ETIOPATHOGENESIS AND MODERN LABORATORY DIAGNOSTICS OF CONNECTIVE TISSUE DISEASES

- Connective tissue diseases (collagenoses)– are immunopathological processes characterized by systemic damage to connective tissue, as well as most other organs and tissues, progressive course and polymorphic clinical manifestations..

COMMON ASPECTS THAT COMBINE UNITING TISSUE DISEASES IN A SINGLE GROUP

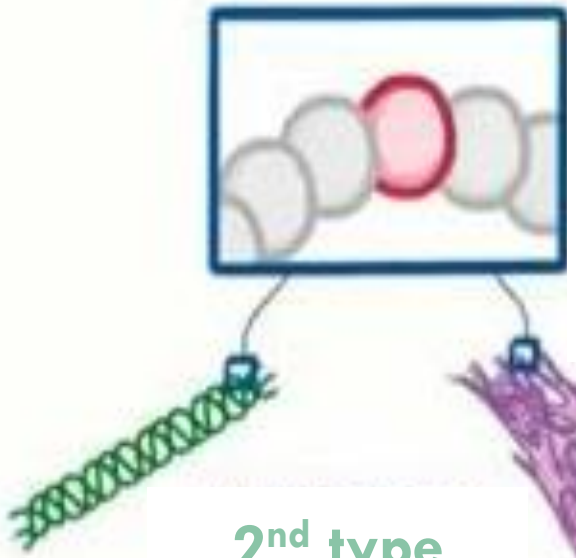
- presence of common mechanisms in pathogenesis (violation of immune homeostasis)
- similarity of morphological changes (fibrinoid changes of collagen)
- having a chronic course
- multisystem damage

RHEUMATOID ARTHRITIS (RA) IS A CHRONIC SYSTEMIC INFLAMMATORY DISEASE OF THE CONNECTIVE TISSUE MAINLY ACCOMPANIED BY EROSIVE-DESTRUCTIVE, PROGRESSIVE POLYARTHRITIS-TYPE DAMAGE TO THE JOINTS.

AETIOLOGY

Rheumatoid arthritis	=	Autoimmun proses
genetic inclination		arthrogenic factors
HLA-DRB 27		viruses (Epstein-Barr, parvovirus B19)
HLA-DR4		other infectious factors (streptococci, mycoplasma)
		Syntrullinated proteins

