Rheumatic diseases. Rheumatic Fever and Rheumatic Heart Disease

Rheumatic diseases

- Rheumatic diseases - a group of diseases characterized by systemic damage to the connective tissue and blood vessels caused by immune disorders.

Common symptoms of the entire group of rheumatic diseases:

- chronic infectious focus;
- disorders of immune homeostasis in the form of hypersensitivity reactions of immediate and delayed types;
- systemic lesion of connective tissue;
- generalized vasculitis;
- chronic course with exacerbations.

Rheumatic diseases

- Rheumatism (Rheumatic Fever and Rheumatic Heart Disease),
- Rheumatoid arthritis,
- Ankylosing spondylitis,
- SLE
- Systemic scleroderma,
- Periarteritis nodosa,
- Dermatomyositis
- Sjögren syndrome.

Connective tissue lesions in rheumatic diseases consist in systemic progressive disorganization of connective tissue .

There are 4 consecutive phases of disorganization:

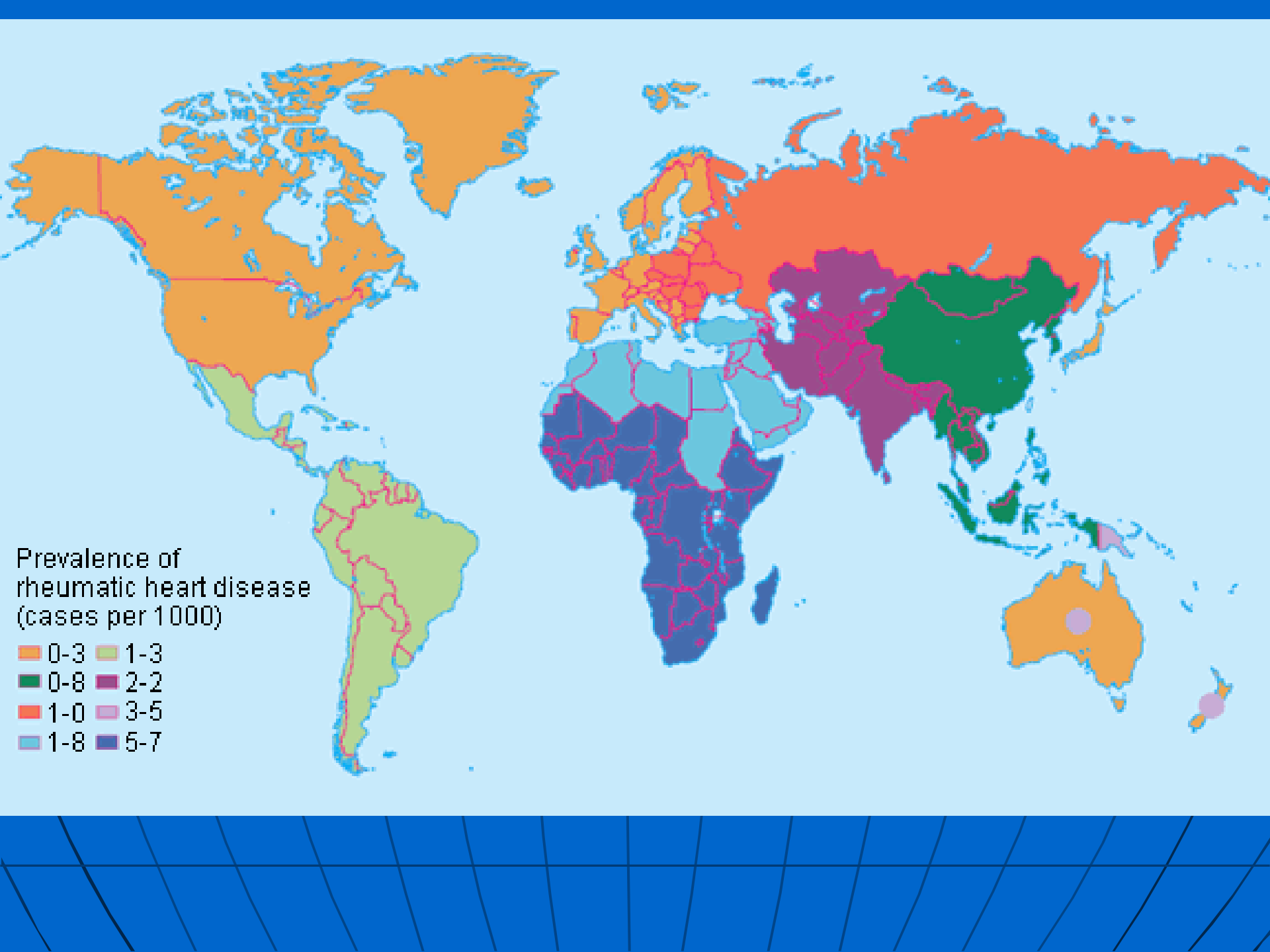
- mucoid swelling;
- fibrinoid changes;
- inflammatory cell reactions;
- sclerosis.

Rheumatic Fever and Rheumatic Heart Disease

- Rheumatic fever is a post-streptococcal (nonsuppurative) autoimmune inflammatory disease with cardiac and extracardiac manifestations.

Incidence

- Although once common worldwide, the incidence has been decreasing for many years. This may be due to the effect of antibiotics, improved socioeconomic conditions and possibly a change in the virulence of the streptococcus. Although acute rheumatic fever has decreased in incidence, the long-term effects on the valves still constitute a cause of chronic valve disease today.


Prevalence of
rheumatic heart disease
(cases per 1000)
0-3
1-3
0-8
2-2
1-0
3-5
1-8
5-7

Rheumatic fever (RF)

1. Epidemiology

a. First attack of RF usually occurs between 5 and 15 years of age.

b. Develops over 1 to 5 weeks (average 20 days) after a group A streptococcal

(Streptococcus pyogenes) pharyngitis

(1) Pharynx is the only site for infection leading to RF.

(2) Nephrogenic strains of group A streptococcus that produce poststreptococcal glomerulonephritis, lack the types of matrix (M) proteins (virulence factors)

in their cell wall that are present in pharyngeal strains; hence they never produce RF.

c. Risk factors for developing streptococcal pharyngitis

(1) Crowding, poverty

- RF is common in impoverished countries.

(2) Young age

(3) Living in Salt Lake City, Utah

- For unexplained reasons, this area in the United States has the highest incidence and prevalence of RF.

d. Recurrent RF produces chronic valvular disease.

Etiology

- Rheumatic fever follows a Group A beta-hemolytic streptococcal infection, usually pharyngitis. The evidence for this association, even though blood cultures of patients with rheumatic fever are sterile, include:
- **epidemiology**: outbreaks of streptococcal pharyngitis are followed by cases of rheumatic fever.
- **patient history**: recurrent attacks and exacerbations of rheumatic fever follow streptococcal infections.
- **serology**: patients typically have elevated levels of anti-streptococcal antibodies.

Pathogenesis

- Presumed due to **cross-reaction of antibodies** to streptococcal antigens **with host cardiac and extracardiac antigens**, leading to tissue damage. Alternatively it has been proposed that there is induction of hypersensitivity or autoimmunity by Streptococcal products.

Pathogenesis

a. Antibody-mediated disease that follows a group A streptococcal infection of the pharynx.

b. Host develops antibodies against group A streptococcal M proteins.

(1) Antibodies that are produced cross-react with similar proteins in human tissue (called mimicry).

- Type II antibody-mediated hypersensitivity reaction (HSR).

(2) Some evidence that cell-mediated immunity (type IV HSR) is also involved; however, this has *not been confirmed.*

- **Clinical manifestations**
  Extracardiac: fever, arthritis, arthralgia, skin lesions, chorea
  Cardiac: pancarditis (inflammation of endocardium, myocardium and pericardium)

Clinical findings in acute RF

a. Migratory polyarthritis (~75% of cases)

(1) Most common initial presentation of acute RF

(2) Involves the large joints (knees), ankles, and wrists

(3) *No permanent joint damage*

b. Carditis (~35% of cases)

(1) Most serious complication

(2) Fibrinous pericarditis presents with precordial chest pain with or without a friction rub.

(3) Myocarditis usually presents with signs of CHF.

(a) Most common cause of death in acute RF

(b) Aschoff bodies are present in myocardial tissue (a postmortem finding).

- Lesions have a central area of fibrinoid necrosis surrounded by Anitschkow cells (reactive histiocytes).

(c) MV regurgitation or AV regurgitation occurs depending upon which valve is inflamed.

- LHF may occur (systolic heart failure).

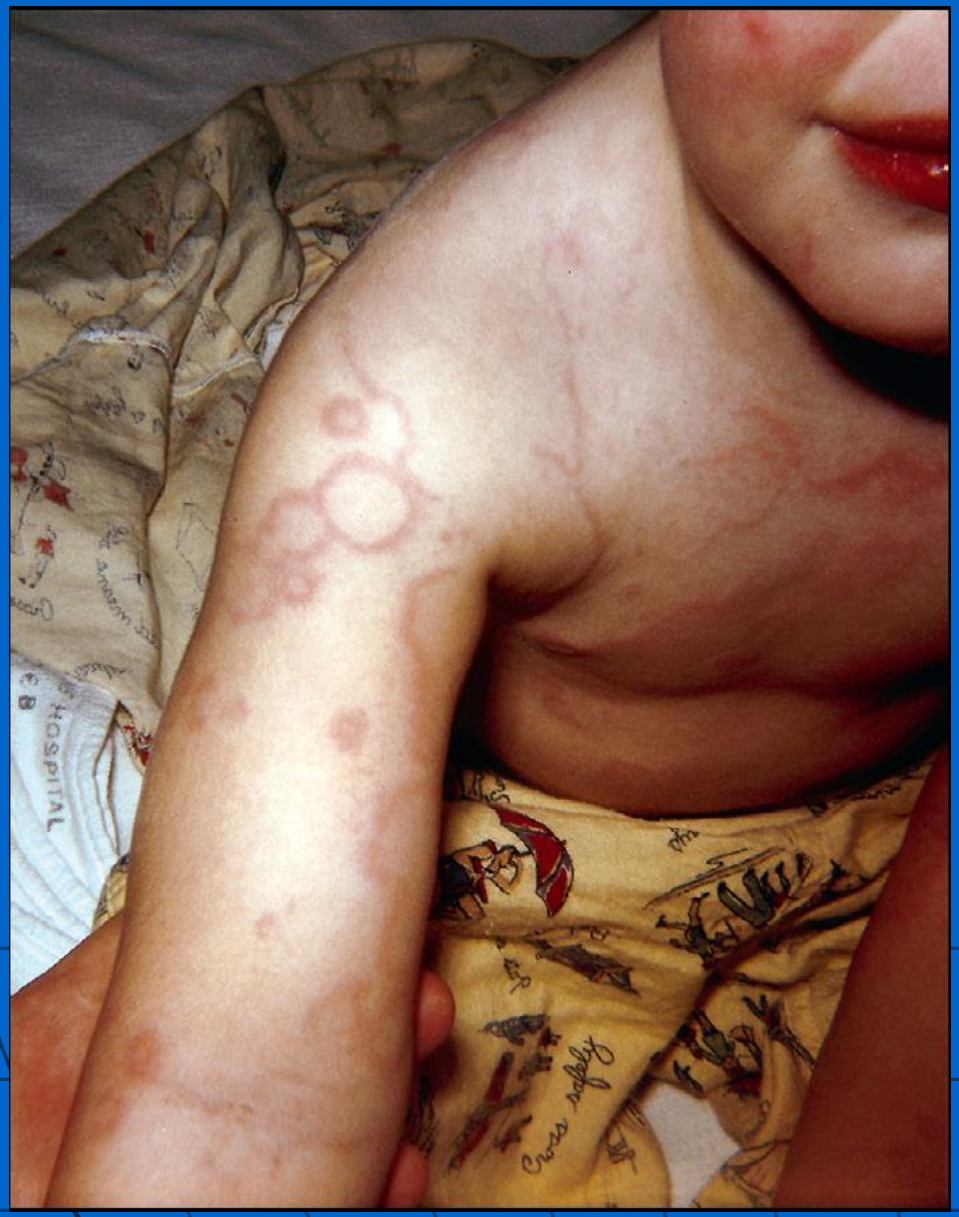
(d) Recurrent infection of the MV or AV over many years leads to stenosis of the respective valves.

c. Subcutaneous nodules (~10% of cases) occur on the extensor surfaces of the forearms.

(1) Nodules are very similar to those seen in rheumatoid arthritis.

(2) Centers of the nodules have fibrinoid necrosis.

- d. Erythema marginatum presents as evanescent circular rings or C-shaped areas of erythema around normal skin (~10% of cases).
- e. Sydenham chorea is characterized by reversible rapid, involuntary movements affecting all the muscles (~10% of cases).



- Erythema marginatum in a child with acute rheumatic fever. Note that most of the erythematous rash has a C-shaped appearance similar to the margin of the mitral valve.
- *from Kliegman R: Nelson Textbook of Pediatrics, 19th ed, Philadelphia, Elsevier Saunders, 2011, p 922, Fig. 176.2, courtesy Schachner LA, Hansen RC, [eds]: Pediatric Dermatology, 3rd ed, Mosby, 2003, p 808.)* A B Carditis: pericarditis, myocarditis, endocarditis (valves) Migratory polyarthritis MC initial presentation M protein antibodies cross-react with human tissue (mimicry) Type II HSR (most common); cell-mediated immunity type IV HSR Endocarditis: MV most often involved, followed by AV; sterile vegetations Myocarditis MCC death in acute RF

(4) Endocarditis refers to inflammation of cardiac valves.

(a) It most commonly involves the MV, followed by the AV, followed by the TV.

