Immune tolerance, autoimmune diseases

Immune tolerance

- Central:
  - negative selection during thymic education
  - deletion of autoreactive B-lymphocytes in the bone marrow

Positive selection in the thymus

Figure 5.19a

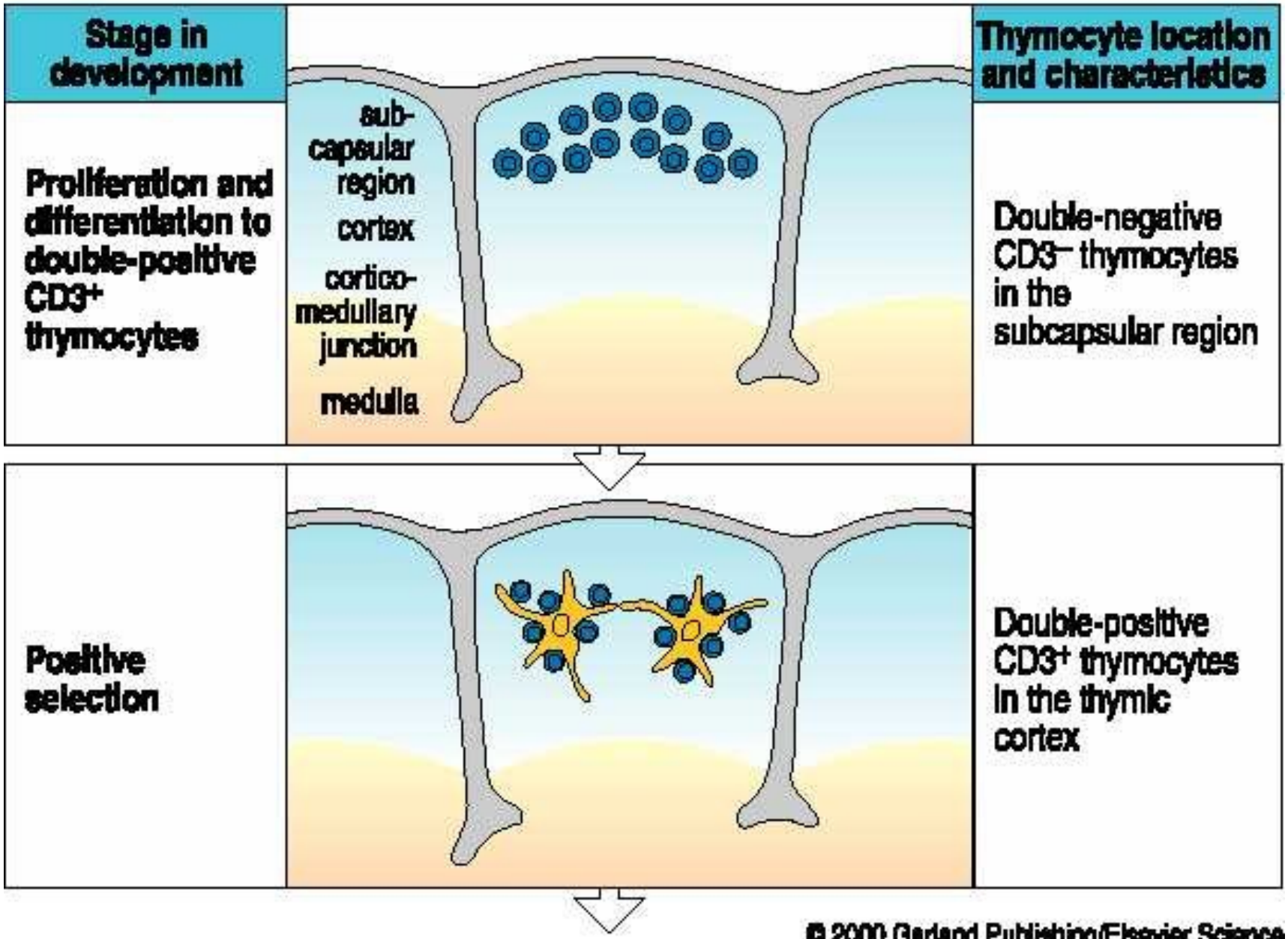
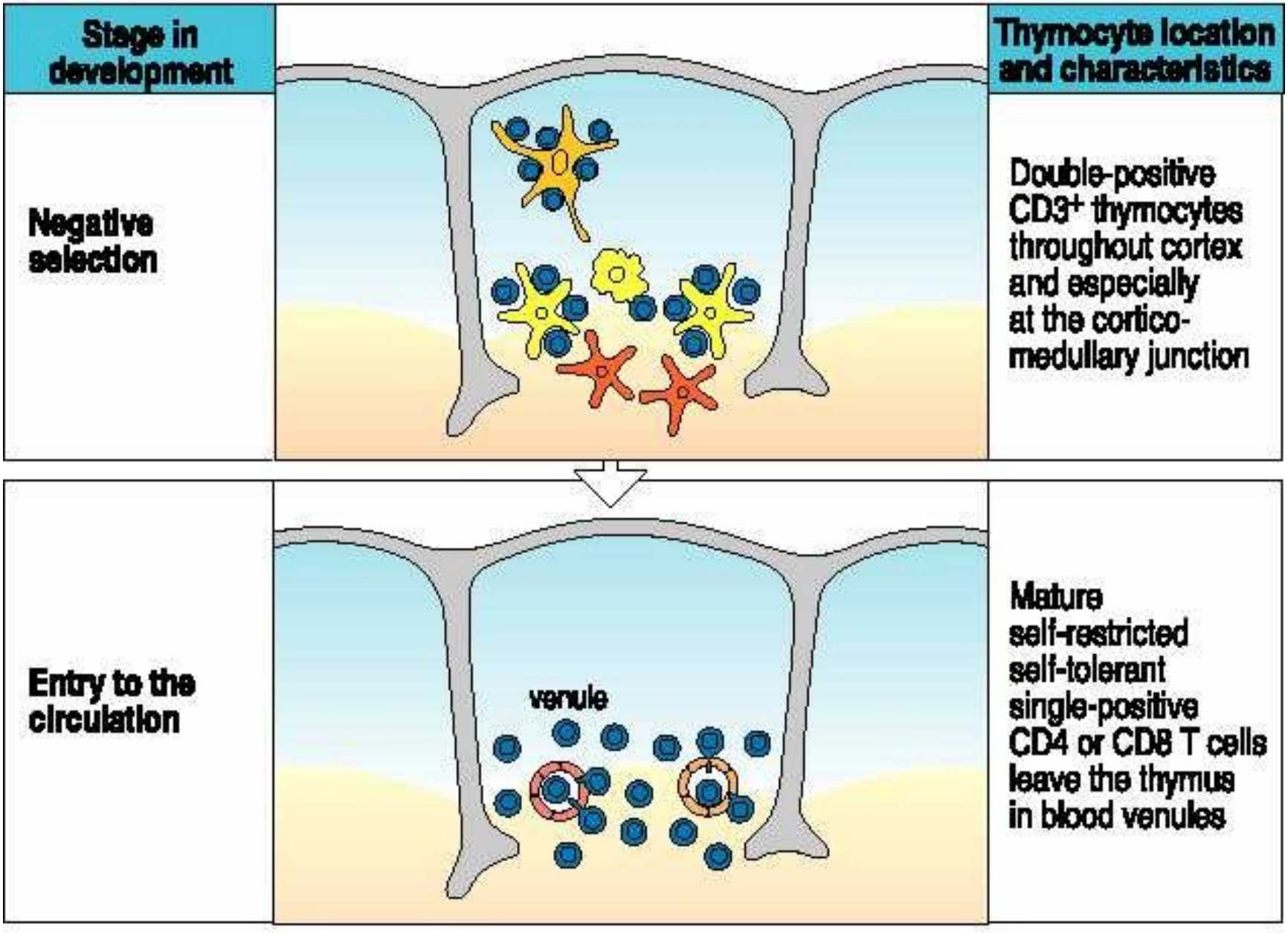


