

Immune tolerance, autoimmune diseases

Immune tolerance

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

Positive selection in the thymus

Figure 5.19a

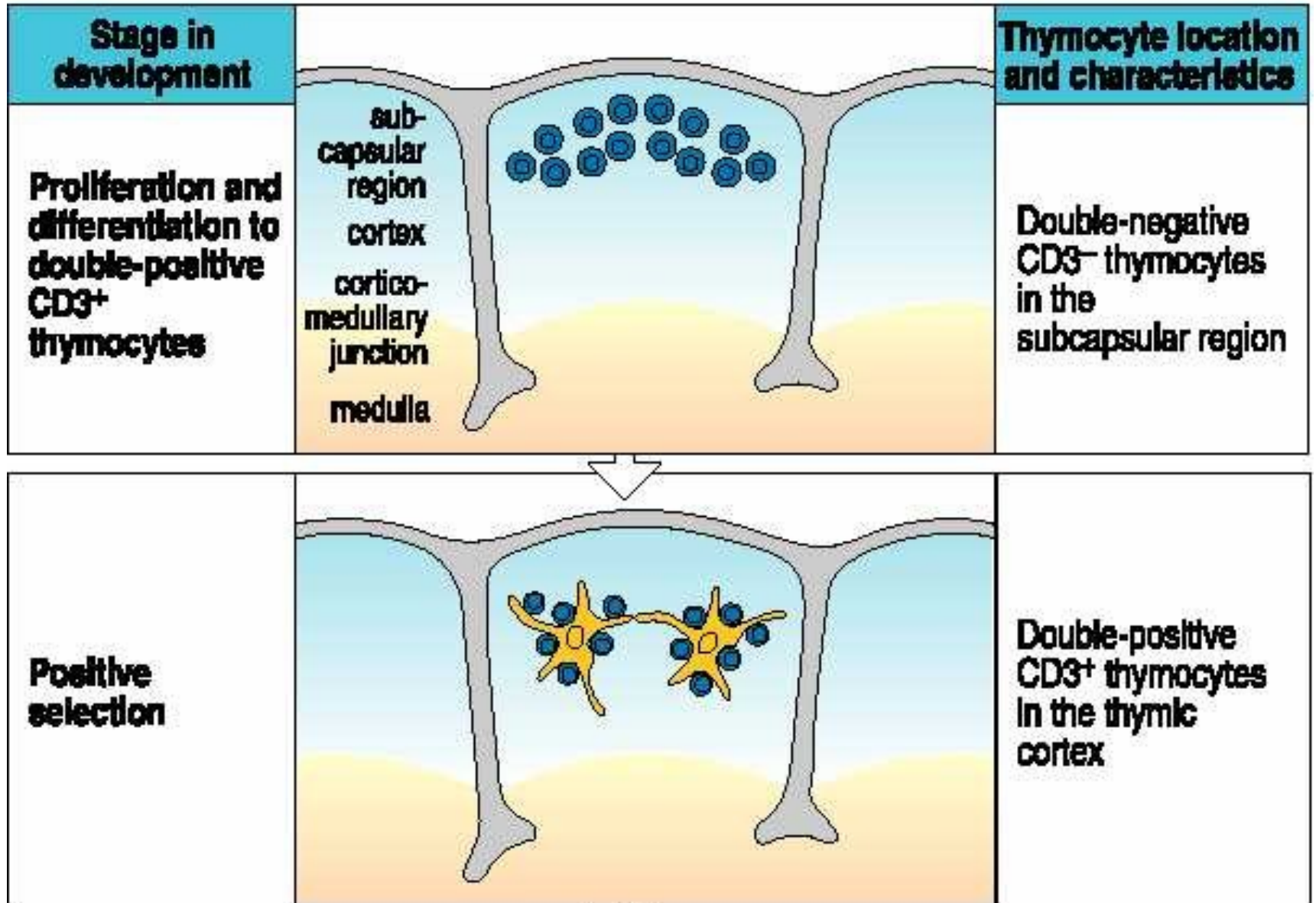
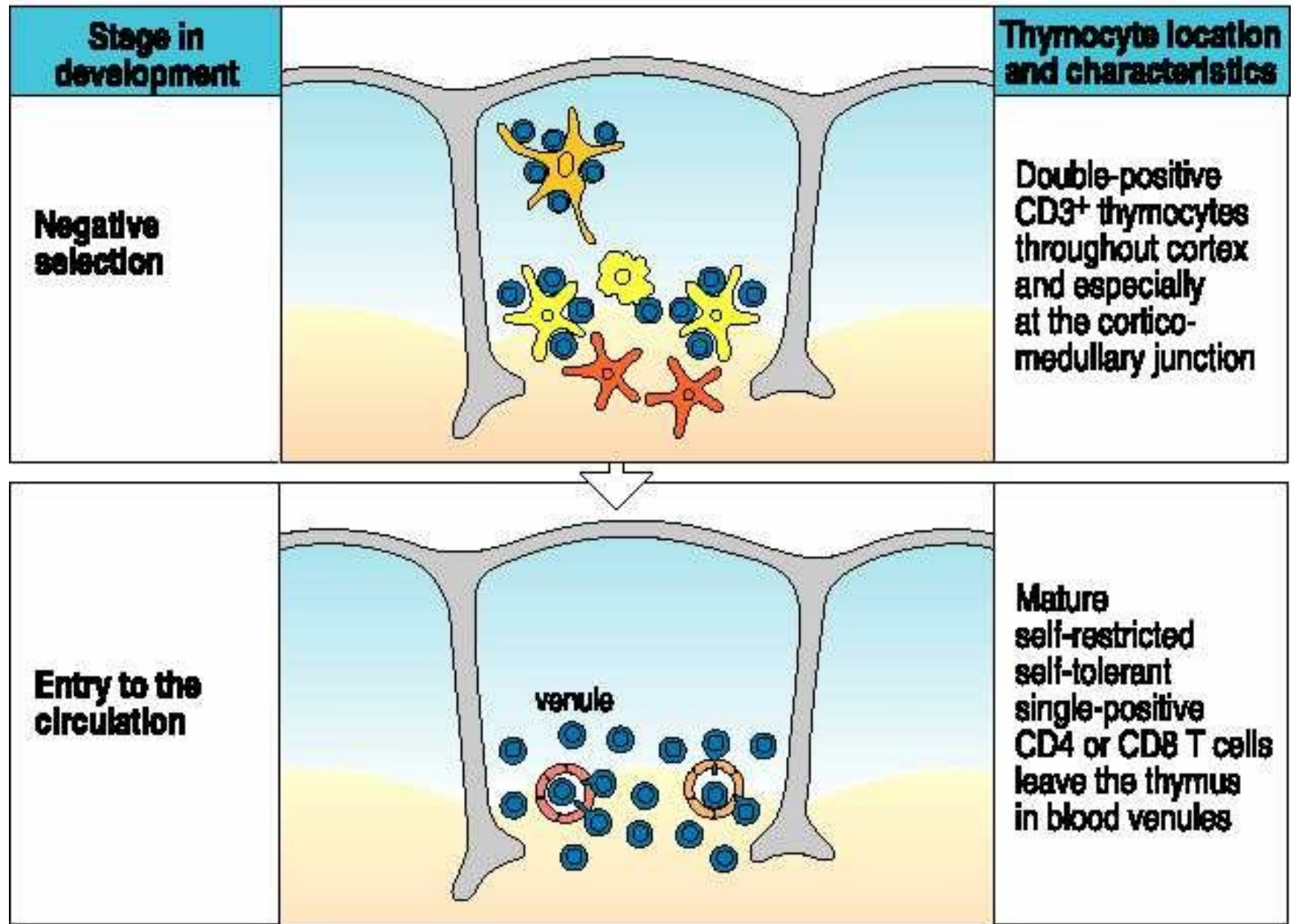