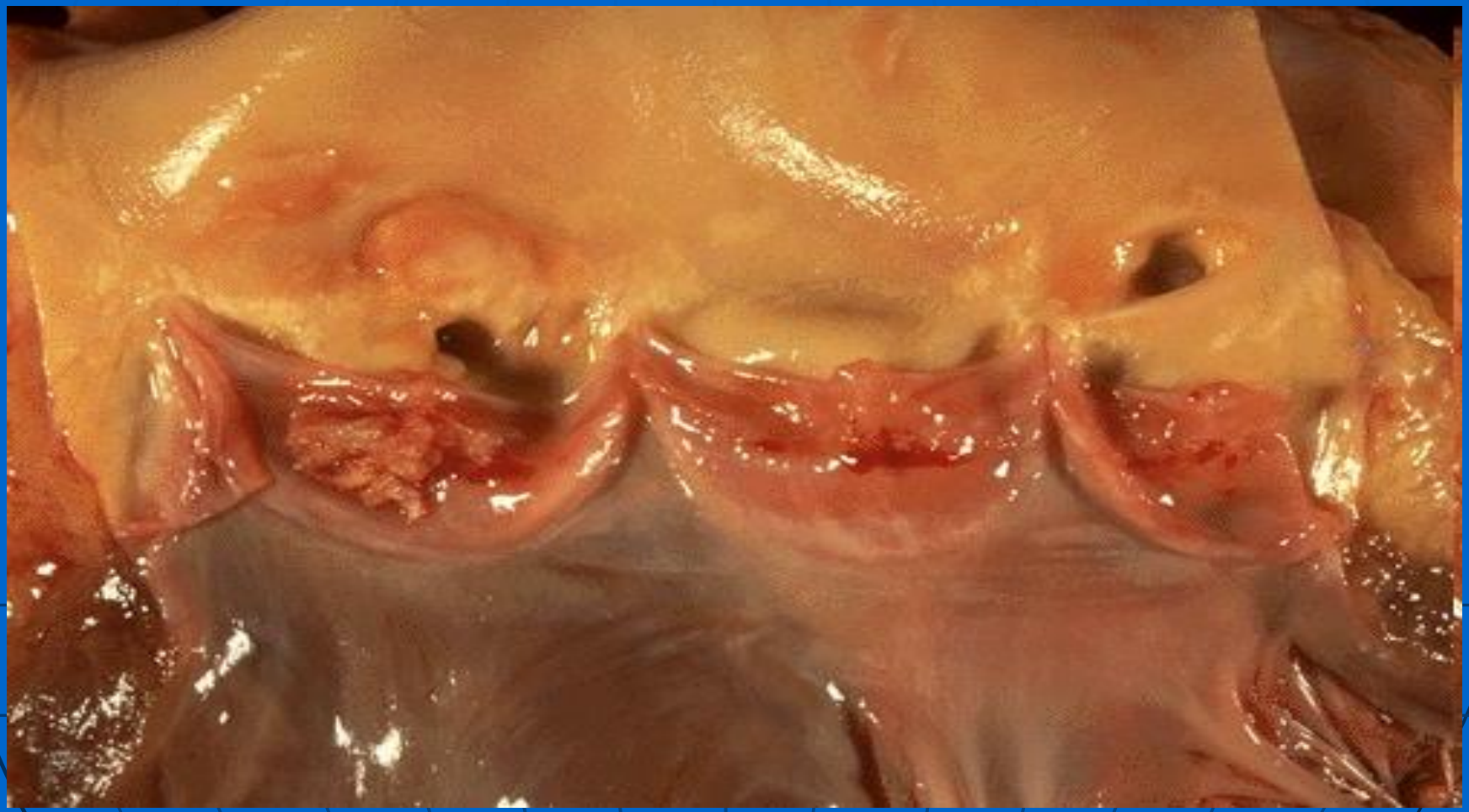
(b) Sterile, verrucous vegetations develop along the line of closure of the valve.

- Embolism is uncommon, but does occur rarely.

4 types of interconnected morphological changes in valves:

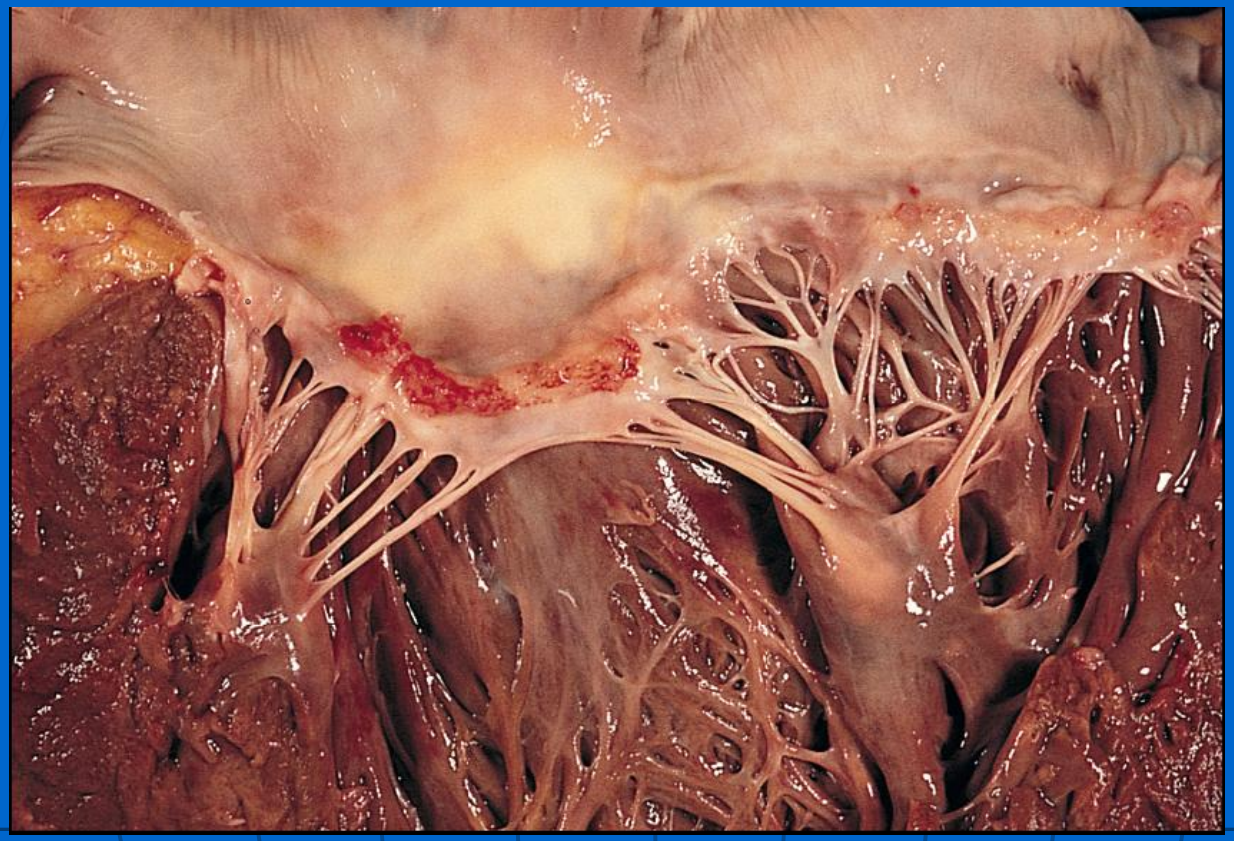
- Diffuse endocarditis (or valvulitis),
- Acute verrucous endocarditis,
- Fibroplastic endocarditis,
- Recurrent-verrucous endocarditis.

Acute verrucous endocarditis



Acute verrucous endocarditis

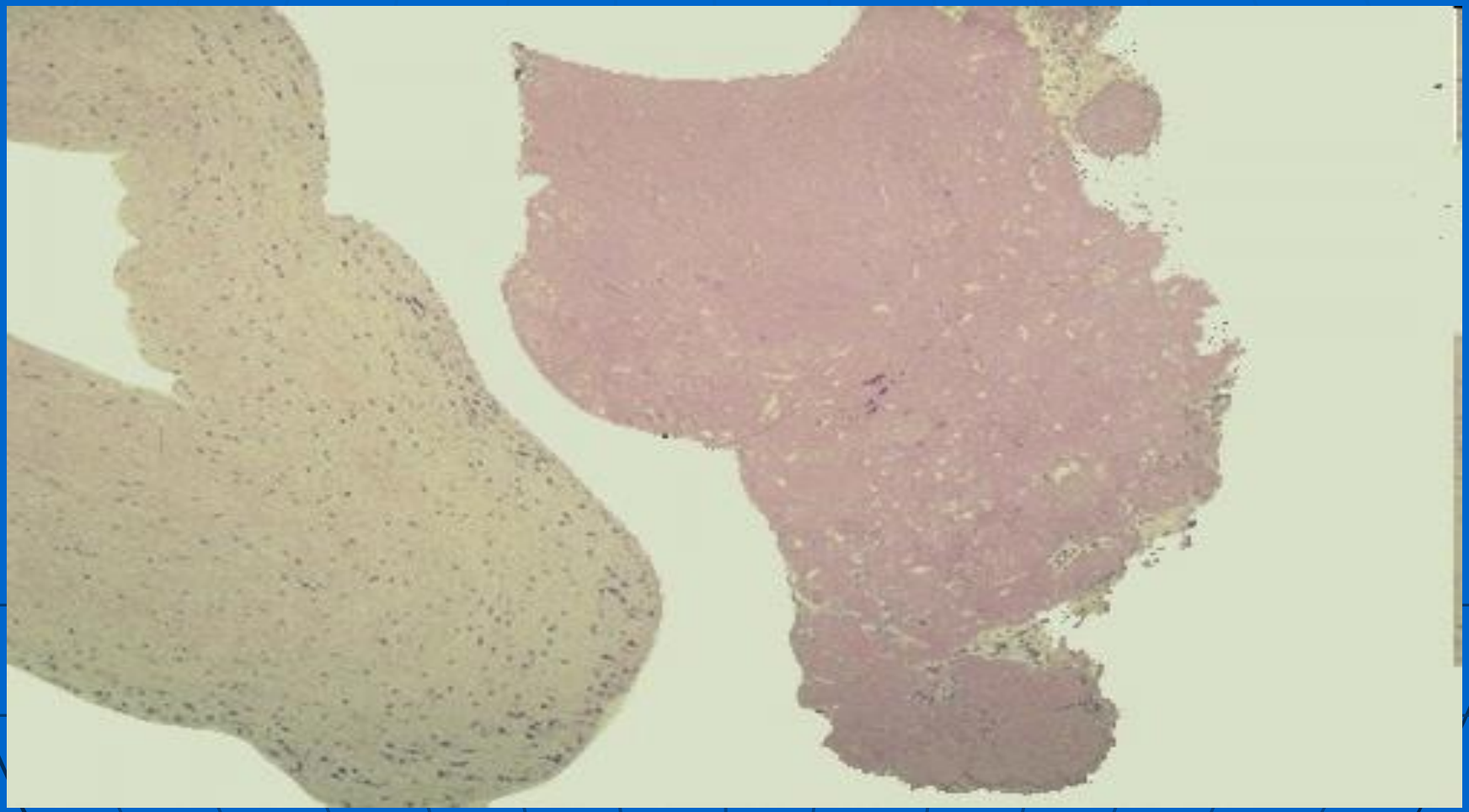
Acute verrucous endocarditis



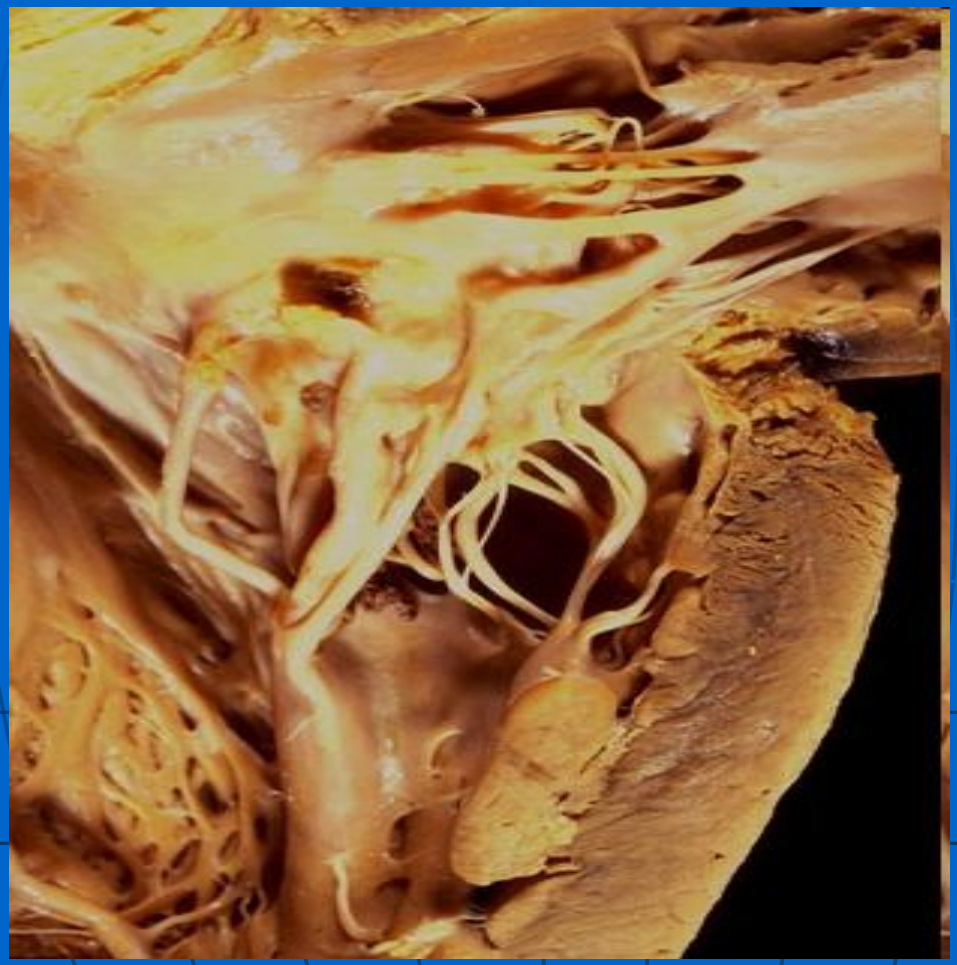
Acute rheumatic fever. Uniform, verrucous sterile vegetations appear along the line of closure of the mitral valve.

from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 13, Fig. 1-22

Acute verrucous endocarditis



Fibroplastic endocarditis



Pathogenetic chain reaction:

- Phase 1 is characterized by pharyngeal infection with b-hemolytic streptococci (group A) leading to formation of antibodies that are directed against streptococcal antigens and against endogenous tissue antigens as a result of an autoimmune cross-reaction. M protein cross-reacts with cardial myosin and sarcolemma's; hyaluronate cross-reacts with connective tissue proteoglycans.

Pathogenetic chain reaction:

- Phase 2, two weeks after the infection, involves postinfectious secondary disease in the form of acute febrile polyarthritis of the major joints (rheumatic fever), endomyocarditis, uveitis (inflammation of the vascular tunic of the eye), or acute glomerulonephritis. Rarely, the brain may be involved in the form of Sydenham chorea (rapid, purposeless contractions of individual muscle groups with grimacing).

- Clinically, involvement of the heart in acute rheumatic fever may result in chamber dilatation and conduction abnormalities.
- Chronic cardiac manifestations include fibrocalcific valvulitis (scarring and calcification of the leaflets) with shortening and fusion of the chordae tendineae.
- *Chronic scarring* of the valves constitutes the most important long-term sequela of rheumatic fever, and usually becomes clinically manifest decades after the acute process.

- The scarring of the valve leaflets converts a translucent, pliable valve into a stiff, thickened structure. The orifice becomes stenotic (narrowed). The distortion and fixation of the valve orifice has been likened to a "fishmouth" or "buttonhole". Occasionally shrinkage of valve leaflets causes mitral insufficiency.

Diagnosis (revised Jones criteria)

a. One major criterion and two minor criteria if supported by evidence of an antecedent group A streptococcal pharyngitis

b. Major criteria include:

- Carditis, migratory polyarthritis, chorea, erythema marginatum, or subcutaneous nodules

c. Minor criteria include:

(1) Previous RF or rheumatic heart disease

(2) Arthralgia (pain without joint swelling)

(3) Fever

(4) Increased acute phase reactants

(a) Increased erythrocyte sedimentation rate (ESR)

(b) Increased C-reactive protein

(c) Absolute neutrophilic leukocytosis

(5) Prolonged PR interval (first-degree heart block)

Laboratory tests

- (1) Increased antistreptolysin O (ASO) titers >400 Todd units
- (a) Titers peak at 4 to 5 weeks after a streptococcal pharyngitis.
- (b) High titers are supportive but *not diagnostic for acute RF.*
- (2) Increased anti–DNase B titers (less reliable than ASO titers)
- (3) Throat cultures possibly positive

The distribution of valve involvement is variable:

- mitral alone: about 50% of cases
- combined mitral/aortic: about 45%
- combined tricuspid and mitral or aortic: about 5-10%
- pulmonic: very rare.

