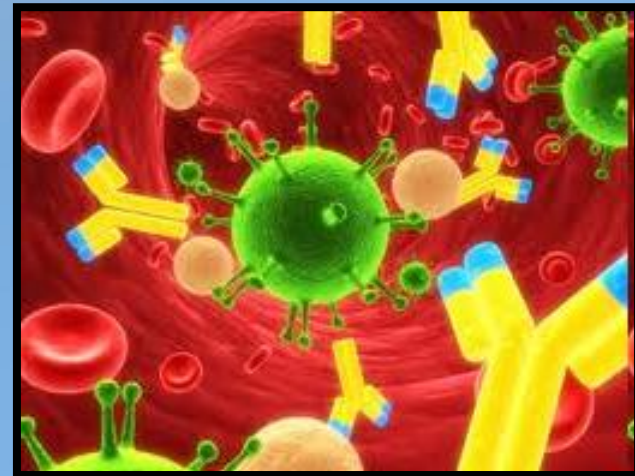
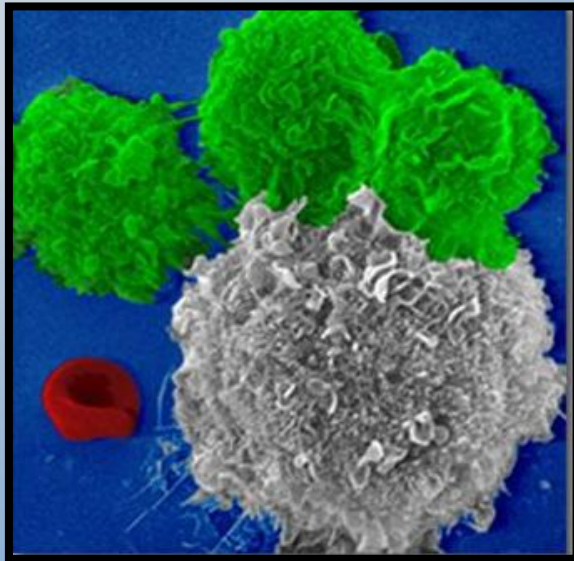


# Diseases of the immune system



## Lecture I.

Ágota Szepesi

I. Department of Pathology

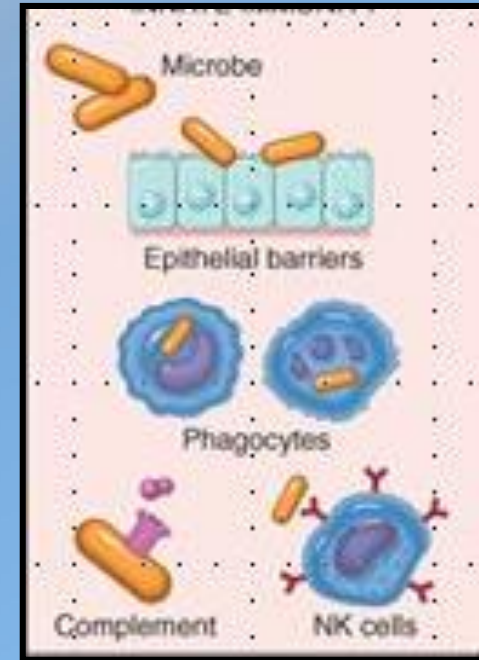
# The normal immune response

## Innate immunity (natural, native)

immediate response to infections

NOT SPECIFIC

NO ADAPTATION- same intensity on repeated exposures



## Adaptive immunity (acquired, specific)

immediate to late response to infection

HIGHLY SPECIFIC

ADAPTATION-improved response

MEMORY

# Adaptive immunity

## Humoral immunity:

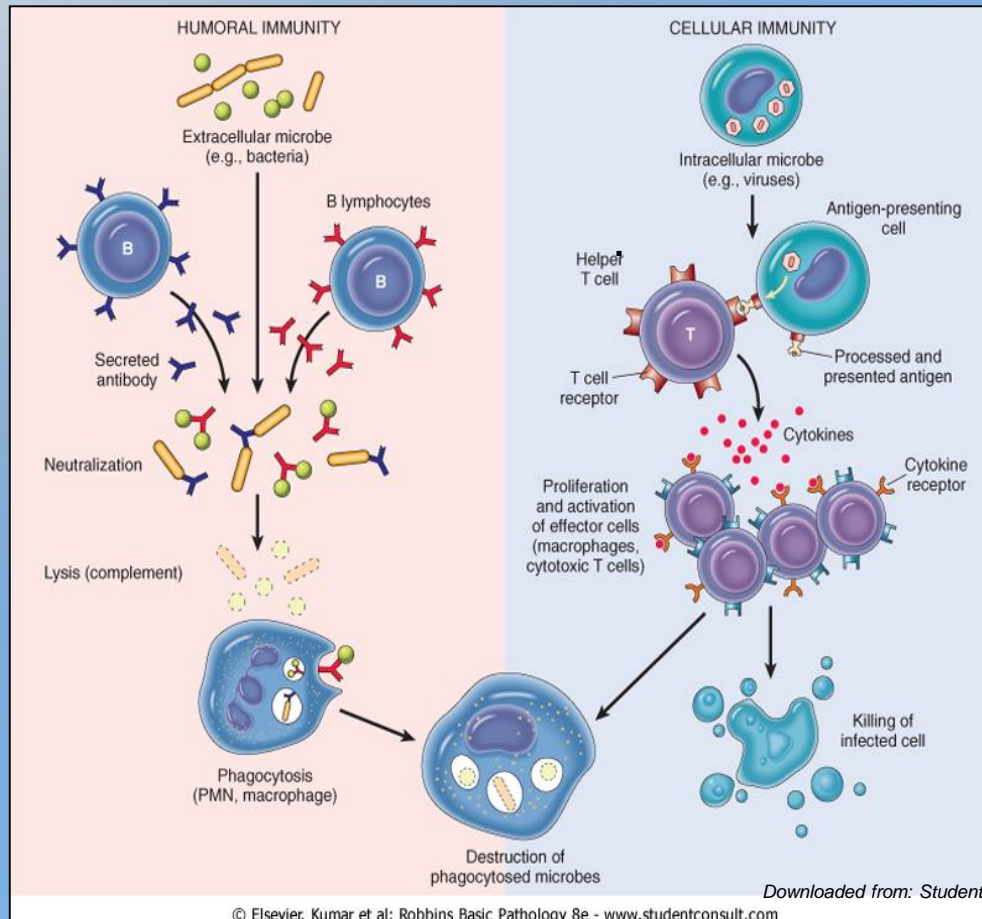
**Effectors:** B-cells, antibodies

**Role:** protection against extracellular microbes

## Cellular immunity:

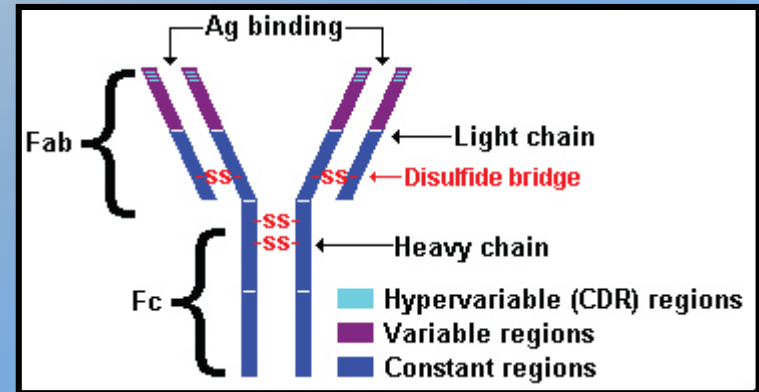
**Effectors:** T lymphocytes

**Role:** protection against intracellular microbes



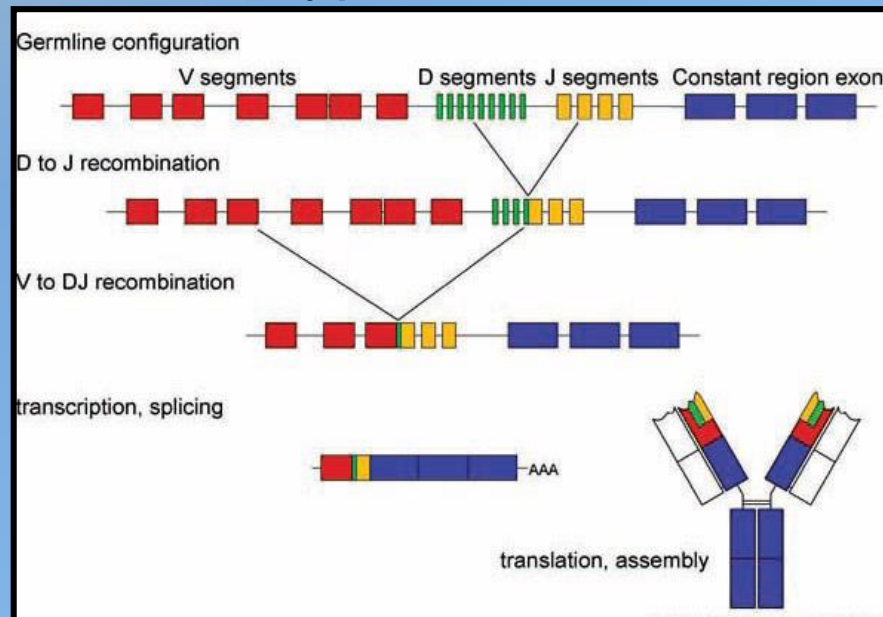
# B-cell function

Immunglobulin (antibody) production



## SPECIFICITY-

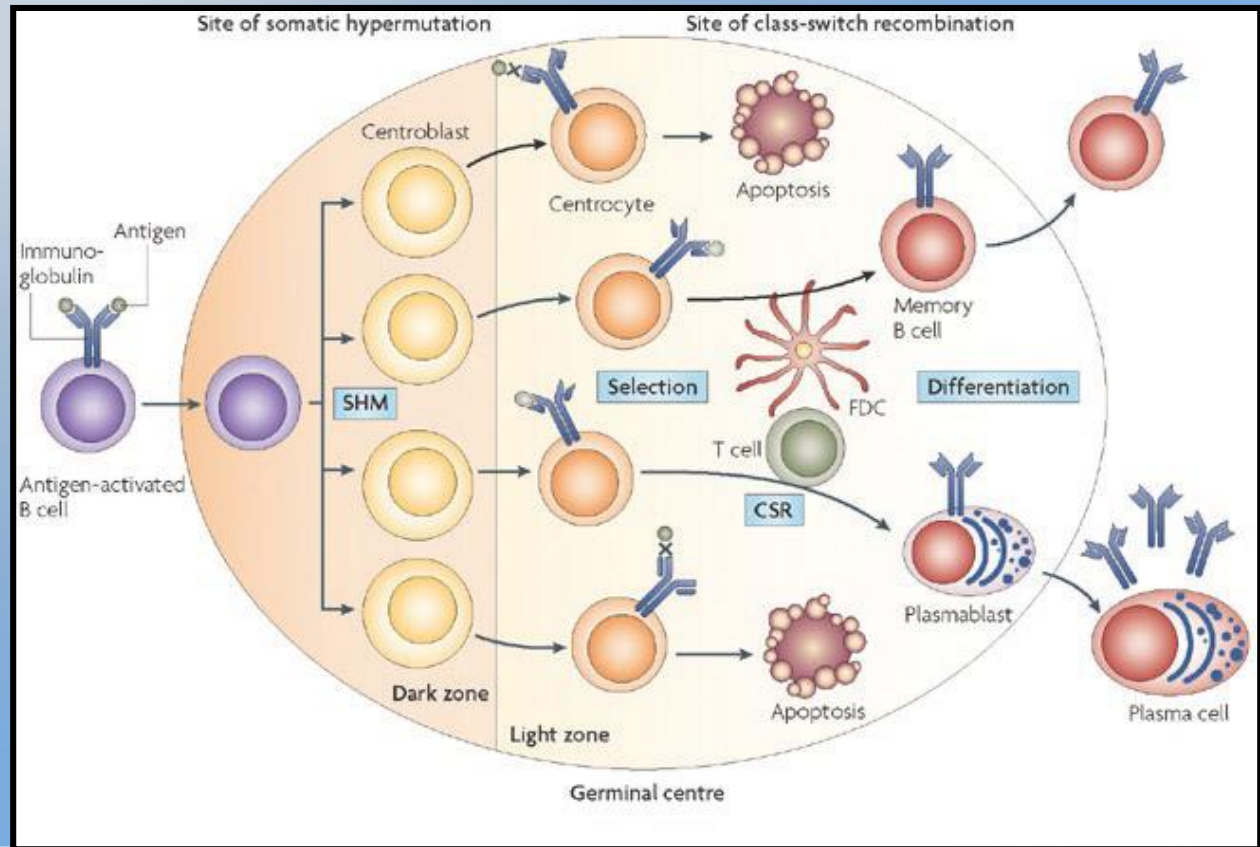
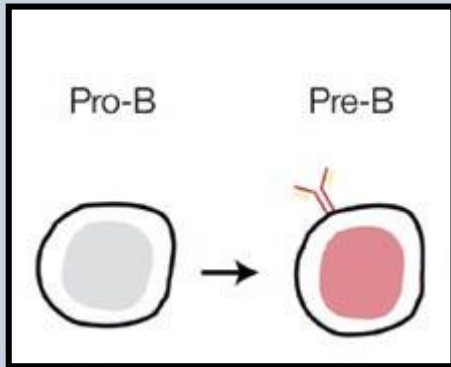
Immunglobulin gene rearrangement  
Somatic hypermutation