Figure 5.15b

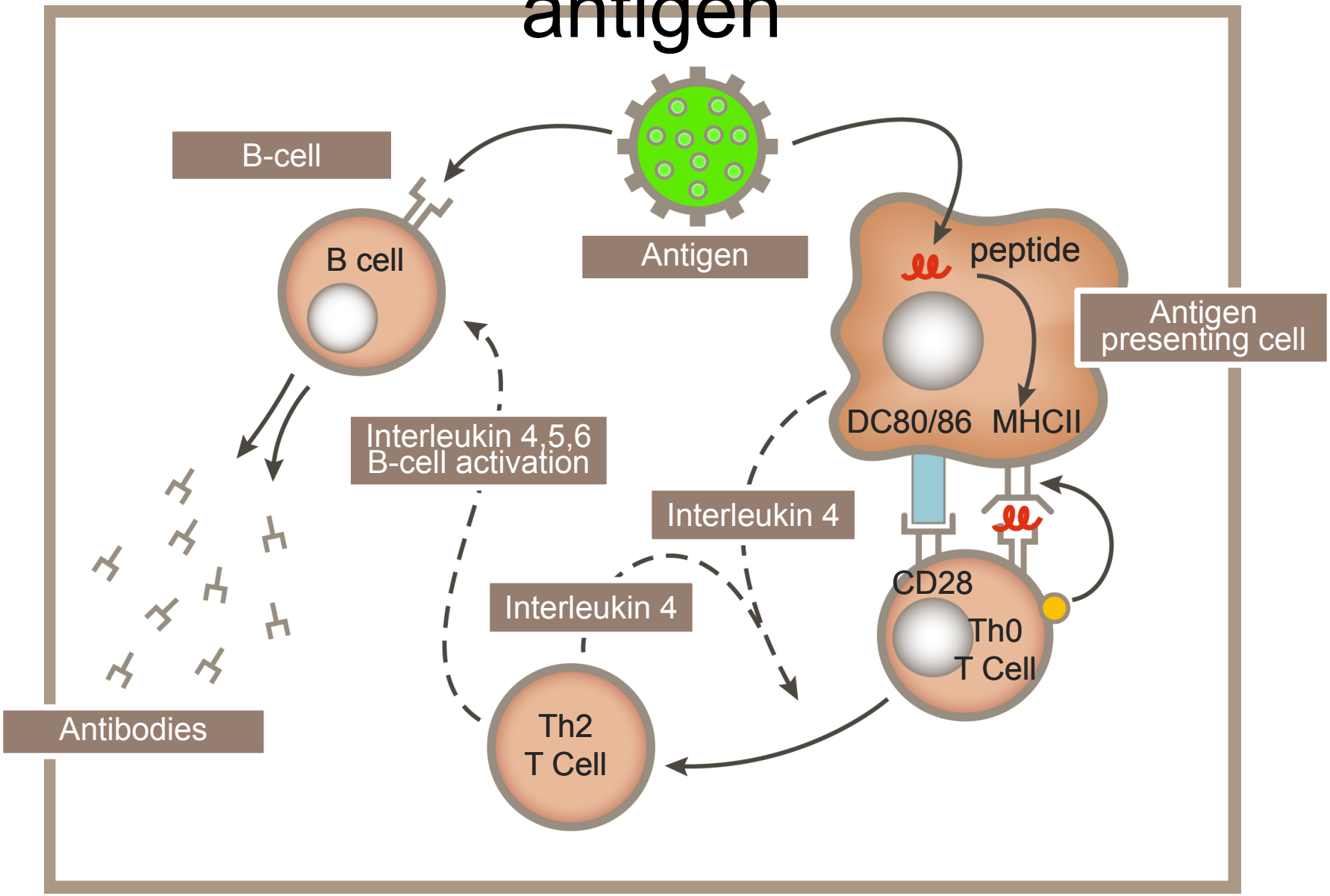
Negative selection in the thymus



Immune tolerance

- Peripheral:
  - Clonal deletion - elimination of autoreactive cells by apoptosis
  - Clonal anergy - costimulatory signals are lacking
  - Clonal ignorance - to low concentration of antigen does not stimulate immune response, the antigen is „hidden“ behind a barrier (eg sperms, lens antigents)
  - Suppression - autoreactivity is blocked by regulatory cells

Activation of immune system by antigen



Regulatory T cells

- T_{reg} cells – naturally occurring regulatory cells causing tolerance of autoantinegens. They cause active tolerance of autoantigens. Development in the thymus. Involved in inborn tolerance. Also inducible in periphery by foreign antigens in some situations.
- T_H3 (T_r1) cells: induced in periphery. They cause acquired tolerance.