Citrullination



arginine

↓

citrulline

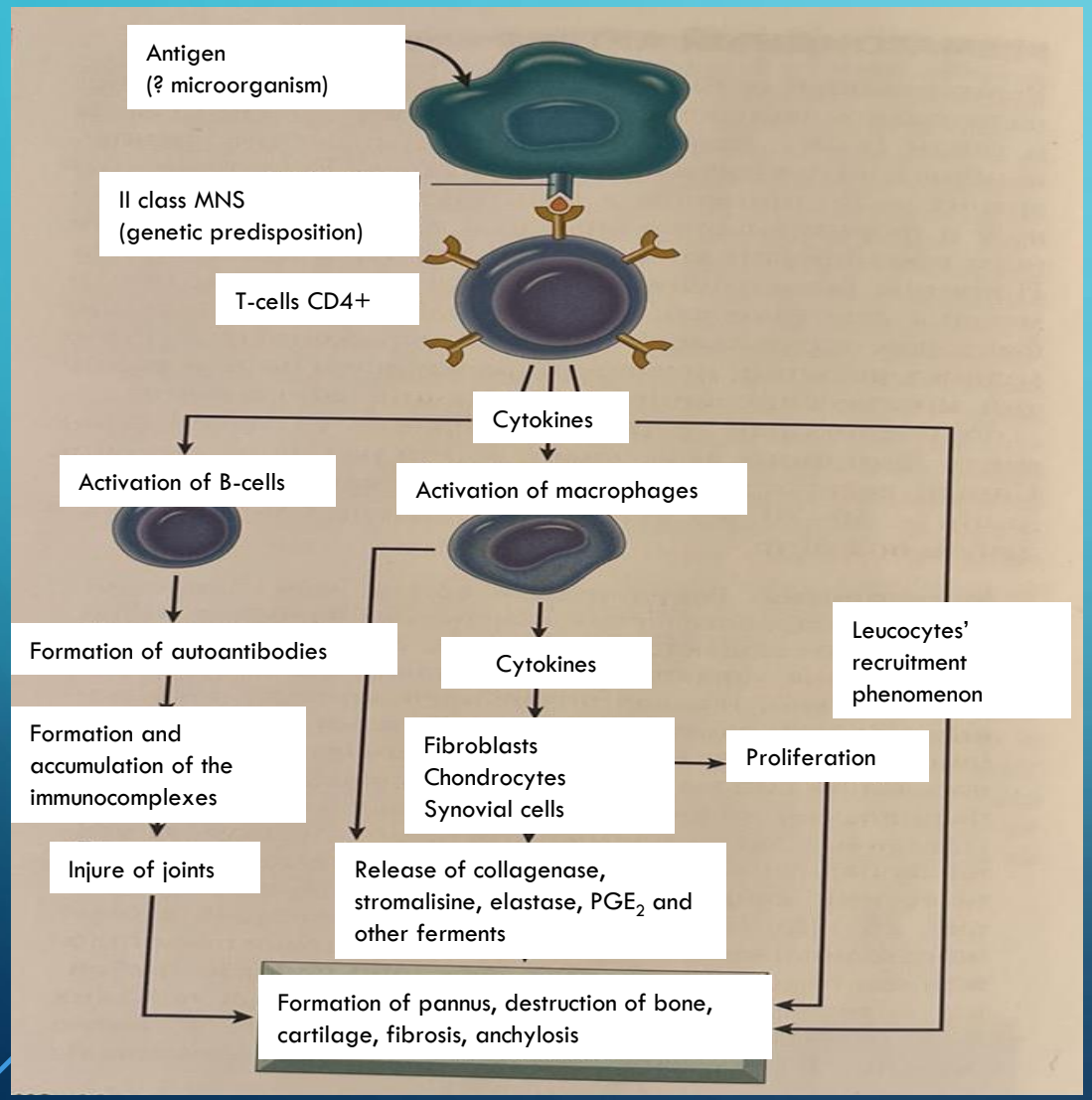
2nd type collagen

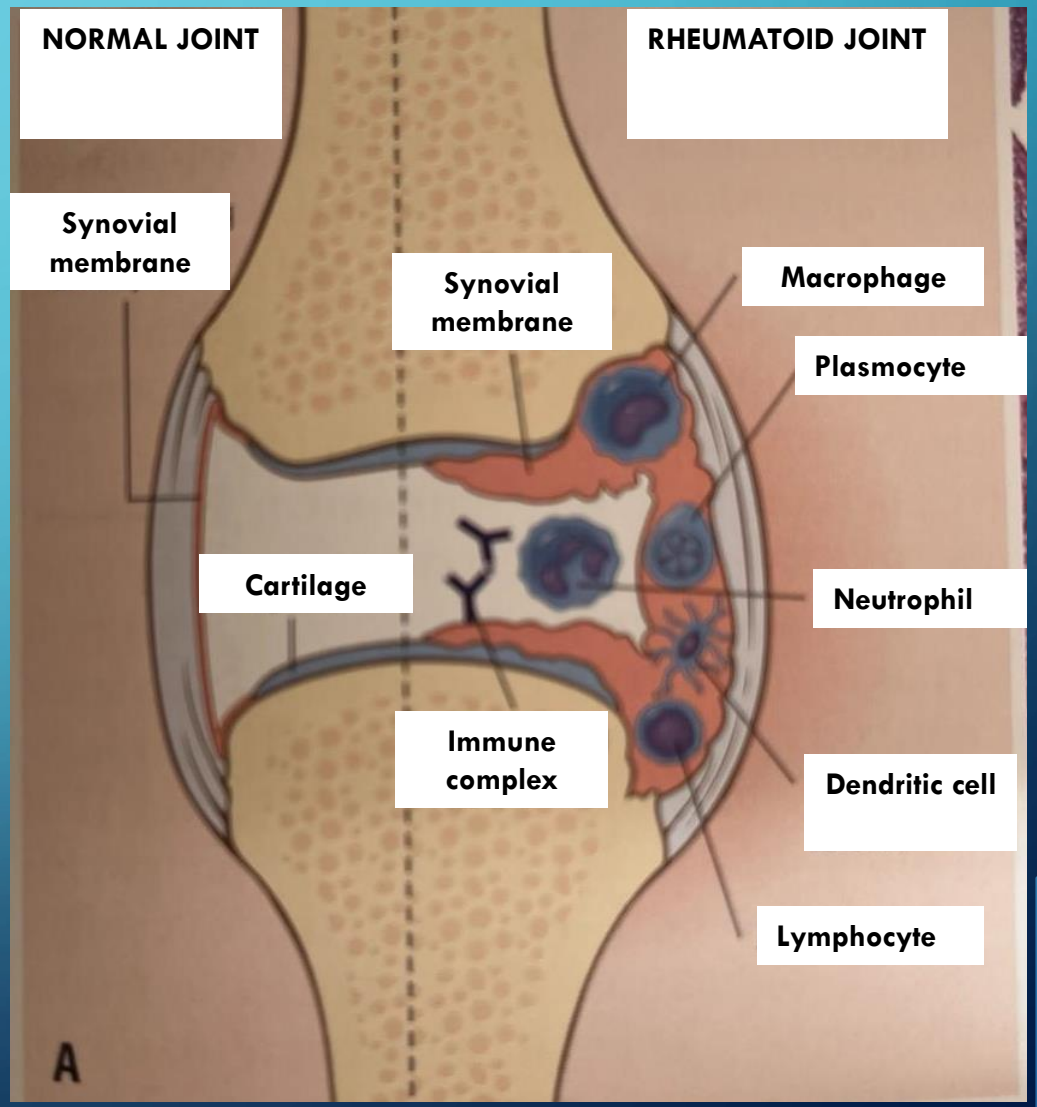
Vimentine

Do you know these guys?

No, I see them first time

PATHOGENESIS

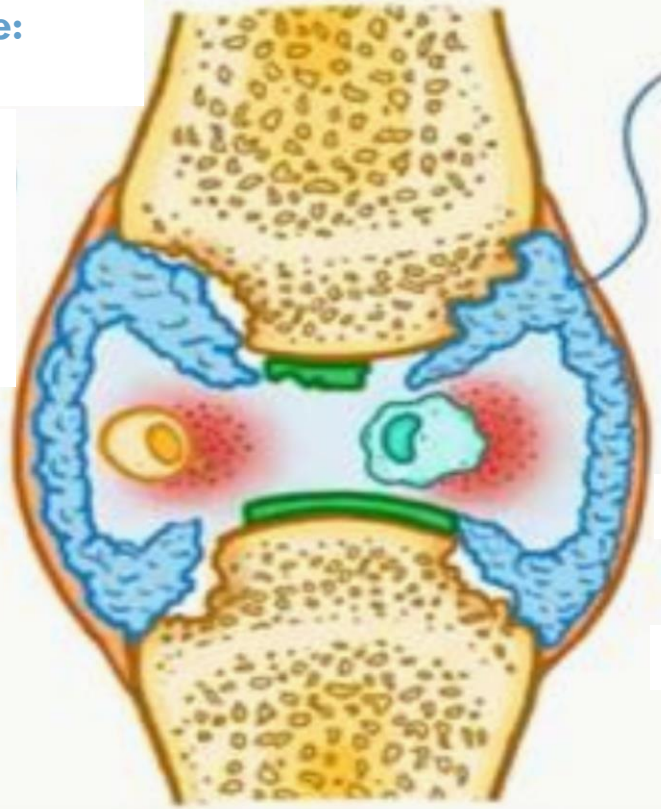




PANNUS IS THE MAIN FEATURE OF RHEUMATOID ARTHRITIS, IT GRADUALLY DESTROYS THE CARTILAGE AND EPIPHYSES OF THE BONES CAUSING FORMATION OF EROSIONS

Over time pannus can damage:

- Cartilage
- Other soft tissues
- May cause erosions on the osseous surfaces



Synovial cell proliferation

PANNUS

thick and edematous tissue

Consists of

Fibroblasts

Inflammatory cells

Miofibroblasts

Classification of rheumatoid arthritis

Forms

Rhematoid arthritis
Polyarthritis
Oligoarthritis
Monoarthritis
RA with systemic symptoms
Main syndromes:
Felty’s syndrome, Sjögren’s syndrome, Still’s syndrome in adults

Clinical-immunological characteristics (based on Rheumatoid factor)

- Seropositive
- Seronegative (ankylosing spondylitis, psoriatic arthritis)

- **Progress**

- Rapidly progressive
- Slowly progressive

- **Activeness**

- I – low
- II – slight
- III – high
- Remission

- **Radiological stage**

- I - osteoporosis
- II -osteoporosis + joint gap narrowing
- III – osteoporosis + erosions
- IV – osteoporosis + ankylosis

