PATHOLOGY LAB -1

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Mutah University
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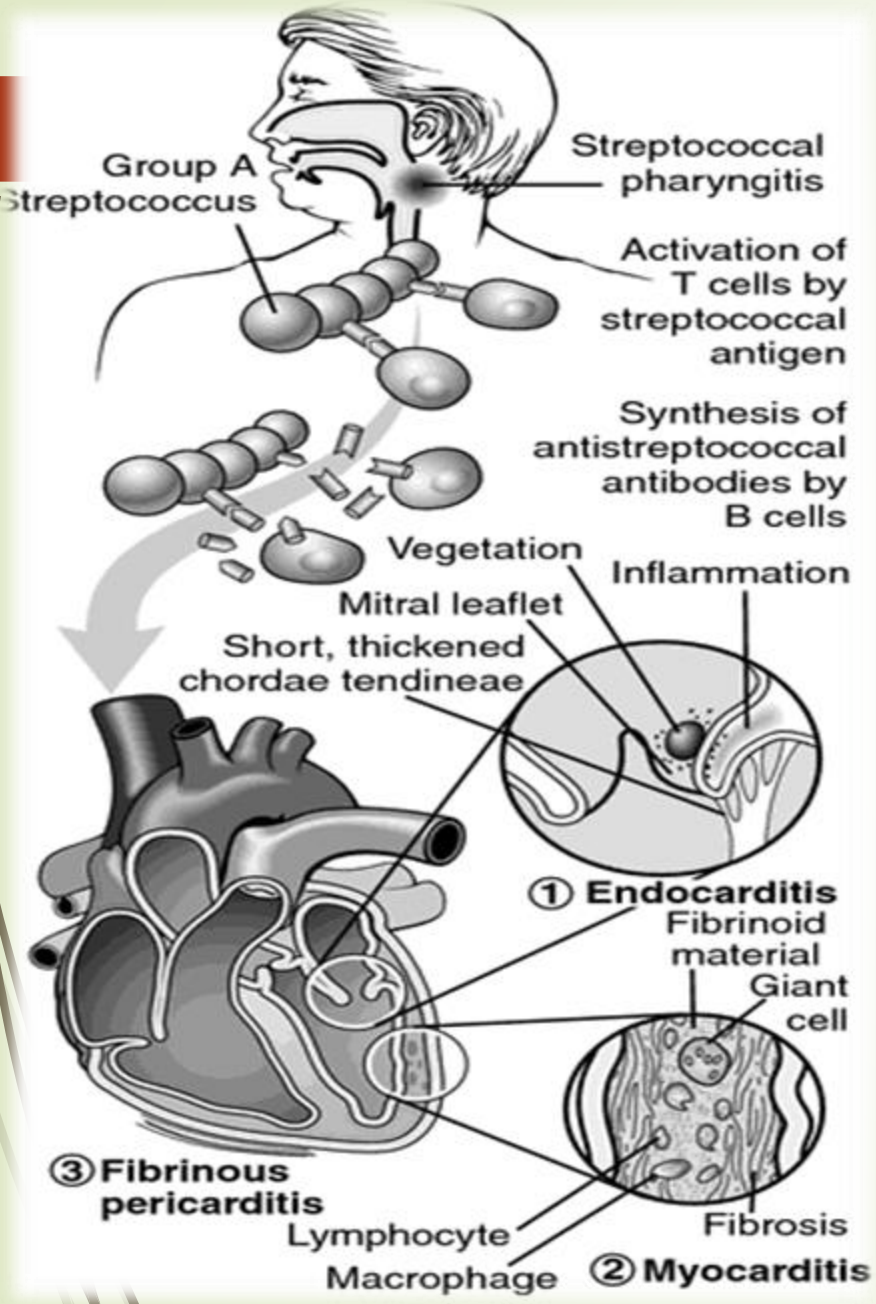
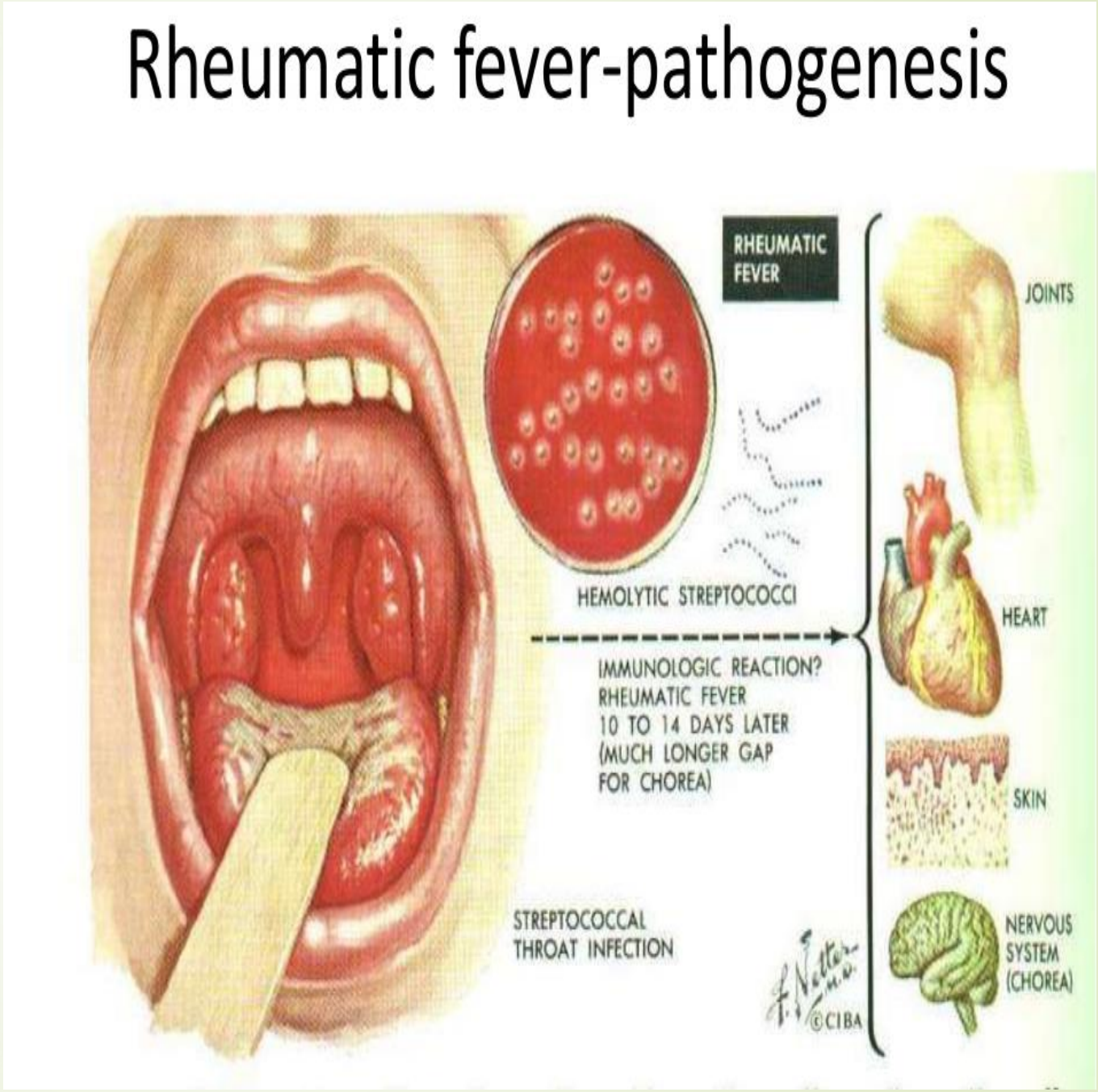
Department of Microbiology & Pathology
CVS lectures 2022