Acquired immune tolerance

- Low-zone tolerance: repeated injections of very low doses of antigen. Suppressor cells are stimulated.
- High-zone tolerance: induced by high-doses of antigen. Clonal deletion is induced.
- Oral tolerance

Mechanisms of breakage of immune tolerance

- Visualization of „hidden antigens“.
- Alteration of body antigens by chemical substances, burns, necrosis
- Cross reactivity of antigens.
- Excessive stimulation of the immune system, abnormal expression of HLA-II antigens.
- Defect of suppressor function of lymphocytes.

Patogensis of autoimmune diseases

- Autoantibodies may induce necrosis, dysfunction but also stimulation of function of the target cells (type-II hypersensitivity)
- Complexes of autoantigen and autoantibodies may play a significant role leading to immunocomplex diseases (type-III hypersensitivity) – typically in SLE.
- In some diseases cell-mediated cytotoxicity seems to play a crucial role (type-IV hypersensitivity) – e.g. multiple sclerosis.

Organ-specific autoimmune diseases

Endocrine system

Autoimmune (Hasimoto's) thyroiditis
Hyperthyroidism (Graves' disease; thyrotoxicosis)

Type I diabetes mellitus (insulin-dependent or juvenile diabetes)

Autoimmune adrenal insufficiency (Addison's disease)

Autoimmune oophritis

Hematopoietic system

Autoimmune hemolytic anemia

autoimmune thrombocytopenia

Autoimmune neutropenia

Neuromuscular system

Myasthenia gravis

Autoimmune polyneuritis

Multiple sclerosis

Skin

Pemphigus and other bullous diseases

Cardiopulmonary System

Rheumatic carditis

Postcardiotomy syndrome (Dressler's syndrome)

Gastrointestina tract

Atrophic gastritis

Crohn´s disease

Ulcerous colitis

Autoimmune hepatitis

Systemic autoimmune diseases

Systemic lupus erythematosus
Rheumatoid arthritis
Sjogren's syndrome
Polymyositis
Dermatomyositis
Scleroderma (progressive systemic sclerosis)

SLE

- A prototypic multi-system autoimmune and immune complex disease
- Involvement of skin, kidneys, lungs, heart blood vessels
- Immunoregulatory abnormalities
- Many autoantibodies
  - ANA
    - ds DNA (inportant marker od aktivity of teh disease)
    - ENA (extractable nucler antigens)
  - Phospholipids

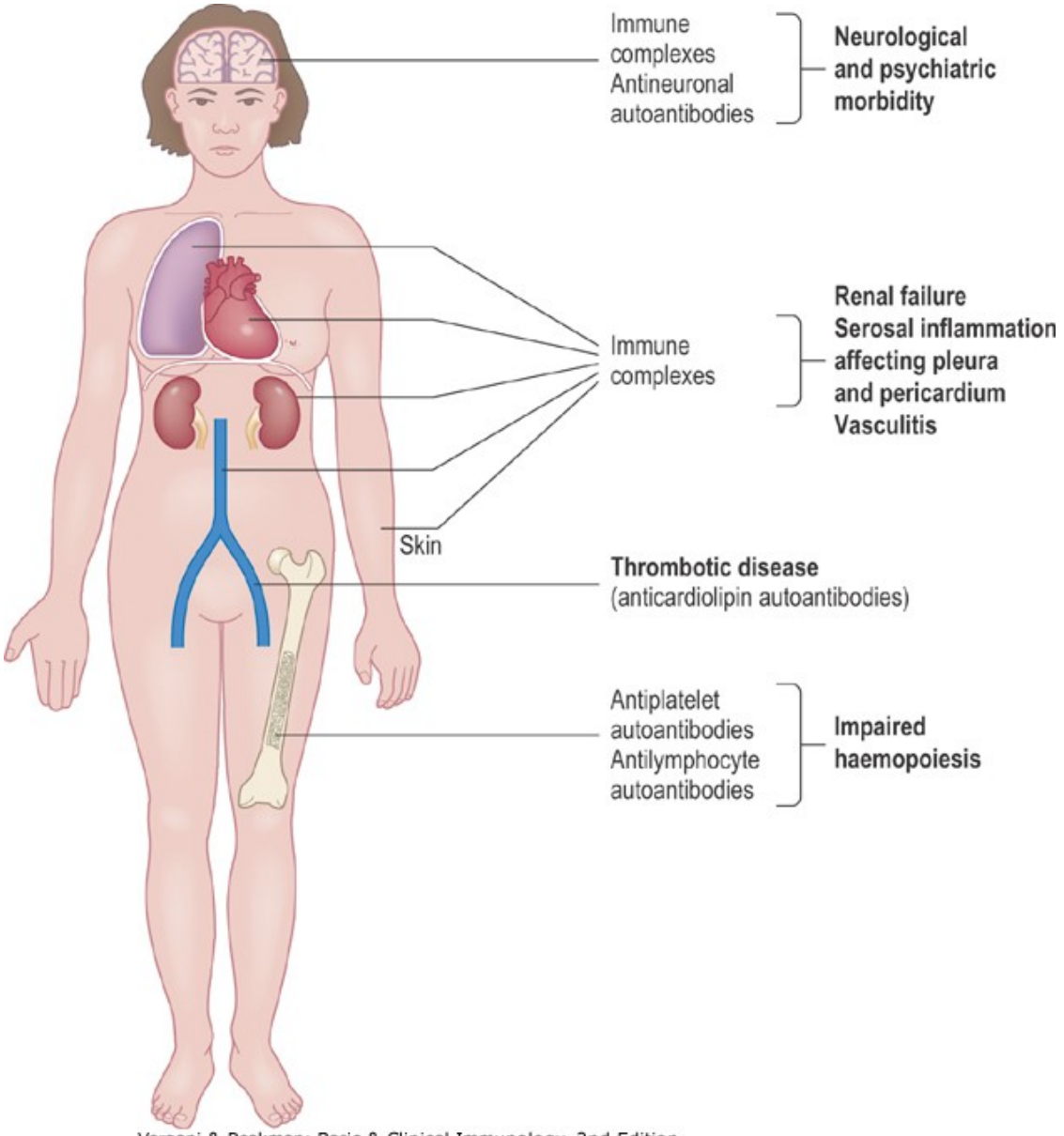
Systemic lupus erythematosus (SLE)

- Systemic autoimmune disease affecting various tissues and organs.
- Many symptoms are caused by deposition of immune complexes (type-III immunopathological reaction).
- Female : male ratio is 10:1.
- Usually begins in early adulthood.