- **Functional feature**

0 – fully stored

I - professional specialty is kept

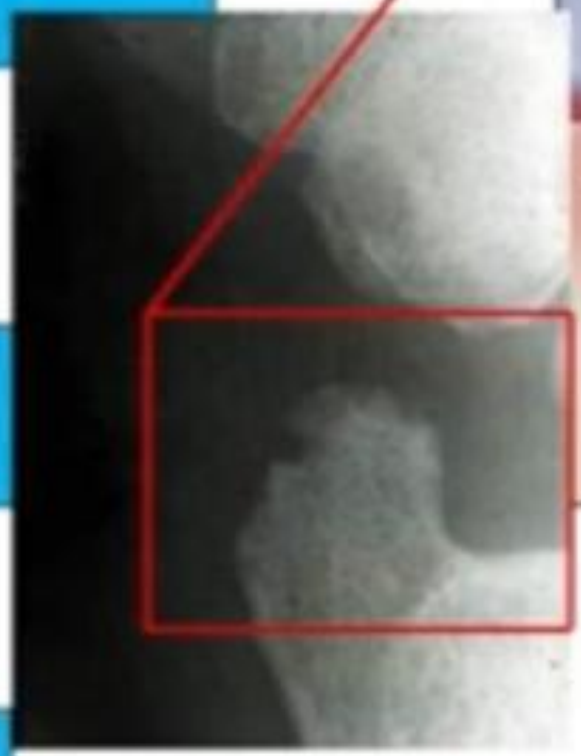
II - professional quality is lost

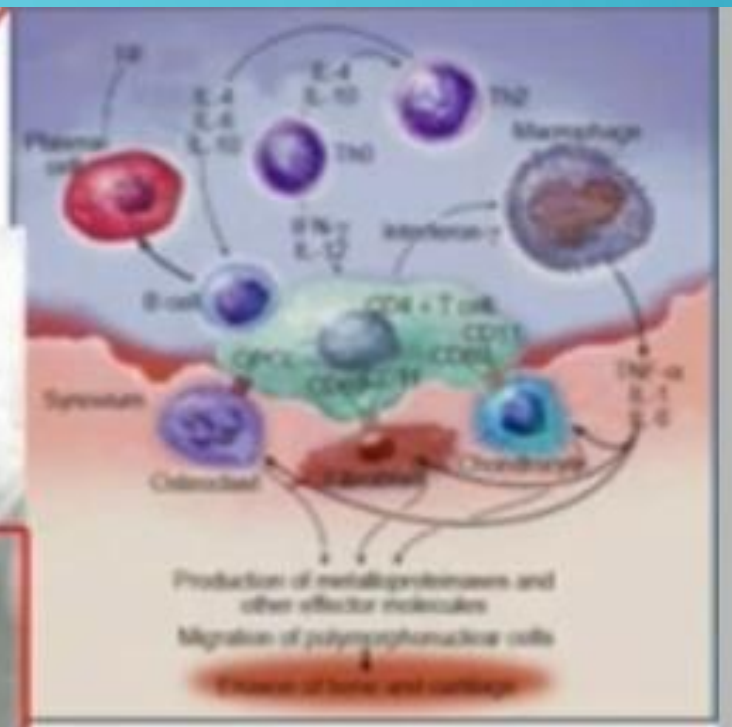
IV – self-serving feature is lost

Inflammation of the synovial membrane

Destruction of joints

Loss of functions





CLINICAL SIGNS

- JOINT SYNDROME

- gradual increase in pain and stiffness in small peripheral joints (wrist, phalangeal-comb, foot-comb)

- joint damage is bilateral, symmetrical

- morning joint pain lasting more than 1 hour

- the pain is more acute in the morning than in the evening

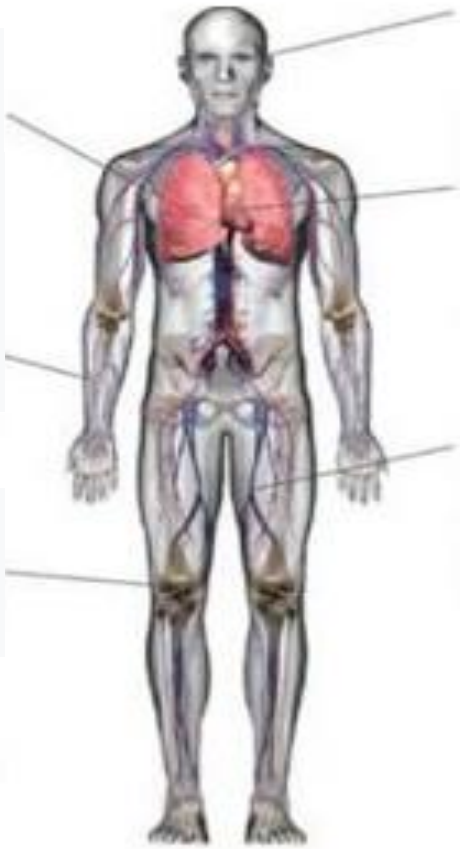
- characteristic inflammatory changes in small peripheral joints: increased skin temperature, swelling, but the skin over the joints is not hyperemic

Extra-articular (outside the joint) manifestations of RA

lung: dry pleurisy, interstitial pulmonary fibrosis

rheumatoid nodules - deposition of immune complexes on damaged joints or in the area of the extensor surface of the ulna