Mitral valve stenosis

1. Epidemiology

a. Most commonly caused by recurrent attacks of RF

b. Twice as common in women than men

2. Pathophysiology

a. Narrowing of the MV orifice (<2.5 cm2 [normal 4–6 cm2])

b. LA becomes dilated and hypertrophied because of increased work imposed on the LA in filling the LV during diastole.

3. Clinical findings

a. Dyspnea and hemoptysis with rust-colored sputum (heart failure cells)

- Due to pulmonary capillary congestion and hemorrhage into the alveoli as blood builds up behind the LA

b. Atrial fibrillation

(1) Atrial fibrillation (irregularly irregular pulse) is a complication of LA dilation and hypertrophy.

(2) Intra-atrial thrombi in the LA develop from blood stasis.

- Systemic embolization occurs in 80% of cases when atrial fibrillation is present.

c. Pulmonary venous hypertension

(1) Due to chronic backup of LA blood in the pulmonary vein

(2) RHF and concentric RVH from the increase in afterload

d. Dysphagia for solids

(1) LA is the most posteriorly located chamber in the heart.

(2) When markedly dilated, it compresses the esophagus, causing difficulty in swallowing solid food.

Murmur of MV stenosis is an opening snap followed by an early to mid diastolic rumble

(1) LA must exert a lot of pressure to open valves that are fibrosed and calcified.

(2) Thickened valves open with a snap and blood from the LA, which should already have been emptied into the LV, gushes into the chamber and produces a diastolic rumble.

(3) Deep held inspiration for 3 to 5 seconds does *not alter the intensity of the opening* snap or middiastolic rumble.

4. Diagnosis is confirmed by echocardiography.
5. Treatment is replacement of the valve.

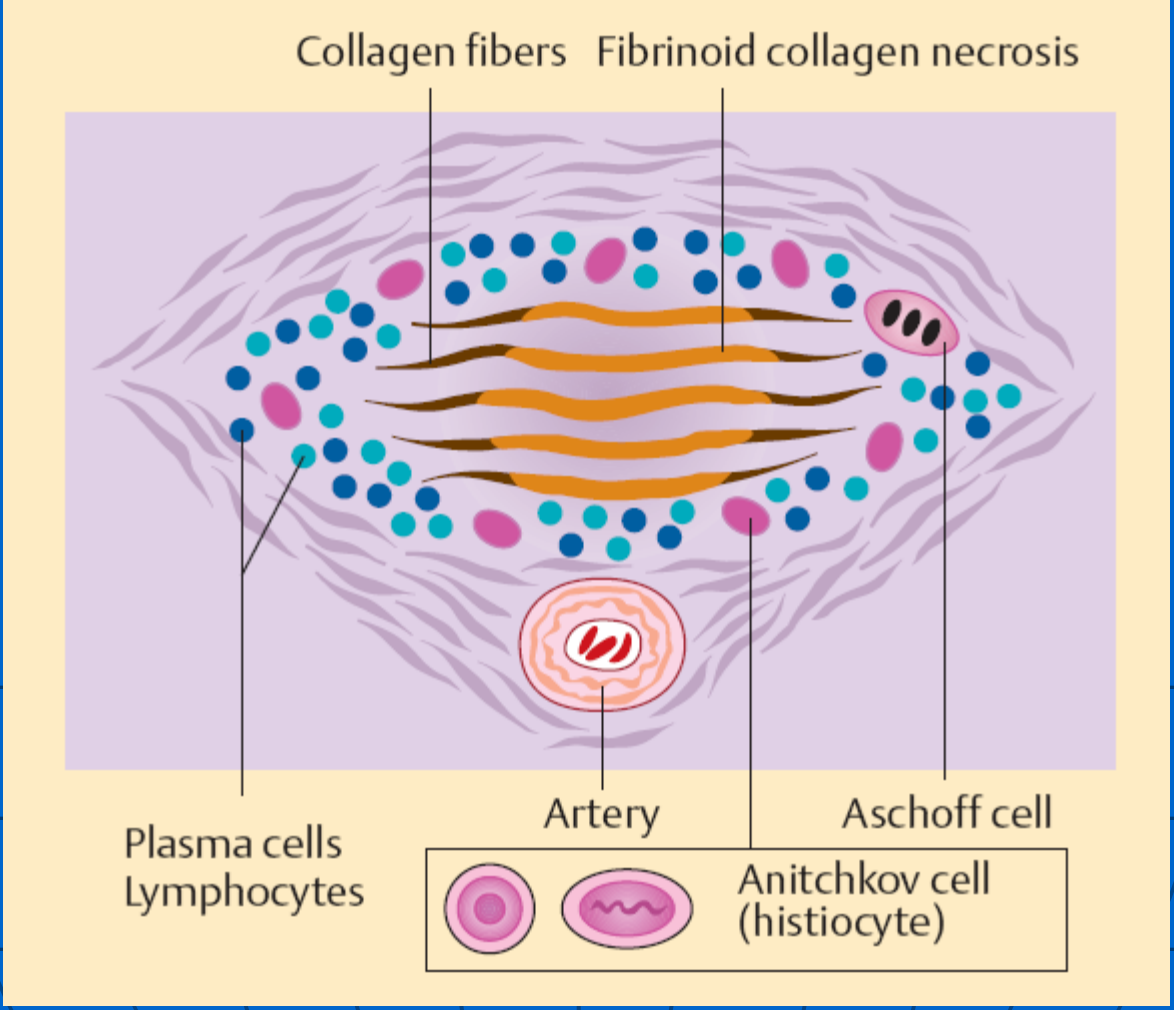
Clinical correlations

- Mitral stenosis may result in left atrial enlargement, elevated pulmonary vascular pressure, atrial fibrillation and atrial thrombosis with the danger of embolization. Aortic stenosis leads to left ventricular hypertrophy.
- The consequences of mitral insufficiency vary depending on the severity of the regurgitation. In some cases it leads to dilatation and hypertrophy of the left ventricle, and dilatation of the left atrium. Aortic insufficiency leads to left ventricular dilatation.
- Patients with chronic rheumatic valvular disease may have severe valvular compromise, and are predisposed to the complications of infectious endocarditis and thromboemboli. They may require long-term antibiotic therapy or valve surgery.

Cardiac Pathology

- The characteristic lesion of acute rheumatic fever is the Aschoff body, consisting of a focus of necrosis (representing the site of antibody-antigen reaction) surrounded by activated histiocytes and lymphocytes. The histiocytes may be mononuclear or multinuclear, and are referred to as Anitschkow's or Aschoff cells. These foci may be found in the pericardium, the myocardium, or in the valves. They ultimately "heal" by fibrosis. Valvular involvement in acute rheumatic fever includes aggregation of fibrin and platelets forming small (1-3 mm) vegetations sometimes called "verrucae" along the lines of closure of the valve leaflets.

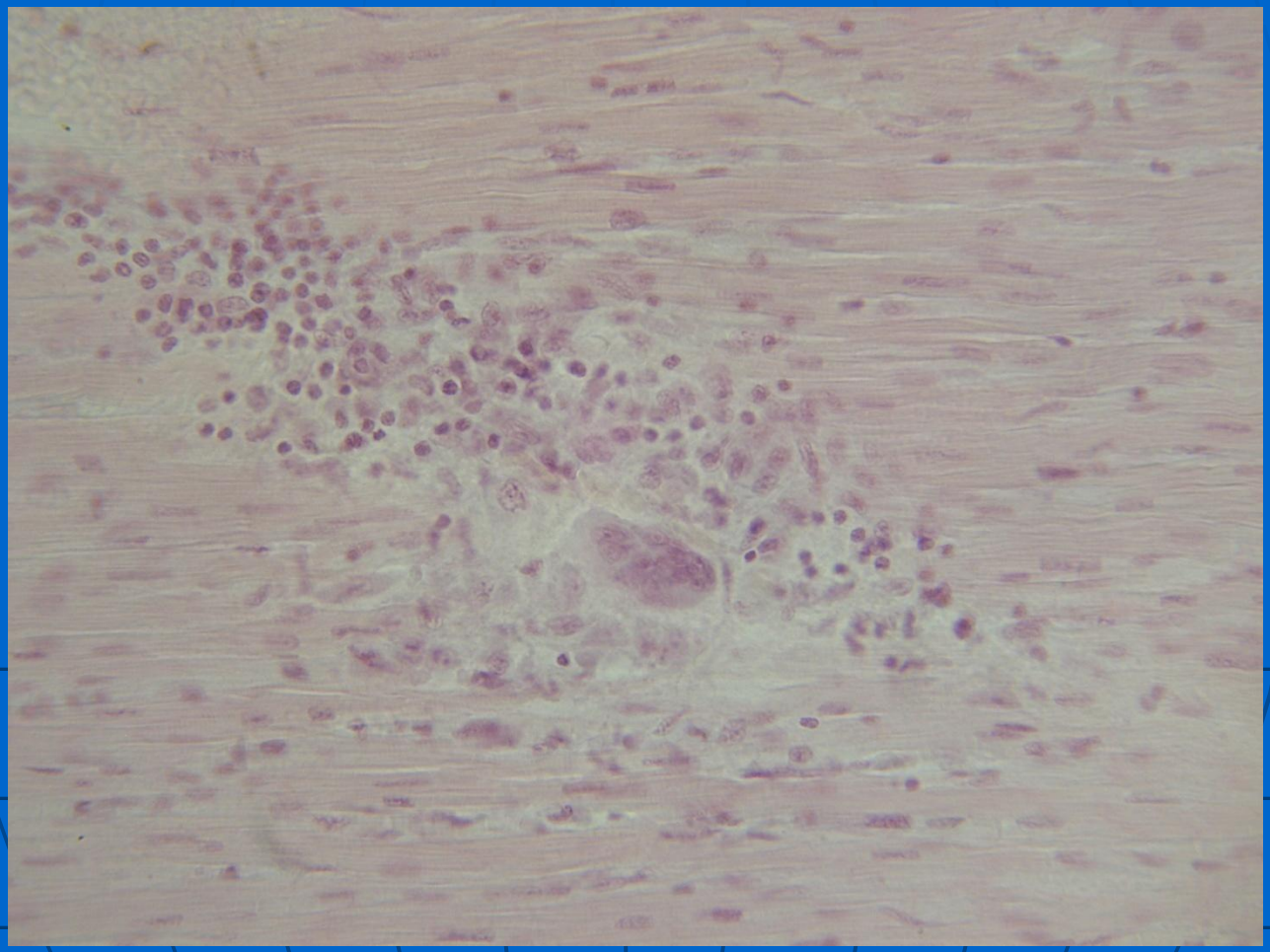
Rheumatic fever. Rheumatic granuloma.



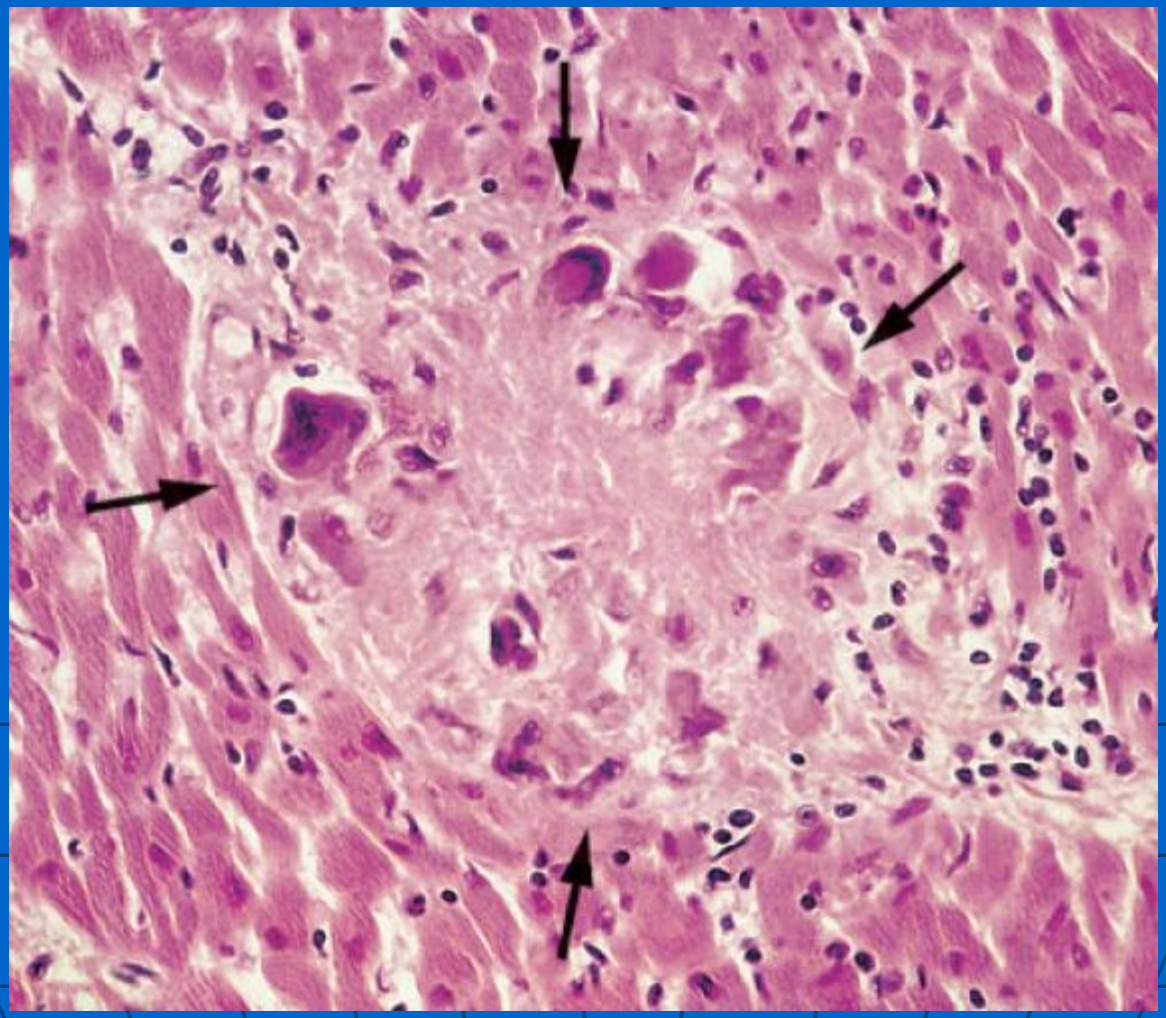
Rheumatic granuloma.

- Definition: Histiocytic granuloma around a core of fibrinoid collagen necrosis, occurring primarily in the myocardium and only with rheumatic fever (acute articular rheumatism).

Rheumatic fever. Rheumatic granuloma.