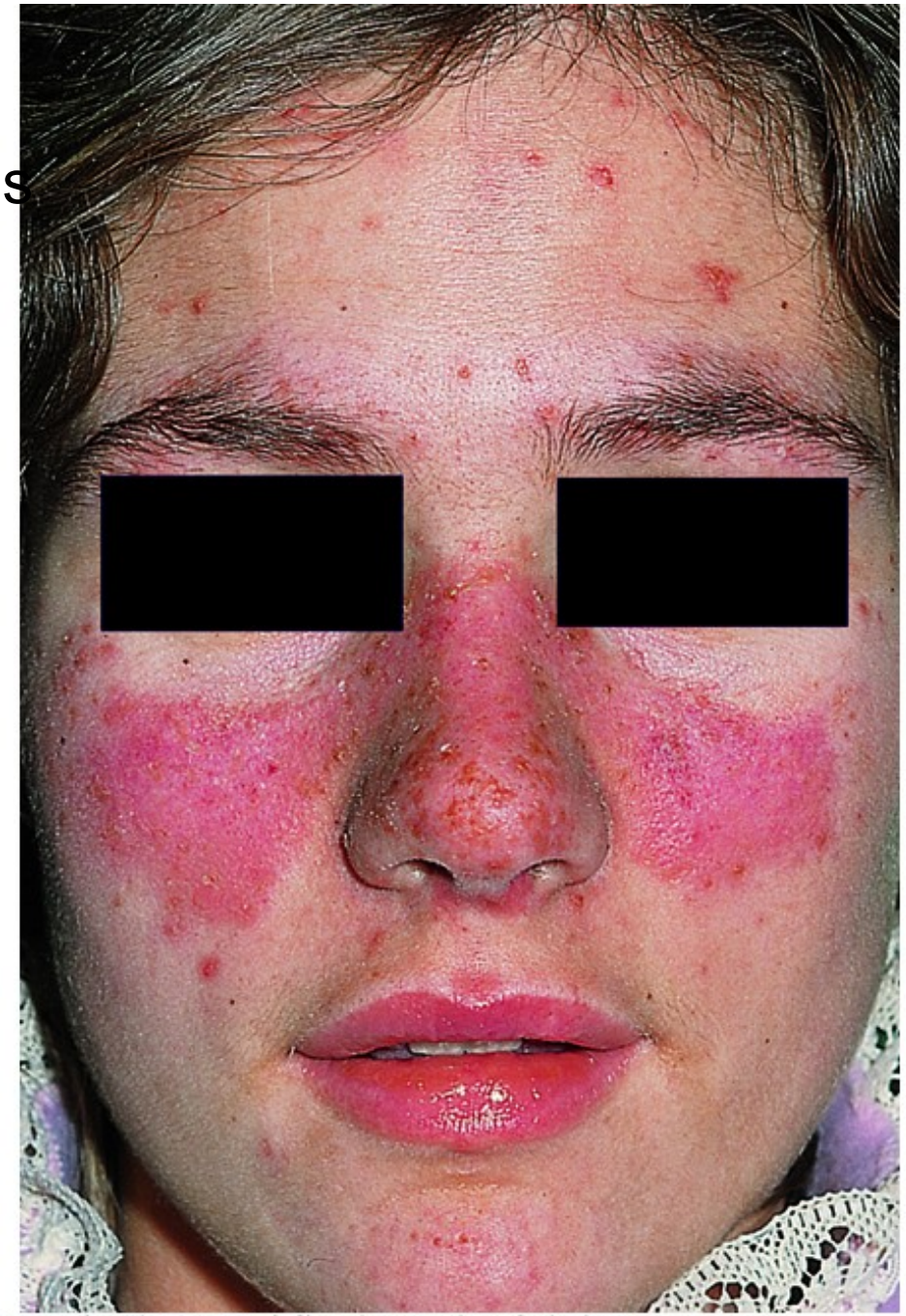
Systemic lupus erythematodes Clinical presentation

- General: fever, malaise, loss on weight
- Artralgia
- Skin: butterfly rash, urticaria
- Vascular: Raynaud´s phenomenon
- Neurological: vasculitis, seisures, neuritis
- Glomerulonephritis
- Haematological: leukopenia, thrombocytopenia anemia
- Recurrent serositis
- Mouse ulcers

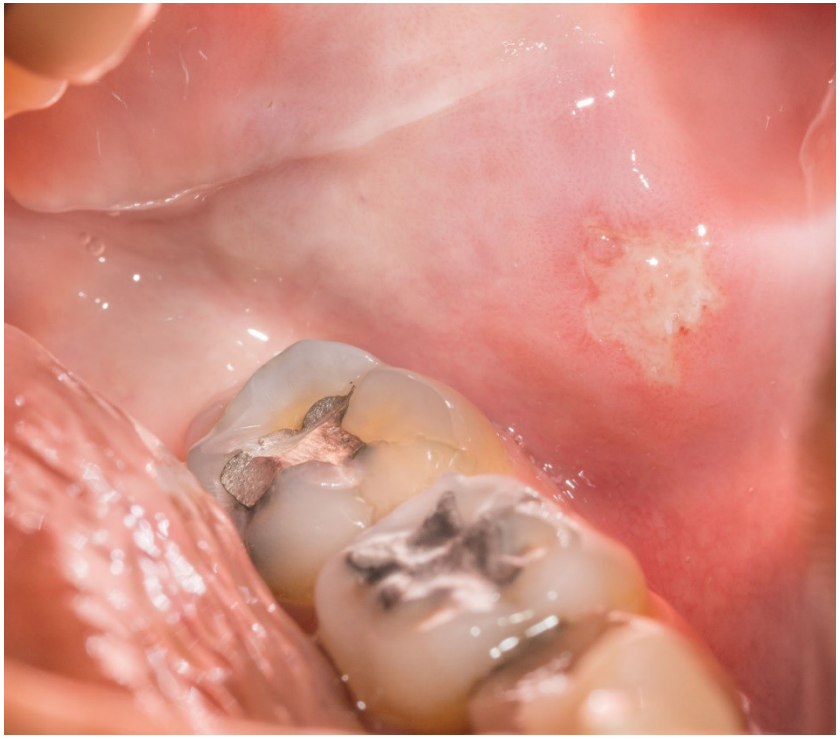
Systemic lupus erythematodes – clinical manifestation