# B-cell development

Bone marrow → Secondary lymphoid organs

Naiv B cells  
Ig rearrangement



**MEMORY**- memory B cells

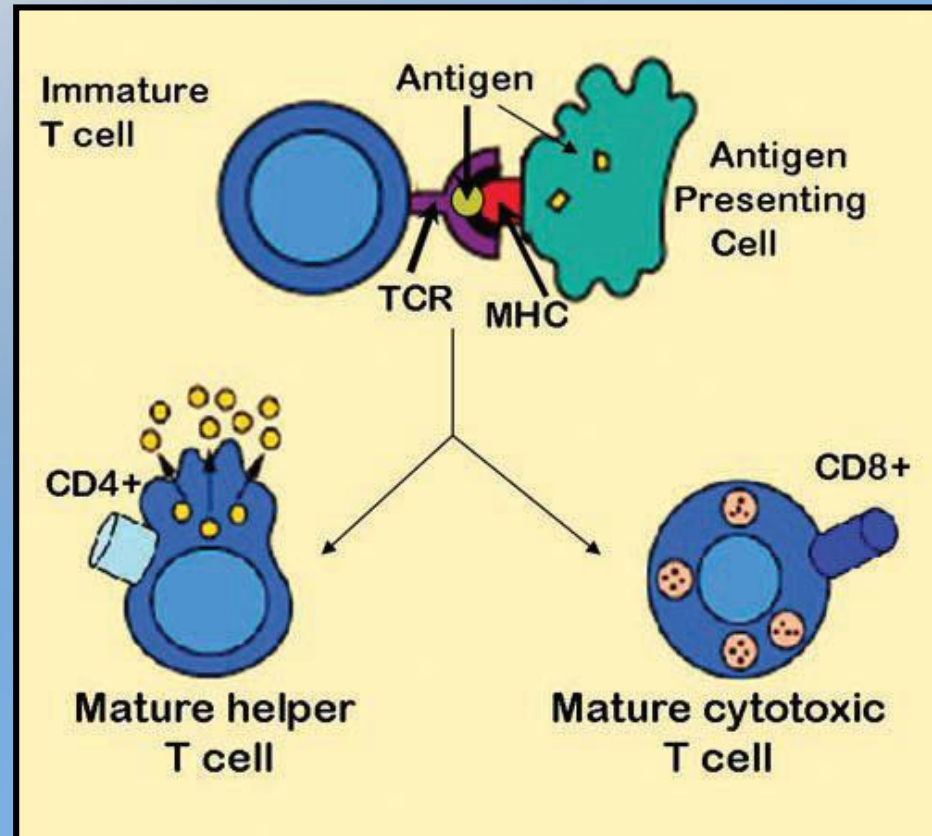


# T cell development

Thymus

Secondary lymphoid organs

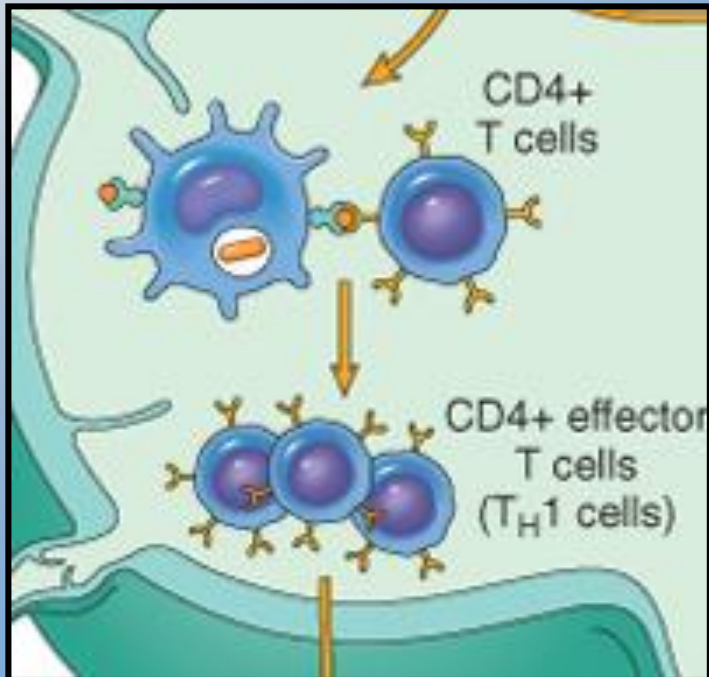
T-cell receptor  
rearrangement



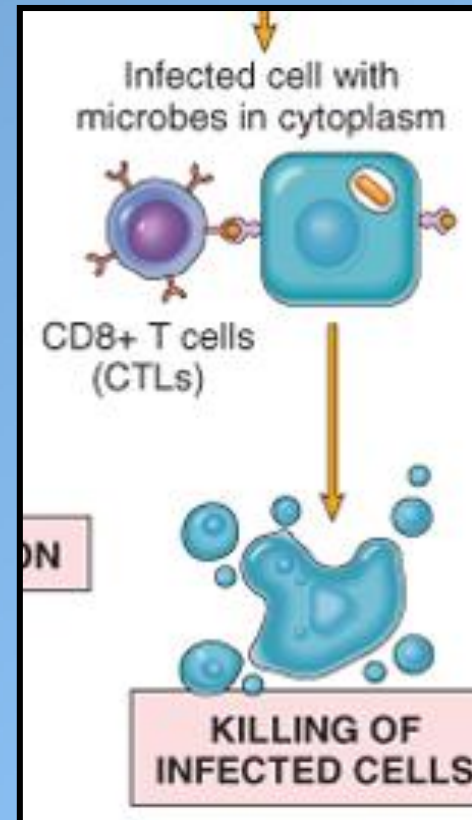
T cells recognize antigens only in association with MHC molecules- **MHC restriction**

# T-cell function

CD4+ helper T cells-  
recognize peptides-deriving from  
extracellular microbes- on APC in  
association with MHC II



CD8+ cytotoxic T cells-  
recognize intracellular  
peptide antigens- tumor  
cells/ viral antigens in  
association with MHC I



# Regulation of the immune response

- **Activation** of innate and specific immunity by **T cells**
- **Duration** and **intensity** is regulated by **cytokines** produced by **T cells** and **macrophages**
- **Genetic control- MHC haplotype** controls antigen recognition by T-cells
  - Genetic predisposition to pathological immune reactions is MHC associated
- **Memory**-long lived **memory cells**- antigen specific B lymphocytes



# Diseases involving the immune system

- Hypersensitivity, allergy
- Autoimmune diseases
- Immunodeficiencies
- Transplantation pathology
- Amyloidosis

# Hypersensitivity reactions

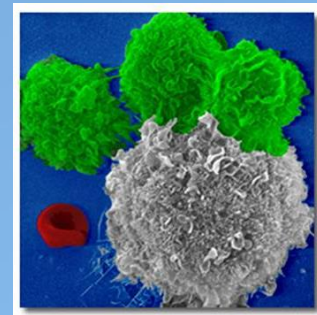
- Abnormal/excessive immune responses in sensitized individuals=**ALLERGY**
- Difficult to control or terminate-
  - immune-mediated injury to host tissues
  - chronic inflammatory reaction
- Association with inheritance of specific susceptibility genes – **MHC/HLA genes**

# Types of hypersensitivity reactions

- Classification is based on the mechanism of immune injury
- Type I-III antibody mediated