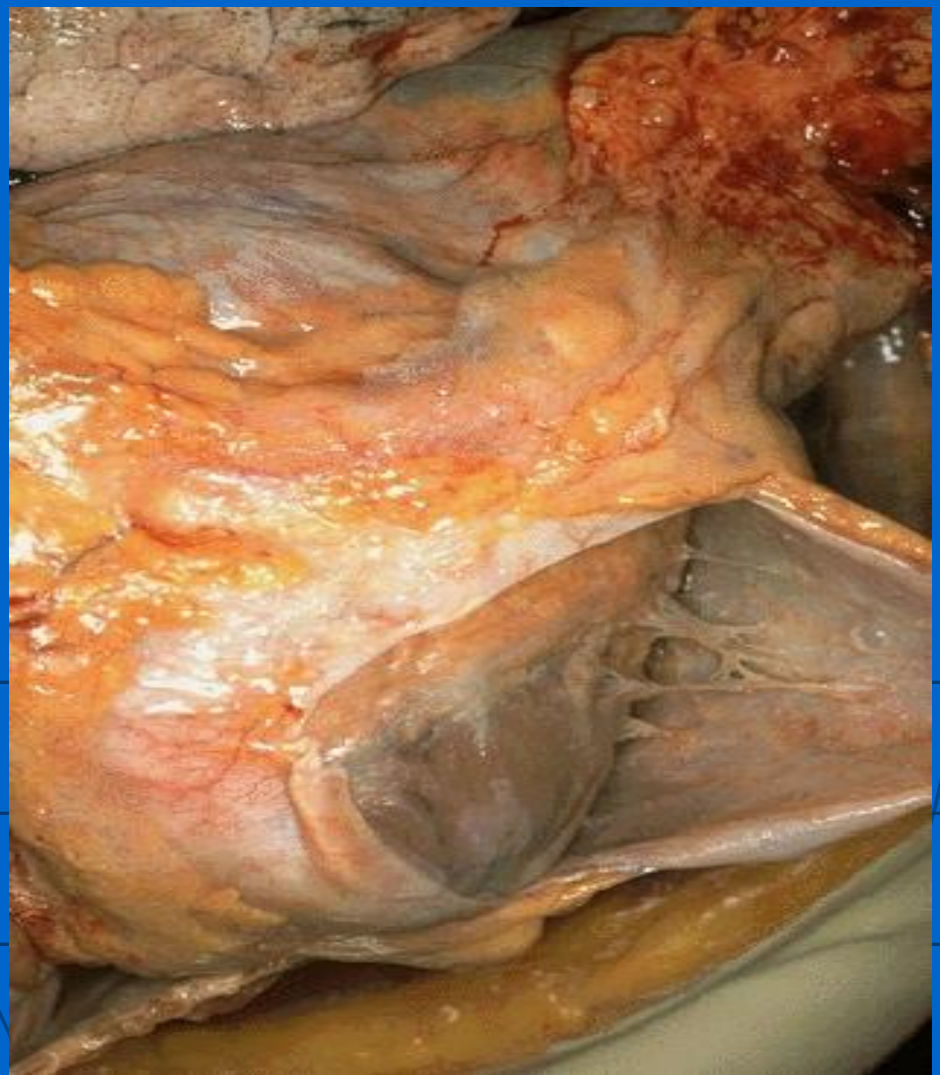
Rheumatic fever. Rheumatic granuloma.



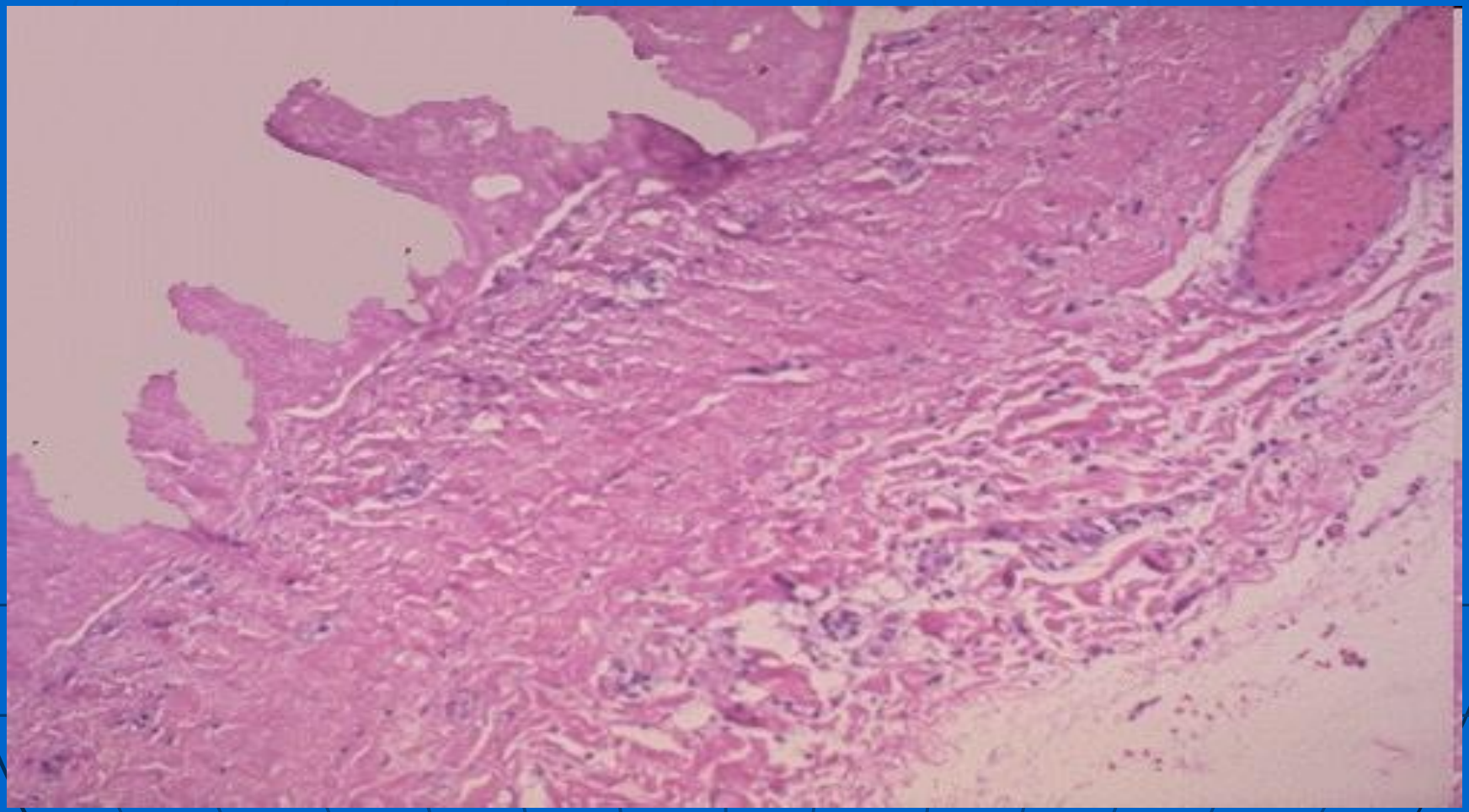
Rheumatic granuloma.

- Histology granuloma: The granuloma occurs in the myocardial interstitium primarily adjacent to minor arteries.
- **Exudative phase:** It is characterized by serofibrinous exudate, with deposits of immune precipitate on collagen fibers that lead to fibrinoid necrosis.
- **Granulomatous phase:** The fibrinoid necrosis is demarcated by specialized histiocytes and a sparse lymphocytic infiltrate with isolated granulocytes and, rarely, inflammatory giant cells (Aschoff cells). The specialized histiocytes or Anitchkov cells resemble epithelioid cells. Their elongated oval nuclei exhibit a flattened bottlebrush like chromatin structure. The morphology changes according to the orientation of the imaging plane. Their cross section resembles a caterpillar; their longitudinal section resembles an owl's eye.
- **Scarring phase:** It is characterized by tissue repair with a spindle-shaped pattern of perivascular scarring (finely nodular fibrosis). Recurrence of the inflammation leads to recurrence of the granuloma.

Acute rheumatic pericarditis



Acute rheumatic pericarditis



Valvular Disease - Endocarditis

- **Endocarditis:**
- **Infective and**
- **Nonbacterial Thrombotic**

Infective Endocarditis (Bacterial Endocarditis)

- This is an acute or subacute inflammatory disease leading to the accumulation of infected thrombotic material ("vegetations") on valves or adjacent endocardium.
- The acute form is usually a rapidly progressive process (days to weeks), due to a highly virulent organism, affecting a previously normal valve, and carrying a poor prognosis.
- The subacute form is more indolent (weeks to months), is caused by an organism of low virulence, and usually affects an abnormal valve.

Etiology:

Acute:

- Staph. aureus 50%
- Streptococci 35%
- other, including fungi 15%

Subacute:

- Strep. viridans 50%
- other Streptococci 15%
- Gram negative bacilli 10%
- other, including fungi 25%

Predisposing factors

- Damaged or congenitally abnormal valves, or valve prostheses. Normal valves can also be affected (especially in the acute form).

Important predisposing conditions include:

- valves damaged by rheumatic carditis
- mitral valve prolapse
- congenital cardiac abnormalities
- atherosclerotic valve disease
- previous cardiac surgery
- prosthetic valves
- intravenous drug addiction
- immunosuppression or immunodeficiency.

Pathogenesis

- The classic initiating event is *transient bacteremia* of S. viridans following dental or oral procedures. Abnormal valves may be prone to the development of sterile thrombi on the endocardial surface. With bacteremia, the thrombus may be colonized, and a fibrinous, bacteria-laden vegetation accumulates on the valve because of altered dynamics of blood flow (less commonly on the endocardium at a congenital septal defect). Any situation in which bacteremia or fungemia occurs may be complicated by the development of endocarditis (e.g. intravenous drug abuse, indwelling catheters, systemic infections, etc.).
- Any valve may be affected, but mitral and/or aortic lesions comprise 75% of the cases. In intravenous drug addicts, the incidence of right-sided lesions is increased.

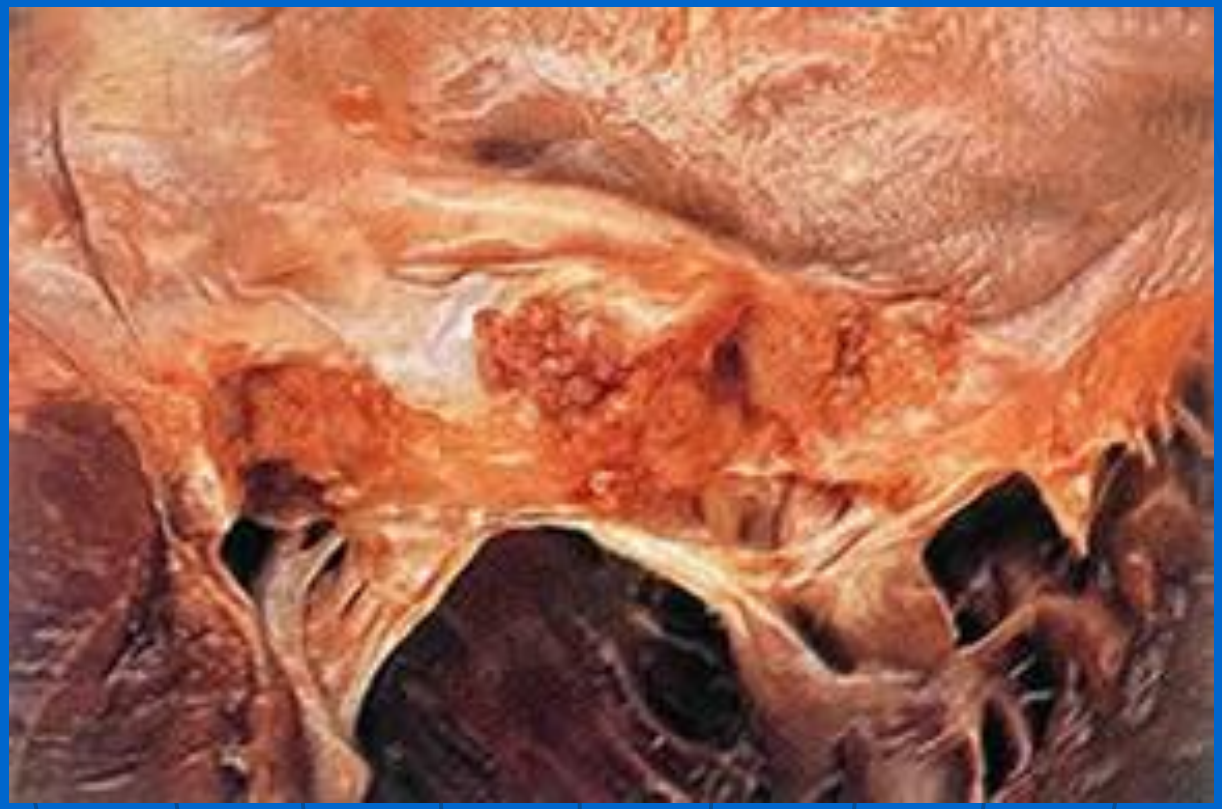
Clinical Manifestations

- fever
- petechiae, splinter hemorrhages
- cardiac murmur (may vary with enlargement or disintegration of the vegetation, or with cusp perforation)
- positive blood culture

Pathology

- Large, friable, infected vegetations composed of fibrin, platelets, and the infecting organisms. In general, the vegetations of acute endocarditis are bulkier than those of the subacute form.
- The gross vegetations may break off to form emboli which, being infected, cause septic infarcts. Erosion or perforation of valve cusps or chordae may cause rapid cardiac decompensation.