Systemic lupus erythematodes
- Butterfly rash



Mouse ulcer in SLE



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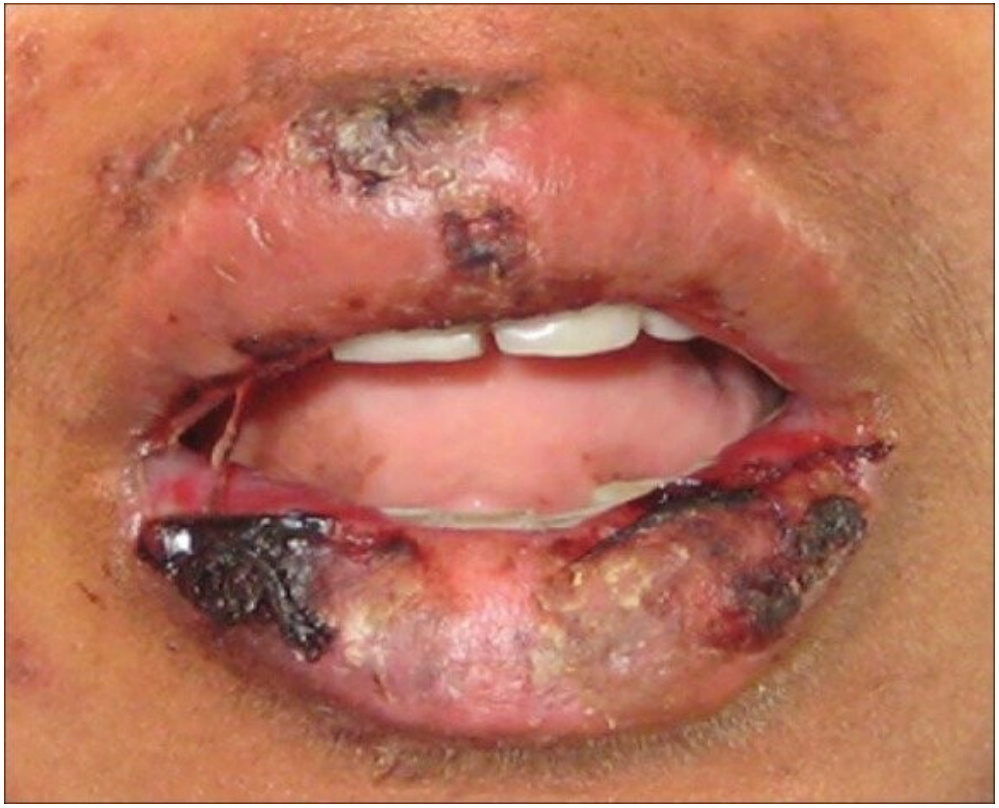
Ulcerations in SLE



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Antiphospholipid syndrome

- It is the most common immunological disorder leading to recurrent miscarriages.
- Patients suffer from recurrent thrombosis (venous and arterial) leading to a variable clinical manifestation according to the affected organs.
- Thrombocytopenia may be present.
- Laboratory: antiphospholipid (anticardiolipin) antibodies, lupus anticoagulant.
- It may be a primary disease or accompany various systemic autoimmune diseases (eg. systemic lupus erythematosus).

Autoantibodies as a diagnostic tool in autoimmune diseases

- Detection of autoantibodies may play a significant role in diagnosis of autoimmune diseases.
- However, only a presence of autoantibodies never makes a diagnosis of a disease! Clinical symptoms must be present!
- Not rarely, these autoantibodies does not cause the disease, they are only an epiphenomenon caused by destruction of many cells and stimulation of the immune system by the released autoantigens.
- Many hundreds of autoantibodies are used for diagnostic purposed with very different sensitivity and specificity.
- However, there are diseases which are definitively of autoimmune origin, however we do knot any autoantibody which might be used for diagnostic purposes (e.s multiple sclerosis, ankylosing spondylitis).

Autoantibodies in SLE - 1

Anti-nuclear anibody (anti-nuclear factor)

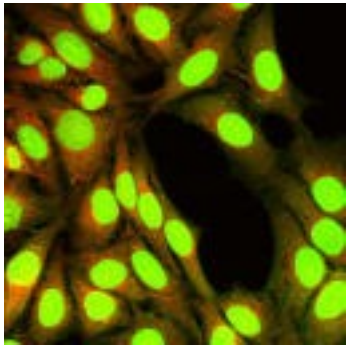
Indirect immunofluorescence on Hep2 cells