Rheumatic fever-pathogenesis

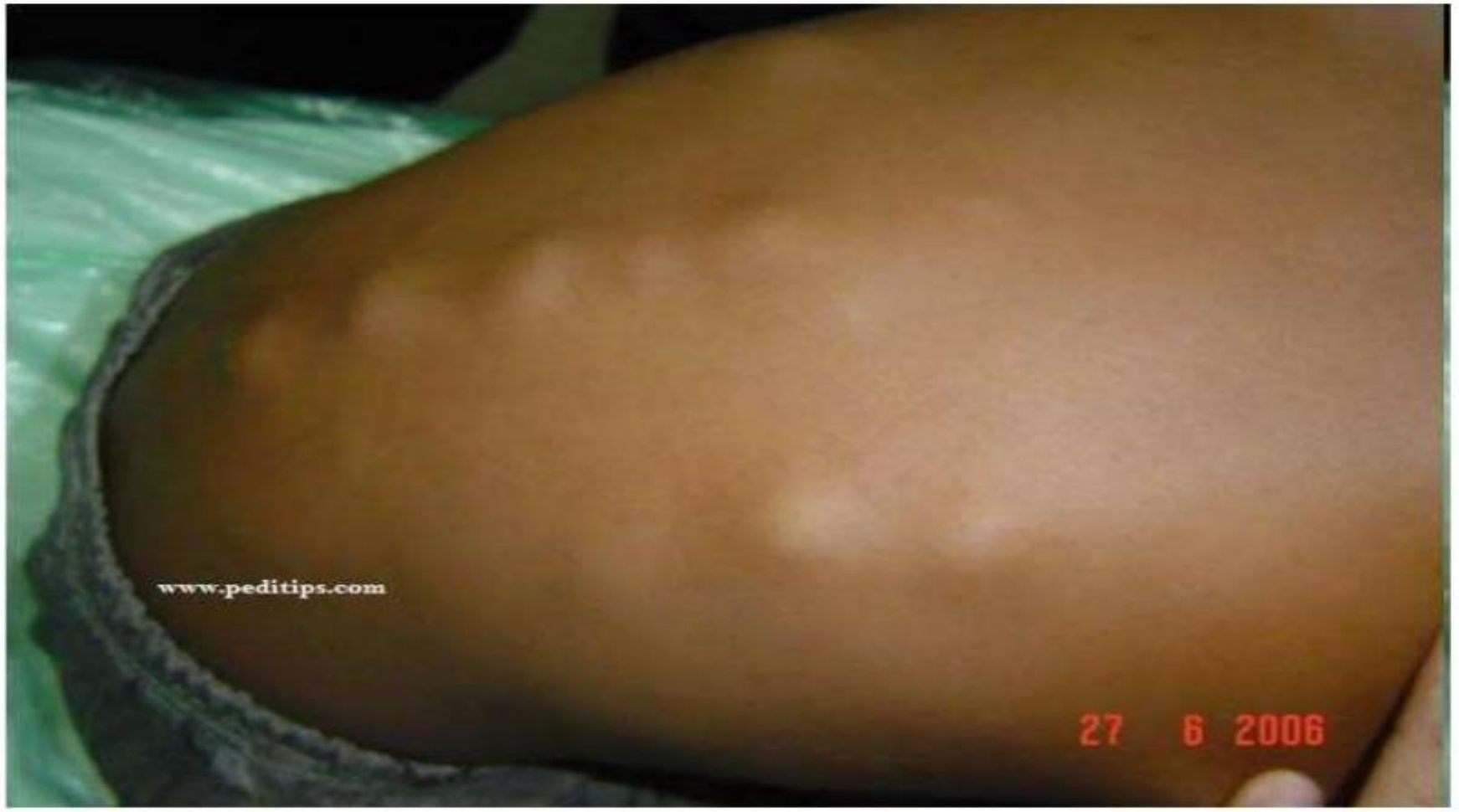




Major Criteria in the Jones System for Acute Rheumatic Fever

Sign	Comments
Polyarthritis	Common; swelling, limited motion, tender, erythema
	•migratory, large joints, no residual deformity, rapid response to aspirin(if aspirin given,24 to 48hrs joint pain will disappear ;thus used as diagnostic test)
Carditis	Common; pancarditis, valves, pericardium, myocardium
	•Murmur(mitral or aortic regurgitation-endocardium involved) •Heart failure •Cardiac enlargement(myocardium involvement) •Pericardial rub or effusion(pericardium involvement)
Chorea (Sydenham disease)	Uncommon; presents long after infection has resolved; more common in females, Spasmodic, unintentional, jerky choreiform movements, speech affected, fidgety, late manifestation
Erythema marginatum	Uncommon; pink macules, ring or crescent shaped, transient patches over trunk and limbs, elicited by application of local heat; nonpruritic
Subcutaneous nodules	Uncommon; Painless, hard nodules beneath skin, over bony prominence, tendons and joints, present over extensor surface of elbows, knees, knuckles, and ankles or scalp and spine. associated with repeated episodes and severe carditis;

