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

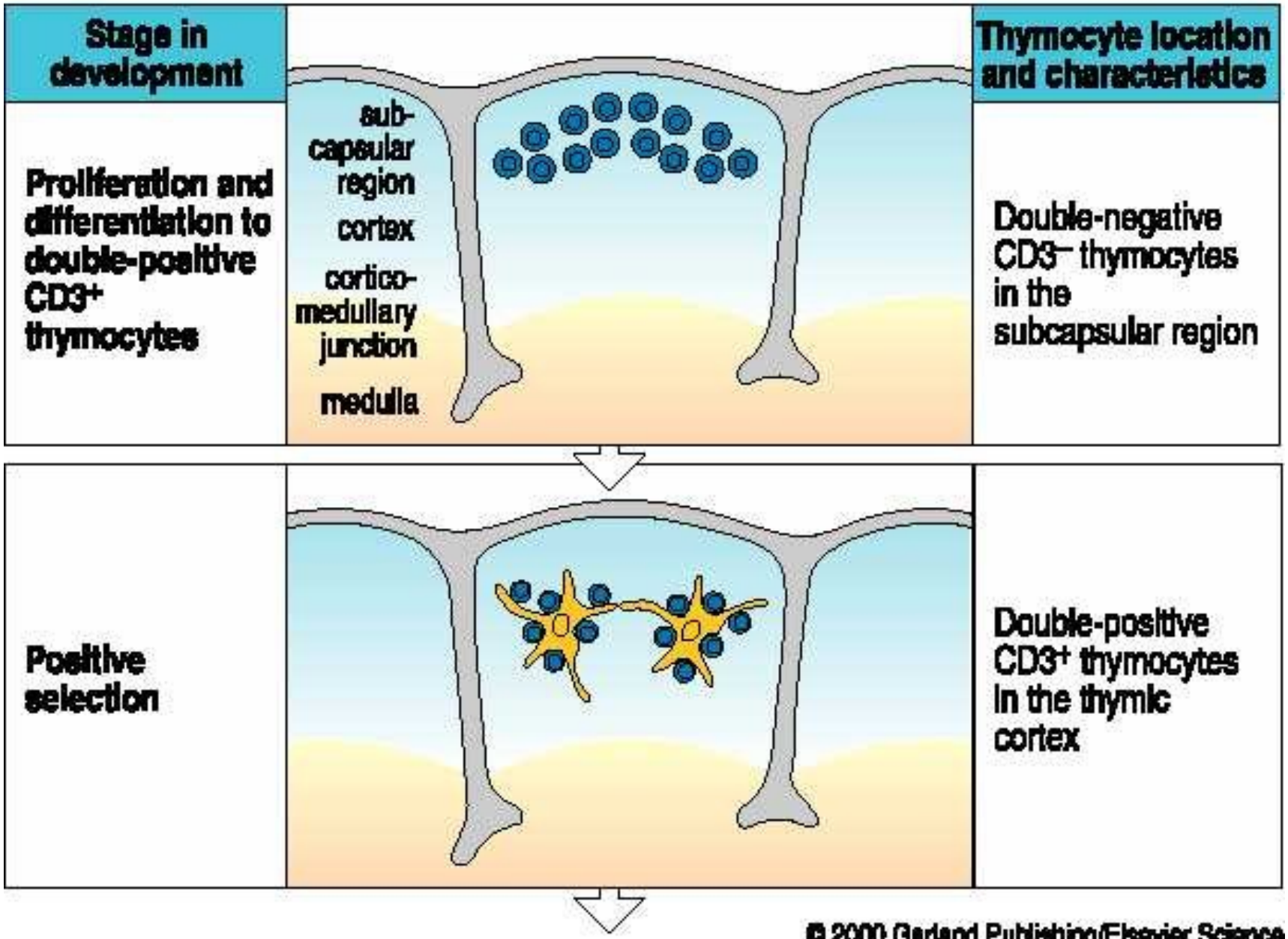
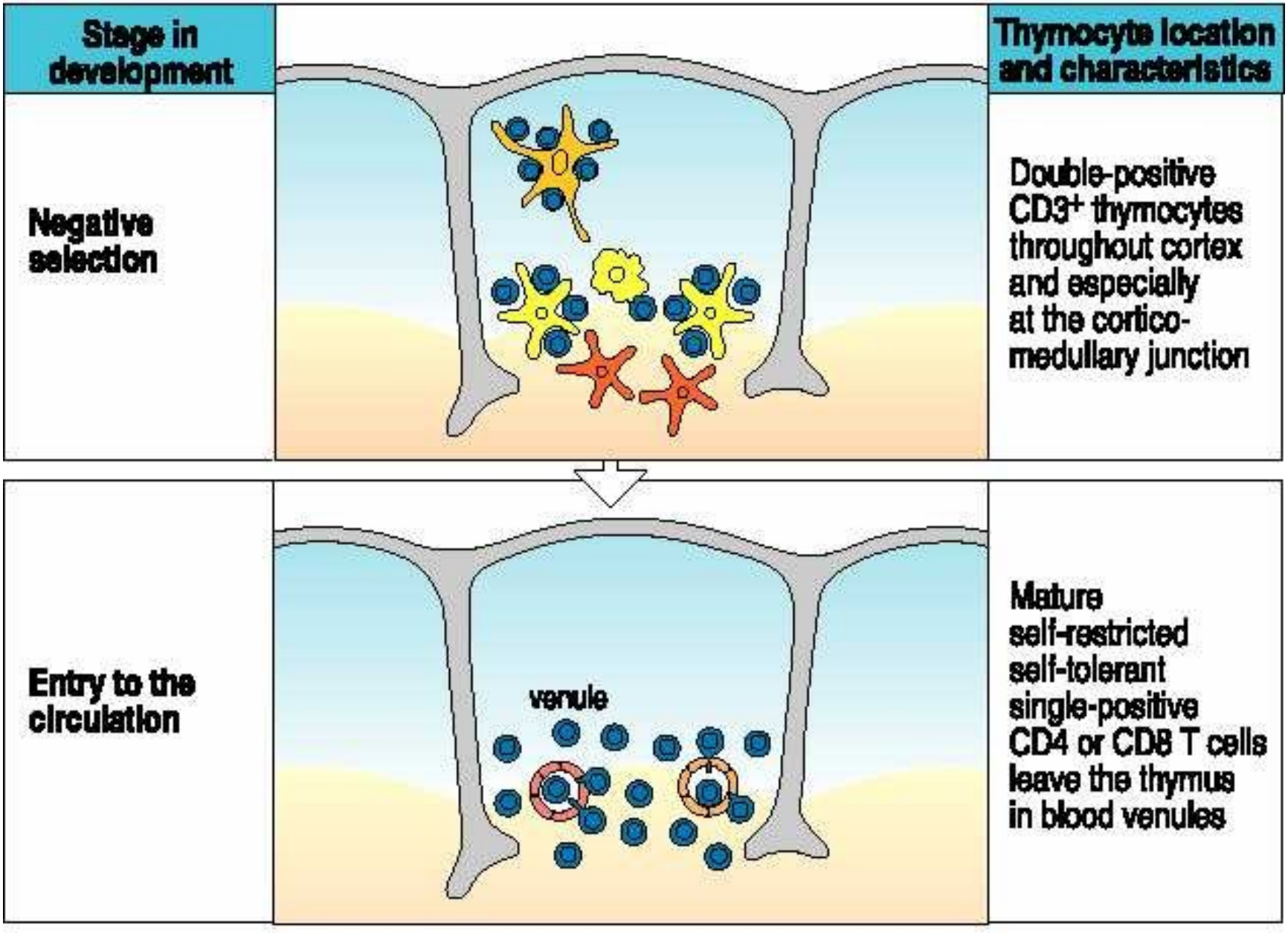
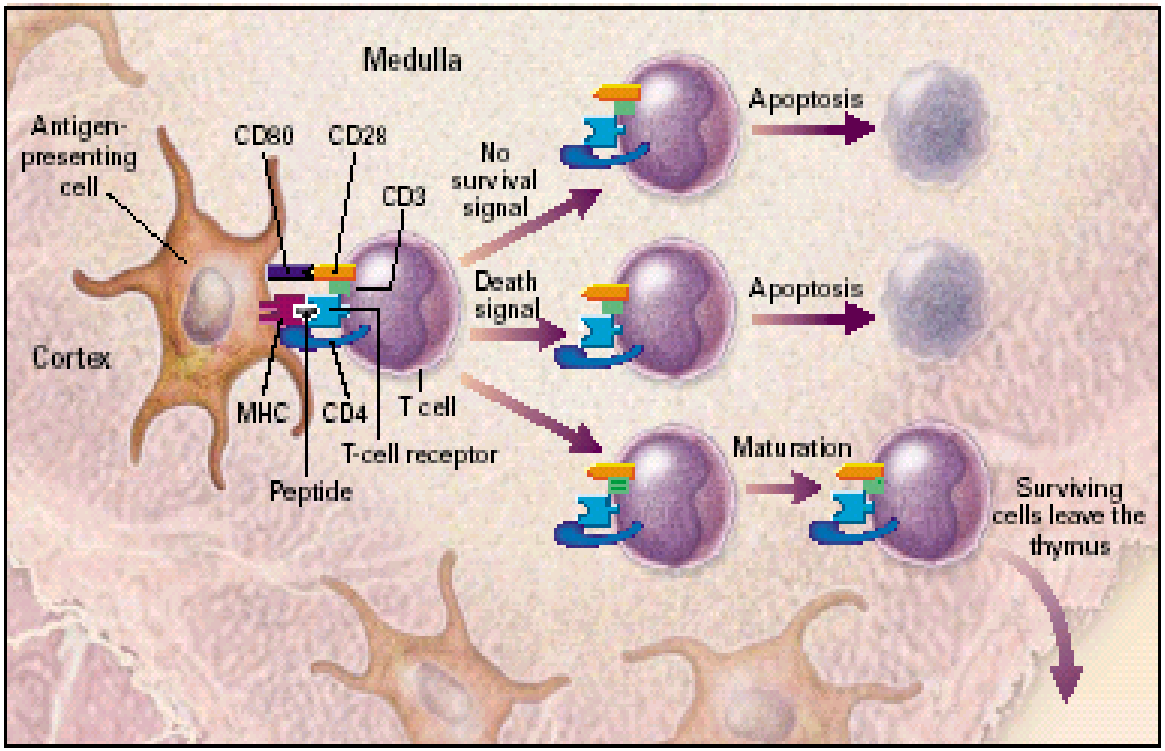