Staining pattern may be clinically useful

Interpretation depends on clinical history, titre and age

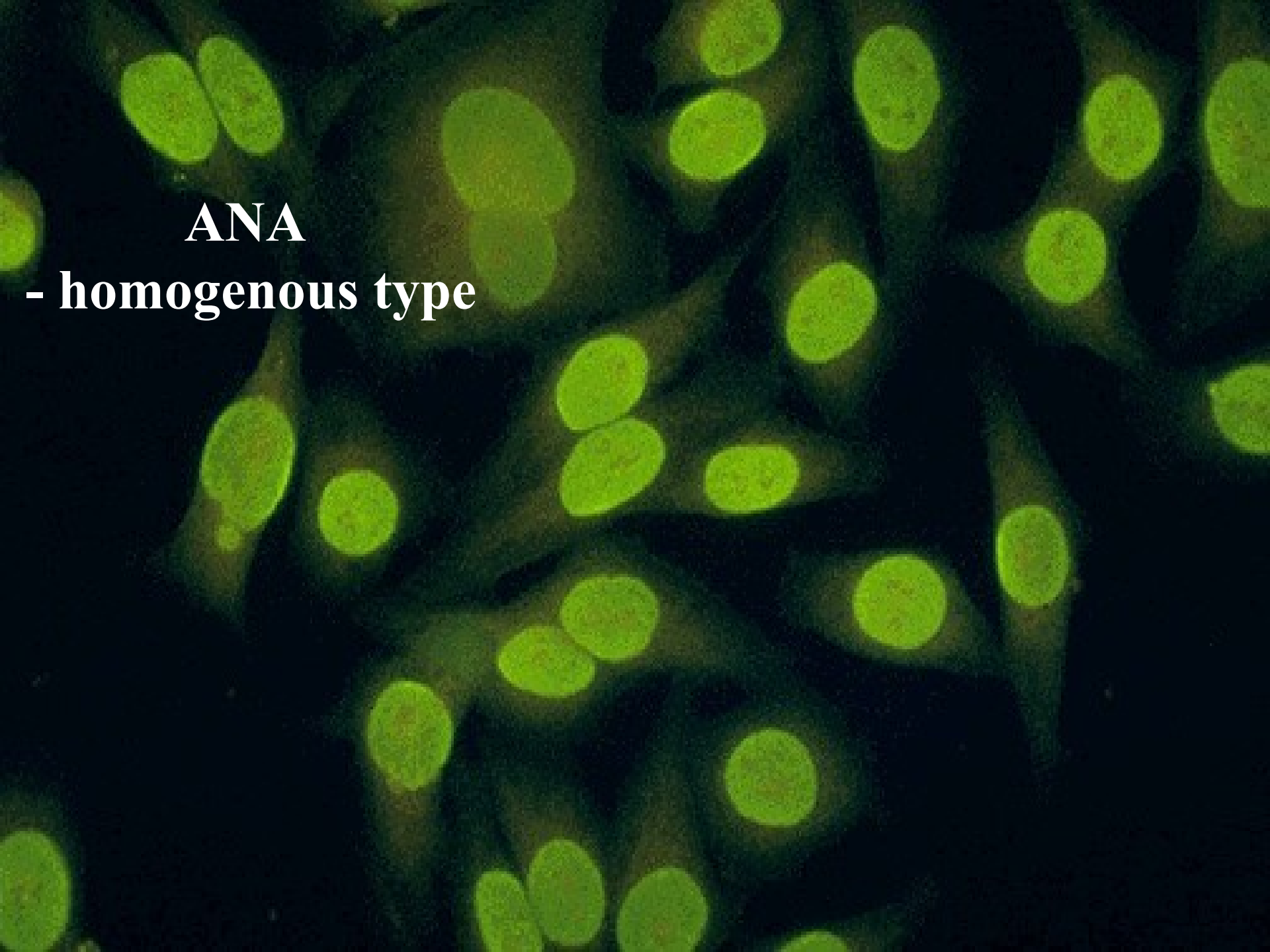
Sensitive but not specific

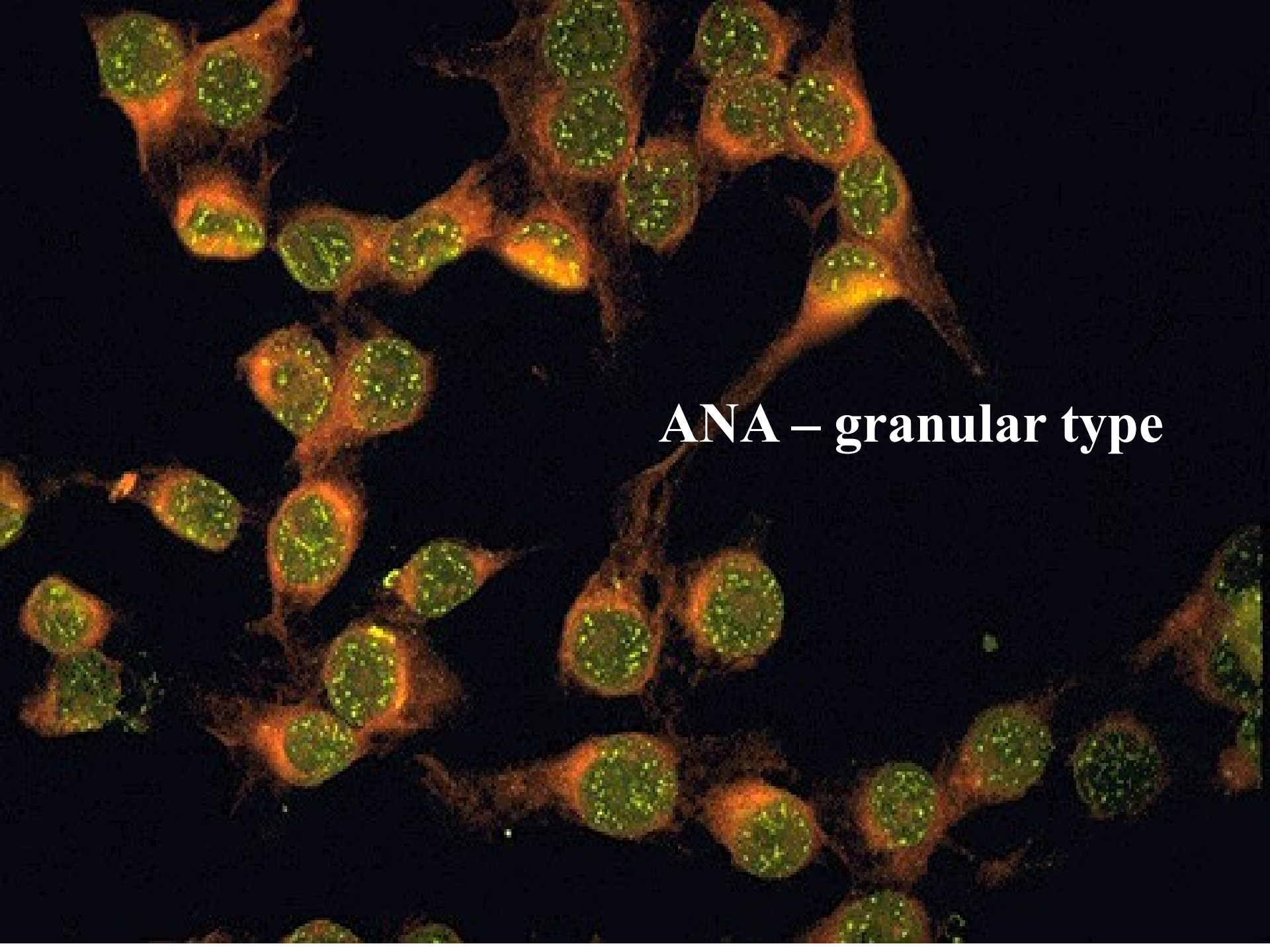
Good screening test for lupus (prevalence ~ 100%)



Positivity of antinuclear antibodies (ANA, ANF)