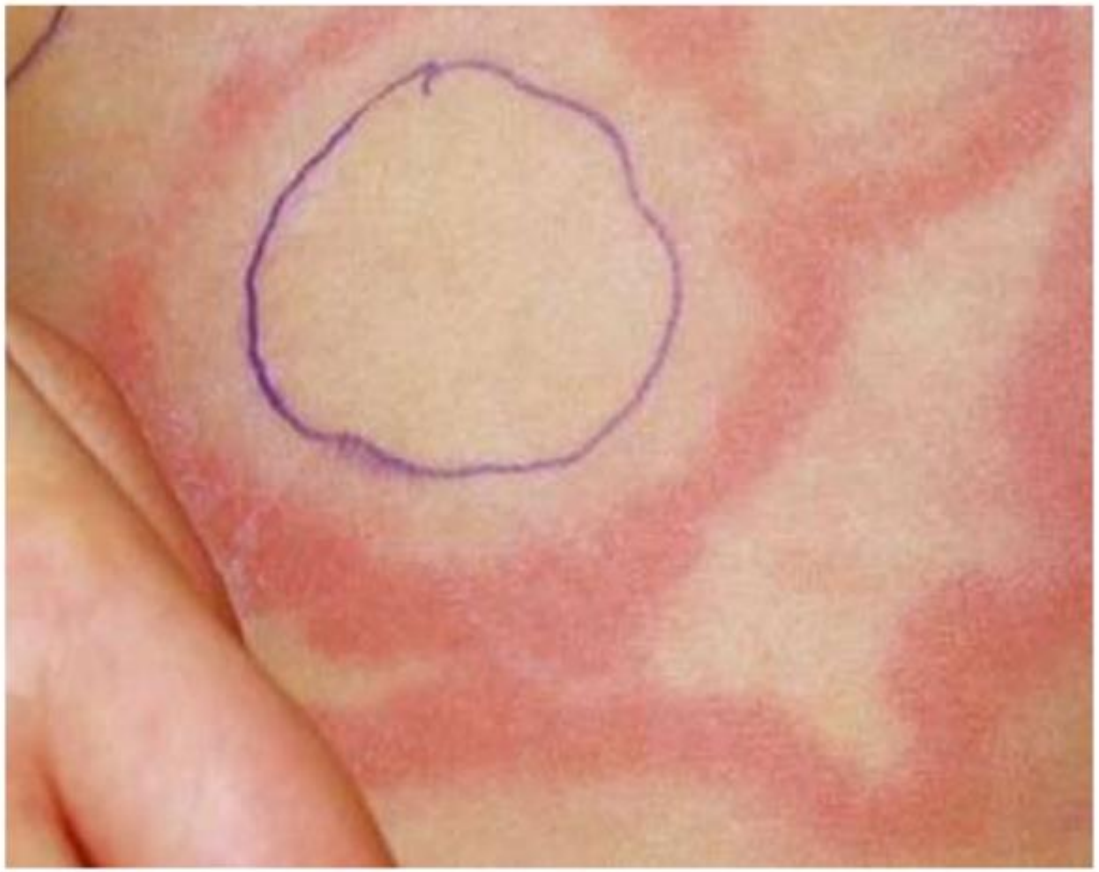
Rheumatic fever-diagnosis



Subcutaneous nodules

(nodules of rheumatoid arthritis are larger)