Figure 5.15b

Negative selection in the thymus

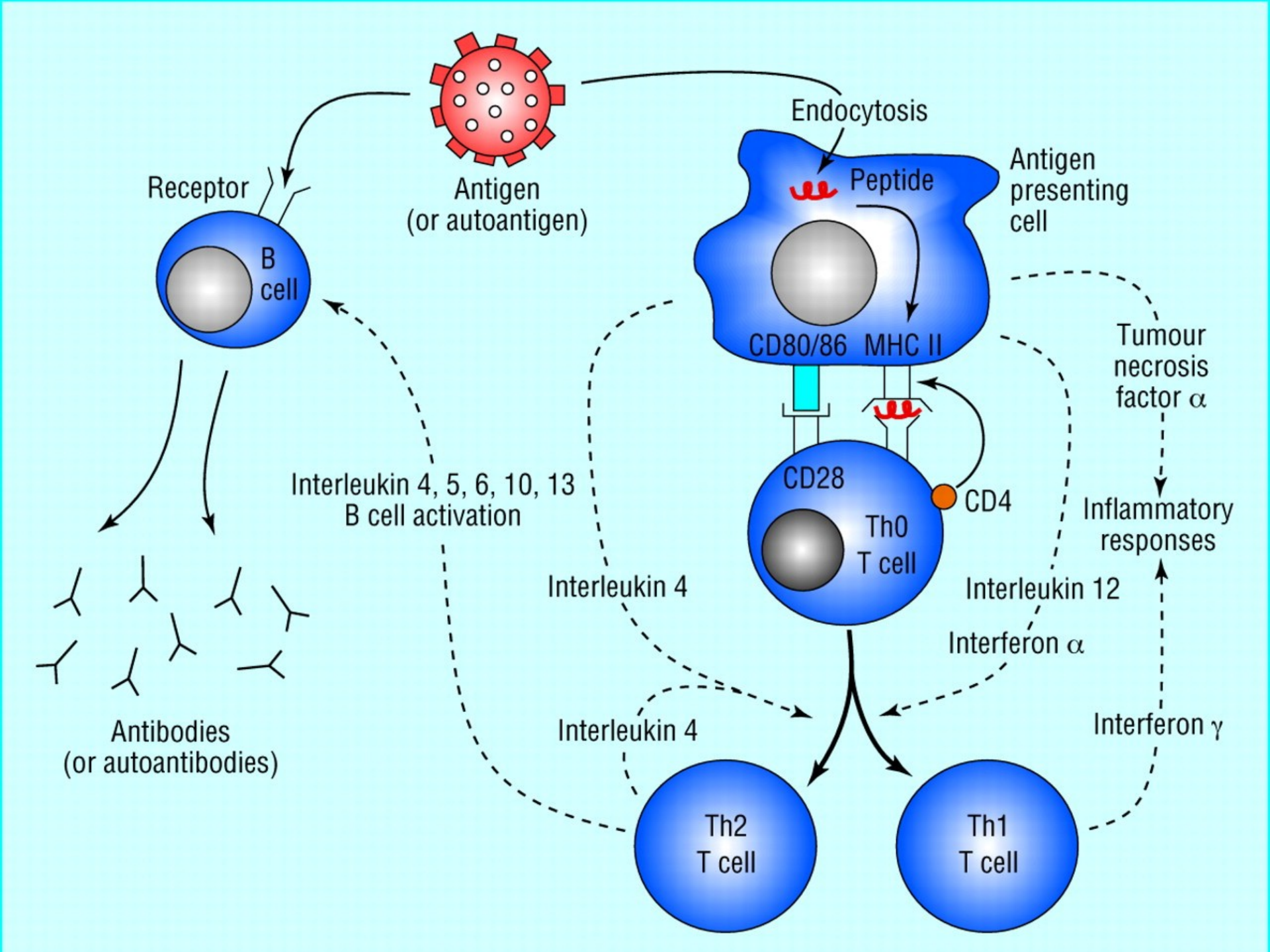


Tolerance
‘Central’

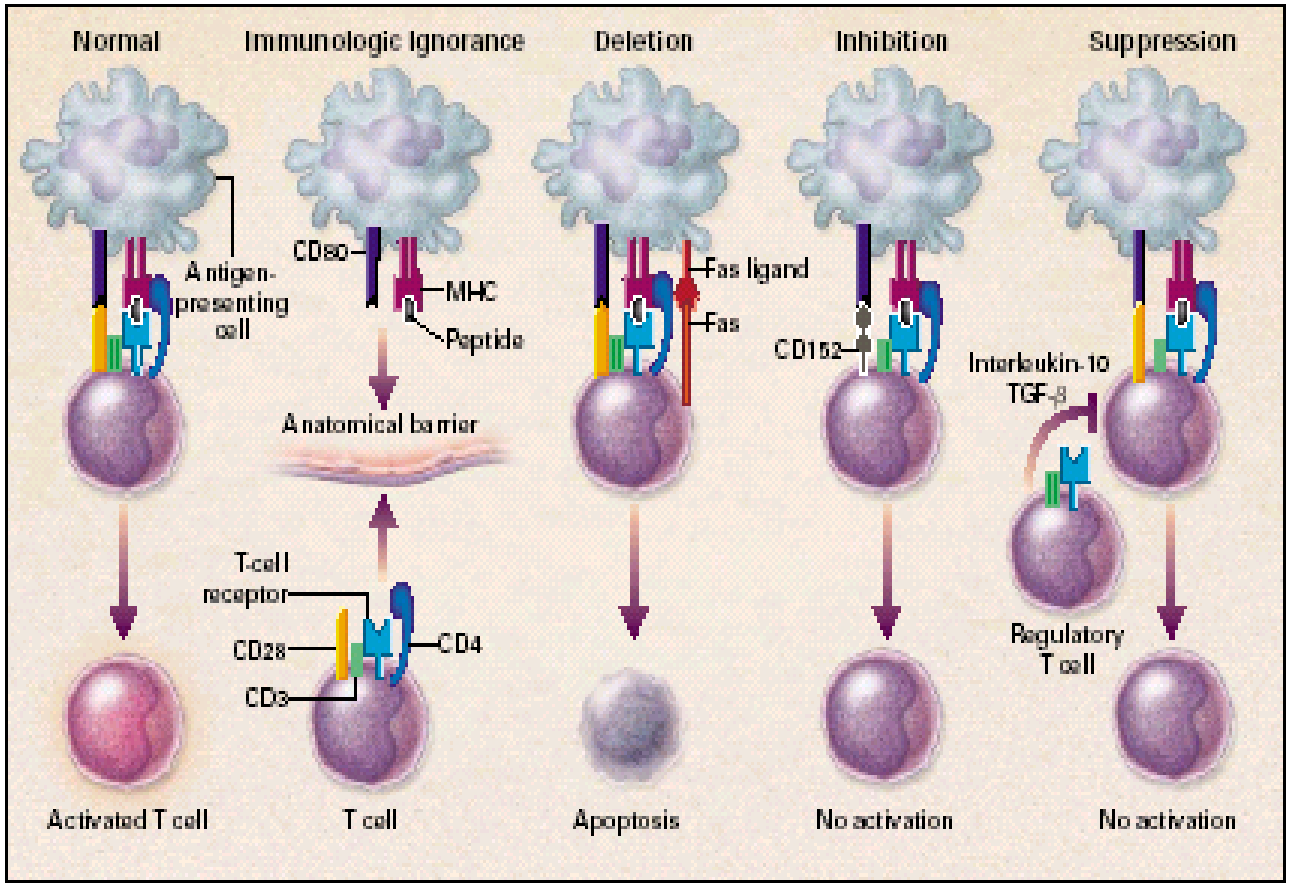


Immune tolerance

- 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


Antigen
(or autoantigen)
Endocytosis
Antigen
presenting
cell
Peptide
Receptor
B
cell
CD80/86
MHC II
Tumour
necrosis
factor α
CD28
CD4
Th0
T cell
Inflammatory
responses
Interleukin 4, 5, 6, 10, 13
B cell activation
Interleukin 4
Interleukin 12
Interferon α
Interleukin 4
Interferon γ
Antibodies
(or autoantibodies)
Th2
T cell
Th1
T cell

Tolerance
‘Peripheral’



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 the induction of these cells in periphery by foreign antigens seems to be possible.
- 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 in 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 etythematodes (SLE)