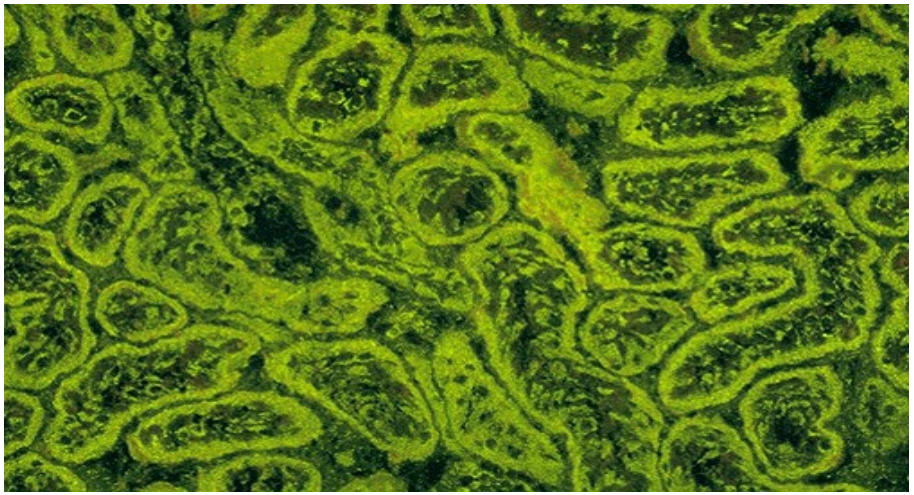
- SLE: 95 - 100 %
- Rheumatoid arthritis: 15 - 30 %
- Systemic scleroderma: 75 -80 %
- Autoimmune hepatitis: 20 -60 %
- **Healthy persons: 0 - 4 %**
- **Seniors: 10 - 20 %**


ANA
- homogenous type


ANA – granular type

Anti-mitochondrial antibodies

- Positive in patiens with primary biliary cirrhosis
- Positivity is highly specific for the disease
- Detected by immunofluorescence



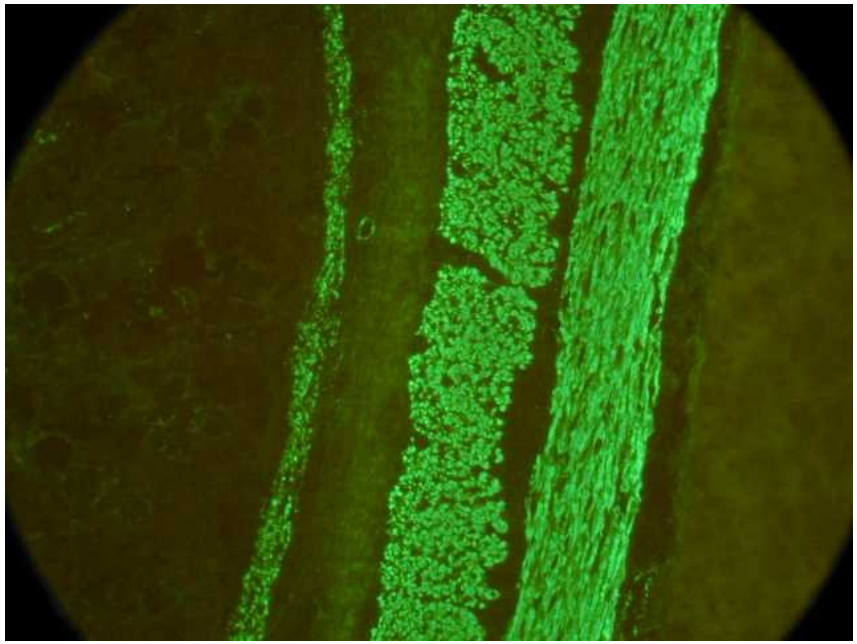
Rheumatoid factor

- Autoantibody against Fc fragment of IgG molecule.
- Positive in 80% of patients with rheumatoid arthritis.
- May be present also in other rheumatic diseases, chronic hepatitis, but also healthy persons, mainly seniors.
- Detected by ELISA or agglutination of latex particles (latex-fixation test)
- Currently antibodies against cyclic citrulinated peptides have higher specificity.

ulnární deviace u pacientky s revmatoidní artritidou

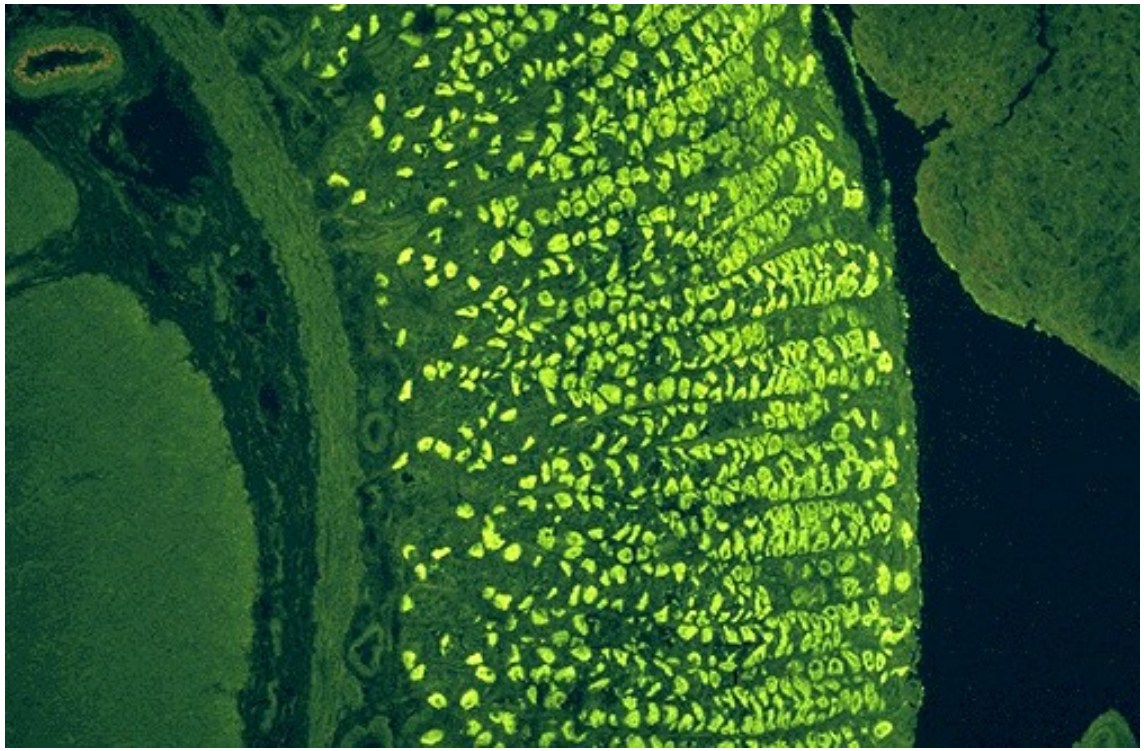
Antibodies against smooth muscle

- Positive in patients with autoimmune hepatitis.
- Specificity is limited, can be observed also in healthy persons or in patients with acute hepatitis.
- Actin is the target antigen.
- Detected by indirect immunofluorescence.