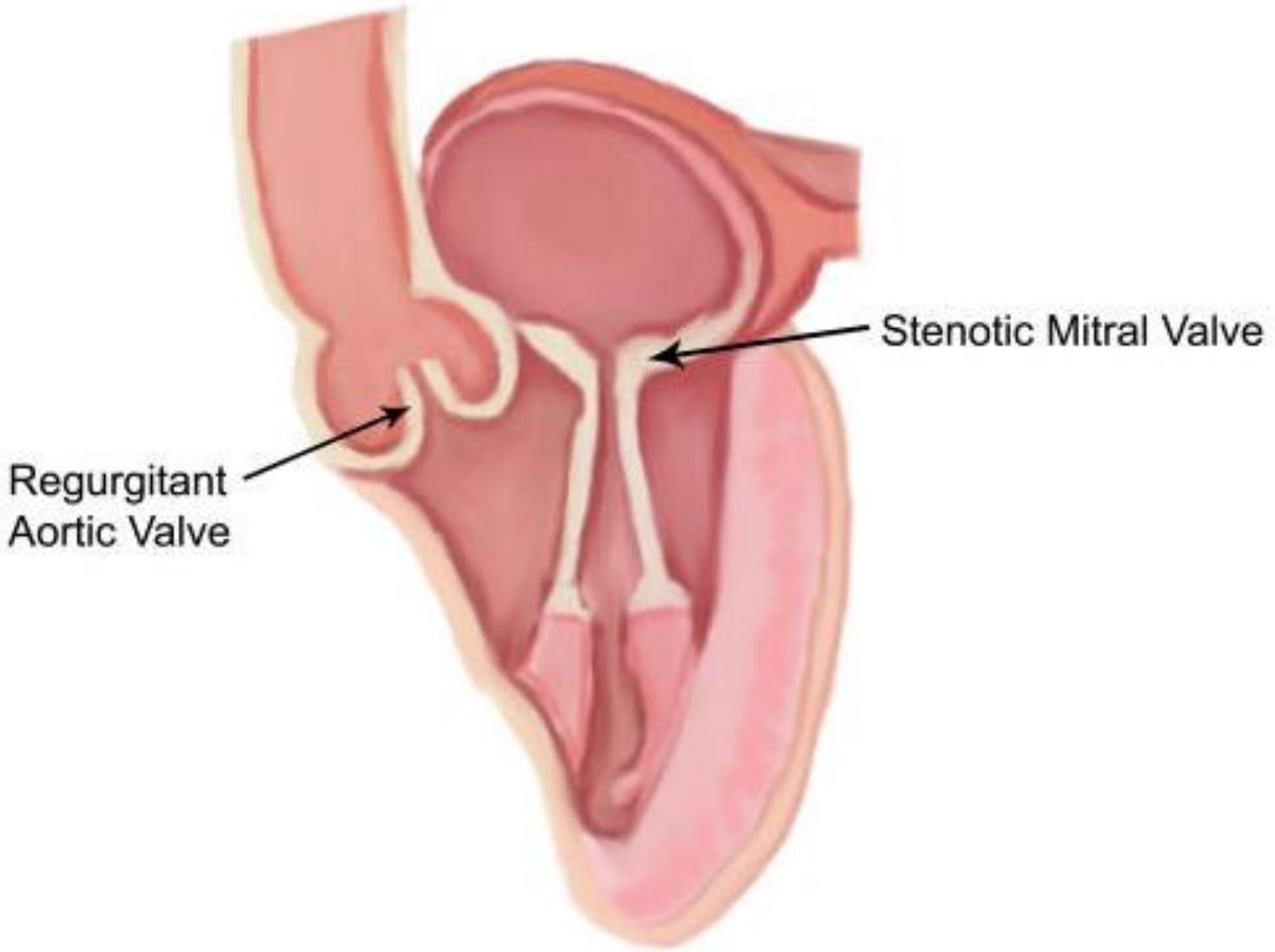
Rheumatic fever-diagnosis



Erythematous patches with central clearing

Erythema marginatum

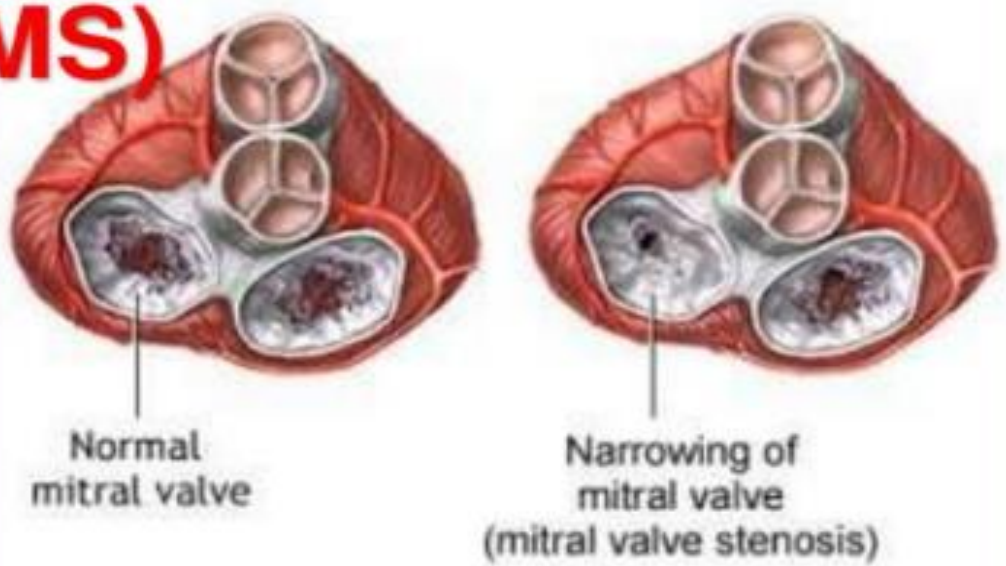
Rheumatic Mitral Stenosis

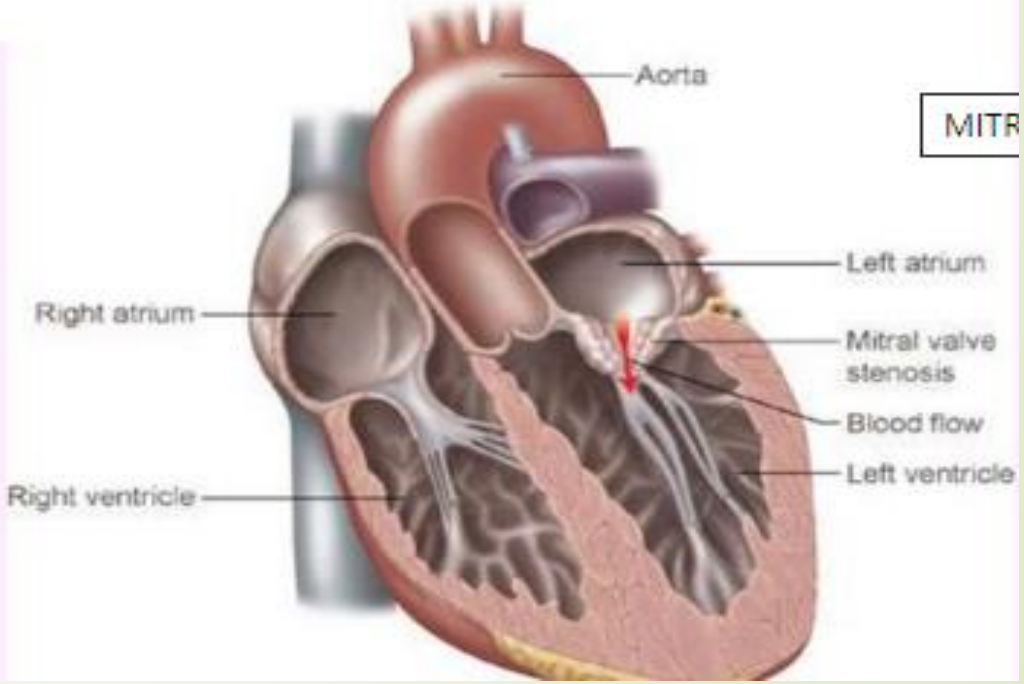


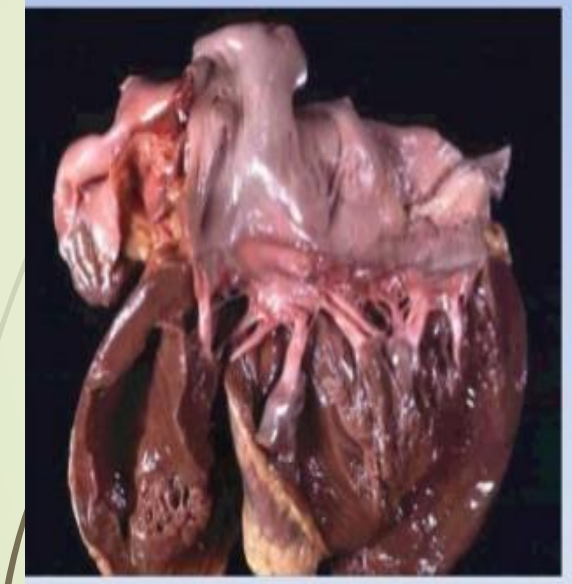
MITRAL STENOSIS (MS)

Pathophysiology

- Thickening of valve leaflets
- Fusion of commissures
- Shortening & thickening of chordae tendineae.
- Funnel shaped valve apparatus → marked obstruction to blood flow from LA to LV
- LA enlargement **(Not LV)**, pulmonary venous congestion, PH, RV & RA dilation
- Right side HF







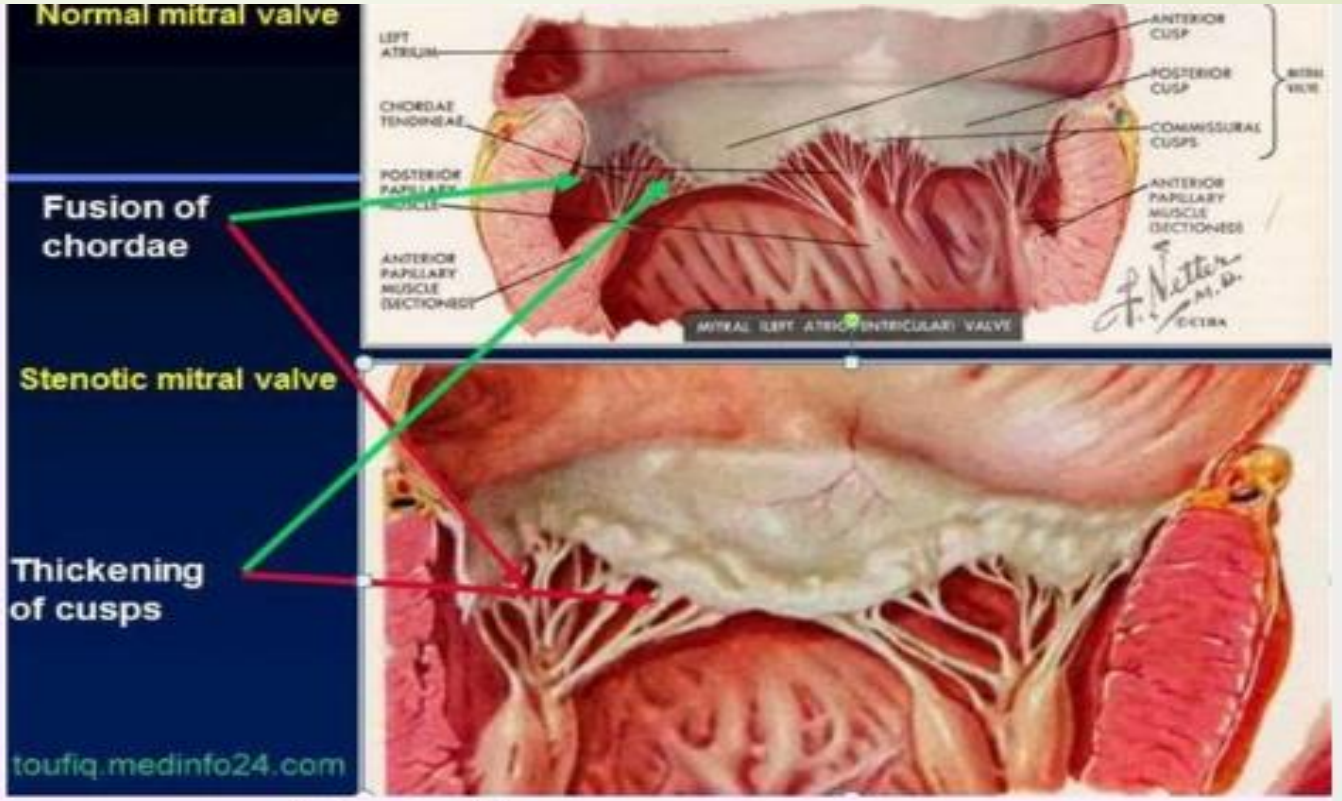
Rheumatic heart disease.