osteoporosis around damaged joints

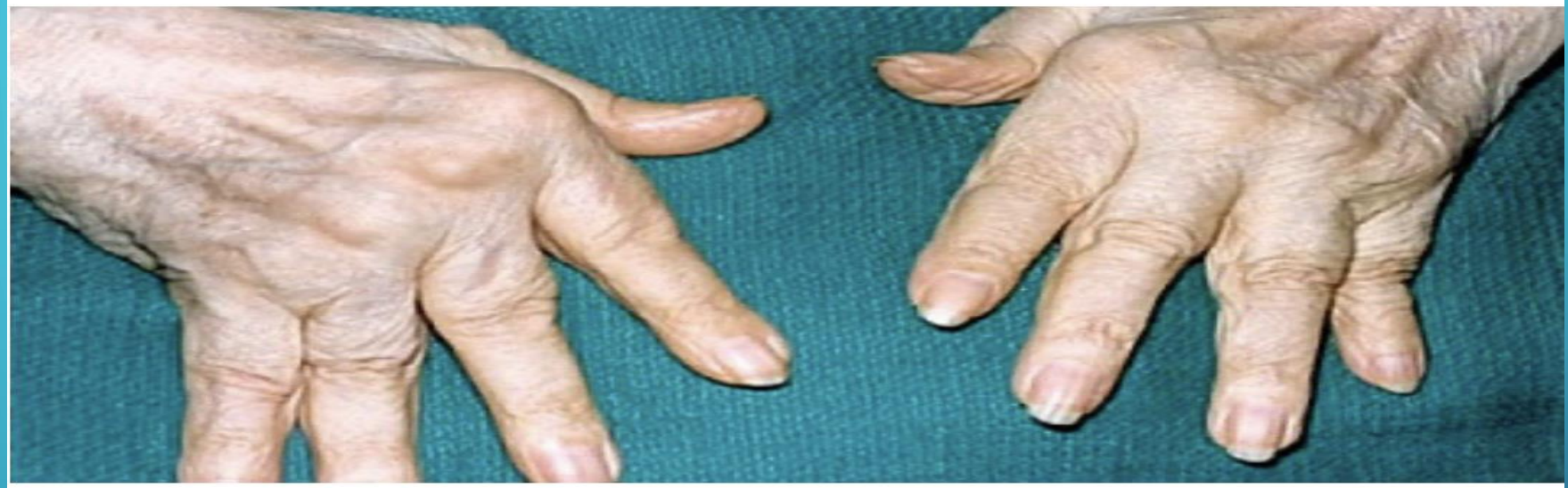


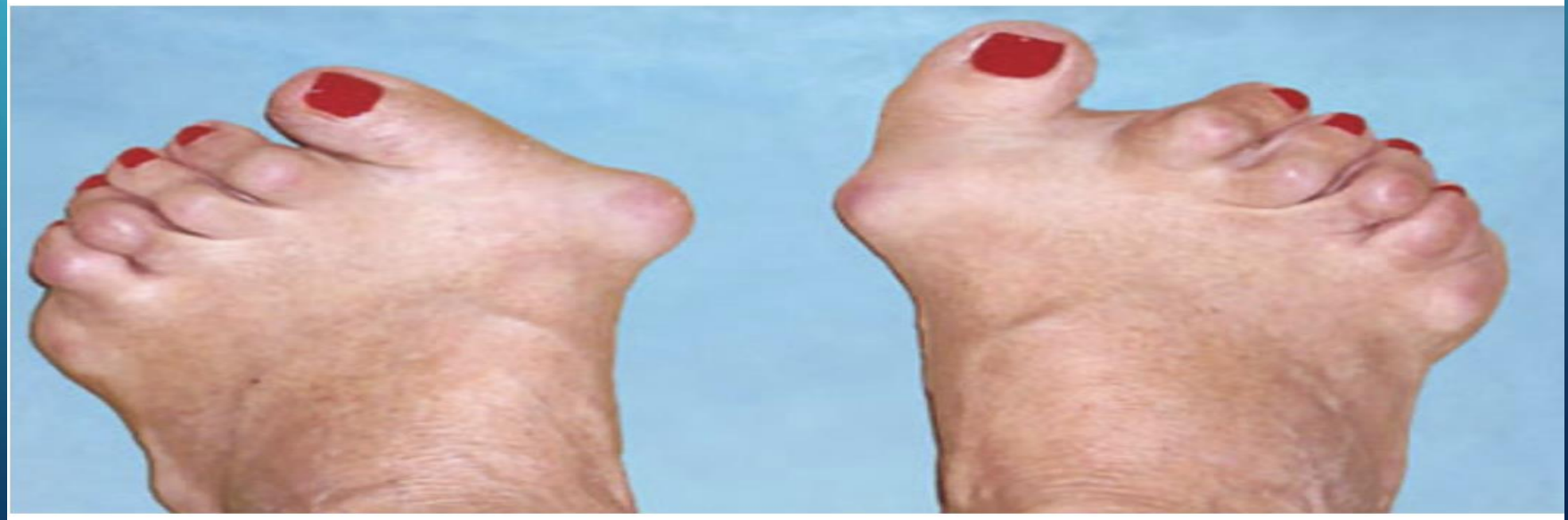
keratoconjunctivitis the ophthalmological symptom of which develops on the background of secondary Sjögren's syndrome

cardiovascular system: pericarditis, "early atherosclerosis", arteritis

hematological: anemia, thrombocytosis, neutropenia in Felty's syndrome

Deformation of joints





Laboratory diagnostics

Blood examination

- inflammatory markers: ERA↑, C-reactive protein↑(CRP) , fibrinogen↑
- leukocytosis, thrombocytosis, neutropenia in Felty's syndrome, thrombocytopenia
- hypochromic anemia (anemia of chronic diseases)
- eosinophilia

Biochemical indicators

- hyperproteinemia or dysproteinemia (α2globulin fraction↑)
- the activity of liver enzymes (ALT, AST) increases.

Immunological indicators

- IgM rheumatoid factor (RF) (in the Vaaler-Rose reaction, the RF titer is considered high if it exceeds 1:10 - 1:20)
- IgG antibodies to cyclic citrulline-containing peptide (ACCP) (7 BV/ml or more indicates a high risk of developing rheumatoid arthritis)

Basic diagnostic laboratory markers of RA

THE MAIN DIAGNOSTIC LABORATORY MARKERS OF RA

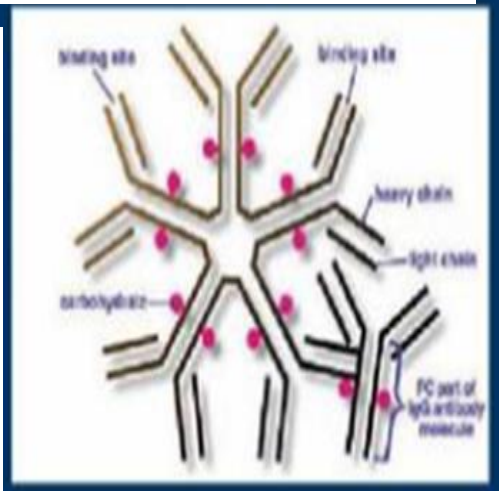
IgM rheumatoid factor (RF)

Autoantibodies of the IgM class reacting with the Fc fragment of IgG

Definition method:

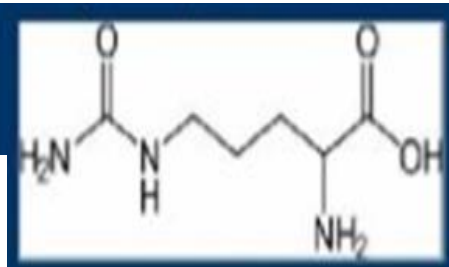
Latex test

(agglutination reaction of sensitized IgG latex particles) - normal < 1:40



Antibodies to cyclic citrullinated peptide (ACCP)

autoantibodies interacting with synthetic peptides containing amino acid i.e. citrulline



Clinical Significance:

- diagnosis of early RA
- Confirmation of the diagnosis of seronegative RA
- Predictor of severe destructive joint damage in RA

ANALYSIS OF THE SYNOVIAL LIQUID

- In rheumatoid arthritis, the synovial fluid usually has an elevated level of turbid protein and a normal or slightly reduced glucose level. Rheumatoid arthritis is characterized by leukocytosis (more than 6x109/l) accompanied by an increase in the number of neutrophils (25-90%).

SYSTEMIC LUPUS ERYTHEMATOSUS

- Systemic lupus erythematosus (SLE) is a chronic disease of young people (mainly women) developing against the background of genetic defects of immune regulatory processes, leading to the uncontrolled synthesis of antibodies against the body's own cells and their components, and resulting in the development of autoimmune and immune complex chronic injuries.