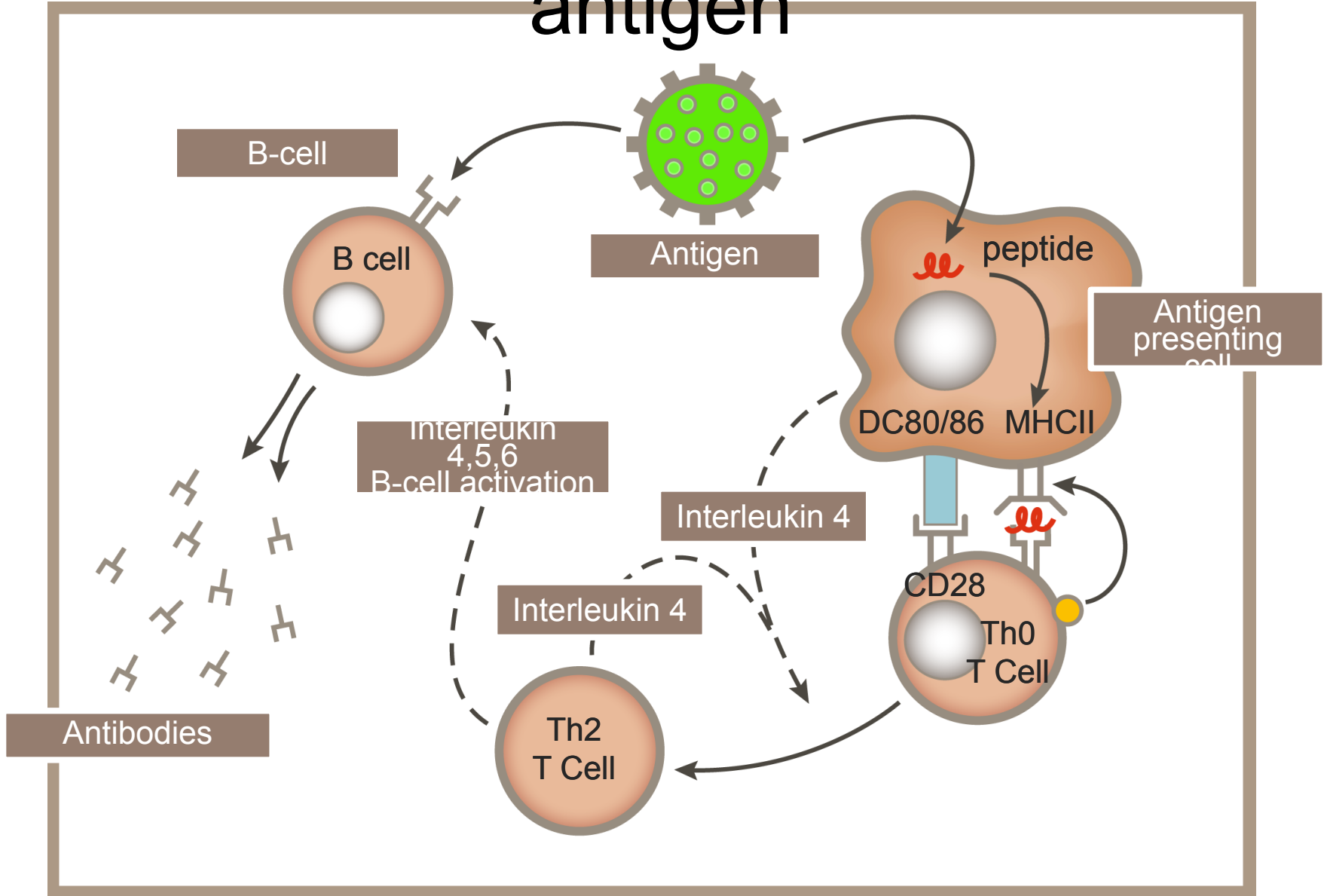
Figure 5.18b Negative selection in the thymus