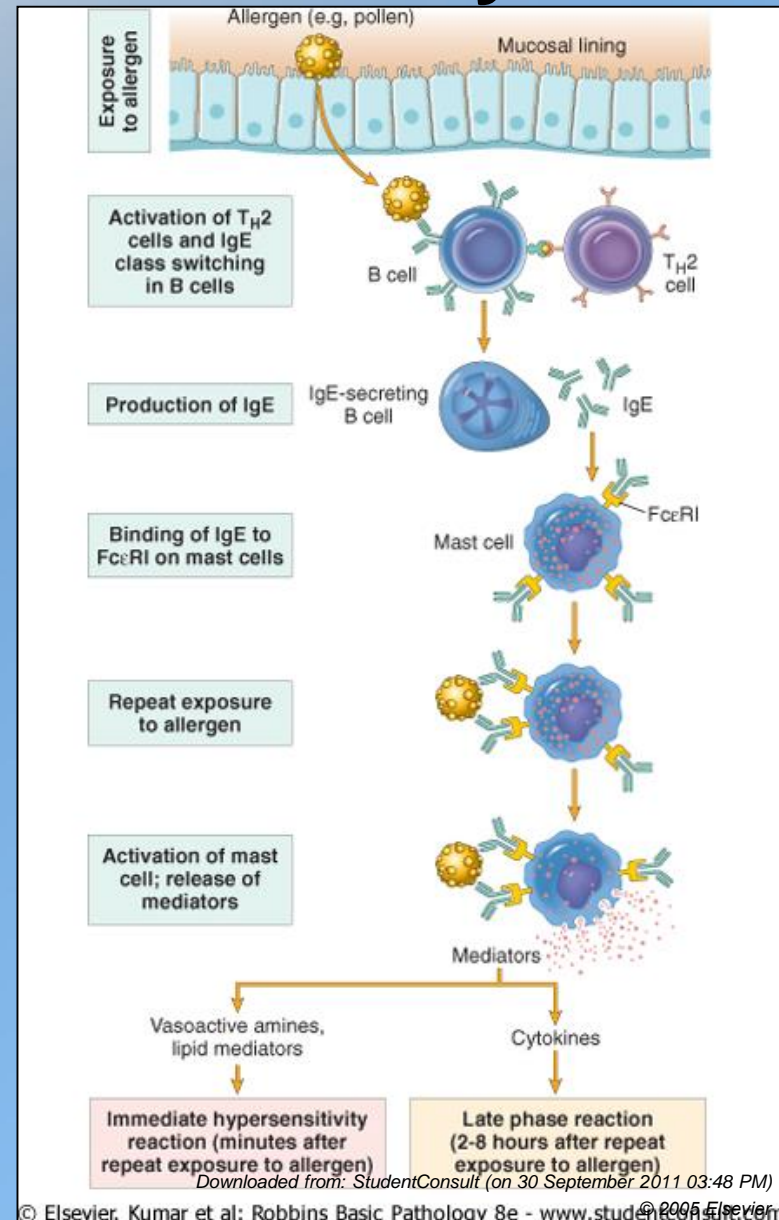
- Type IV cell mediated



- Antigen- ALLERGEN

# Type I Immediate hypersensitivity

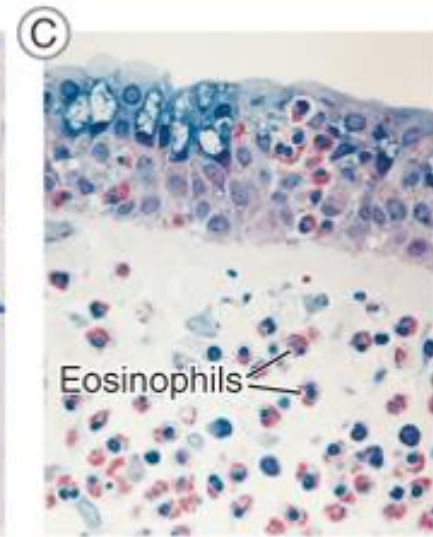
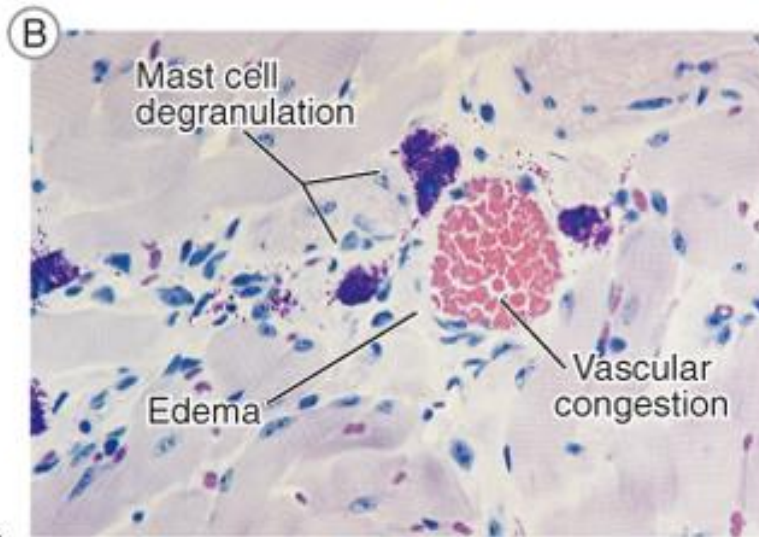
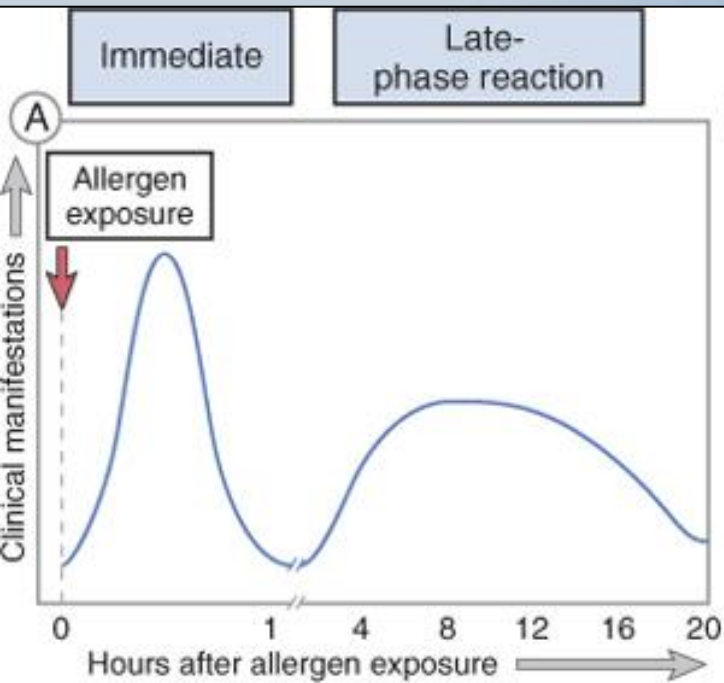
- Sensitization (antibody production) against environmental antigens (allergens: pollens, house dust)
- Immediate reaction in minutes
  - IgE antibody mediated
  - Main effector cells: Mast cells
- Late phase: tissue infiltration by eosinophils, neutrophils



- Mast cell mediators:
  - Vasoactive amines released from granule stores- HISTAMINE
  - Newly synthesized lipid mediators: PROSTAGLANDINS, LEUKOTRIENES
  - Cytokines: TNF, PAF, CHEMOKINS
- Action:
  - Vasodilatation, increased vascular permeability
  - Smooth muscle spasm
  - Cellular reaction



# Tissue reactions in type I hypersensitivity



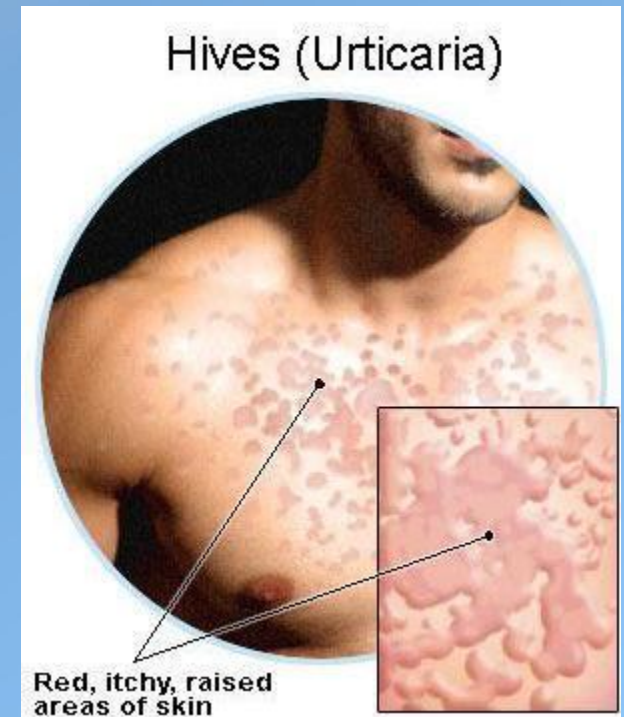
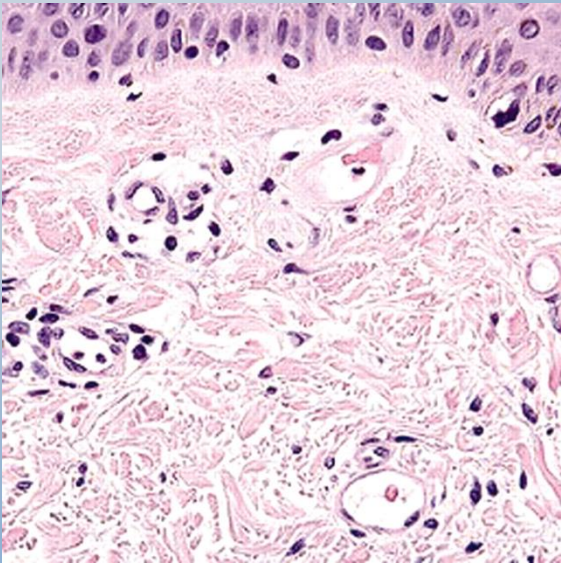
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# Extension of the reaction

- Depending on the portal of entry of the allergen
  - **Local**: entry through skin, mucous membranes (respiratory tract, GI tract)
  - **Systemic reaction = anaphylaxis**, due to blood injection of the allergen

# Local immediate hypersensitivity

- Skin
  - Urticaria (hives, nettle rash)



- Allergens:
  - GI: drugs (penicillin), food (milk, eggs),
  - contact allergens: chemicals, metals

# Local immediate hypersensitivity



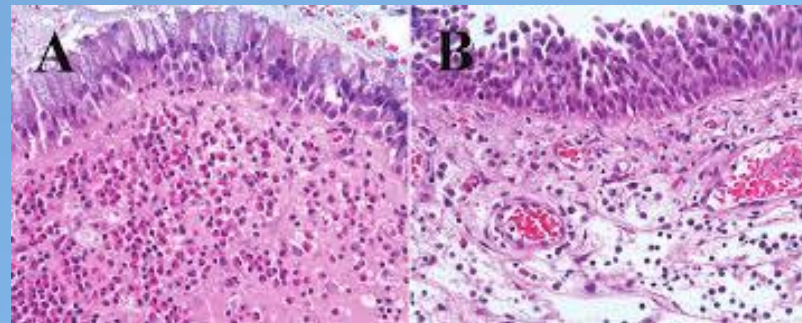
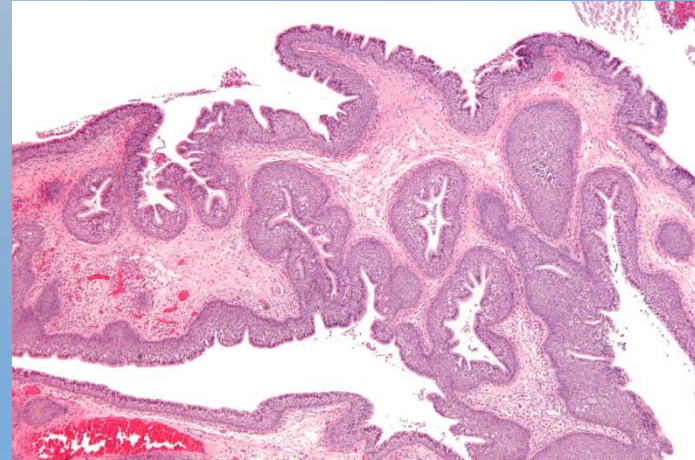
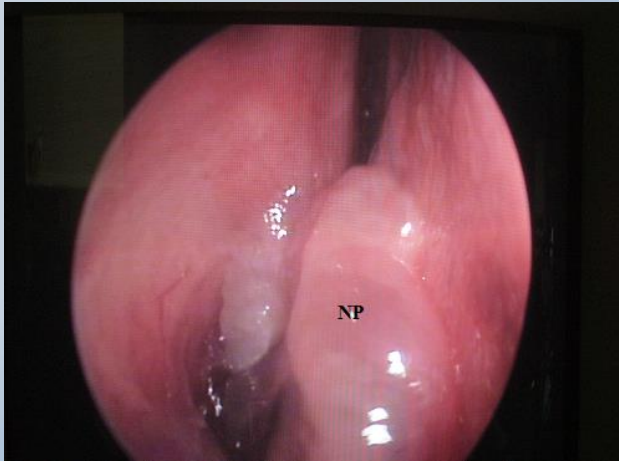
- Respiratory tract: nose, sinuses
  - **Hay fever/** allergic rhinitis, sinusitis
    - Serous exudate
    - Chronic allergic sinusitis-sinusitis polyposa
    - Secondary bacterial sinusitis

Allergens: pollen (ragweed), house dusts (mite,tick), animal dander, and food.