Abnormal mitral valve. Thick, fused chordae

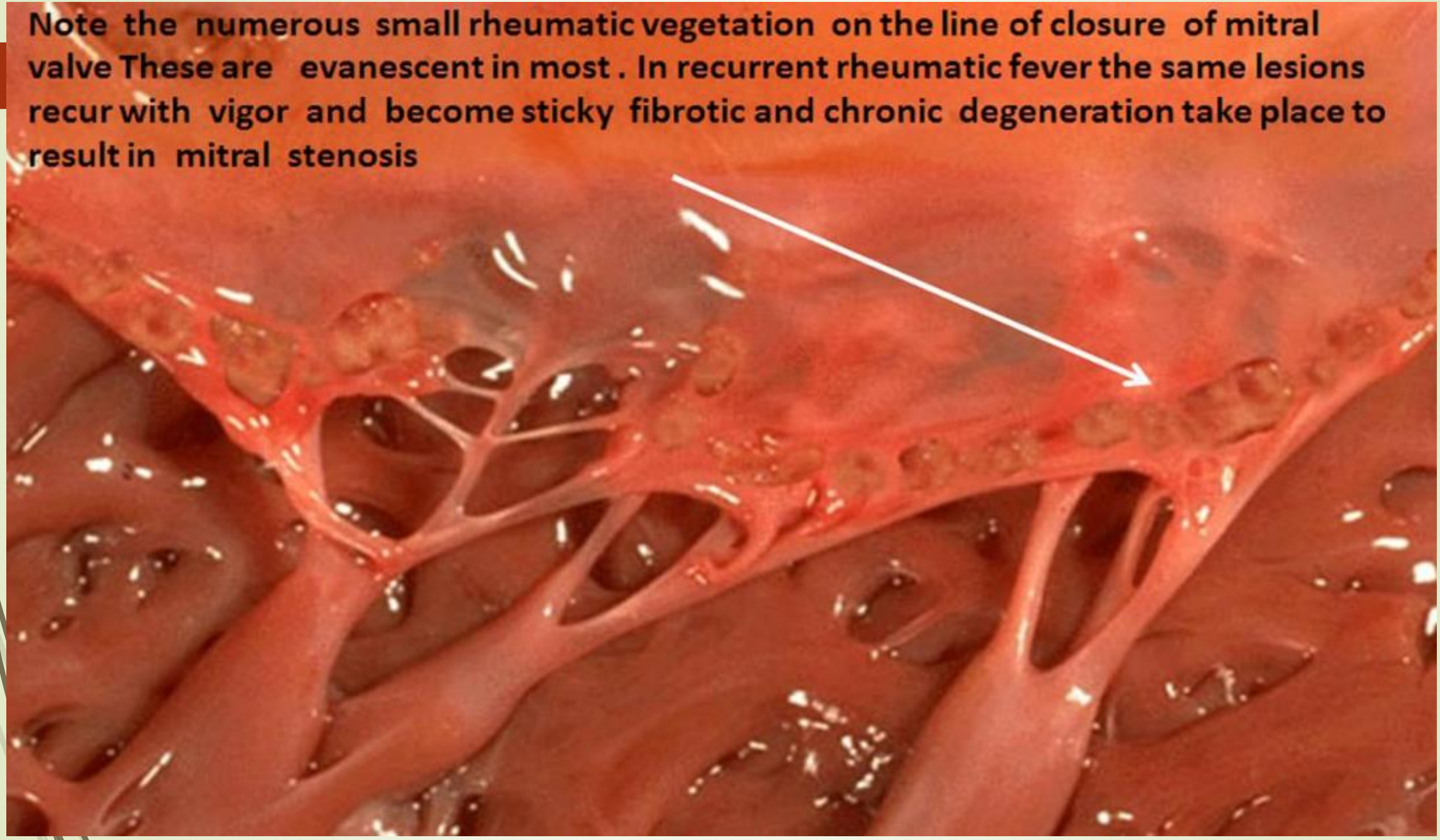
Another view of thick and fused mitral valves in Rheumatic heart disease

Pathophysiology

Healing of ARF results in



- Fibrosis & contracture of leaflets
- Shortening & thickening of chordea tendinea.
- Leaflets cannot coapt and separated
- LA and LV volume overload and enlargement.
- Pulmonary venous congestion, PH, RVH


Note the numerous small rheumatic vegetation on the line of closure of mitral valve These are evanescent in most . In recurrent rheumatic fever the same lesions recur with vigor and become sticky fibrotic and chronic degeneration take place to result in mitral stenosis