Bacterial endocarditis:



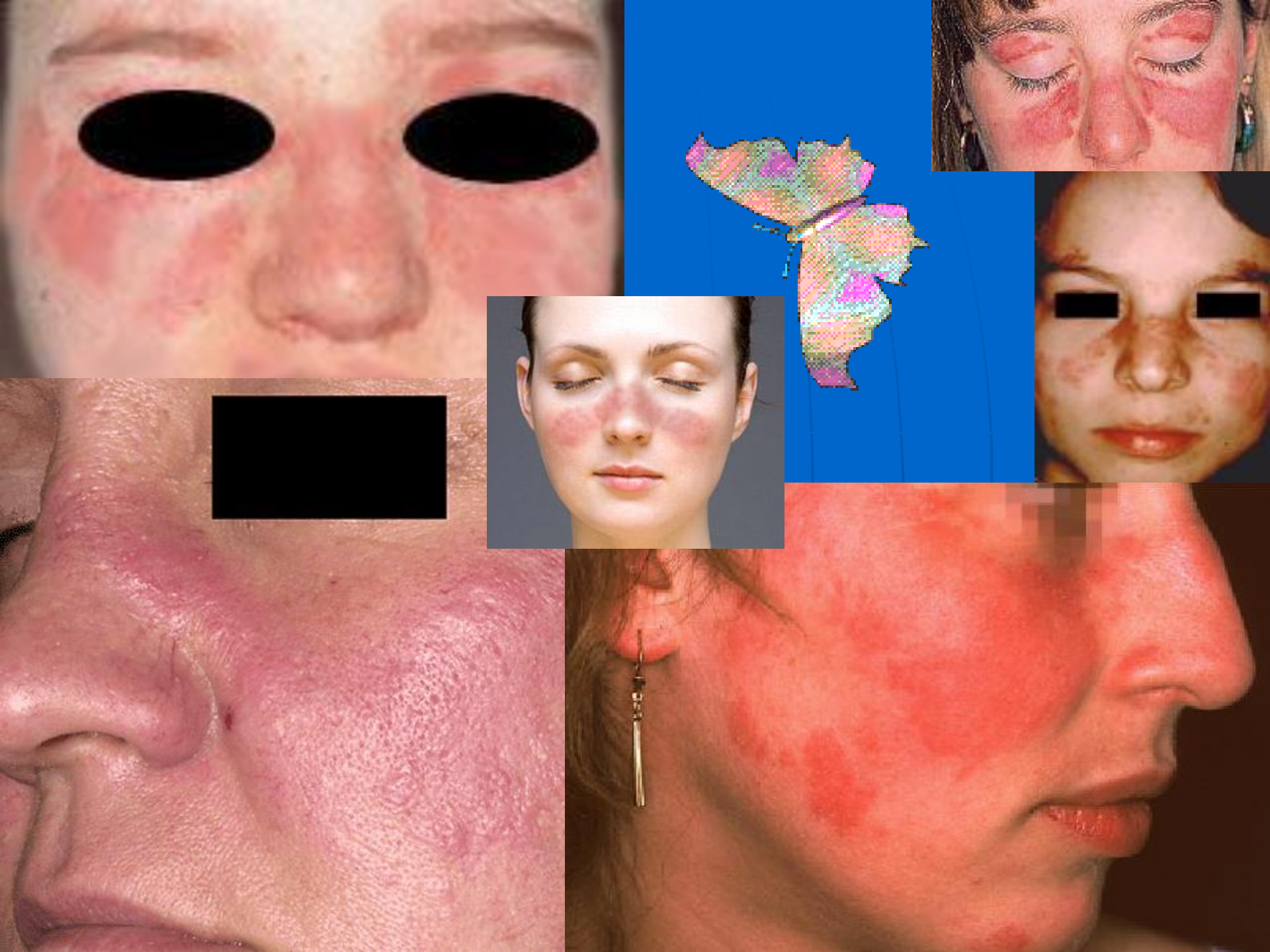
- The heart is opened to visualize the mitral valve. There are warty excrescences on the surface of the mitral valve which, are called vegetations. These vegetations lie along the edge of the cusp (valve). They consist of fibrin, necrotic cells. Occasionally, organisms (bacteria, fungi, etc.) can be found. These vegetations are friable, where they can break off (embolize) and travel to distant sites.

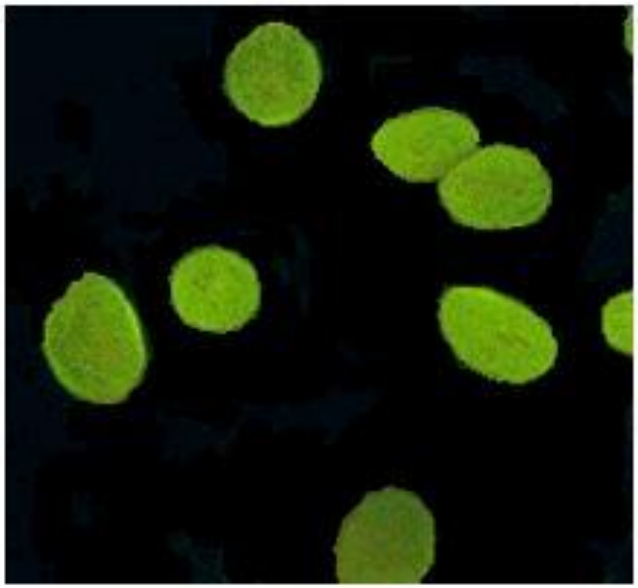
Complications

- embolization (and infarcts)
- perforation of valve cusps
- rupture of chordae
- sepsis
- arrhythmia
- dehiscence of prosthetic valve
- valve ring or myocardial abscess
- deposition of circulating immune complexes in the kidney may result in diffuse glomerulonephritis.

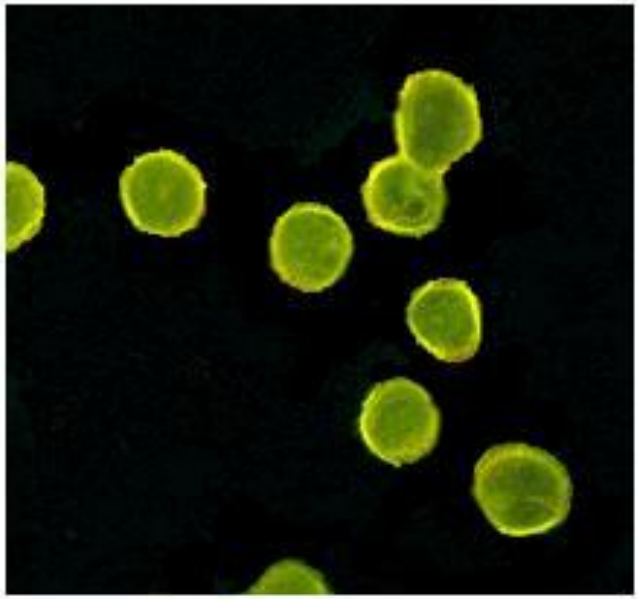
LUPUS (SLE)

- **Etiology:** Antibodies (ABs) directed against the patient's own DNA, HISTONES, NON-histone RNA, and NUCLEOLUS
- **Pathogenesis:** Progressive DEPOSITION and INFLAMMATION to immune deposits, in skin, joints, kidneys, vessels, heart, CNS
- **Morphology:** "Butterfly" rash, skin deposits, glomerolunephritis (NOT discoid)
- **Clinical expression:** Progressive renal and vascular disease, POSITIVE A.N.A.