AETIOLOGY

Systemic lupus erythematosus = Autoimmune process

-genetic inclinations

- HLA-DQ

- deficiency of the early components

of the complement system (C2, C4 and C1q)

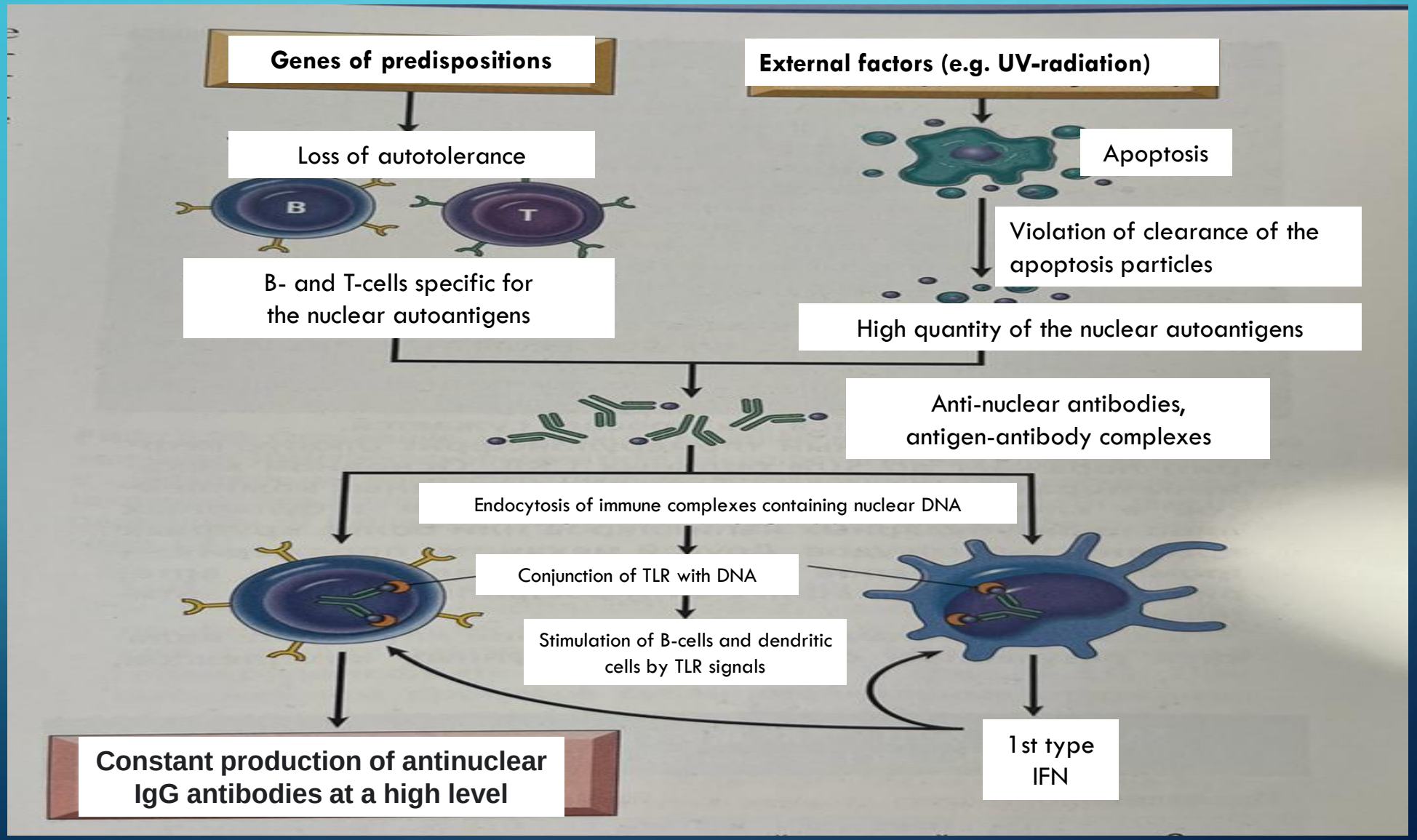
- environmental factors

- ultraviolet radiation,

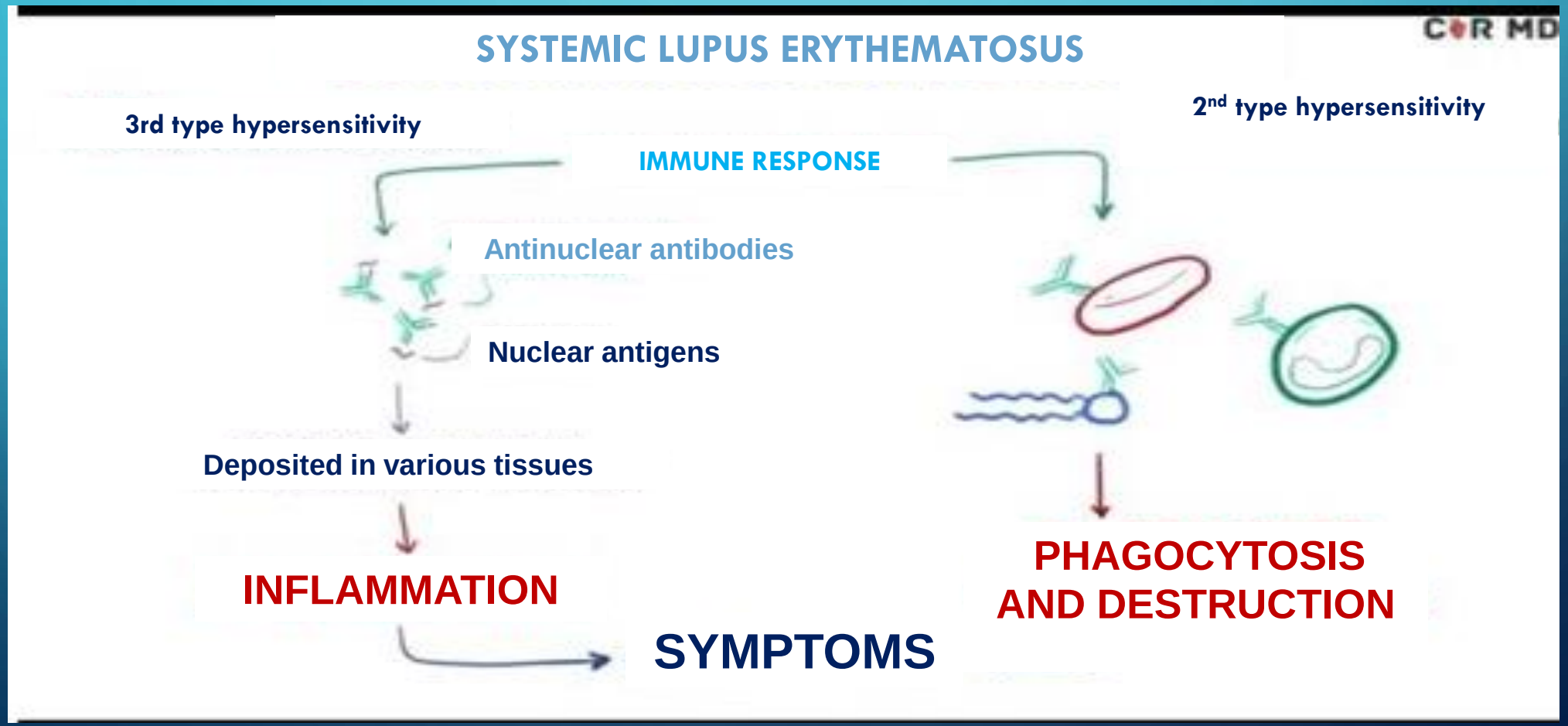
- sex hormones (estrogens)