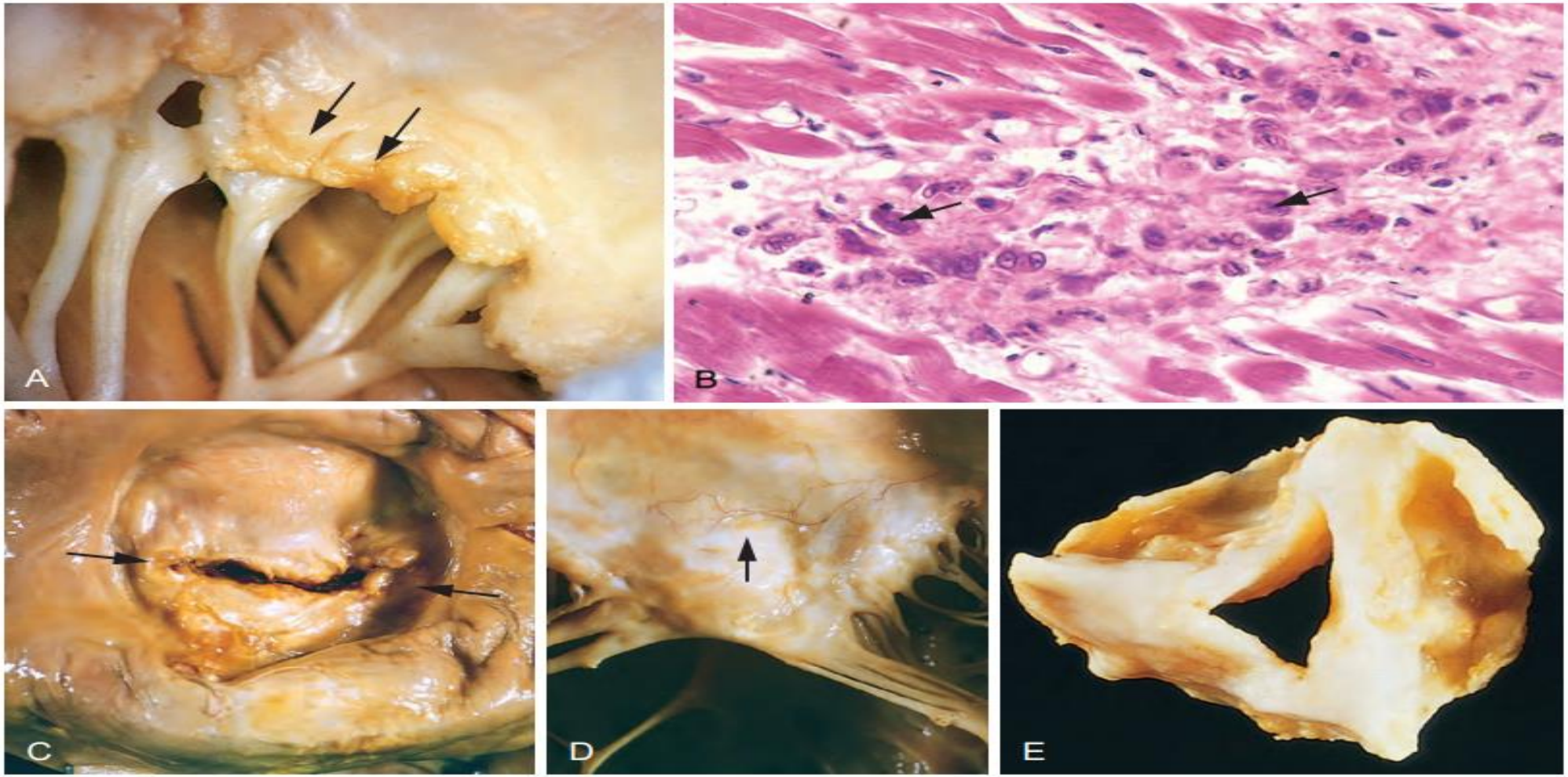


Figure 12.22 Acute and chronic rheumatic heart disease. (A) Acute rheumatic mitral valvulitis superimposed on chronic rheumatic heart disease. Small vegetations (verrucae) are visible along the line of closure of the mitral valve leaflet *(arrows)*. Previous episodes of rheumatic valvulitis have caused fibrous thickening and fusion of the chordae tendineae. (B) Microscopic appearance of an Aschoff body in a patient with acute rheumatic carditis. The myocardium exhibits a circumscribed nodule of mixed mononuclear inflammatory cells with associated necrosis; within the inflammation, large activated macrophages show prominent nucleoli, as well as chromatin condensed into long, wavy ribbons (caterpillar cells; *arrows*). (C and D) Mitral stenosis with diffuse fibrous thickening and distortion of the valve leaflets and commissural fusion (*arrows*, C), and thickening of the chordae tendineae (D). Note the neovascularization of the anterior mitral leaflet (*arrow*, D). (E) Surgically resected specimen of rheumatic aortic stenosis, demonstrating thickening and distortion of the cusps with commissural fusion. (E, Reproduced from Schoen FJ, St. John-Sutton M: Contemporary issues in the pathology of valvular heart disease, *Hum Pathol* 18:568, 1967.)

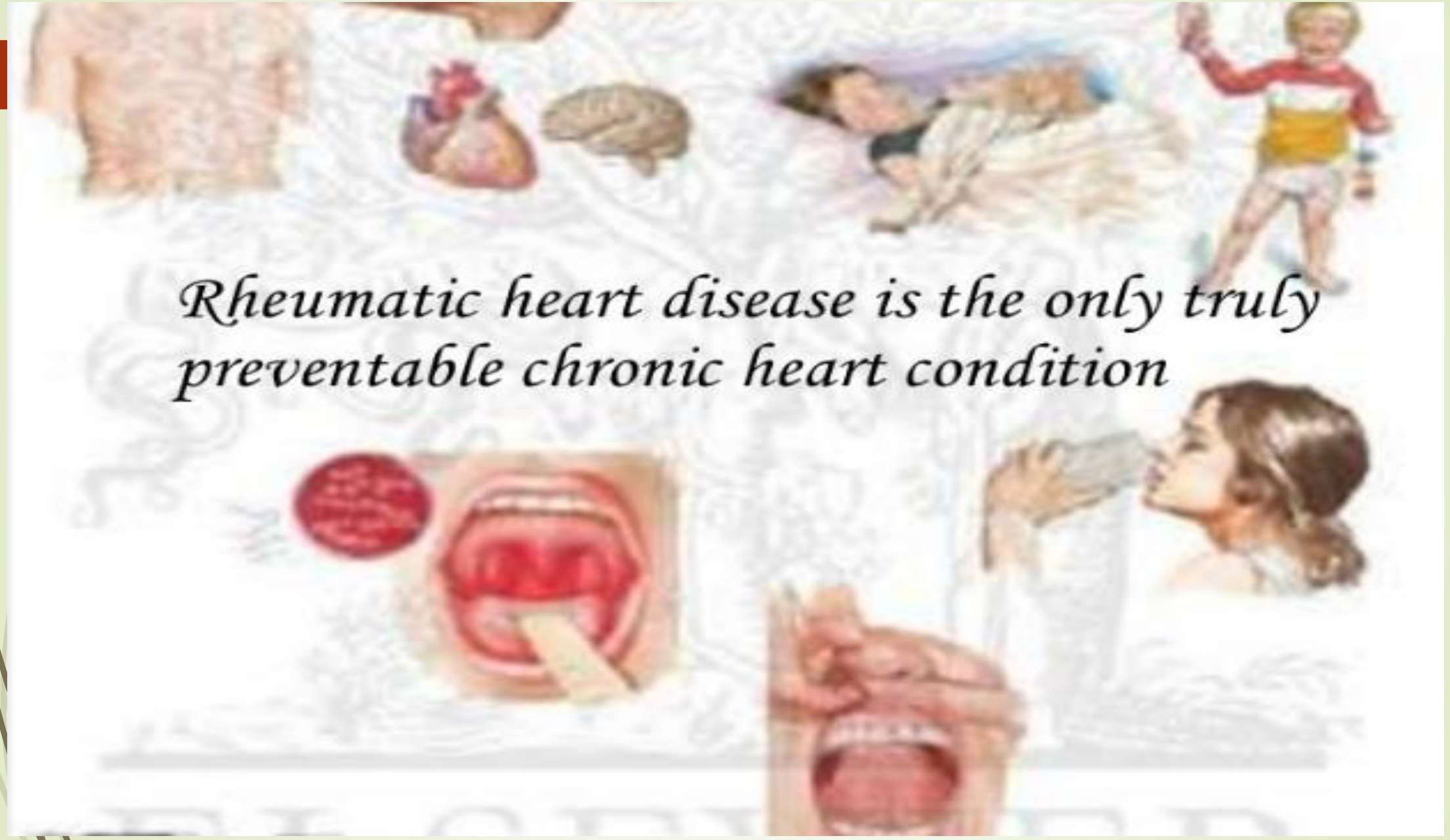
❖ Minor criteria includes:

Clinical finding:

1. fever (38.2°C to 38.9°C)
2. Arthralgia(joint pain without swelling)
3. Previous rheumatic fever