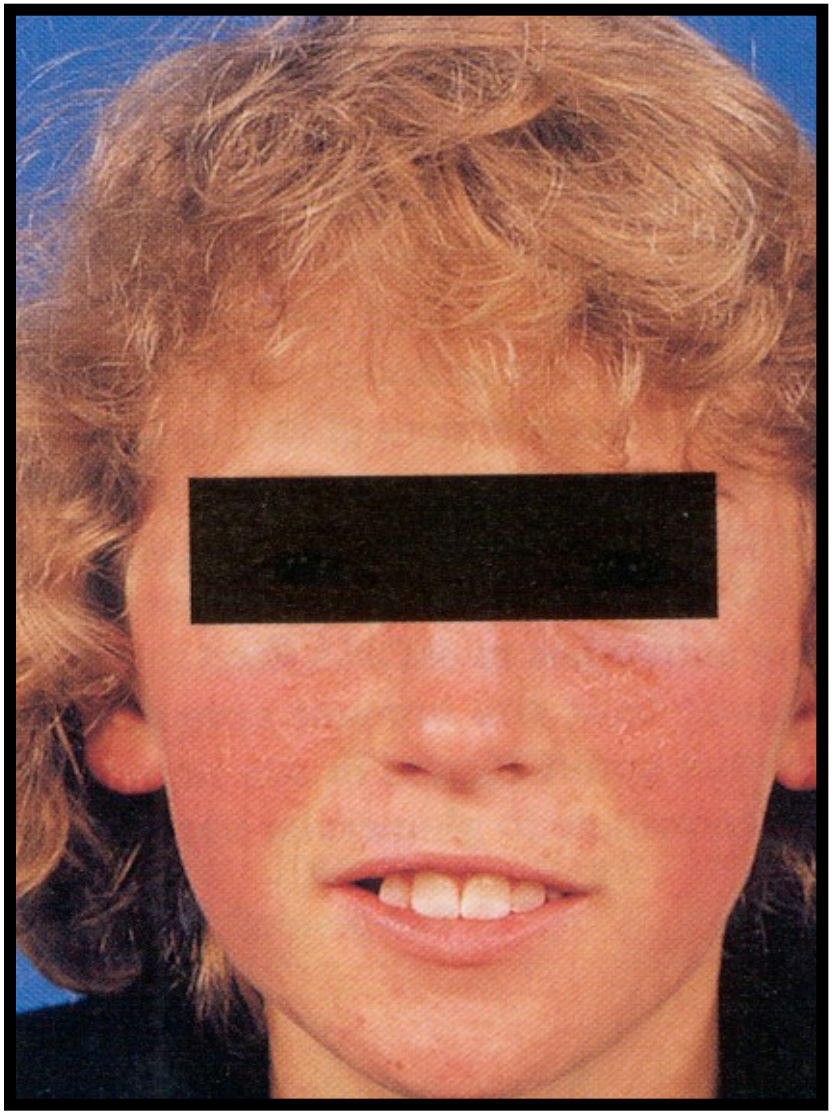
- Systemic autoimmune disease affecting various tissues and organs
- Many symptoms are caused by deposition of immune complexes (type-III immunopathological reaction)
- Female : male ratio is 10:1
- Usually begins in early adulthood

Systemic lupus erythematodes Clinical presentation

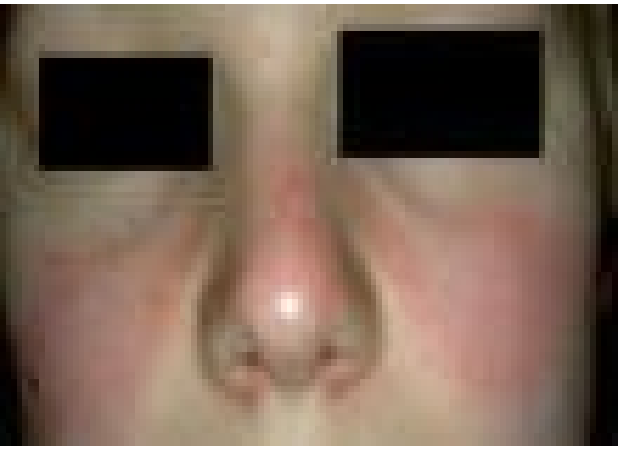
- General: fever, malaise, loss on weight
- Artralgia
- Skin: butterfly rash, urticaria
- Vascular: Raynaud´s phenomenon
- Neurological: vasculitis, seisures, neuritis
- Glomerulonephritis
- Haematological: leukopenia, thrombocytopenia anemia
- Recurrent serositis