- Eye: allergic conjunctivitis



# Allergic nasal polyps





# Asthma bronchiale

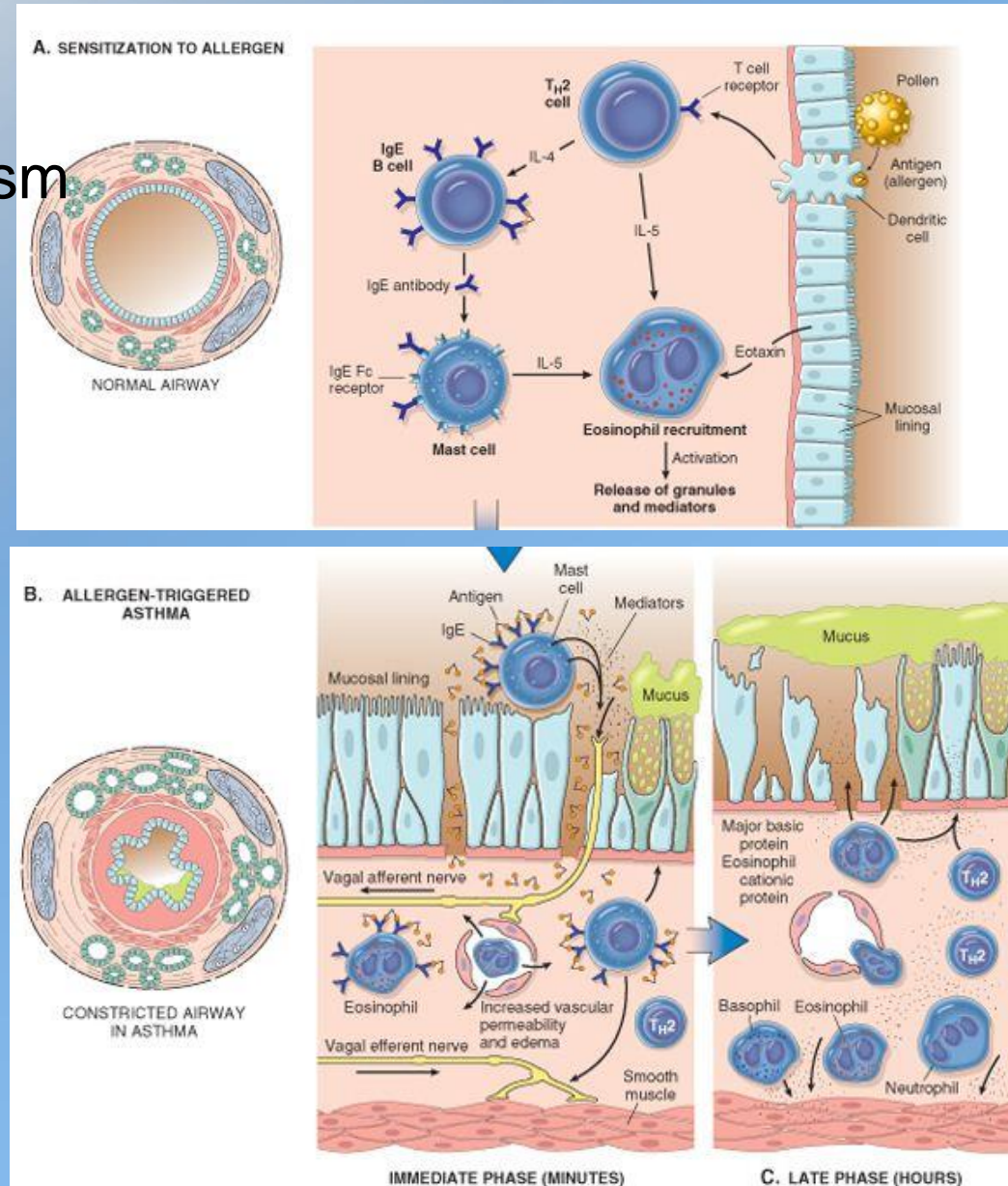
## Clinical symptoms due to airway obstruction

**Immediate reaction:**  
oedema, smooth muscle spasm

**Late phase:** increased  
mucus production, smooth  
muscle hypertrophy.

**Cellular reaction:**  
infiltration by eosinophils

**Allergens:** dusts,  
pollen, animal dander,  
and foods



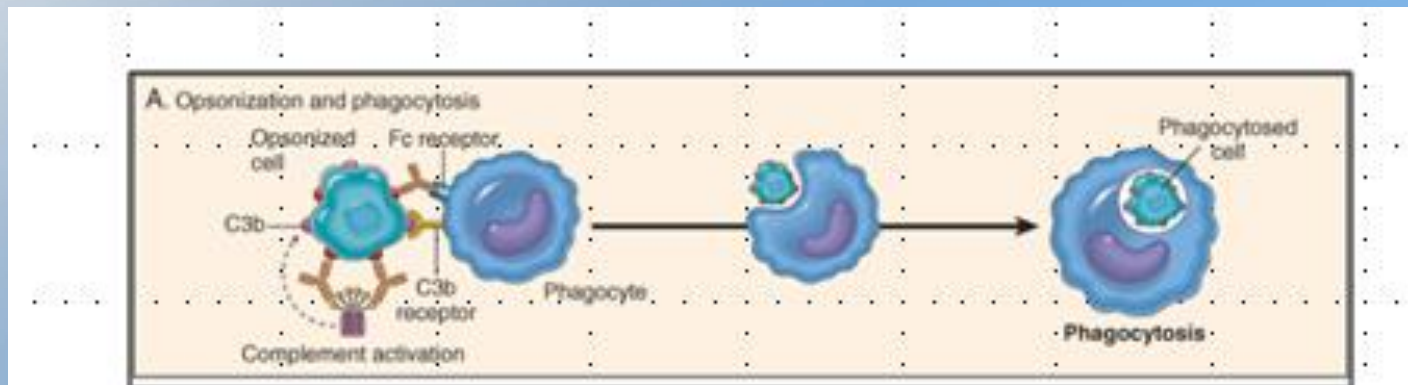
# Systemic hypersensitivity=Anaphylaxis

- Vascular reaction: severe hypotension, Circulatory collapse
  - systemic vasodilatation, increased vascular permeability
  - tissue hypoperfusion, severe hypoxia
- Skin: itching, urticaria, erythema
- Respiratory tract: difficulty in breathing
  - Contraction of respiratory bronchioles, mucus secretion
  - Laryngeal oedema
- Allergens: foreign proteins (vaccine), drugs (antibiotics), food allergens (peanut), insect toxins (bee venom)

# Type II

## Antibody mediated hypersensitivity

- Antibodies bind to cell surface antigen
  - A. Opsonization, cytolysis and phagocytosis



- Transfusion reaction (A,B, Rh)
- Hemolytic disease of the newborn (anti-Rh)
- Autoimmune cytopenias: hemolytic anemia (AIHA), immun thrombocytopenia (ITP)

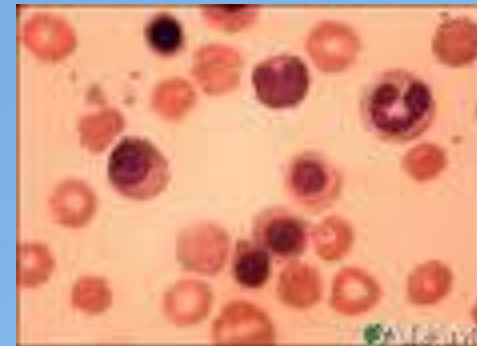
# Hemolytic disease of the newborn

IgG molecules against Rh blood group antigens, produced by the Rh-, sensitized mother, pass through the placenta

Severe hemolysis, hypoxia:  
Hydrops fetalis



Mild hemolysis:  
Erythroblastosis fetalis

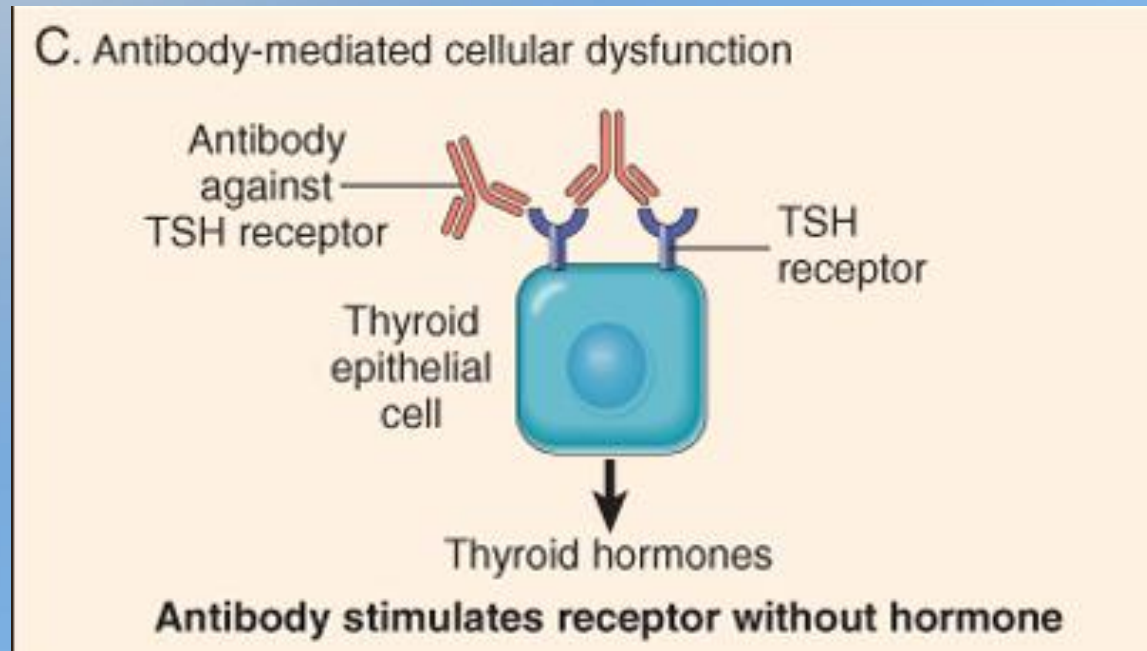


Erythroid regeneration: erythroblasts  
, reticulocytes in the circulation

B. Antibodies bind to cell surface RECEPTORS influencing cell functions:

## Graves disease, diffuse goiter

-Stimulating antibodies against TSH receptors of the thyroid gland.

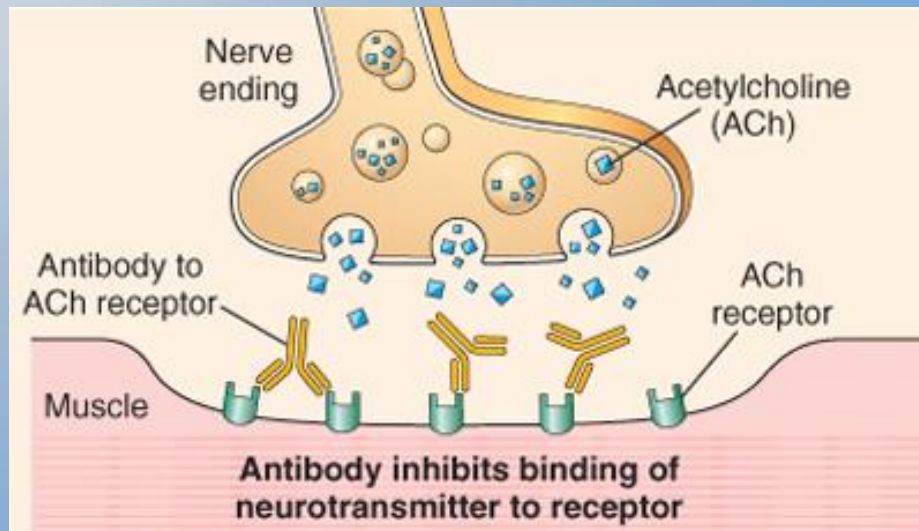




# Myasthenia gravis

Inhibiting antibodies against the acetylcholine receptors at the neuromuscular junction.