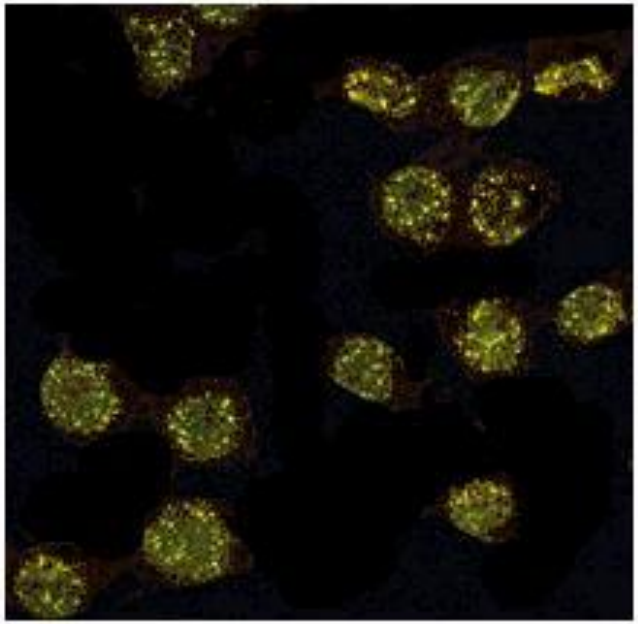




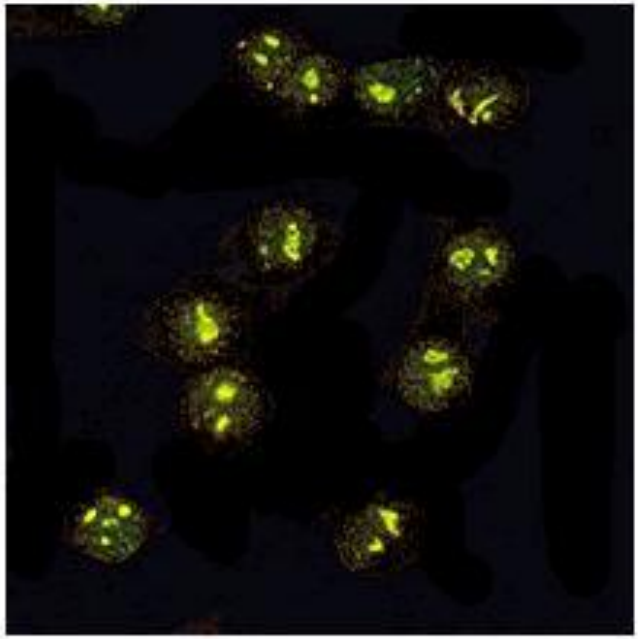
Homogenous pattern



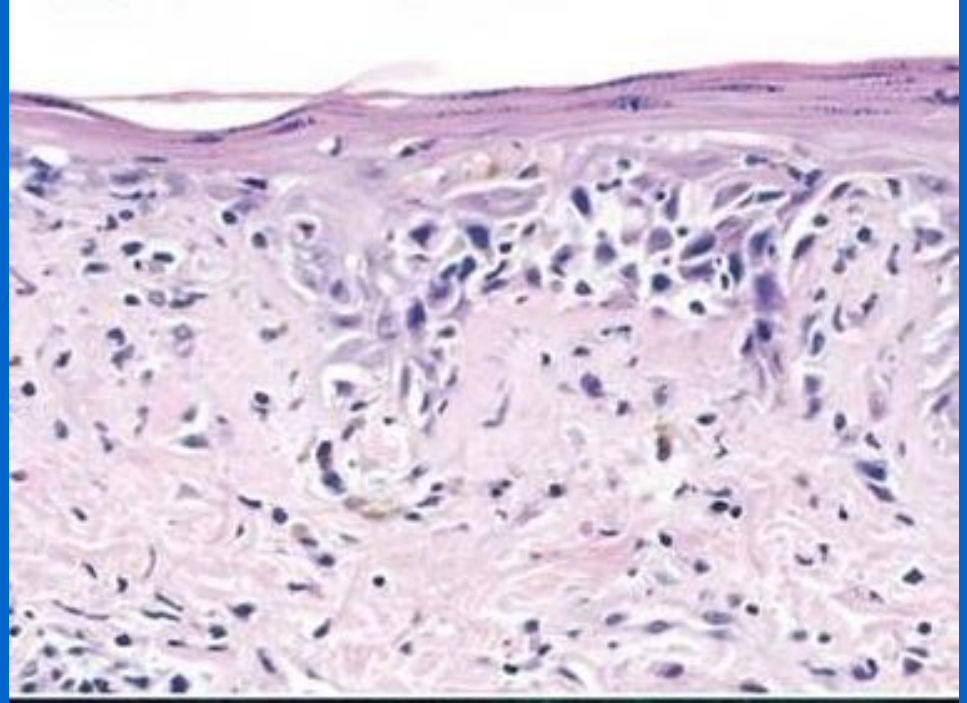
Rim pattern

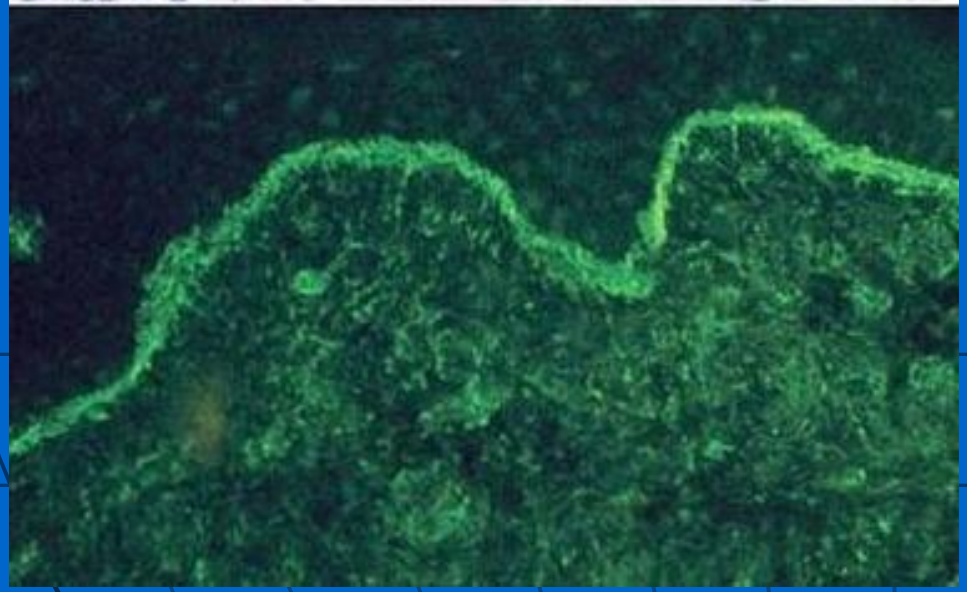


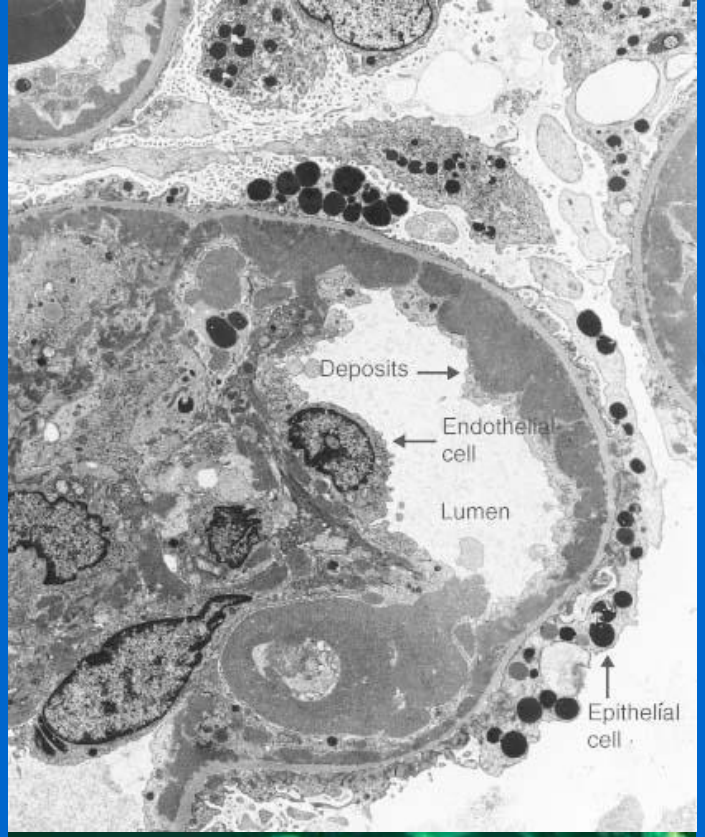
Speckled pattern

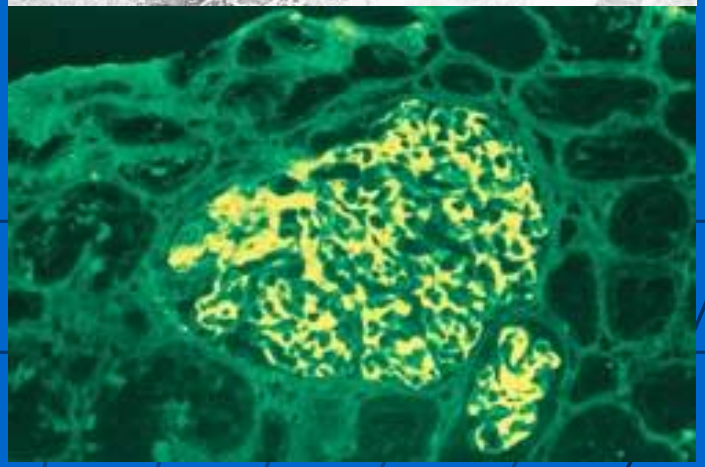


Nucleolar pattern









SLE, SKIN **LE, GLOMERULUS**

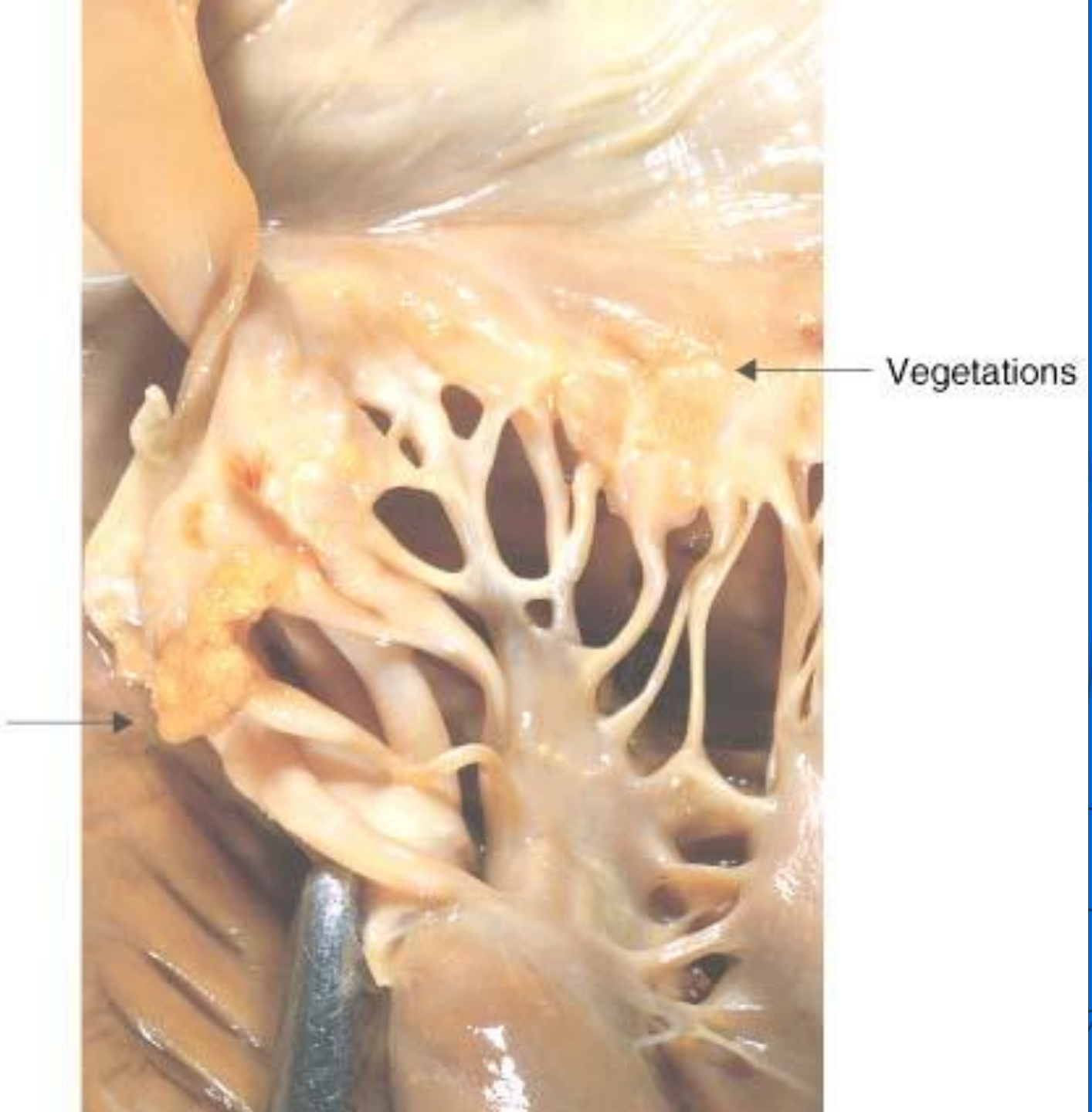

Vegetations

TABLE 6-10 -- Clinical and Pathologic Manifestations of Systemic Lupus Erythematosus

Clinical Manifestation	Prevalence in Patients, %
Hematologic	100
Arthritis	90
Skin	85
Fever	83
Fatigue	81
Weight loss	63
Renal	50
Central nervous system	50
Pleuritis	46
Myalgia	33
Pericarditis	25
Gastrointestinal	21
Raynaud phenomenon	20
Ocular	15
Peripheral neuropathy	14

RHEUMATOID ARTHRITIS

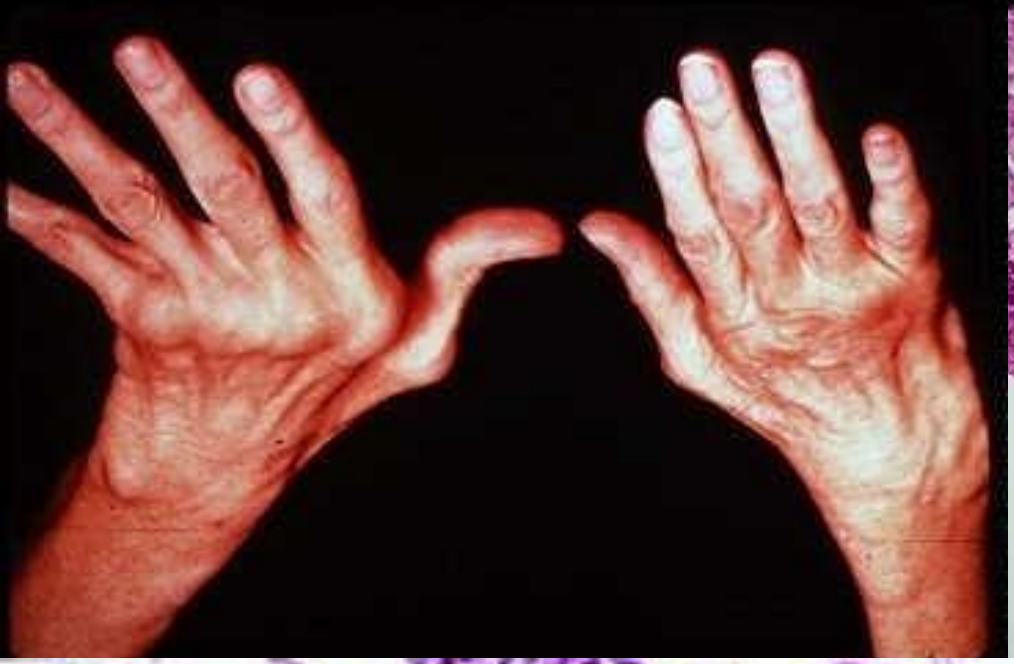
- Rheumatoid arthritis is a chronic autoimmune disease, its basis is systemic disorganization of the connective tissue with progressive damage to mainly peripheral joints, the development of productive synovitis in them, destruction of the articular cartilage with subsequent deformity and ankylosis of the joints.
- Epidemiology. The prevalence of rheumatoid arthritis among the adult population is 0.6–1.3%. The incidence among women is about 3 times higher than among men. With age, the risk of developing rheumatoid arthritis increases.

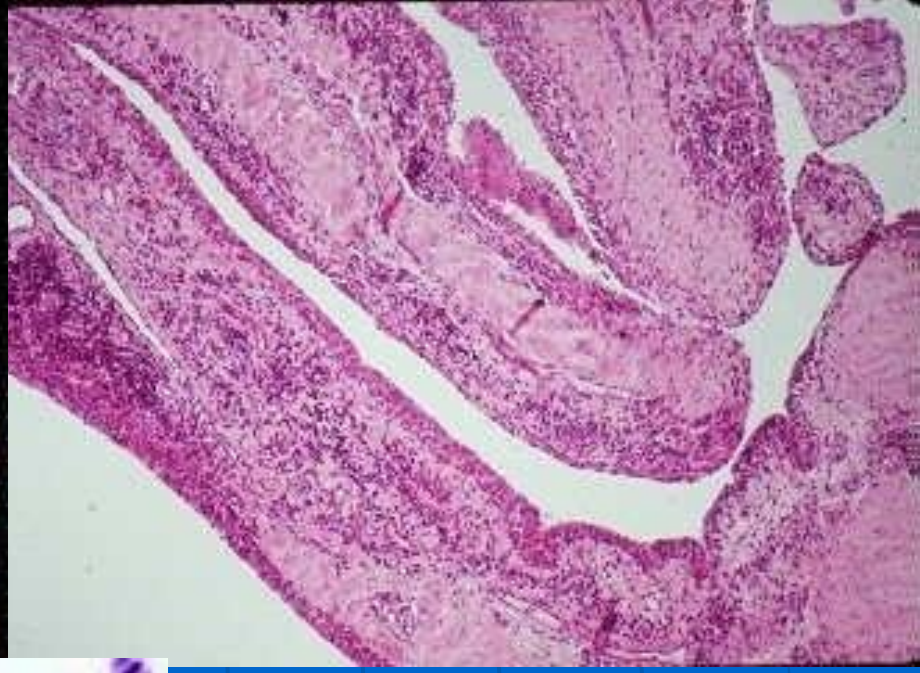
The main manifestations of rheumatoid arthritis.

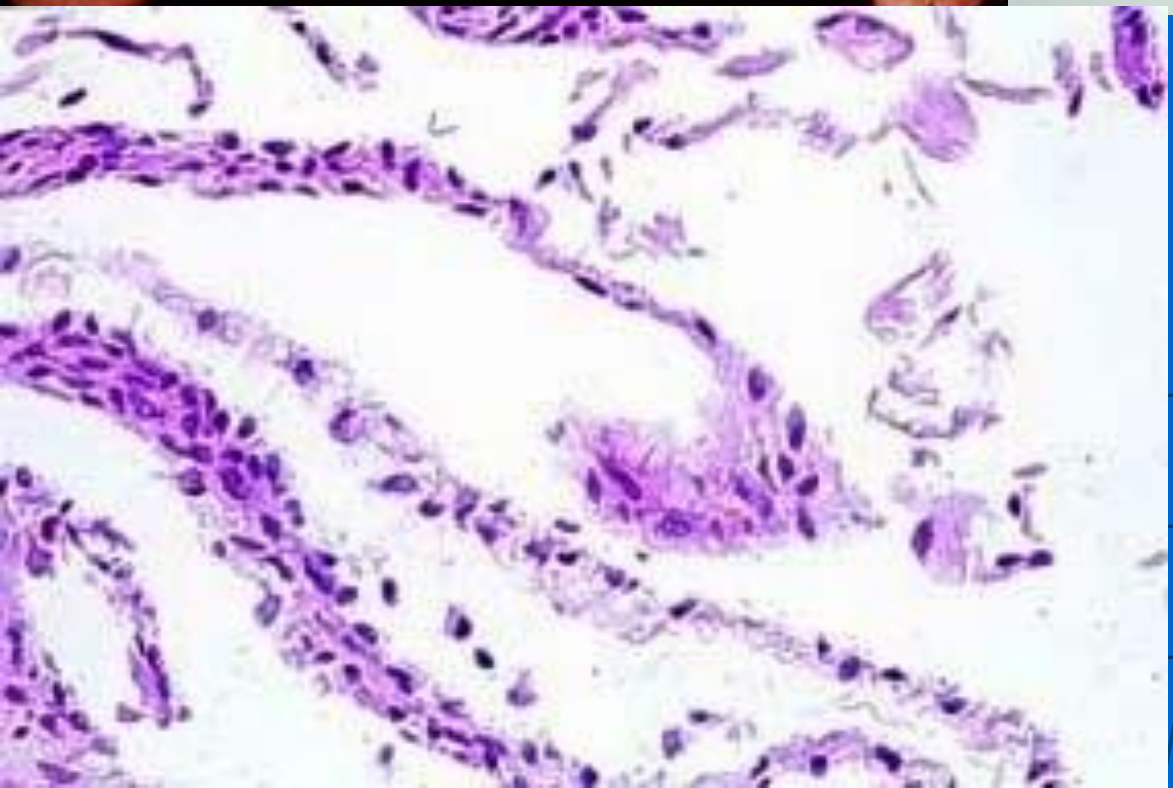
- • Joint damage: arthritis and ankylosis.
- • Inflammatory lesions of periarticular tissues: tendosynovitis, bursitis, synovial cyst around the joint, amyotrophy, damage to the ligaments with the development of hypermobility and deformities, myositis, etc.
- • Systemic manifestations: rheumatoid nodules, ulcers on the skin of the legs, eye, heart, lung, kidney, neuropathy, vasculitis, anemia.
- Morphogenesis. The main morphological changes in rheumatoid arthritis are found in the joints and in the entire connective tissue.

Joint damage:

- hyperplasia and fibrinoid changes in the synovial membranes of the villi with their rejection into the articular cavity;
- proliferation of synoviocytes;
- productive vasculitis in the synovial membrane;
- perivascular stromal infiltration with the formation of lymphoid aggregates consisting of CD4+ T-lymphocytes, as well as plasma cells and macrophages;
- the formation in the articular cavity of serous fluid with neutrophils;
- formation of pannus - a layer of granulation tissue with inflammatory infiltration, which destroys and replaces articular cartilage;
- increased osteoclasia, especially in the area of the subchondral plate and in the place of attachment of the articular capsule with the formation of subchondral cysts, osteoporosis of the articular ends of bones
- development of fibrous and bone ankylosis.