- drugs (hydralazine) D-penicillamine

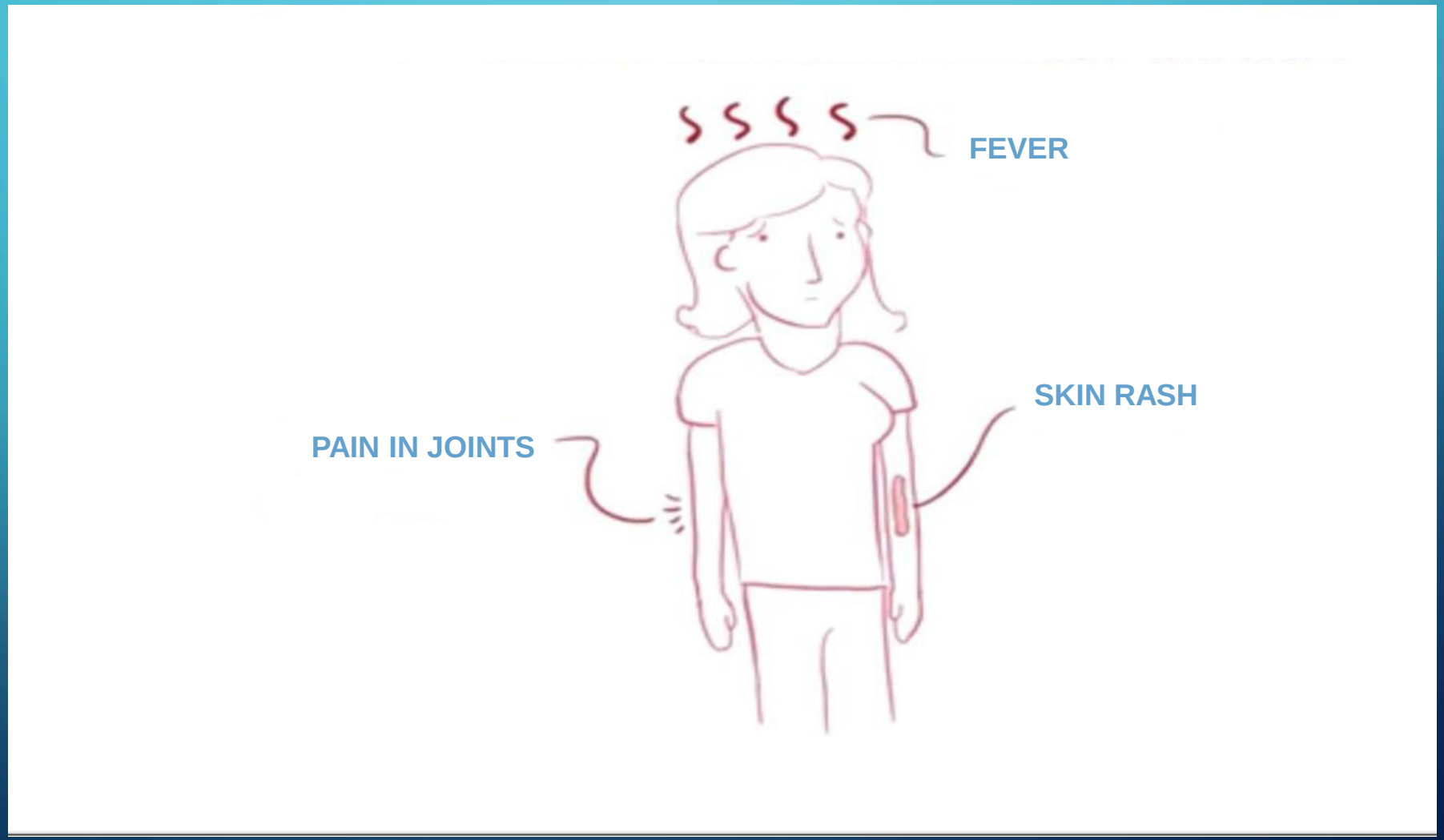
PATHOGENESIS



PATHOGENESİS



CLINICAL SIGNS



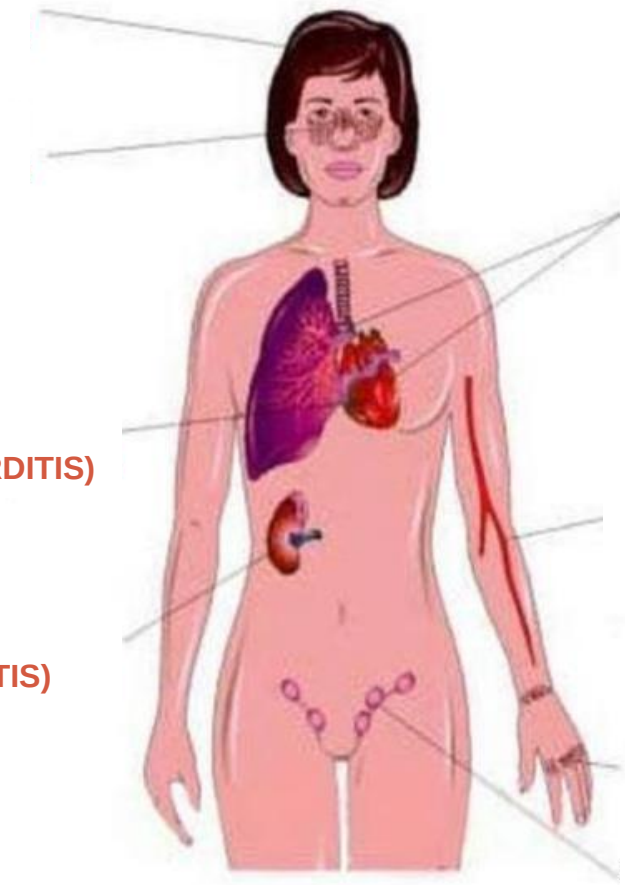
CLINICAL SIGNS

CNS
(SEROSITIS, STROKE)

SKIN
(BUTTERFLY-SHAPED RASHES)

HEART
(PERICARDITIS, MYOCARDITIS)

KIDNEYS
(GLOMERULONEPHRITIS)



LUNGS
(PLEURISY, PNEUMONITIS)

BLOOD
(ANAEMIA, LEUKOPENIA, THROMBOCYTOPENİA)

JOINTS
(ARTHRITIS)

INFLAMMATION OF GLANDS
(LYMPHADENITIS)

LABORATORY DIAGNOSTICS

- GENERAL ANALYSIS OF BLOOD
- ERA↑
- AUTOIMMUNE HEMOLYTIC ANEMIA
- LEUKOPENIA
- THROMBOCYTOPENIA
- GENERAL URINE ANALYSIS - In the general analysis of urine, proteinuria, hematuria, leukocyturia are detected, their significance depends on the clinical-morphological variant of lupus nephritis.
- Elevation of CRP is not characteristic, it increases in the presence of concomitant infection.