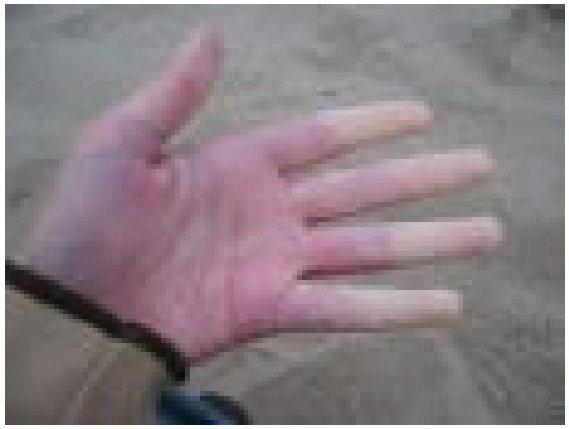
Systemic lupus etythematodes

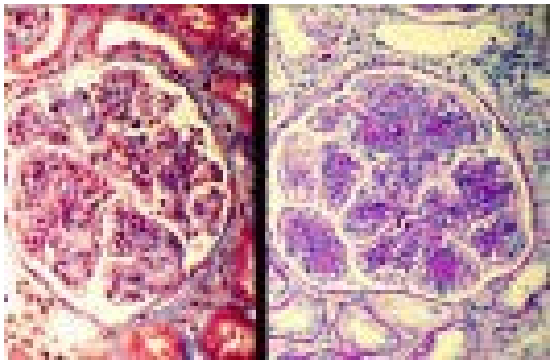
- **Butterfly rash**

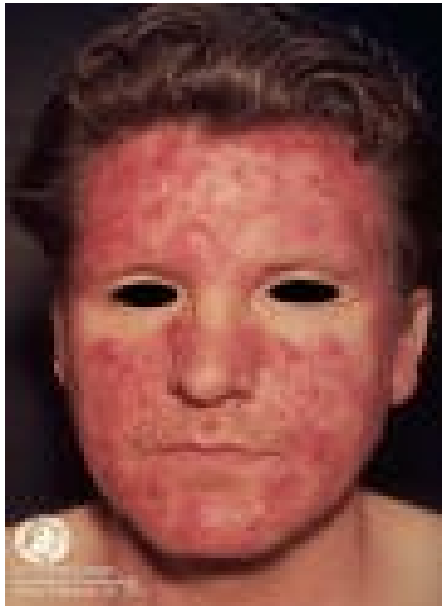


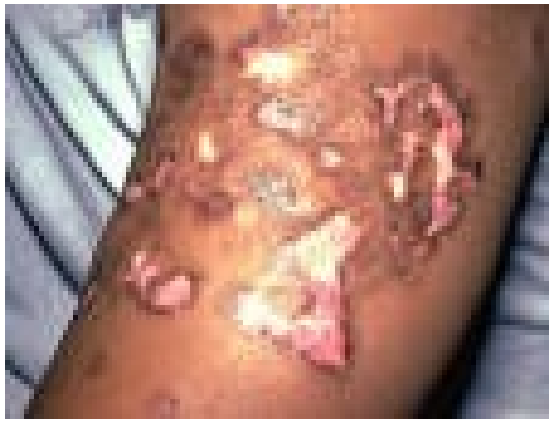
Systemic lupus etythematodes

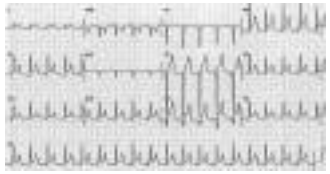


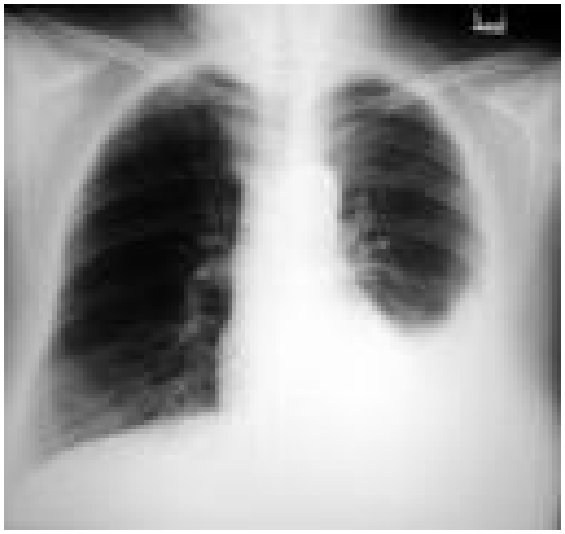












Autoantibodies in SLE - 1

Anti-nuclear anibody (anti-nuclear factor)

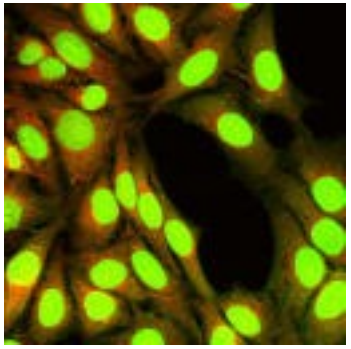
Indirect immunofluorescence on Hep2 cells