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
 - 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 autoantigens. 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.

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
 - ENA
 - Phospholipids

Systemic lupus erythematoses (SLE)

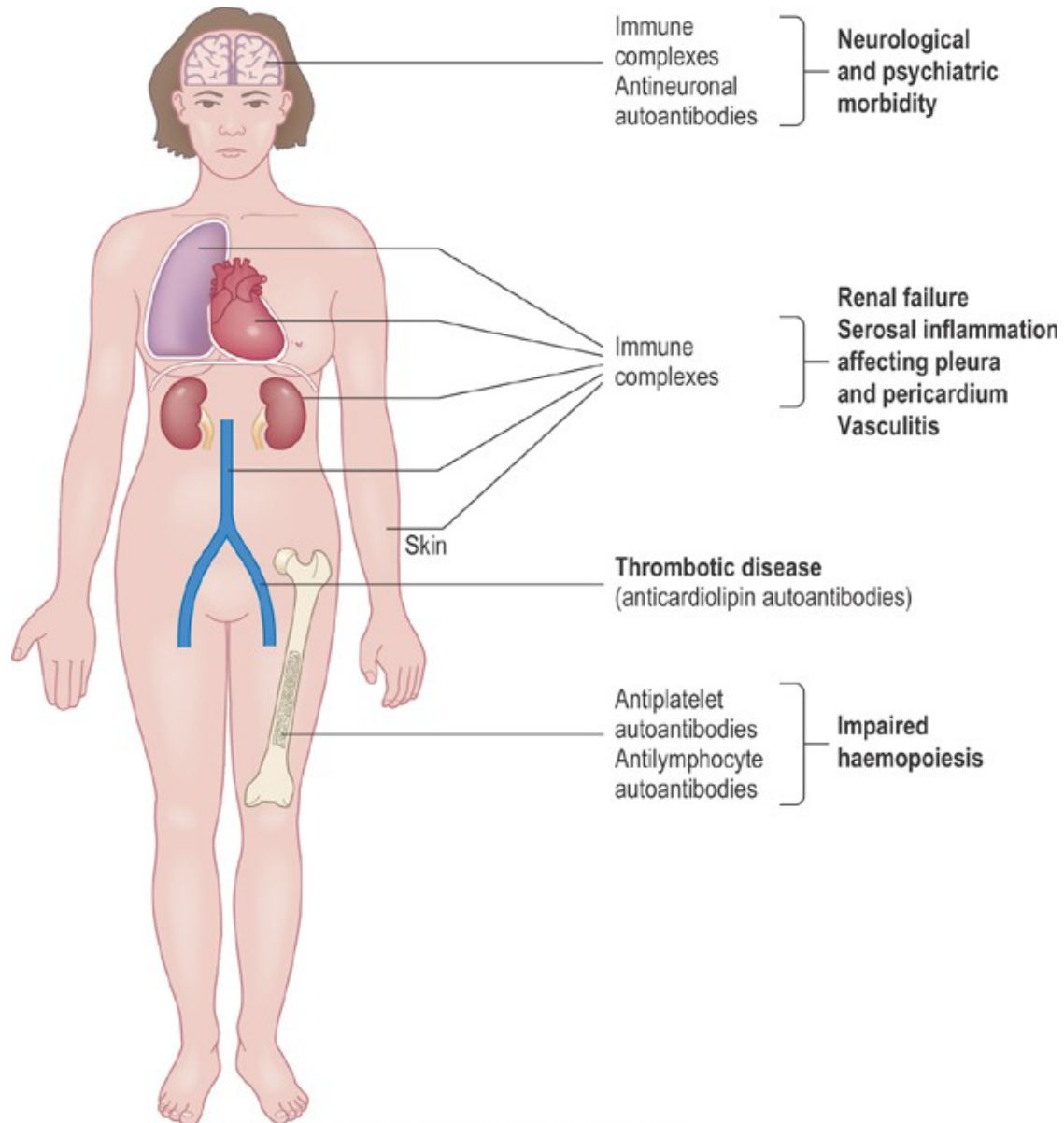
- Systemic autoimmune disease affecting various tissues and organs.
- Many symptoms are caused by deposition of immune complexes (type-III immunopathological reaction).
- Female : male ratio is 10:1.
- Usually begins in early adulthood.

Systemic lupus erythematoses

Clinical presentation

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

Systemic lupus erythematoses – clinical manifestation



Systemic lupus erythematoses - Butterfly rash



Autoantibodies in SLE - 1

Anti-nuclear antibody (anti-nuclear factor)

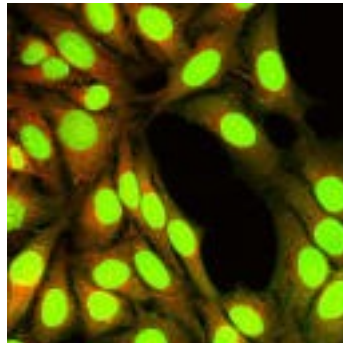
Indirect immunofluorescence on Hep2 cells

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 %

A fluorescence micrograph showing numerous cells with bright green, oval-shaped nuclei. The cells are distributed across the field of view, with some appearing in small clusters and others in isolation. The background is dark, making the green nuclei stand out prominently. The text 'ANA' is overlaid in the upper left quadrant.

ANA

- homogenous type

A fluorescence micrograph showing numerous cells with bright green granular cytoplasm and orange-brown nuclei, characteristic of ANA granular type cells. The cells are scattered across a dark background, with some showing more prominent granulation than others. The overall appearance is that of a dense population of these specialized cells.