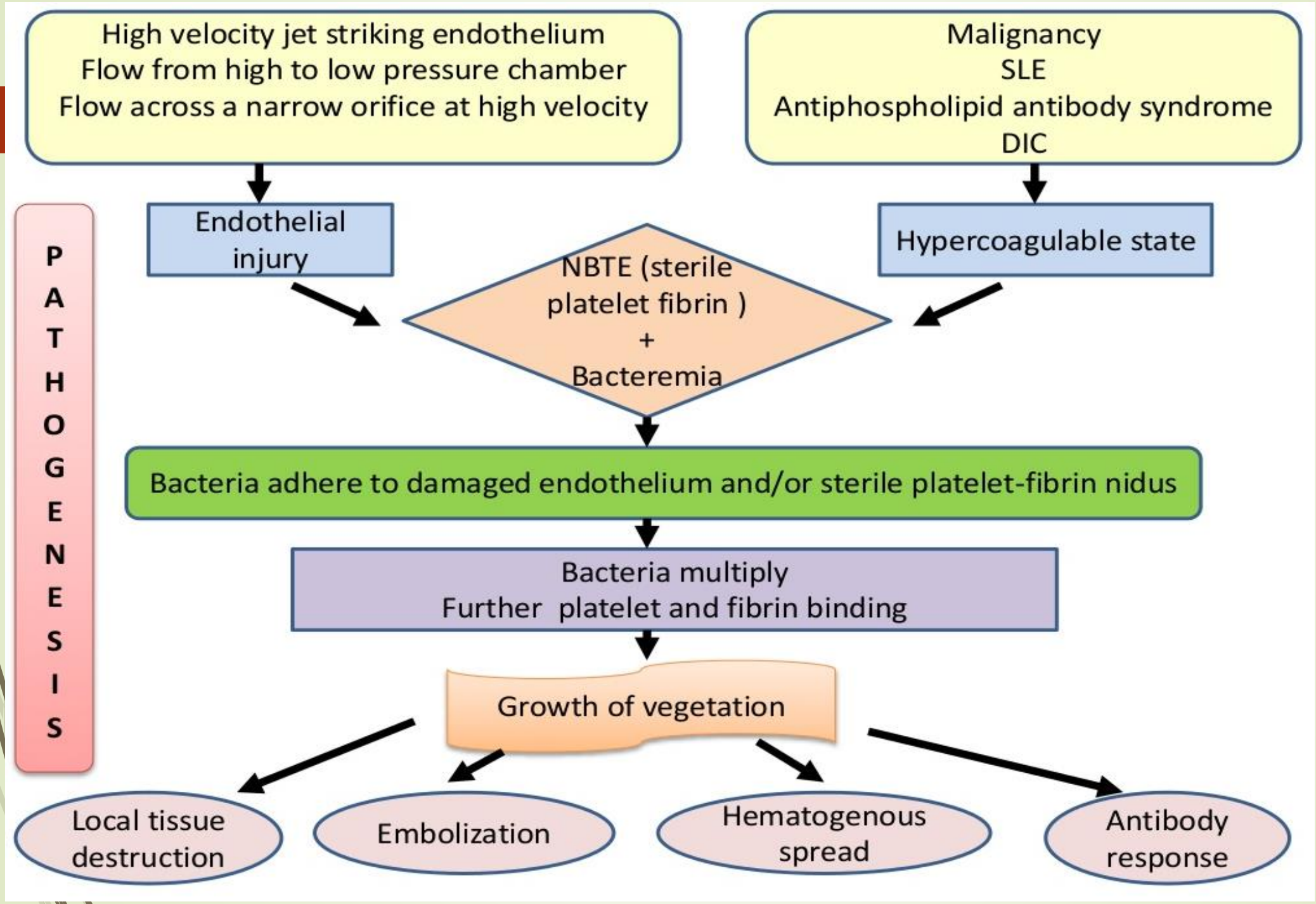
Laboratory finding:

1. Elevated erythrocyte sedimentation rate (ESR)
2. Elevated C-reactive protein (CRP)
3. ECG: prolonged P-R interval.


Rheumatic heart disease is the only truly preventable chronic heart condition

Distinction between Acute and Subacute Bacterial Endocarditis

Feature	Acute	Subacute
Underlying Heart Disease	Heart may be normal	RHD,CHD, etc.
Presentation	Toxic presentation Progressive valve destruction & metastatic infection developing in days to weeks	Mild toxicity Presentation over weeks to months
Organism	S. aureus, Pneumococcus S. pyogenes, Enterococcus	viridans Streptococci, Entercoccus


High velocity jet striking endothelium
Flow from high to low pressure chamber
Flow across a narrow orifice at high velocity
Malignancy
SLE
Antiphospholipid antibody syndrome
DIC
PATHOGENESIS
Endothelial injury
Hypercoagulable state
NBTE (sterile platelet fibrin) + Bacteremia
Bacteria adhere to damaged endothelium and/or sterile platelet-fibrin nidus
Bacteria multiply
Further platelet and fibrin binding
Growth of vegetation
Local tissue destruction
Embolization
Hematogenous spread
Antibody response