Staining pattern may be clinically useful

Interpretation depends on clinical story, titre and age

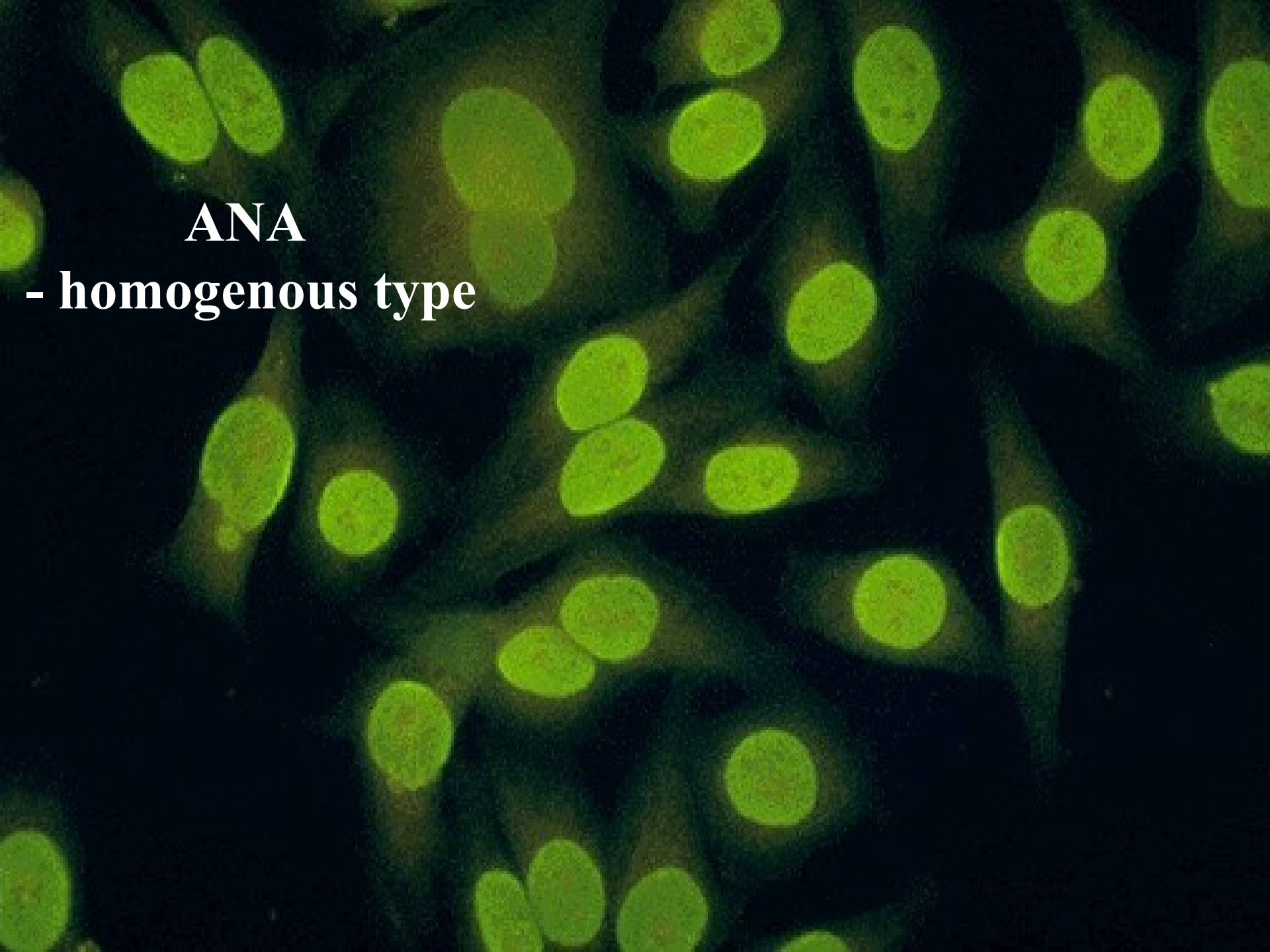
Sensitive but not specific