Anti- parietal cells antibodies

Present in patients with autoimmune atrophic gastritis.
Disturbed production od the gastric juice (incl. intrinsic factor) leads to vitamin B12 deficiency – leading to pernicious anemia.

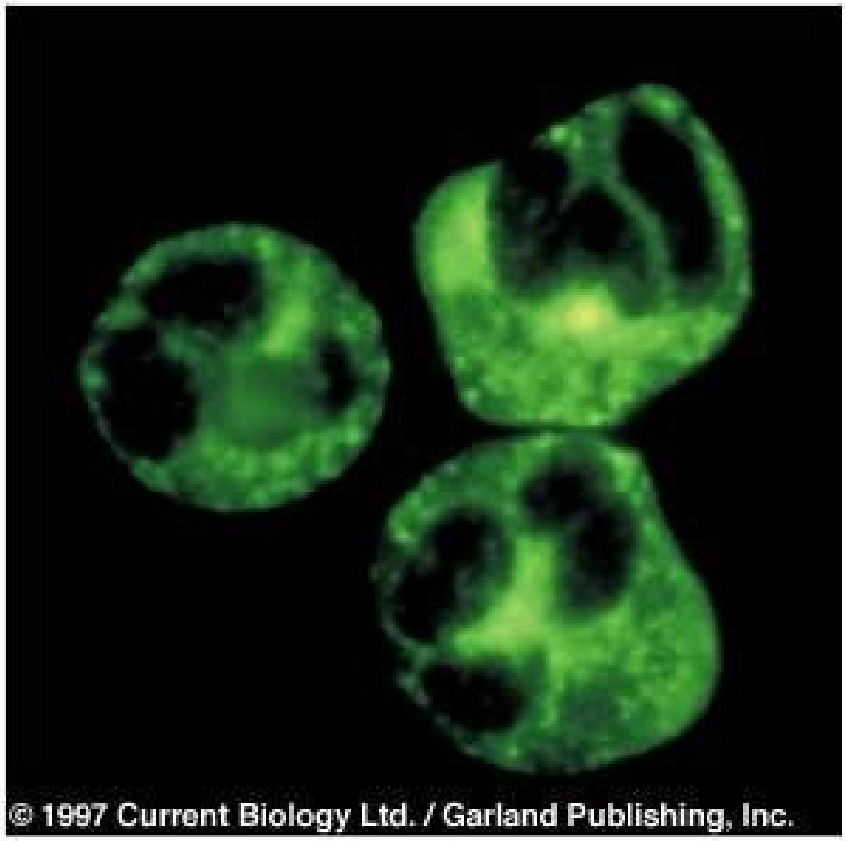


Pernicious anemia

- Antibodies against gastric parietal cells cause atrophic gastritis.
- Decreased production of gastric juice results in dyspeptic problems.
- Also production of intrinsic factor is decreased causing disturbed resorption of vitamin B_{12}.
- Low serum levels of vitamin B_{12} results in megaloblastic anemia.

Anti-neutrophil cytoplasmatic antibodies (ANCA)

- c-ANCA (common ANCA) – highly specific for Granulomatosis with Polyangiitis (Wegener´s Granulomatosis)
- p-ANCA (perinuclear AČA) less sensitive for several other vasculitis
- Detected by indirect immunofluorescene, concrete antigens by ELISA.
- **ANCA lead to activation of neutrophils (not to death of the cells)!**



Antibododies in coeliac disease

- Abs against tissue transglutaminase – detected by ELISA. Most specific.
- Abs against endomysium of smooth muscle – detected by immunofluorescence.
- Abs against deaminated gliadin – used mainly in infancy.

Autoantibodies against the thyroid gland

- Antibodies against thyroid microsomal peroxidase and against thyreoglobulin are present in autoimmune thyroiditis – Hashimoto thyroiditis (gradually leading to hypothyreosis). However, Hashimoto thyroiditis is mainly T-cell mediated disease, the mentioned autoantibodies are supposed to be an epiphenomenon.
- Antiboidies against thyroid-stimulating hormone receptor stimulates the receptor leading to Graves-Basedow hyperthyreosis.

Anti-receptor antibodies

- Stimulatory –
  - Graves disease. Antibodies against TSH-receptors stimulate function of thyroid gland causing hypertyreosis.
- Inhibitory
  - Myastenia gravis. Antibodies against acetylcholine receptor block activation of muscle in neuromuslular junction.

Please note!!

- Some autoantibodies are relatively very specific for some diseases. Thy are very rare in general population – ANCA, antimitochondrial antibodies (they have high positive predictive value).

- Other autoantibodies are relatively common, even in healthy population but their negativity almost excludes the disease (ANA in SLE) – they have high negative predictive value).

- Many are somewhere between these extremes.

Treatment of autoimmune diseases

- Substitution of function of the affected organ (insulin treatment, parenteral treatment by vitamin B12….)
- Anti-inflammatory drugs
- Immunosuppressive treatment
- Tolerance induction

Systemic Immunosuppression

- High-dose steroids
- Purine antagonists: Azathioprin
- Alkylating agents: Cyclophosphamide
- Anti-pholates: Methotrexate
- Calcineurin antagonists: Cyclosporine A, Rapamycin, Tacrolymus
- Block of purins synthesis: Mycophemolate
- Monoclonal antibodies: anti-CD20, anti-CD54...

Imunostimulatory drugs

- Cytokines: IL-2, interferons
- Check point (CTLA-5, PD-1) inhibitors
- Thymic hormones
- Bacterial immunomodulators: Broncho-vaxom, Luivac,