ANA – granular type

Organ-specific autoimmune diseases

Endocrine system

Autoimmune (Hashimoto's) thyroiditis

Hyperthyroidism (Graves' disease; thyrotoxicosis)

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

Autoimmune adrenal insufficiency (Addison's disease)

Autoimmune oophoritis

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)

Gastrointestinal tract

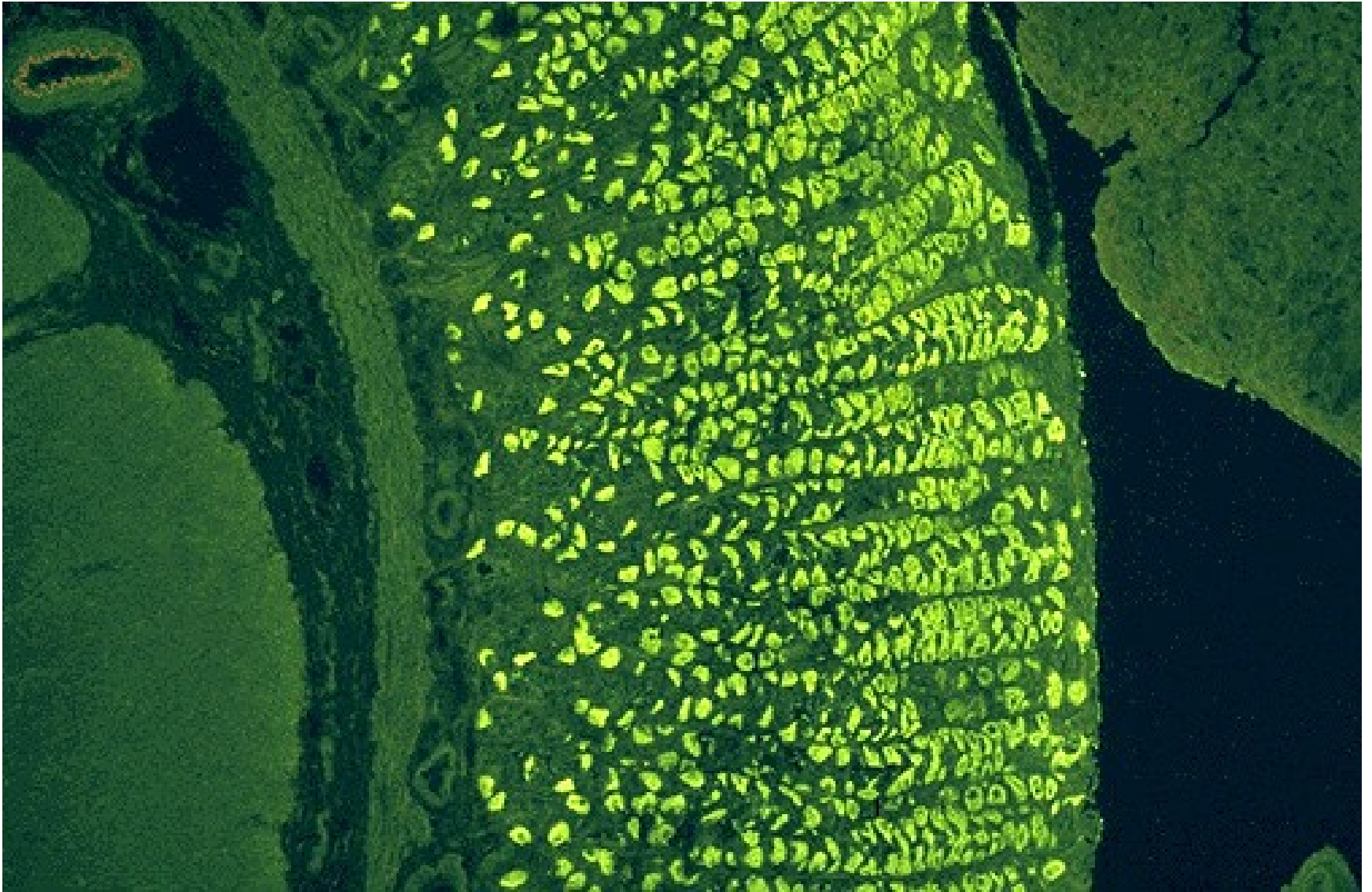
Atrophic gastritis

Crohn's disease

Ulcerous colitis

Autoimmune hepatitis

Anti- parietal cells antibodies



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 B₁₂.
- Low serum levels of vitamin B₁₂ results in megaloblastic anemia.

Anti-receptor antibodies

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

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-folates: Methotrexate
- Calcineurin antagonists: Cyclosporine A, Rapamycin, Tacrolimus
- Block of purins synthesis: Mycophemolate
- Monoclonal antibodies: anti-CD3, anti-CD20, anti-CD54...

Imunostimulatory drugs

- Synthetic immunostimulators: inosiplex
- Cytokines: IL-2, interferons
- Thymic hormones
- Bacterial immunomodulators: Ribomunyl, Broncho-vaxom, Luivac, Imudon, Biostim...