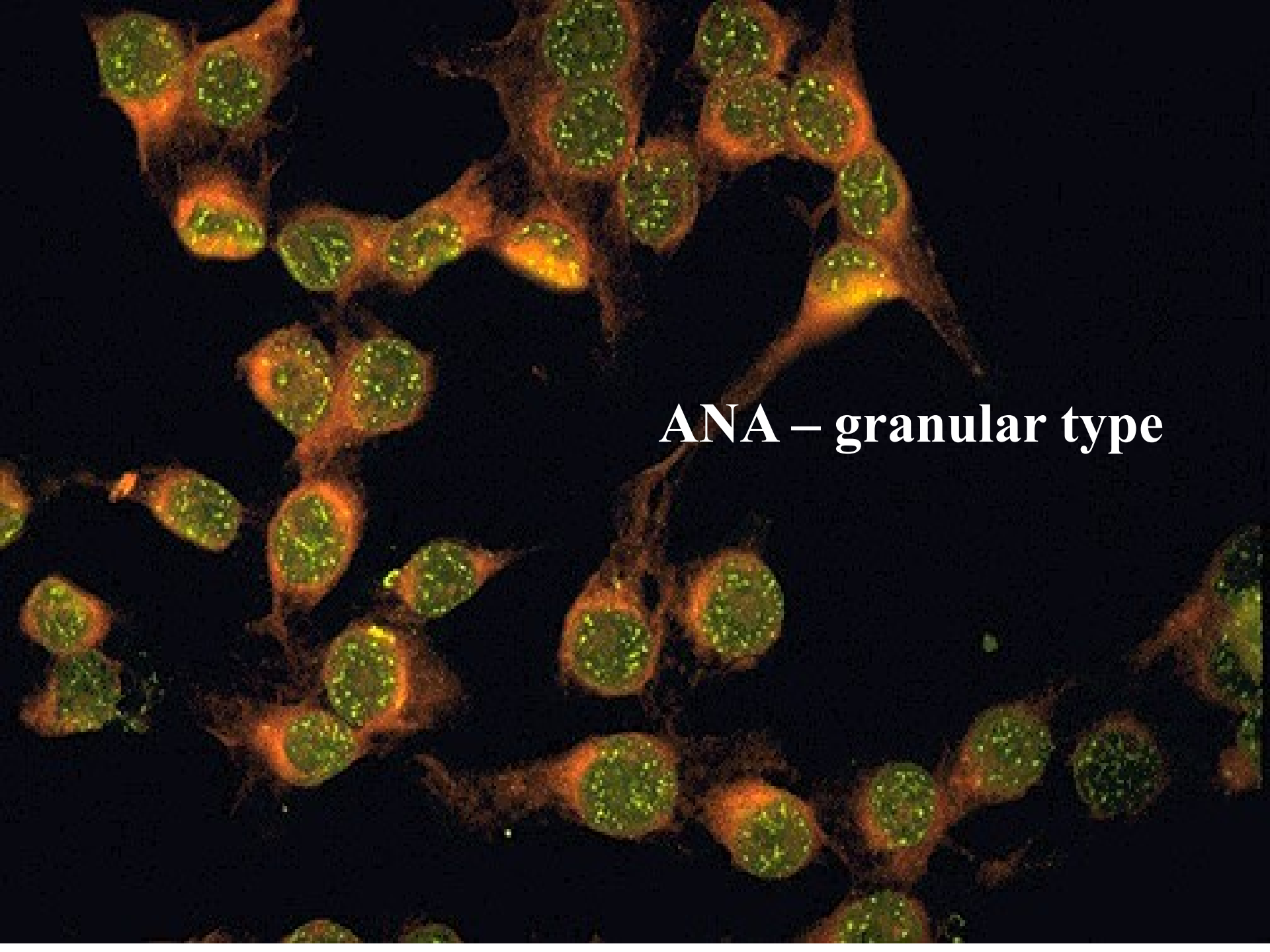
Good screening test for lupus (prevalence ~ 100%)



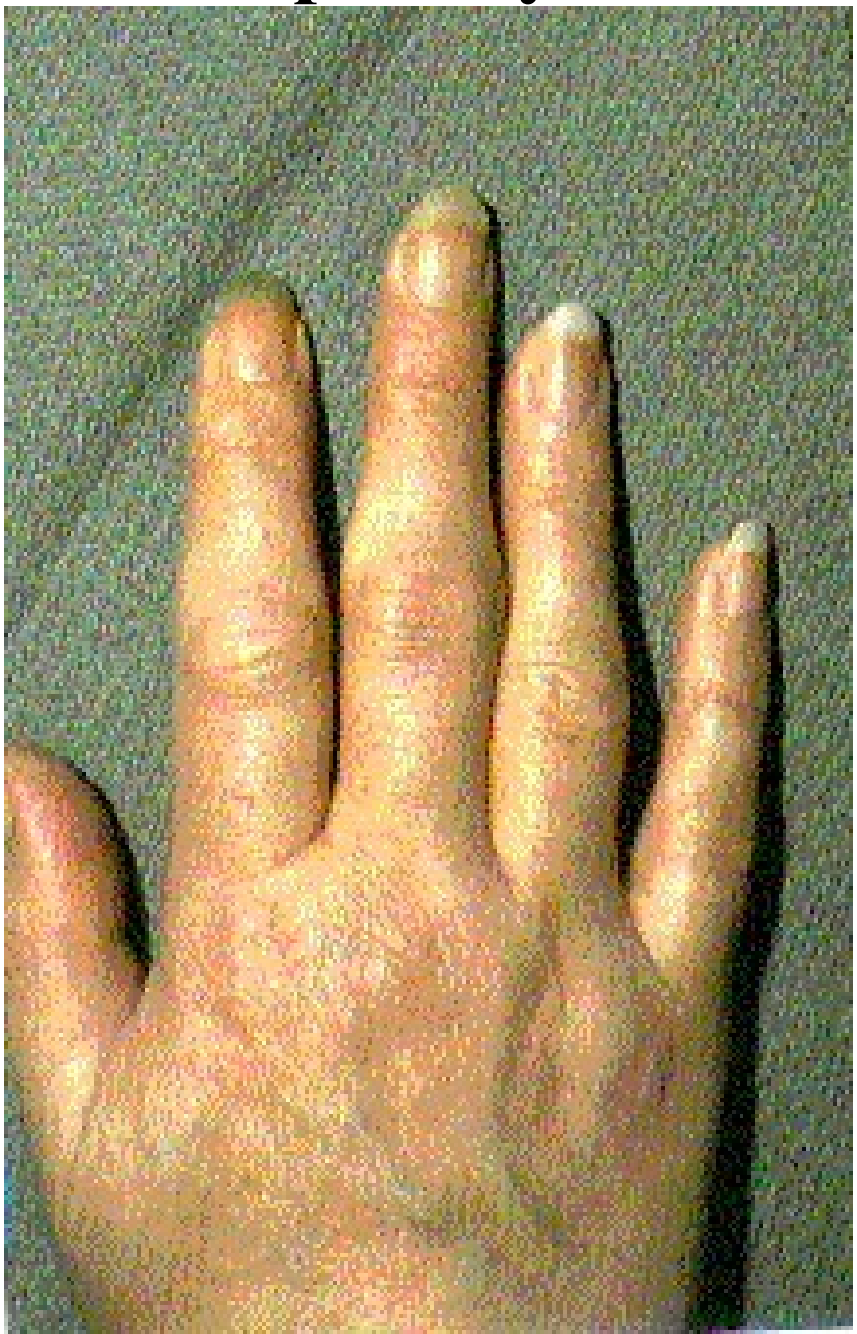
Positivity of antinuclear antibodies (ANA, ANF)