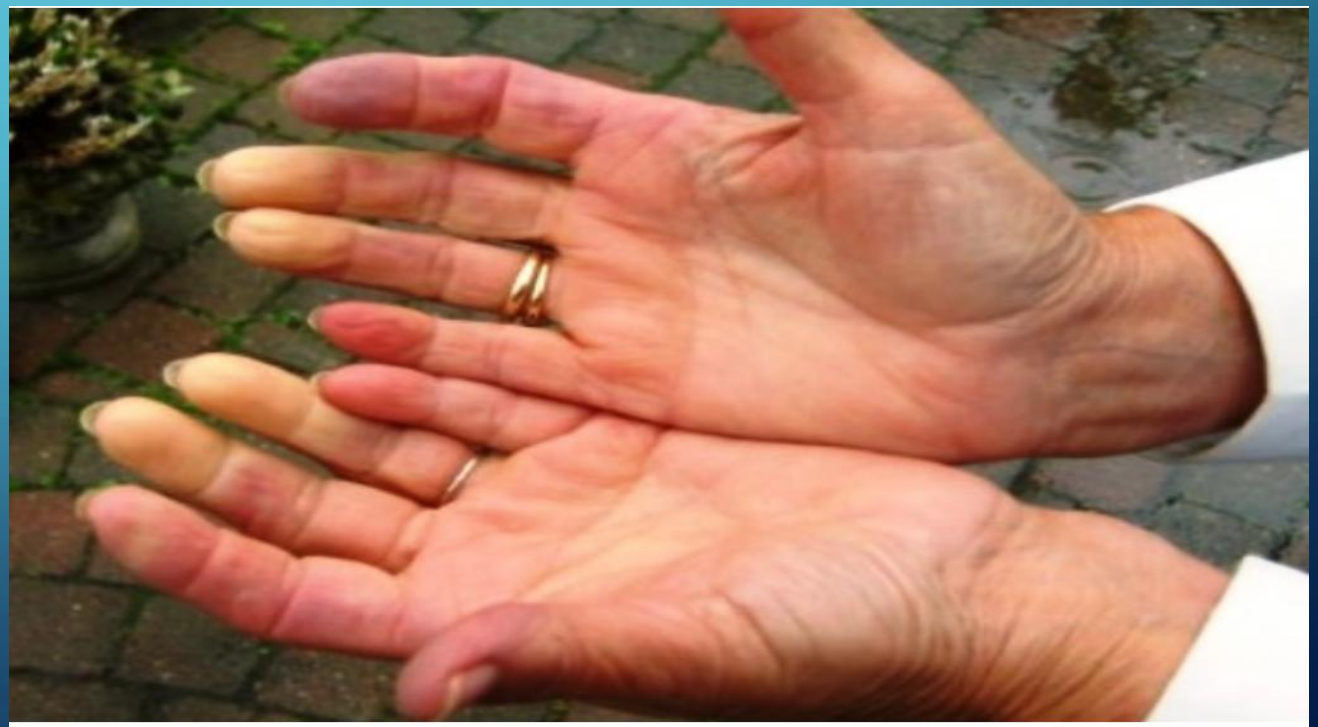
IMMUNOLOGICAL MARKERS

- Antinuclear antibodies (ANA- antinuclear antibodies) are a heterogeneous group of autoantibodies directed against components of their own nucleus. ANA is detected in 98% of patients with SLE. Therefore, a negative test result negates the diagnosis of SLE. These antibodies are not specific for SLE : they are also present in the blood during other diseases (other connective tissue diseases, autoimmune pancreatitis, primary biliary cirrhosis, some malignant tumors). There are several methods of determining ANA in blood. Using human epithelial cells (HEp-2), the non-uniform fluorescence reaction allows determination of the titer and type of illumination. SLE is characterized by homogeneous, peripheral (marginal) and granular illumination.
- Anti-dsDNA antibodies (anti-dsDNA) are autoantibodies directed against a person's own double-stranded DNA. Anti-dsDNA is detected in approximately 70% of patients with SLE. Although the sensitivity of anti-dsDNA against SLE is low, their specificity reaches 100%. This high sensitivity means that a positive test result confirms the diagnosis of SLE.
- Antiphospholipid antibodies are a heterogeneous group of autoantibodies directed against phospholipids and their associated proteins. This group includes beta-2-glycoprotein, annexin V, phosphatidylprothrombin, etc. include antibodies against Antiphospholipid antibodies are detected in 40-50% of SLE patients. The most commonly detected type of antiphospholipid antibody is anticardiolipin antibodies AKA and lupus anticoagulant.

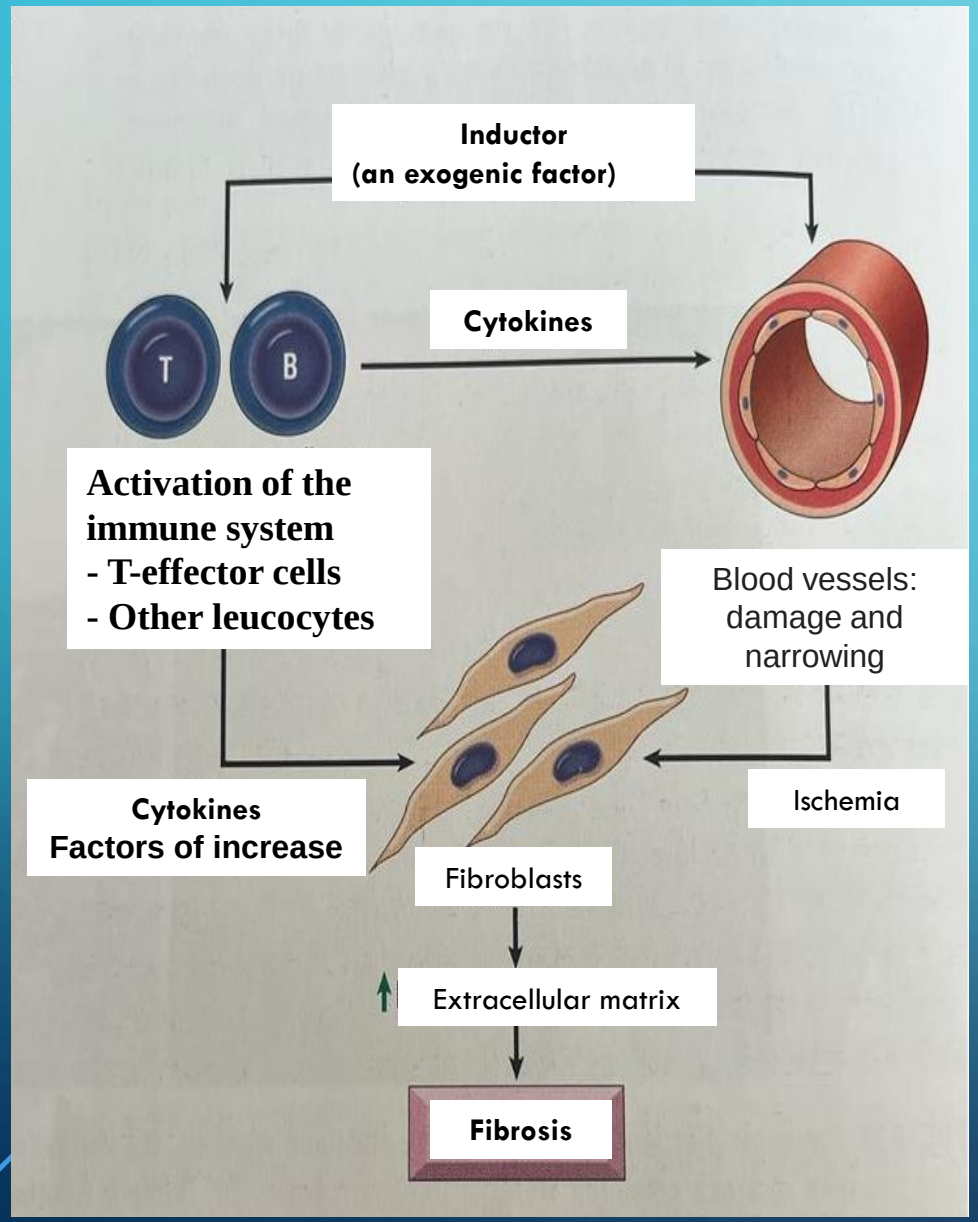
Laboratory signs of SLE	Frequency of appearance in patients (%)
Anti-dsDNA	80
Antinuclear antibodies (immunoglobulin G)	95
Deposition of IgG, complement C3 and C4 components during skin biopsy	75
Increase in the level of IgG in the blood serum	65
Decreased levels of complement components C3 and C4	60
Cryoglobulinemia	60
Antithrombocytic antibodies	60
Antibodies against phospholipids	30-40
RNA (antibodies against ribonucleoprotein-containing molecules)	
-Sm (Smith antigen)	30
SS-A (Ro)	30
SS-B (La)	15
Low titer of rheumatoid factor	30
Increase in ESR	60
Proteinuria	30
Leukopenia	45
Pseudo Wasserman reaction	10
Anticoagulant for lupus erythematosus	10-20