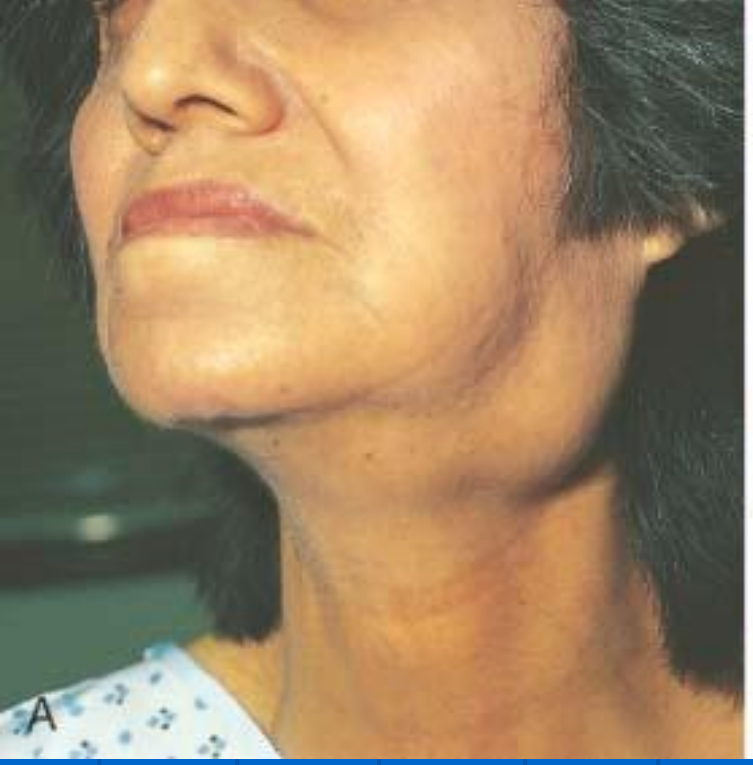


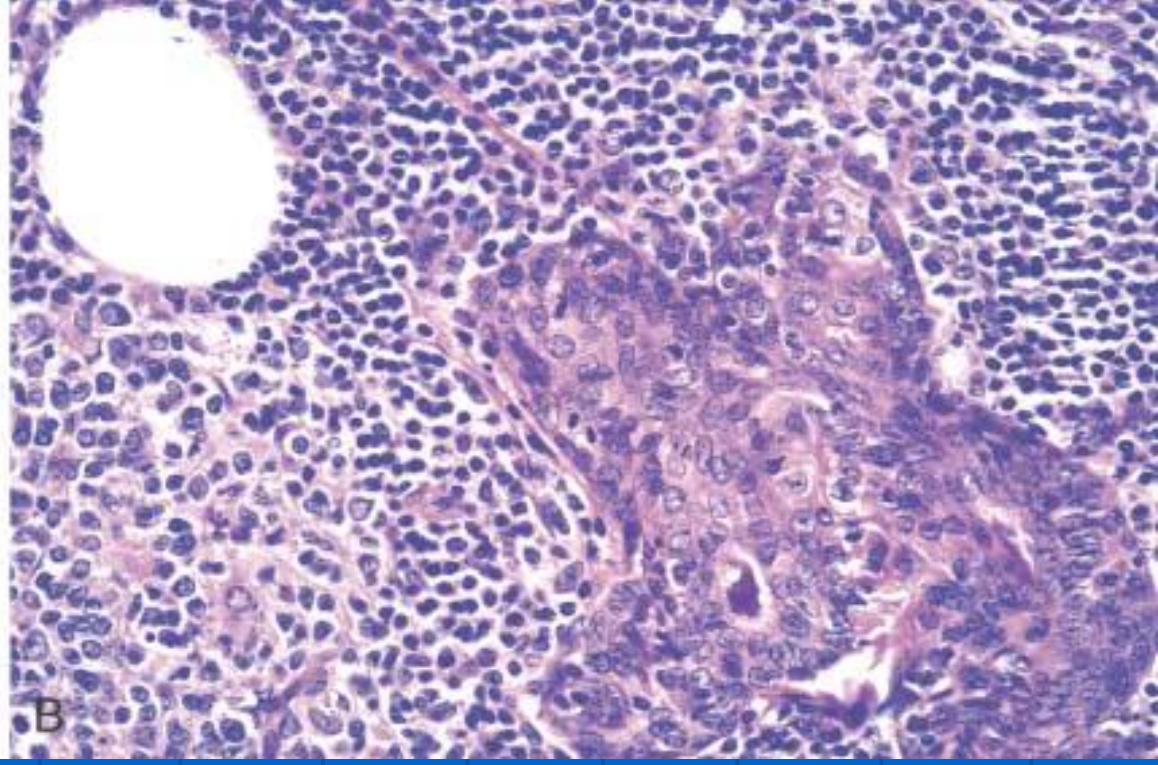




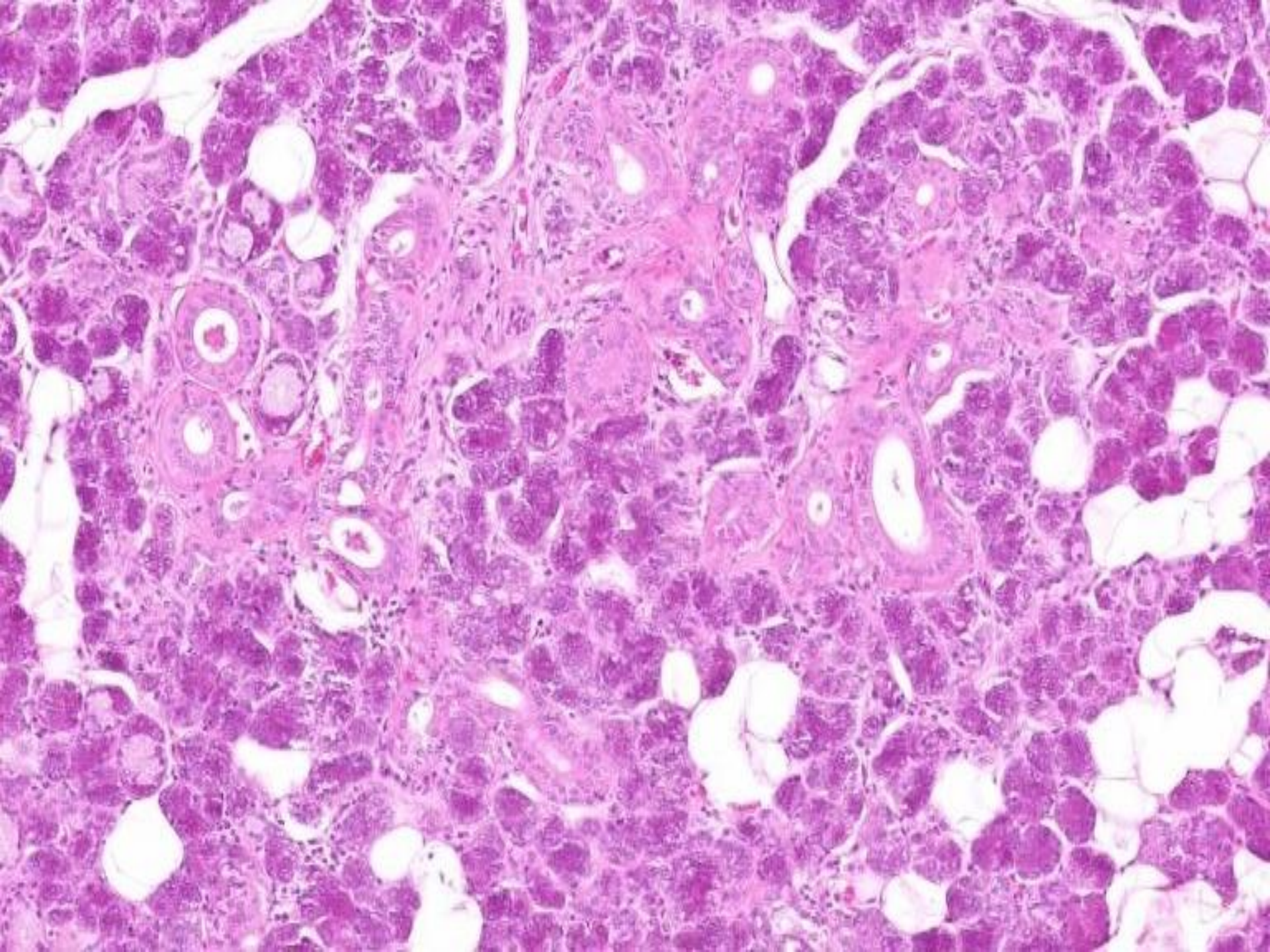
Destructive Rheumatoid Synovitis

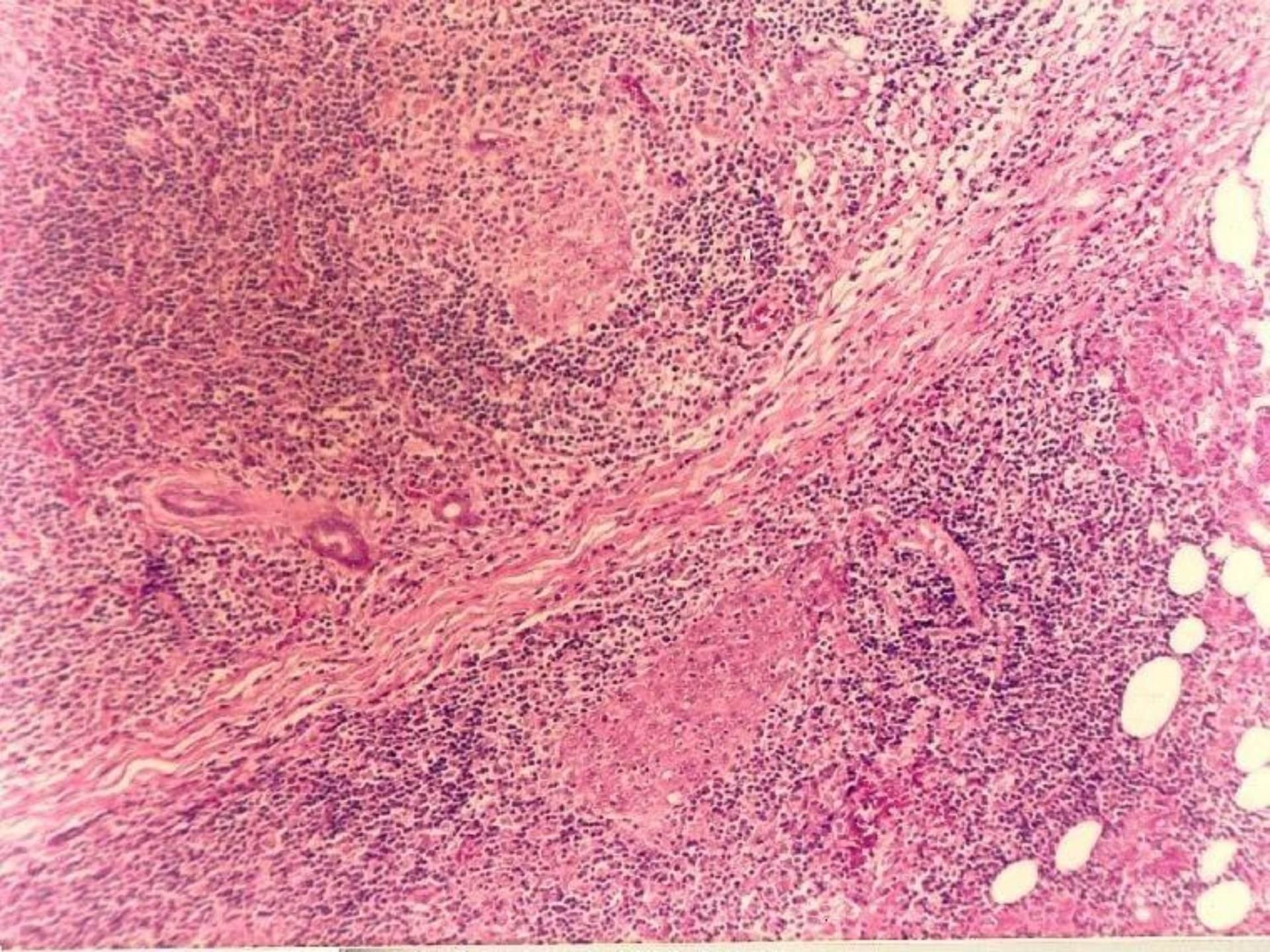
←**NORMAL** Bi-Layered Synovium

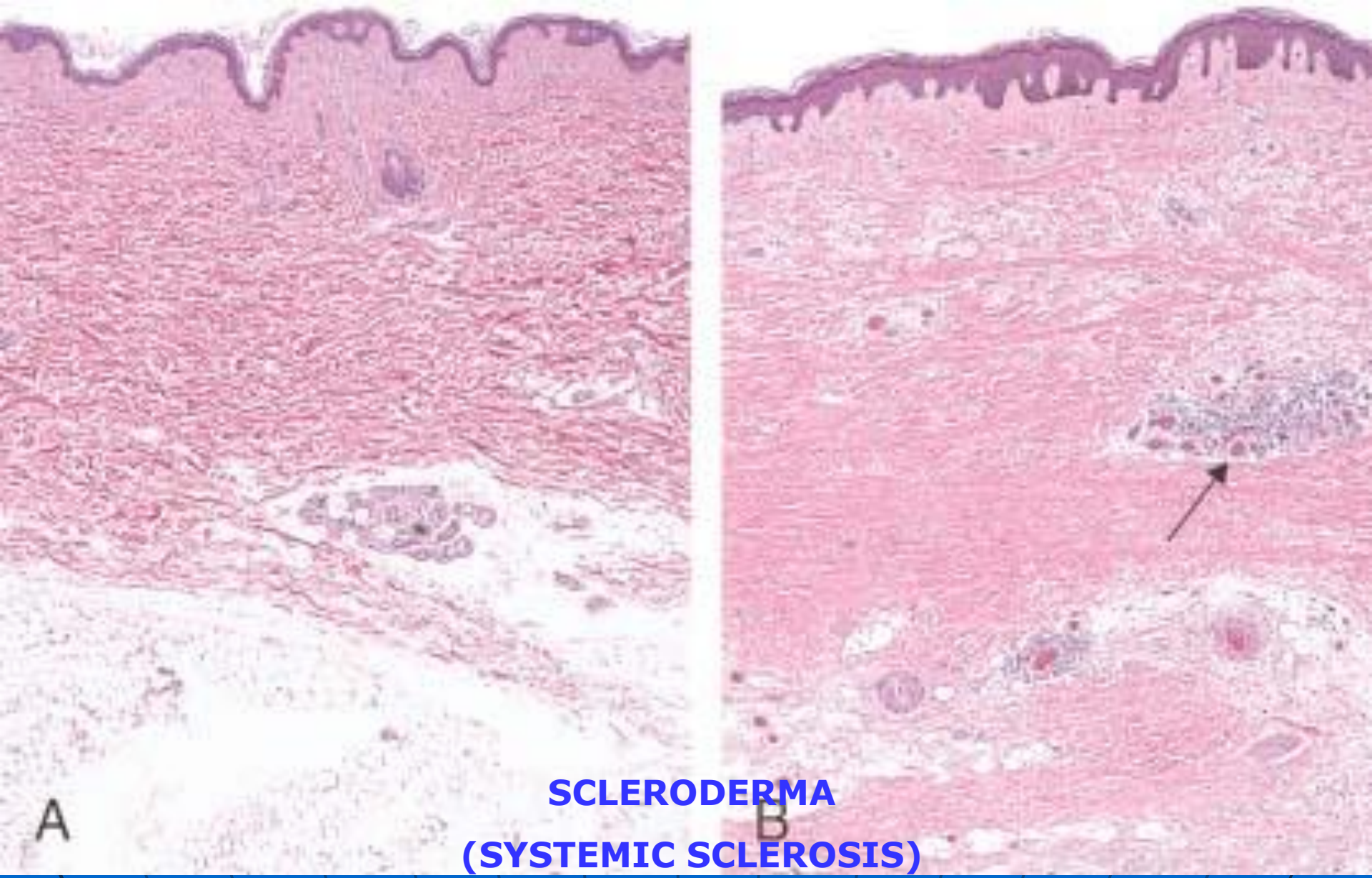




SJÖGREN SYNDROME







SCLERODERMA

(SYSTEMIC SCLEROSIS)