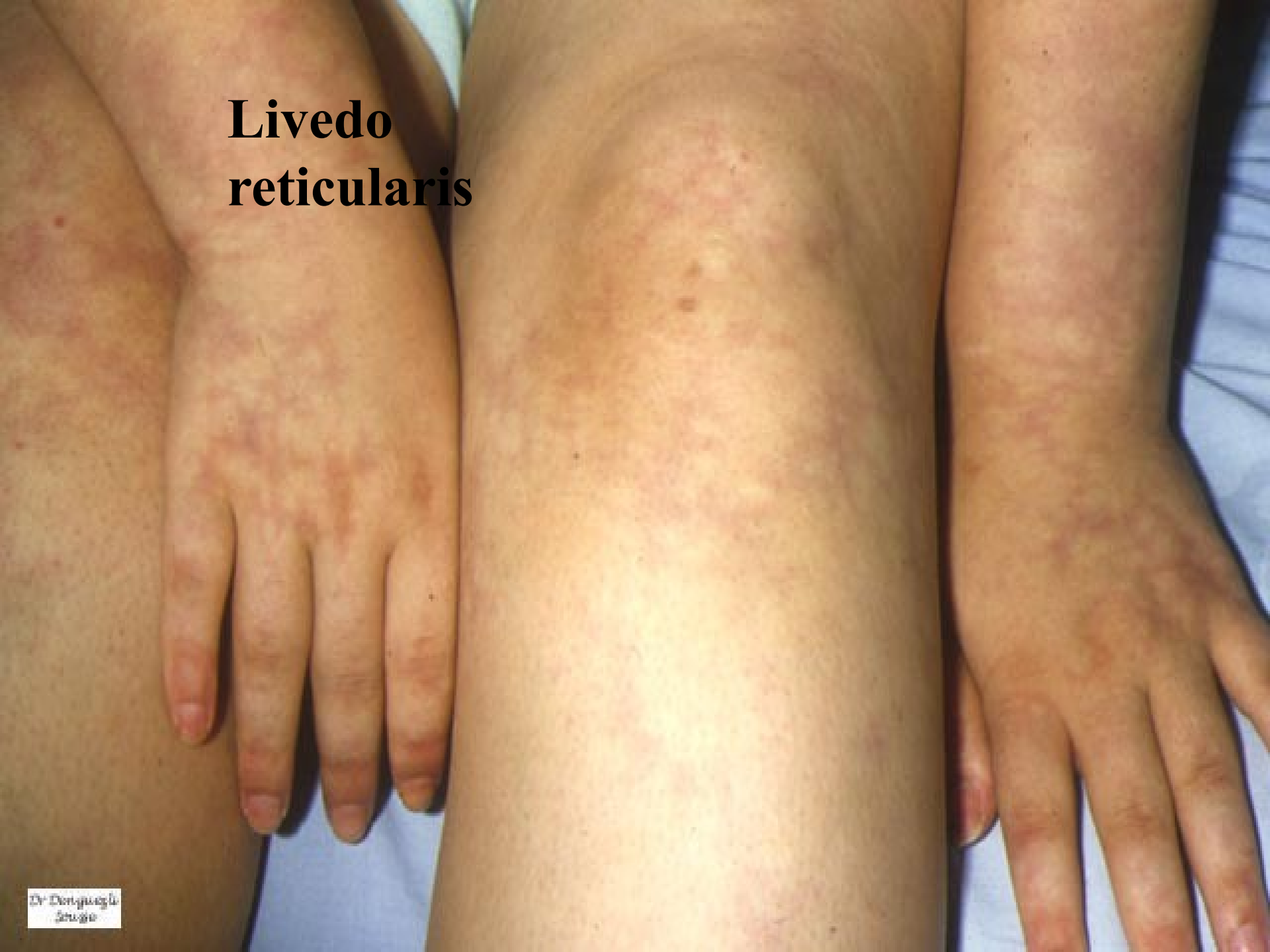
- SLE: 95 - 100 %
- Rheumatoid arthritis: 15 - 30 %
- Systemic scleroderma: 75 -80 %
- Autoimmune hepatitis: 20 -60 %
- Healthy persons: 0 - 4 %
- Seniors: 10 - 20 %