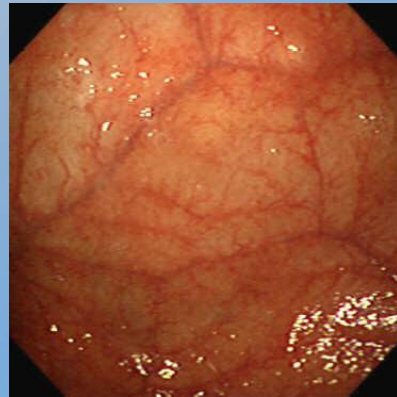
**Symptoms:** muscle weakness, ptosis, diplopia



Associated: thymus hyperplasia or thymoma

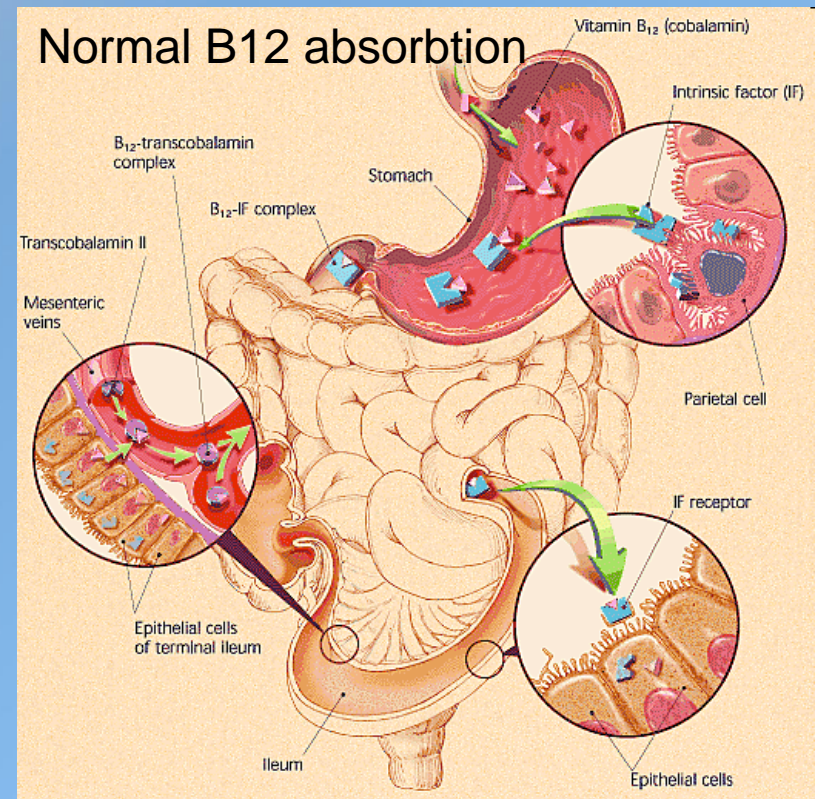
# Autoimmune gastritis/anaemia pernicioosa

- Antibodies against gastric parietal cells/ intrinsic factor-
- Inhibiting the intrinsic factor-B12 complex ileal absorbtion
- Chronic atrophic gastritis
  - Atrophy and lymphocytic infiltration



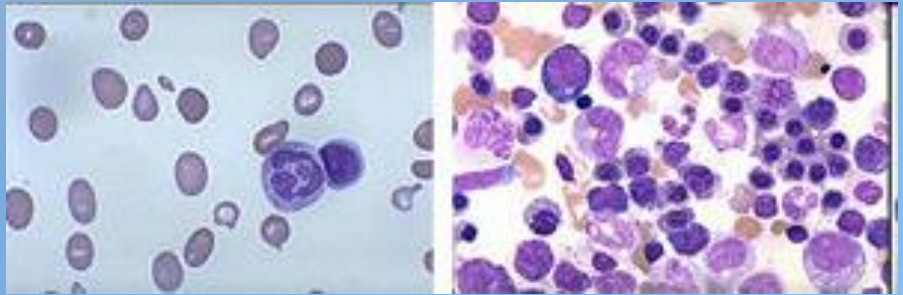
- Increased risk of gastric carcinoma

- Vitamine B12 defficiency



# Vitamin B12 deficiency

- Bone marrow: Megaloblastic erythroid hyperplasia
  - Impaired DNA synthesis- Cytoplasmic-nuclear asynchrony
  - Ineffective erythropoiesis
- Peripheral blood: Macrocytic anaemia



- Peripheral neuropathy: due to demyelination of the spinal cord tracts



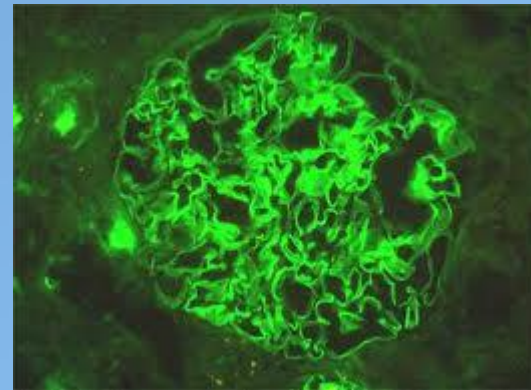
- Atrophic glossitis



# Goodpasture syndrome

- Anti-basal membrane antibodies (type IV collagen)
- Organs: kidney, lung

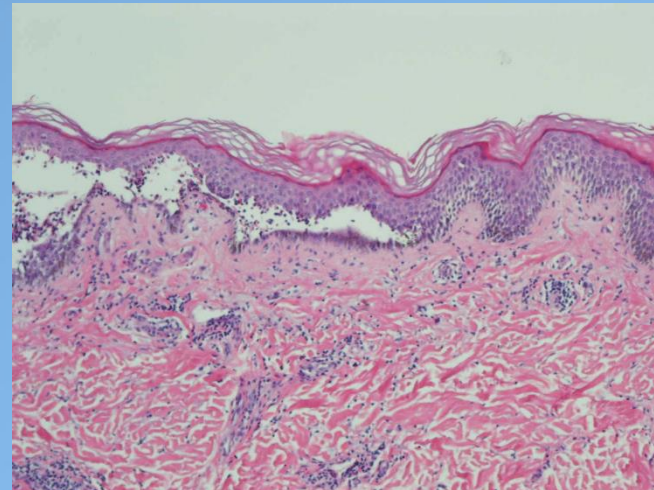
Haemorrhagic interstitial pneumonitis



Chronic glomerulonephritis

# Pemphigus vulgaris, pemhigoid

- Vesiculo-bullosus disease of the skin and oral mucosa
- Antibodies (IgG) against the desmosome proteins
- Acantholysis- suprabasal, subepidermal





# Type III

## Immunocomplex mediated hypersensitivity

- **Systemic:** antigen-antibody complexes are formed in the circulation in large amount and deposited in blood vessels
- **Local:** complexes are formed and deposited in a specific site.

### Antigen:

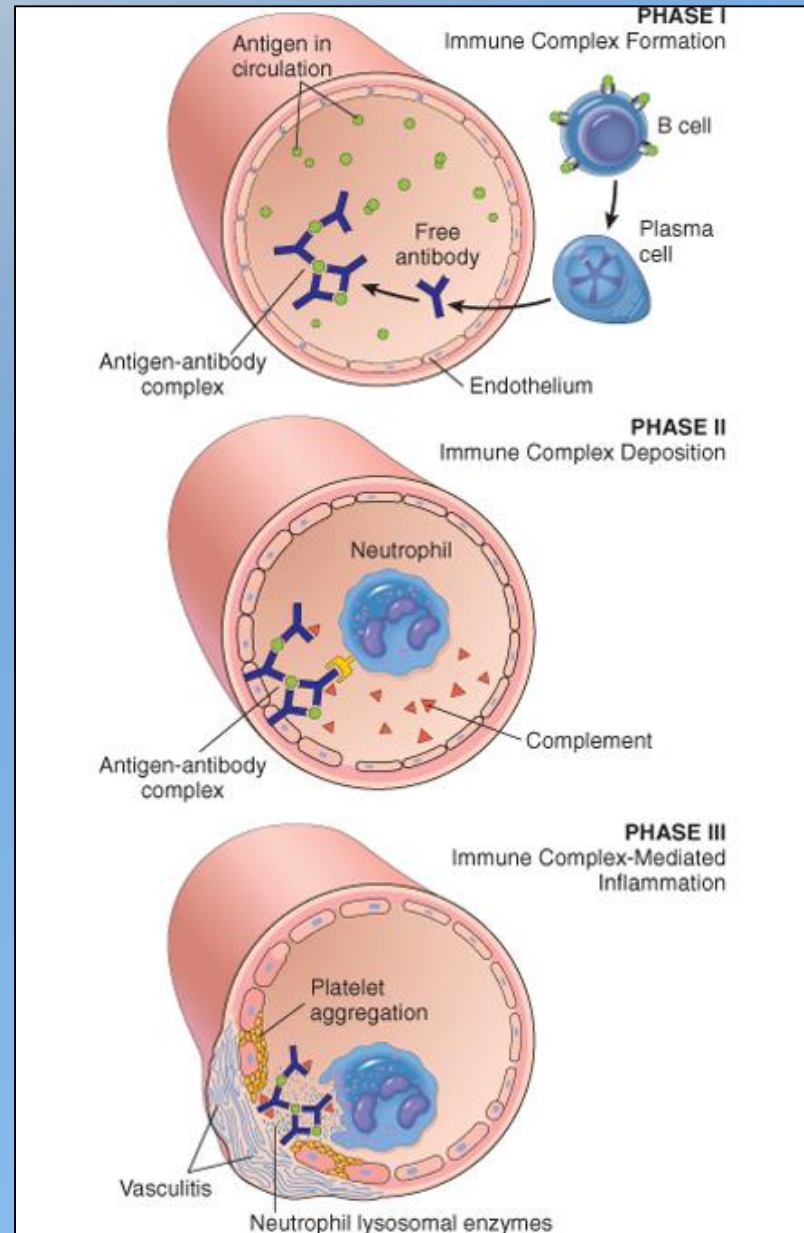
1. exogenous- microbial proteins- postinfectious  
glomerulonephritis-streptococcus, hepatitis B,  
treponema pallidum
2. endogenous (nucleoproteins)=self antigens-  
autoimmun disease - SLE

# Vasculitis

Mechanism: immune complex deposition- complement and neutrophil, monocyte activation and acute inflammation

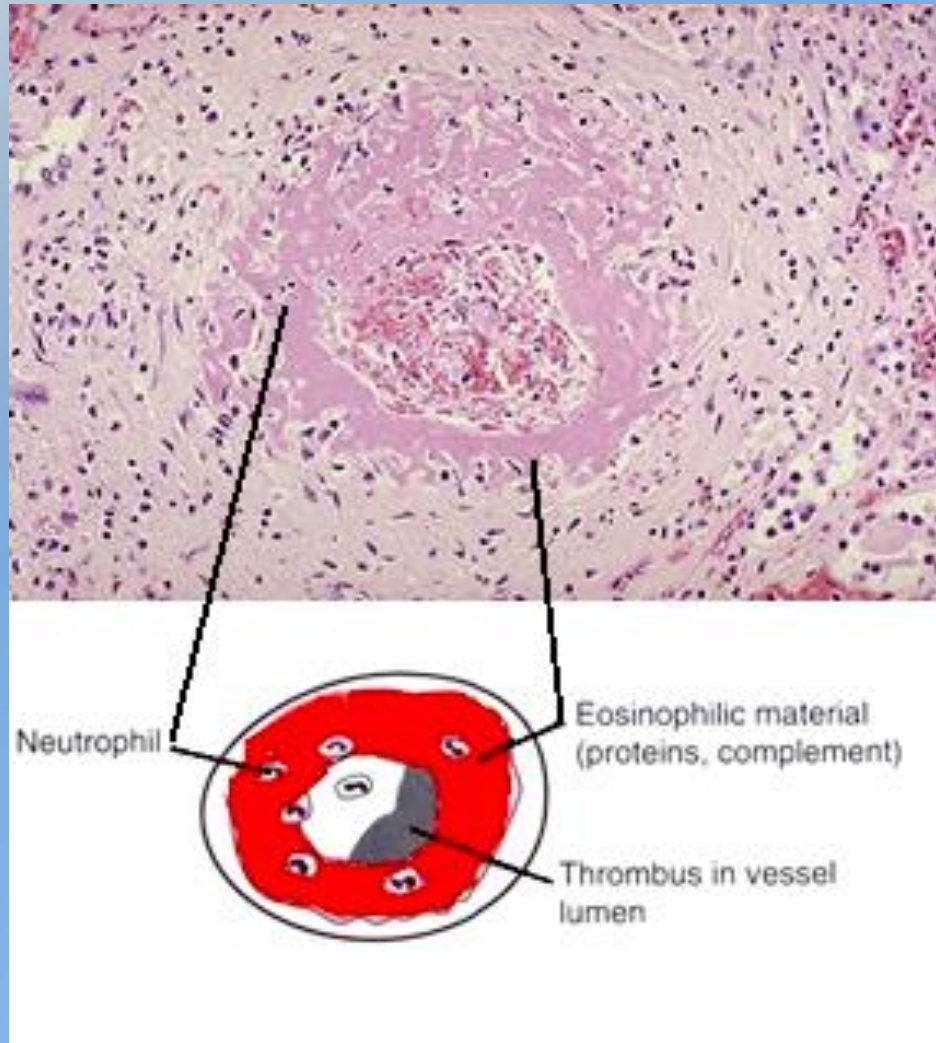
Organs involved: **kidneys, joints, skin** and small blood vessels in many tissues.