SYSTEMIC SCLEROSIS

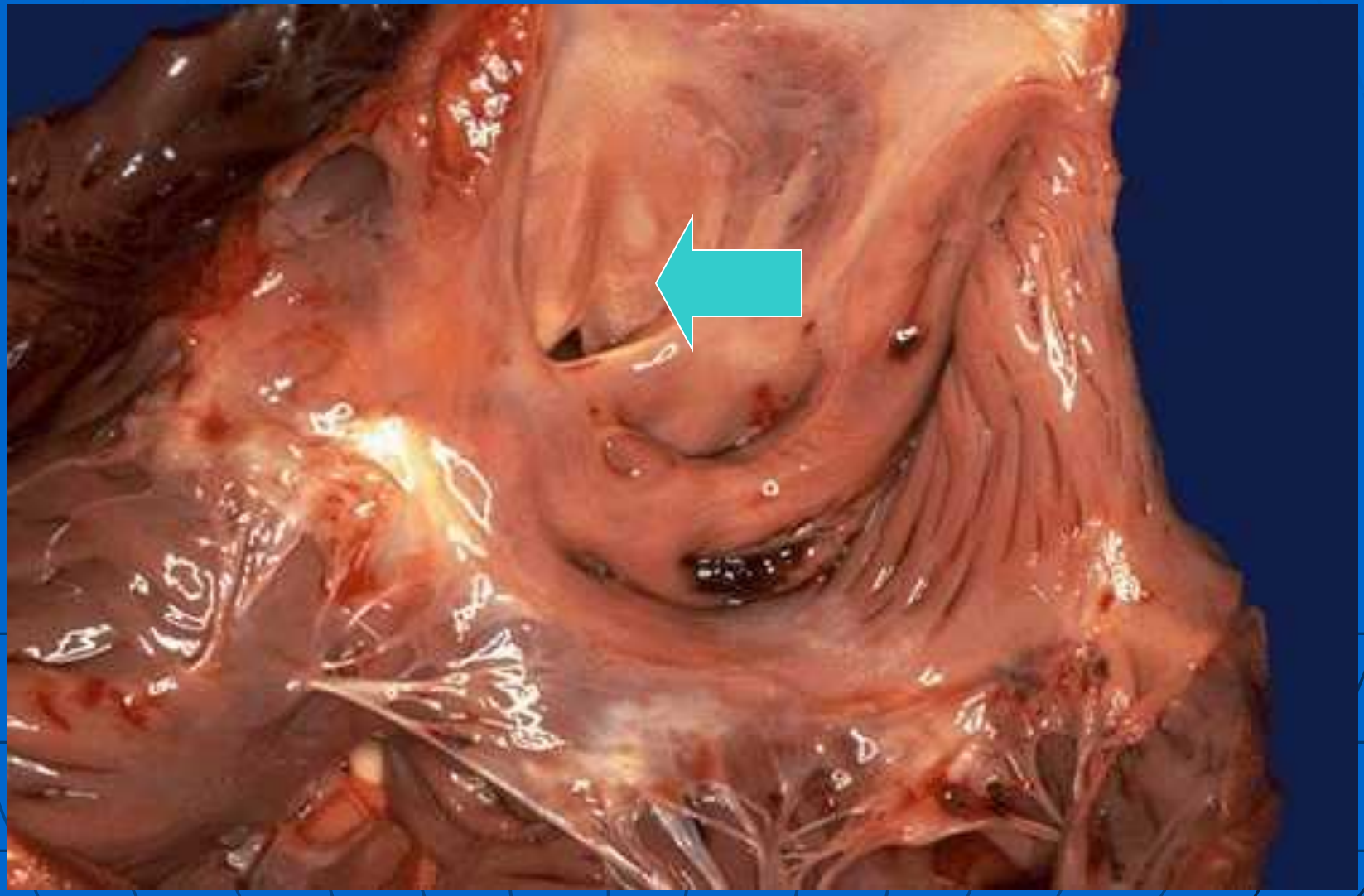
(SCLERODERMA)

Congenital Heart Diseases

Congenital Heart Diseases:

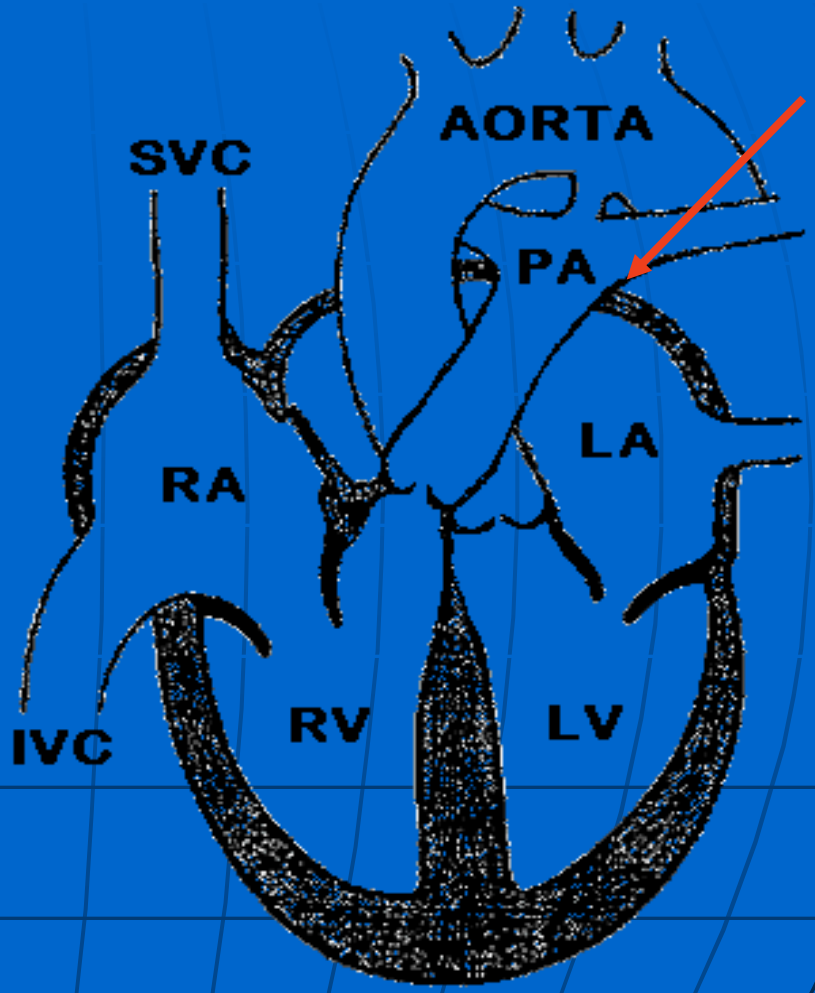
- **Left-to-Right shunts.**
  - Atrial Septal Defect (ASD)
  - Ventricular Septal Defect (VSD)
  - Patent Ductus Arteriosus (PDA)
- **Right-to-Left shunts**
  - Transposition of Great Arteries
- **Obstructions**
  - Coarctation of Aorta
- **Others.**

Atrial Septal Defect (ASD)

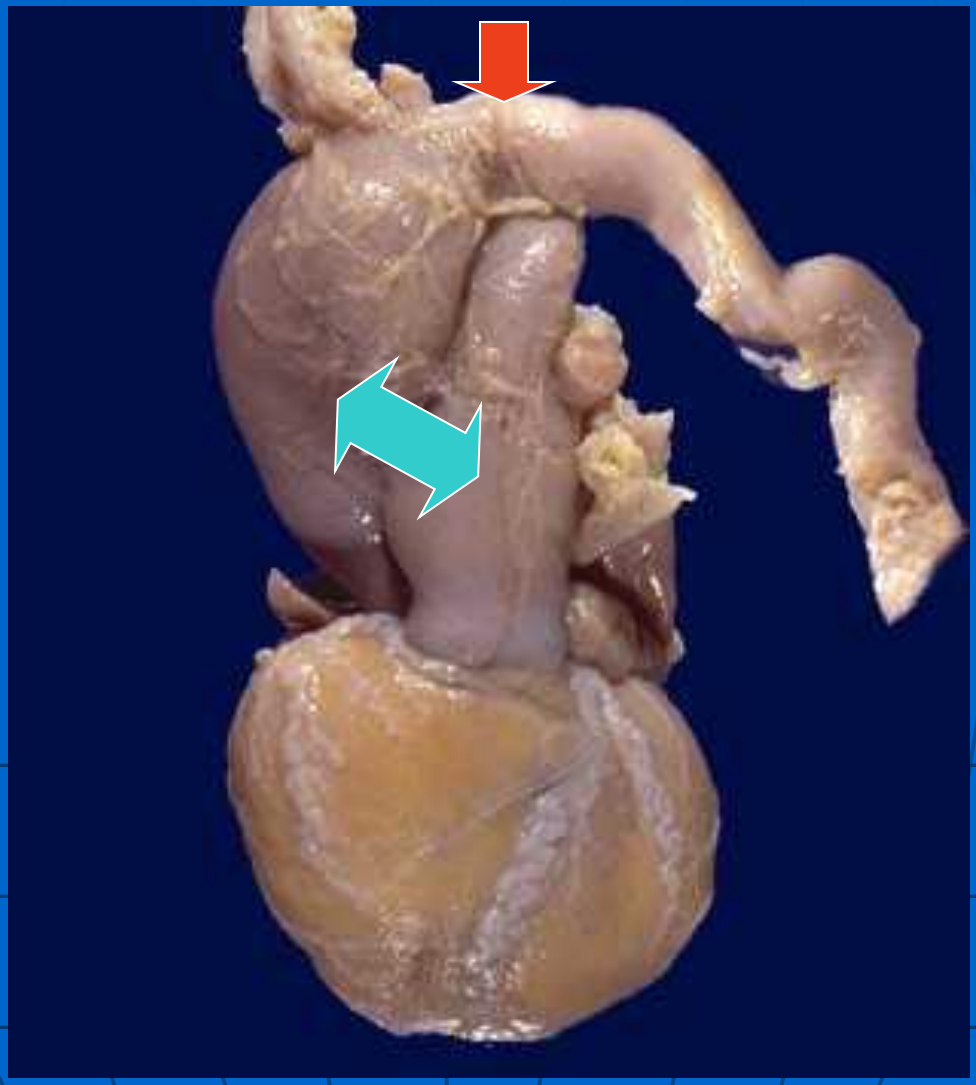


Patent Ductus Arteriosus (PDA)

- The ductus arteriosus, serves to shunt blood from pulmonary artery to aorta during intrauterine life. Persistence of ductus, which normally closes soon after birth, results in left-to-right shunt.



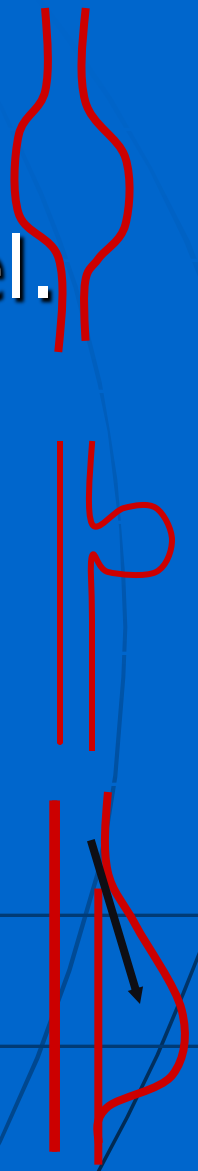
Coarctation of Aorta - Infant



Aneurysms & Varicose Veins

Aneurysms:

- Abnormal dilatation of blood vessel.
- Fusiform, Saccular & dissecting.
- Atherosclerosis, Syphilitic & congenital.
- Berry aneurysms – Base of brain.
- Complications:
  - Thrombosis
  - Embolism
  - Rupture



Berry Aneurysm:

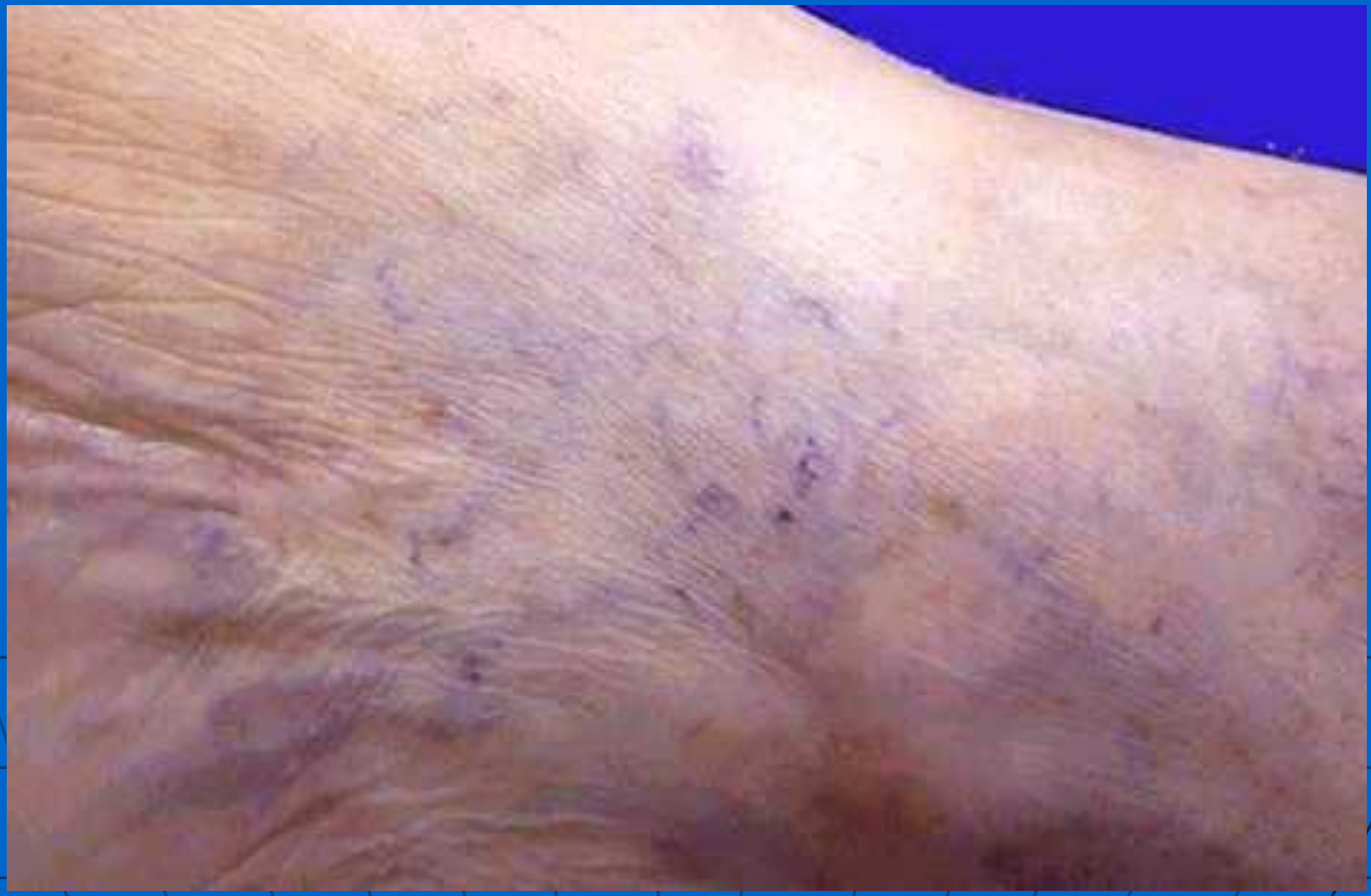
Complications of Aneurysms:

- Thrombosis
- Embolism
- Rupture

Varicose Veins:

- Abnormal diffuse dilatation of veins.
- Lower limbs- common
- Congenital or acquired
- Pathogenesis:
  - Damage to valves
  - Stagnation
  - Increased pressure → dilatation.
- Chronic ulcers.

Varicose Veins:



Thank You…