ANA
- homogenous type

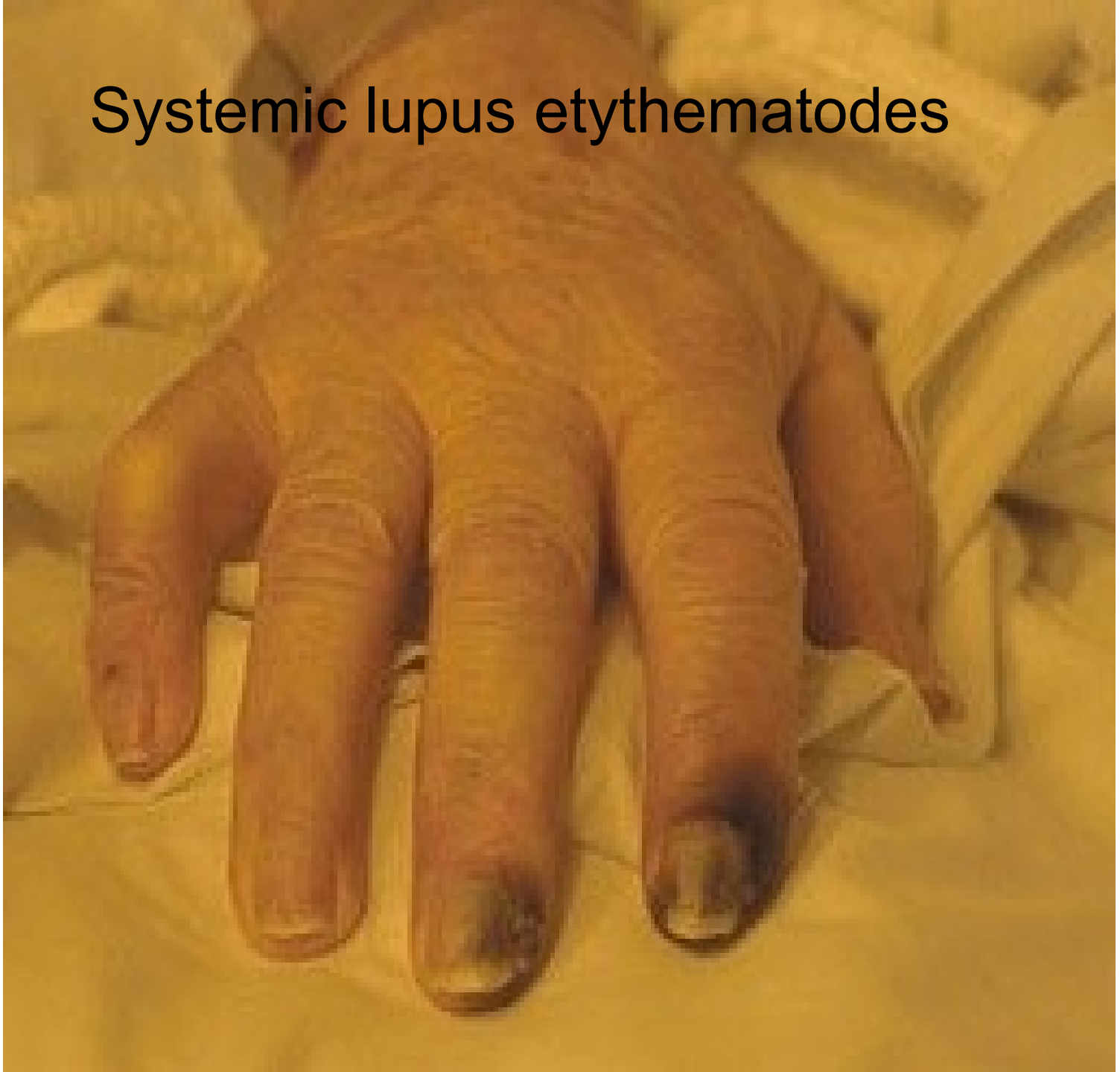

ANA – granular type

Systemic lupus erythematosus




Livedo
reticularis

Systemic lupus etythematodes



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

Hermatopoietic 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

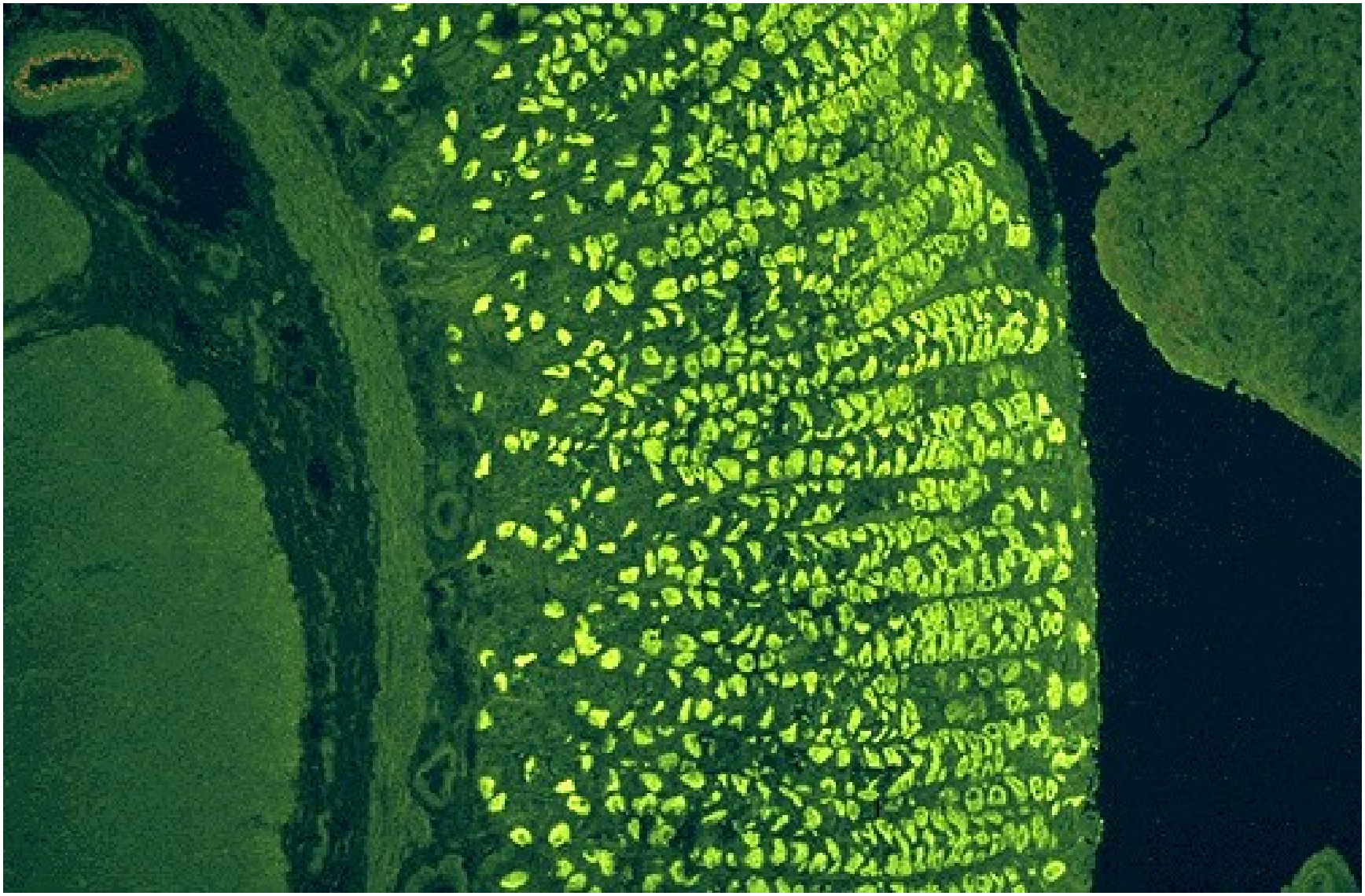
Atrophic gastritis

Crohn´s disease

Ulcerous colitis

Autoimmune hepatitis

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 B_{12}.
- Low serum levels of vitamin B_{12} result in megaloblastic anemia.

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.

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
- Antilymphocytic serum
- Monoclonal antobodies: 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...