kidney- **glomerulonephritis**  
joints- **arthritis**



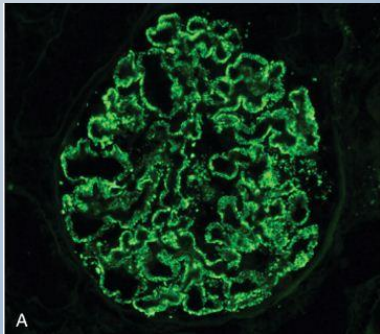
# Histology: Fibrinoid necrosis

Consequences:  
thrombosis of the  
small vessels,  
tissue ischemia,  
necrosis

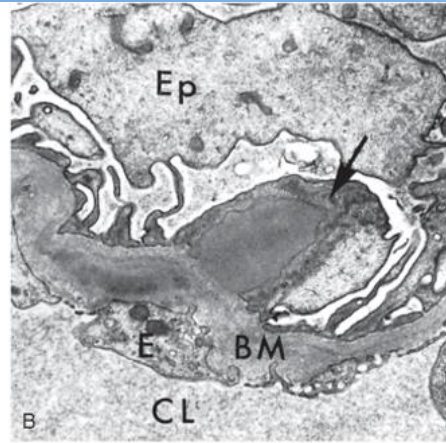
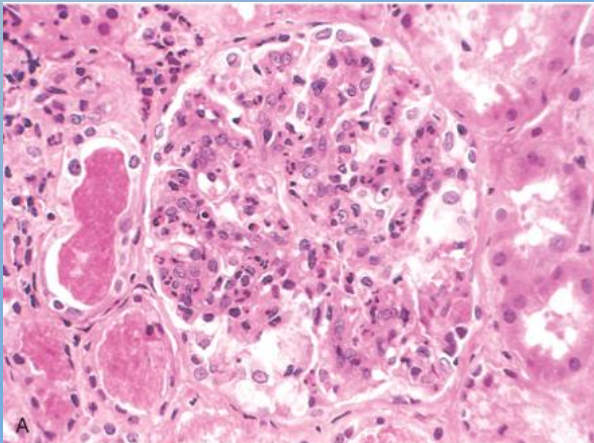


# Post-streptococcal acute glomerulonephritis

- 1-4 week after  $\beta$ -hemolytic streptococcal infection
- nephritic syndrome
- antibodies to streptococcal antigens (streptolysin O or DNAase)



-Granular deposition  
of IgG and  
complement



subepithelial "hump"  
(*arrow*) and  
intramembranous deposits



# Rheumatic fever

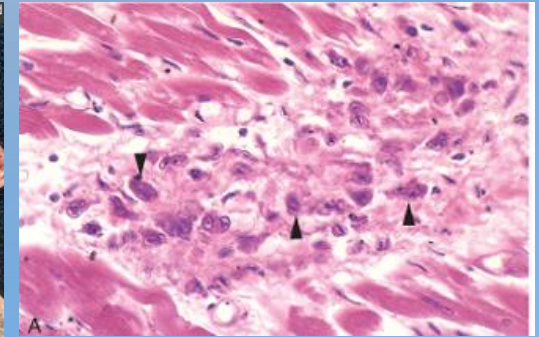
- Post-streptococcal secondary, immun-mediated disease
- Diagnosis: Jones criteria (5)
  - **Pancarditis**- Mechanism: type II hypersensitivity by antibody mimicry, crossreaction between streptococcal and fixed cardiac antigens
  - **Polyarthritis**:Mechanism: type III hypersensitivity=immun-complex deposition.  
Migratory, serous inflammation of the large joints
  - **Subcutaneous rheumatoid nodules**
  - **Erythema marginatum**
  - **Chorea minor**



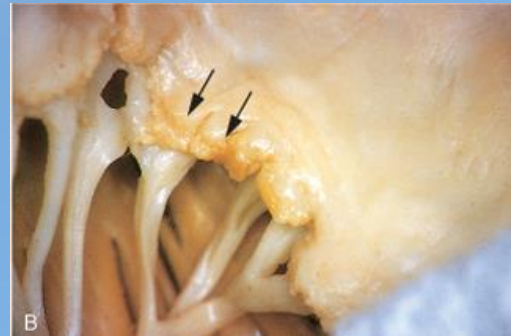
# Heart- pancarditis

Acut phase: pancarditis

1. Acut fibrinous pericarditis
2. Granulomatous myocarditis:
3. Acut endocarditis:

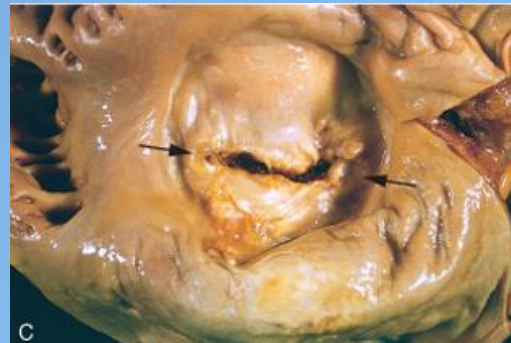


**Aschoff body**  
**Anitschkow cells**



vegetations

Chronic phase:  
chronic endocarditis  
Aortic and mitral valves



Mitral stenosis

thickening and  
distortion of the  
cusps with  
commissural fusion

# Type IV

## Delayed type Hypersensitivity (DTH)

Cell mediated:  
**T cells,**  
**macrophages**  
against intracellular  
pathogens,  
(mycobacteria,  
viruses, fungi,  
parasites).

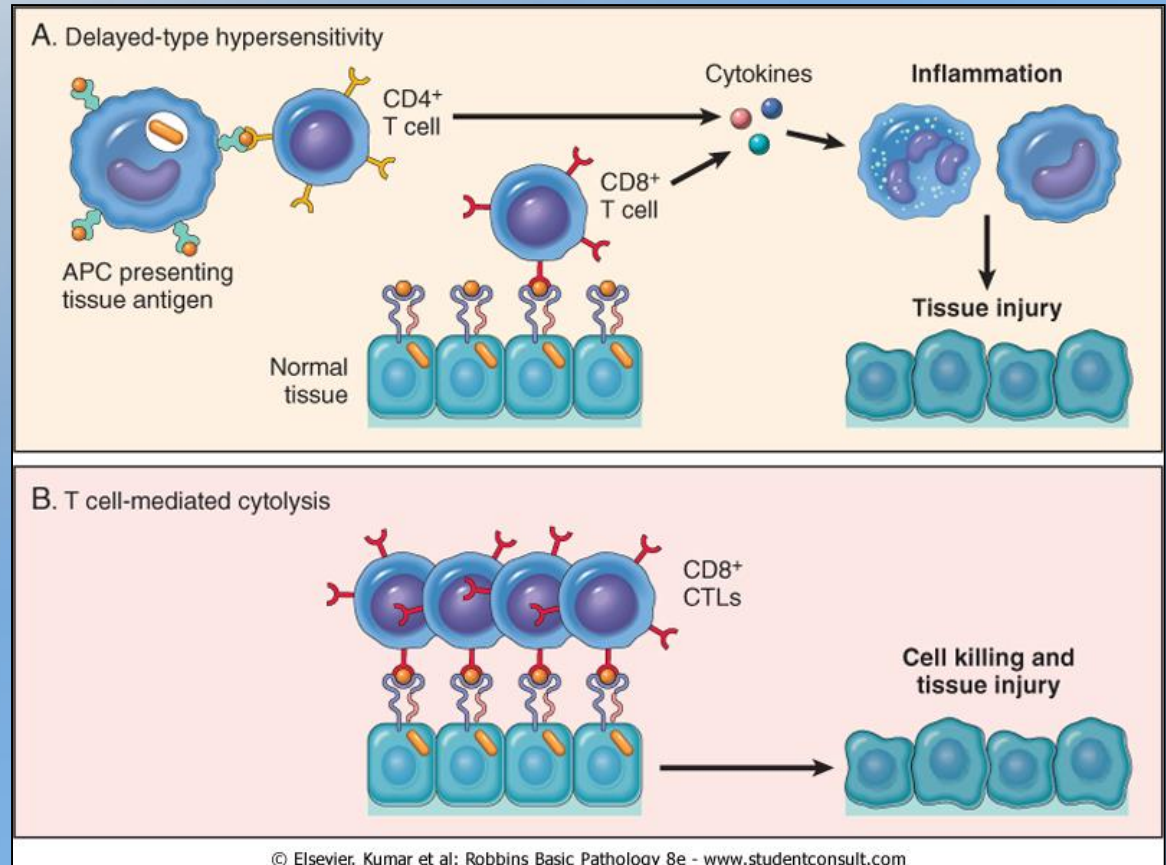


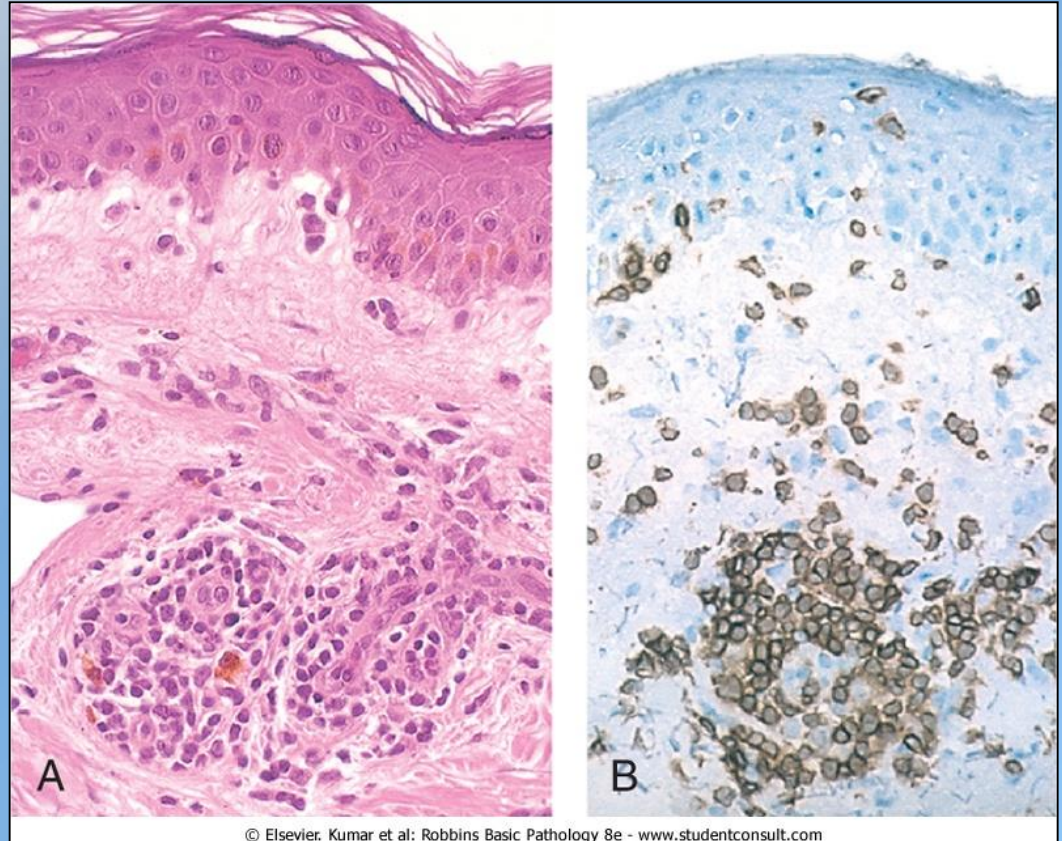
Figure 5-13 Mechanisms of T-cell-mediated (type IV) hypersensitivity reactions. A, In delayed-type hypersensitivity reactions, CD4<sup>+</sup> T cells (and sometimes CD8<sup>+</sup> cells) respond to tissue antigens by secreting cytokines that stimulate inflammation and activate phagocytes, leading to tissue injury. B, In some diseases, CD8<sup>+</sup> CTLs directly kill tissue cells. APC, antigen-presenting cell.