SYSTEMIC SCLEROSIS

- Systemic sclerosis (scleroderma) is a chronic disease characterized by inflammation of autoimmune origin, widespread damage to small blood vessels, progressive interstitial and perivascular fibrosis in the skin and many organs.



PATHOGENESIS



- Autoimmune reaction
- Damage of vessels
- Excessive collagen accumulation

CLINICS

Diffuse scleroderma is characterized by extensive skin damage from the beginning, rapid progression and early spread of the process to internal organs.

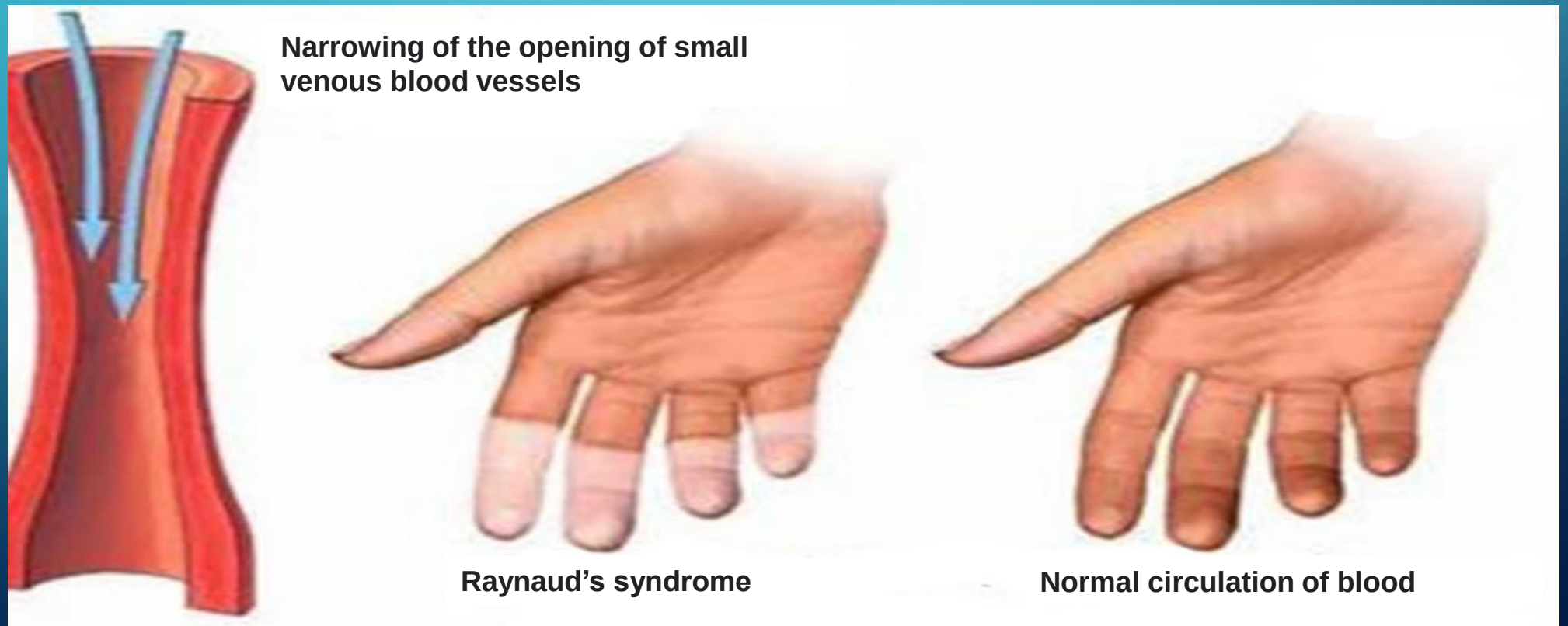
In localized scleroderma, the skin of the fingers, shoulder, and face is affected, but the internal organs are affected late, and therefore the clinical course is relatively benign. Patients with local scleroderma often develop CREST syndrome.

CREST SYNDROME

- C – calcinosis
- R – Raynaud’s syndrome
- E – esophagitis
- S – sclerodactyly
- T – telangiectasia

RAYNAUD'S SYNDROME

- Raynaud's syndrome is characterized by reversible vasospasm of the arteries feeding the fingers



LABORATORY DIAGNOSTICS

General analysis of blood

- CRP ⬆
- ERA ⬆
- Fibrinogen ⬆
- Hypochromic anemia
- Hypergammaglobulinemia

Immunological markers

Two types of ANA are distinguished in systemic sclerosis:

DNA-topoisomerase 1 (anti-Scl 70) ⬆

Anticentromeric antibodies (İgG ⬆)

Autoantibodies detected during systemic scleroderma

Autoantibodies	***Disease form***
Antibodies against Scl-70 antigen	Diffuse
Antibodies against centromeres	Local (GREST syndrome)
Antibodies against RNA polymerases I, II and III	Diffuse
Antibodies against Th-ribonucleoprotein	Local
Antibodies against U3-ribonucleoprotein	Diffuse