# Tuberculin reaction

CD4+ T cell mediated  
due to the circulating  
memory T cells specific  
for mycobacterial  
proteins

-screening populations  
for tuberculosis

Macroscopy: erythema  
and induration  
(dermal edema and  
fibrin deposition )





# Granulomatous inflammation

Prolonged DTH reactions  
persistent stimuli

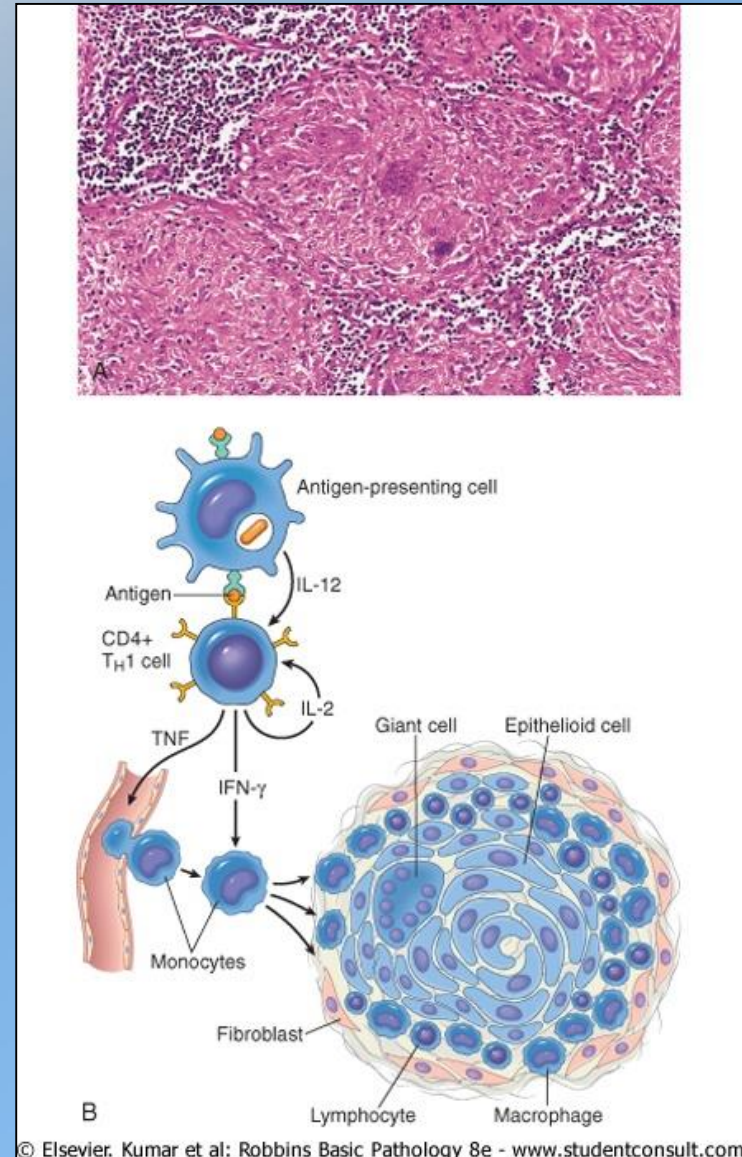
After 2-3 weeks- granuloma formation:

Epithelioid cells: activated tissue macrophages

Langhans type giant cells: epithelioid cell fusion

Lymphocytes-T-cells

Fibrous capsule – in old granulomas



# Granulomatous inflammation

- Infectious granulomas:
  - Tuberculosis
  - Syphilis
  - Fungal, parasitic infections
- Non-infectious granulomas
  - Rheumatic fever- Aschoff granuloma-
  - Sarcoidosis
  - Crohn disease
  - Foreign body granulomas



# Contact dermatitis/ ekzema

Allergen- exogen (poison ivy, poison oak)

Antigen presentation by Langerhans cells

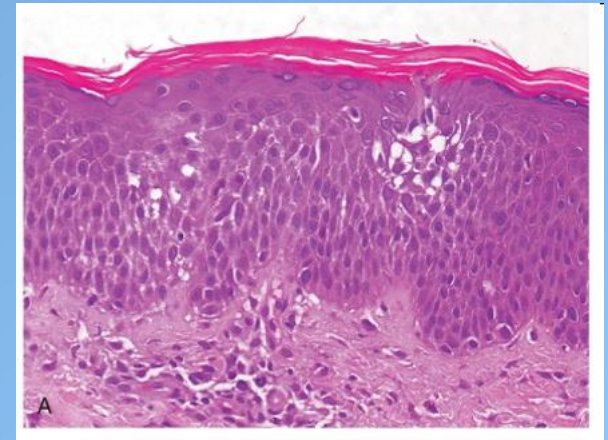
CD4+ cell response (48-72 hours) - activation of macrophages and keratinocytes-

Histology: Macrophage and T cell and eosinophil cell infiltration

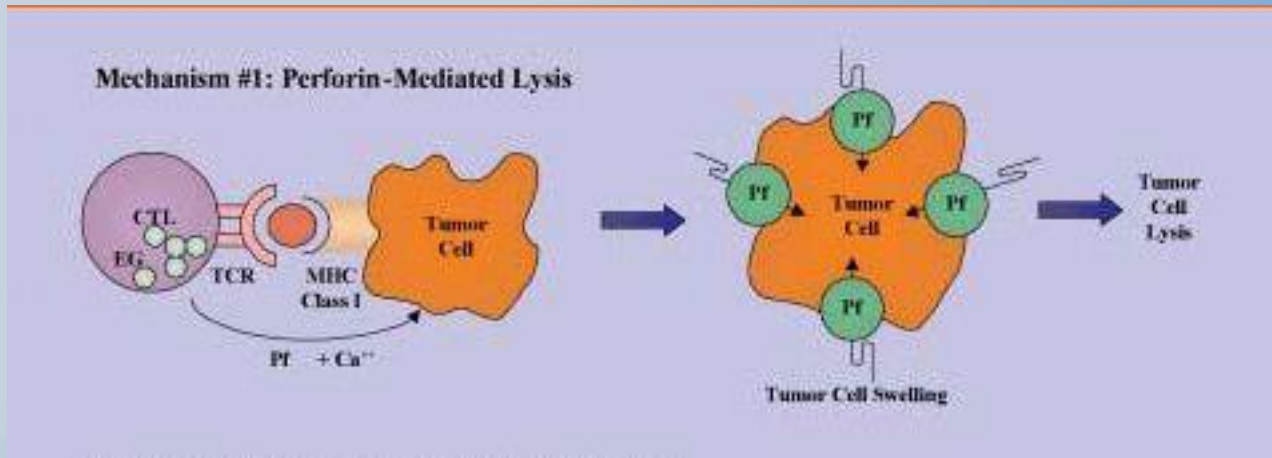
Damage to keratinocytes- intraepidermal vesicle formation.



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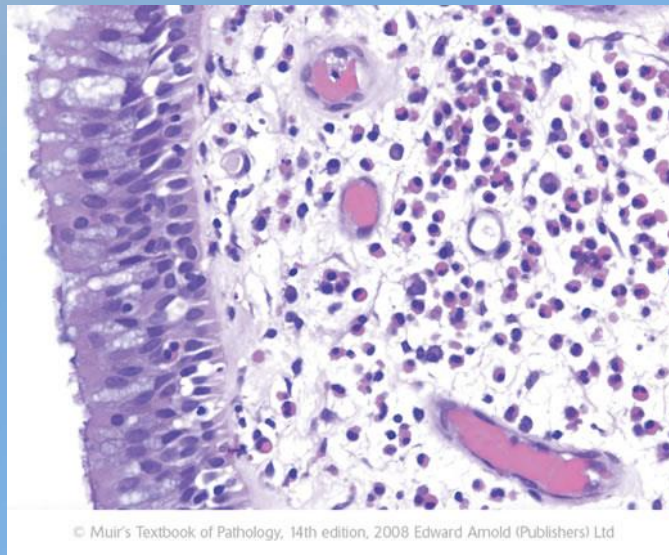
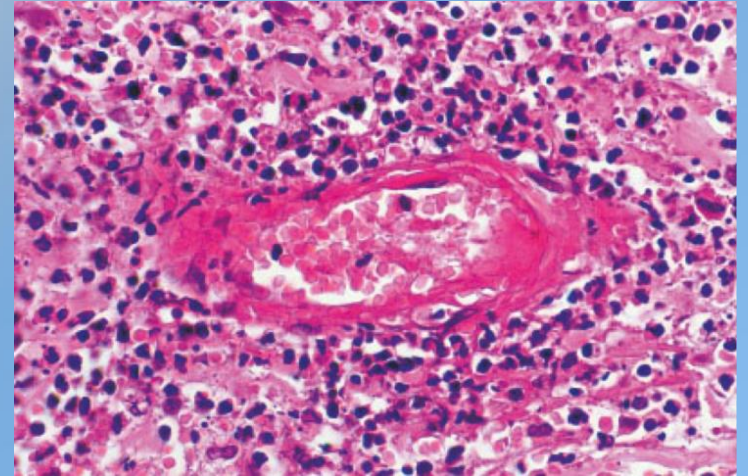
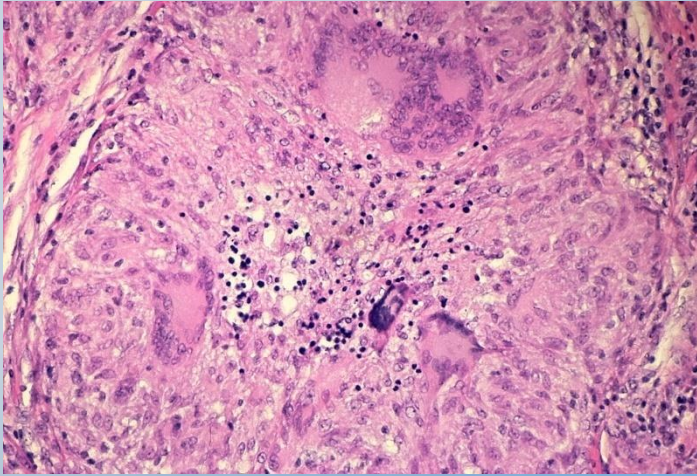


# T-Cell-Mediated Cytotoxicity



- Effector cells: CD8+T cells.
- Antigens are intracellular
- Mechanism: Perforin-granzyme system- activating the caspase system leading to apoptosis
- Roles
  - Killing of viral infected cells
  - Anti-tumor immunity
  - Rejection of solid-organ transplants
  - Autoimmune diseases-against self antigens

# Histological findings in hypersensitivity reactions



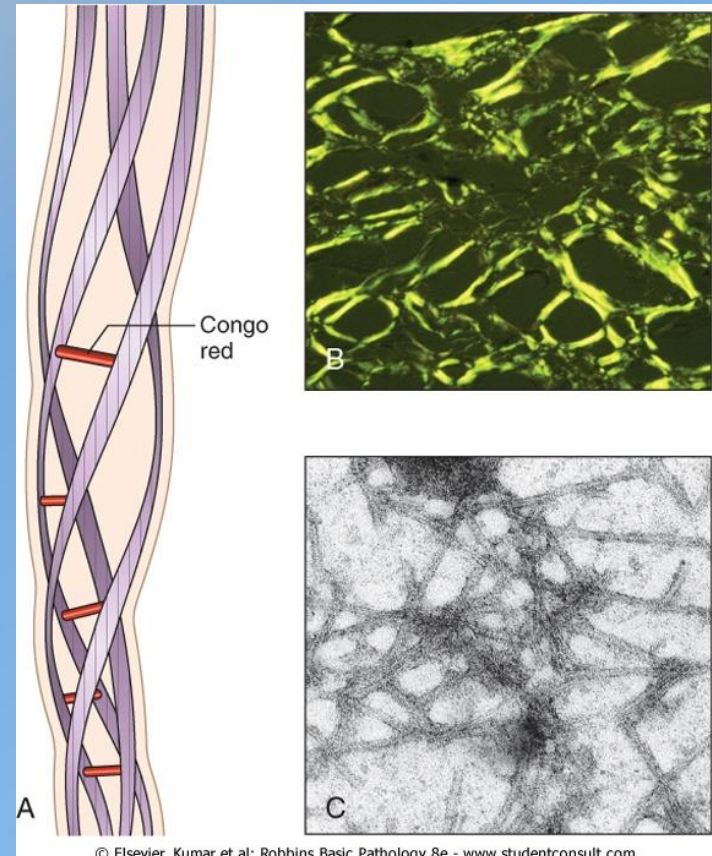
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I. III. IV.



# Amyloidosis

- Extracellular aggregation and deposition of fibrillary misfolded proteins
- Biochemically distinct ~20 proteins with similar structure:  $\beta$ -sheet polypeptide chains
- Diagnosis: histology,



7.5-10 nm amyloid fibrils

# Classification of amyloidosis

## I. Systemic

- **Primary**- plasma cell neoplasia- AL amyloid
- **Secondary**-chronic inflammation-SAA amyloid
  - Osteomyelitis, bronchiectasy, tuberculosis

## II. Localized

Brain-Alzheimer disease- A $\beta$  amyloid

Endocrine- thyroid medullary cancer- calcitonin

Hereditary (familial): mutation of Transtiretin-transport protein for thiroxin, retinol

Senile- transtiretin (heart)

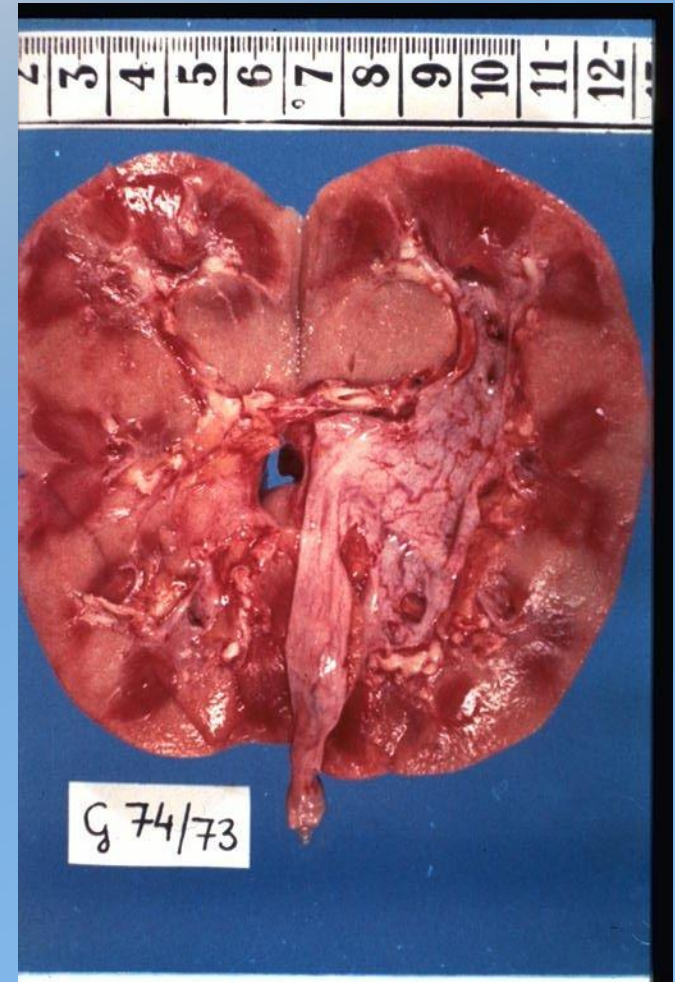


Organ involvement: Kidney, spleen, liver, GI, heart,

Macroscopic picture: large, light organs

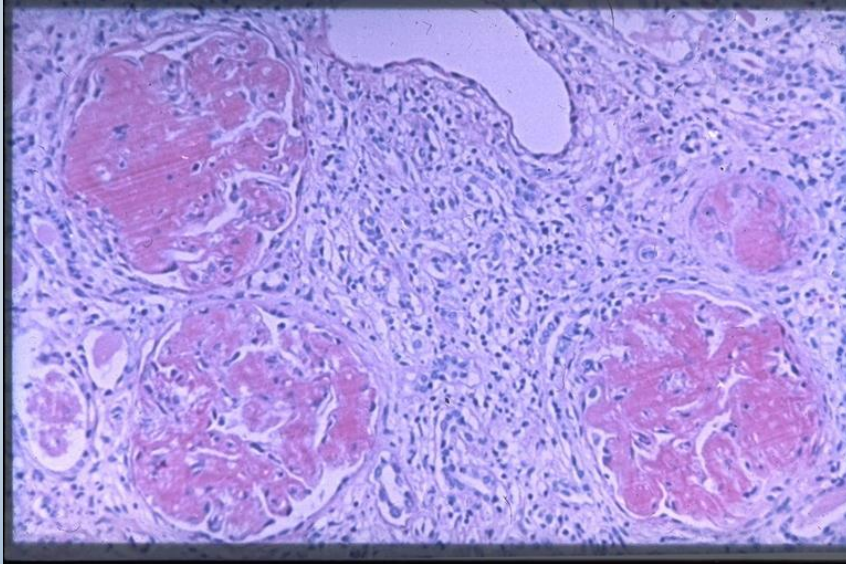
Kidney: chronic renal failure

Heart: restrictive type cardiomyopathy

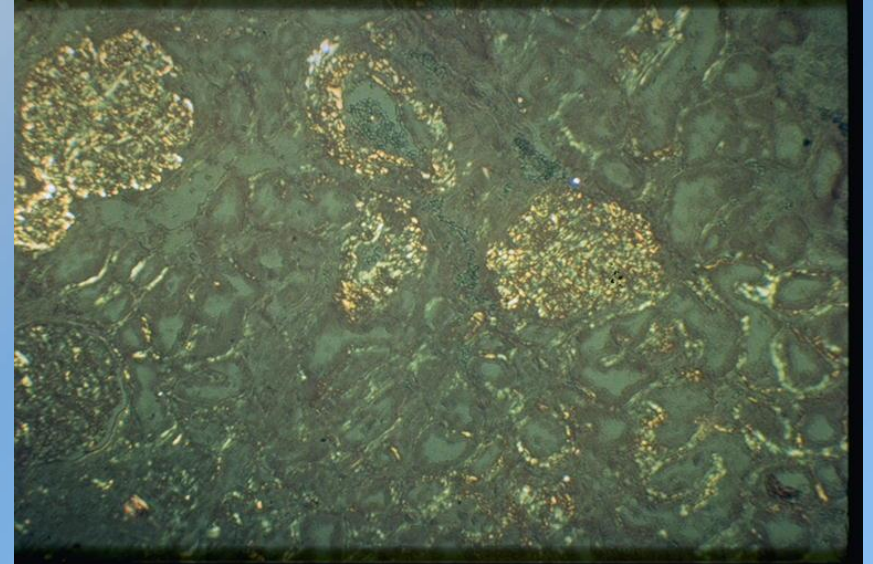


Macroscopic detection: Lugol solution: cut organ is painted with iodine and sulfuric acid. This yields mahogany brown staining of the amyloid deposits

# Microscopic detection: congo red stainig



Congo red



Polarization microscopy:  
green birefringence

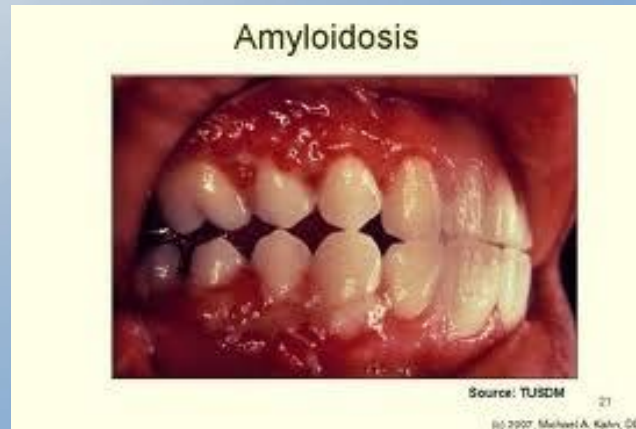
Diagnosis is based on histology!!



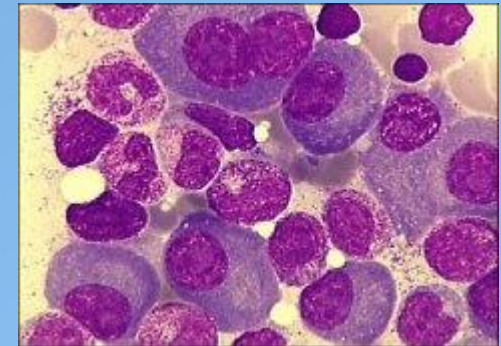
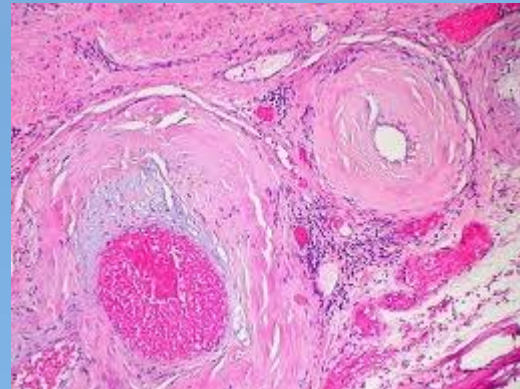
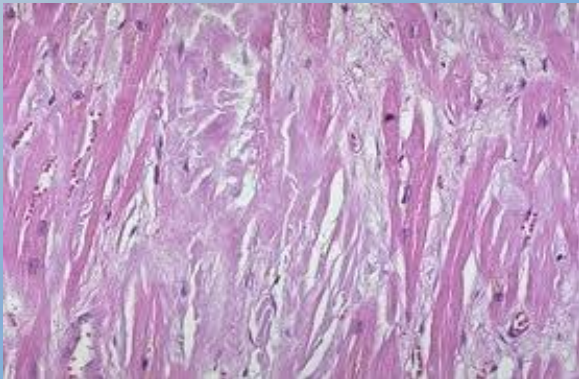
# Amyloidosis- tongue, gingiva



macroglossia



Plasma cell tumor



Thank You!