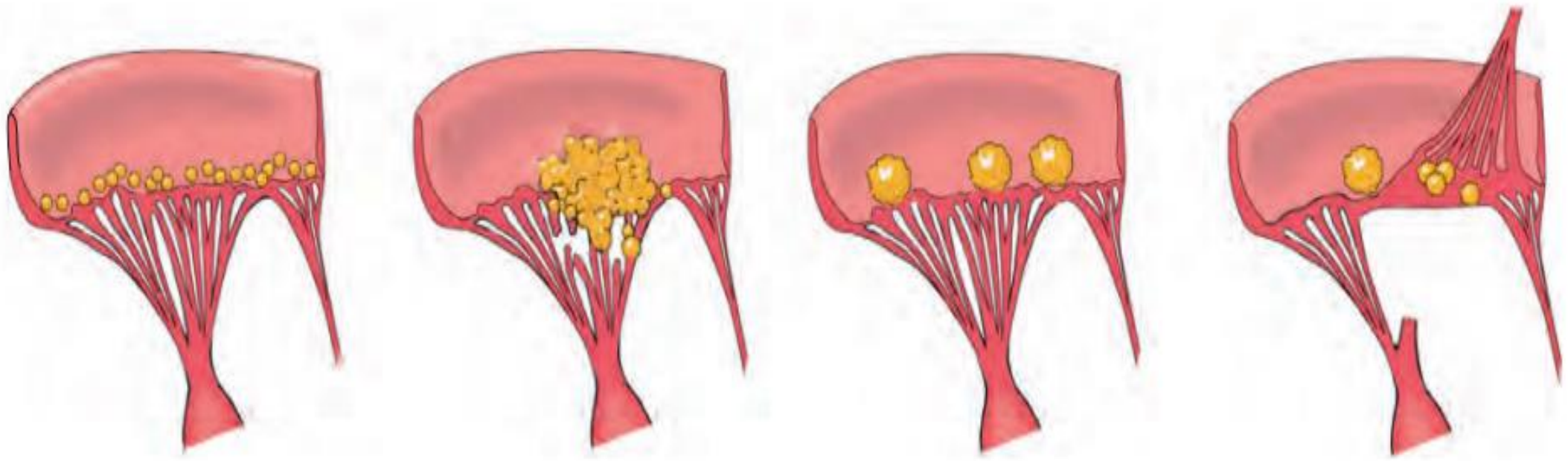
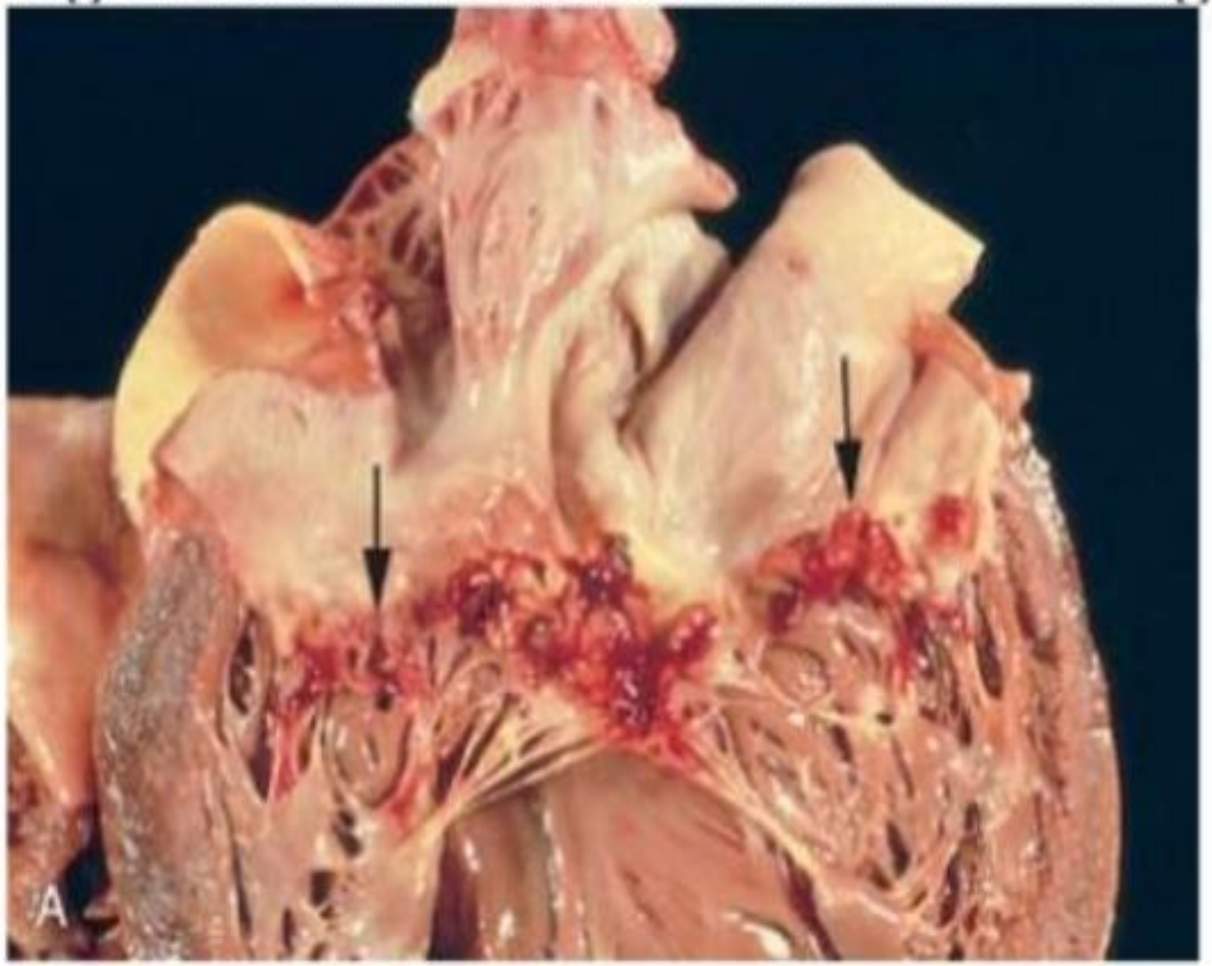
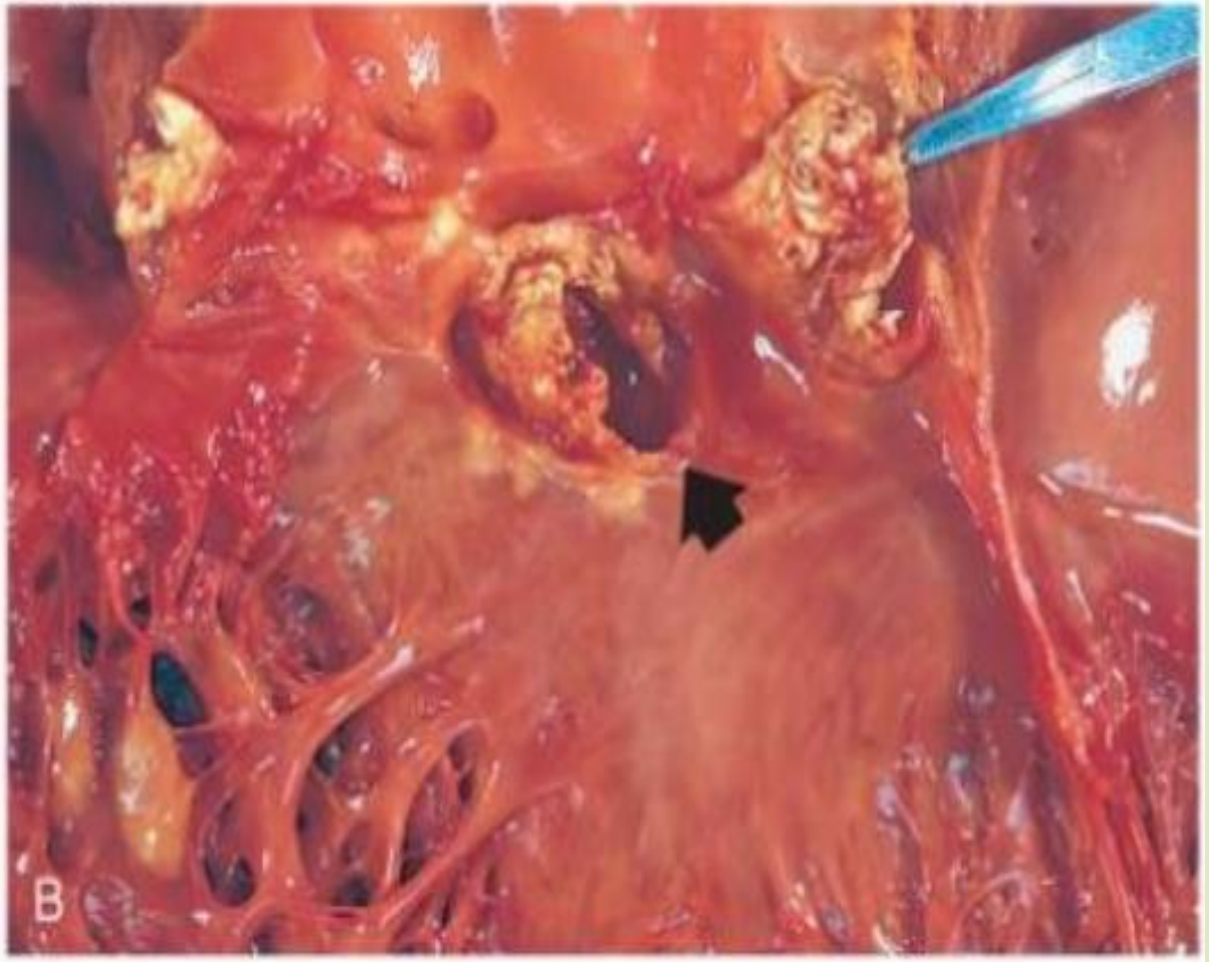
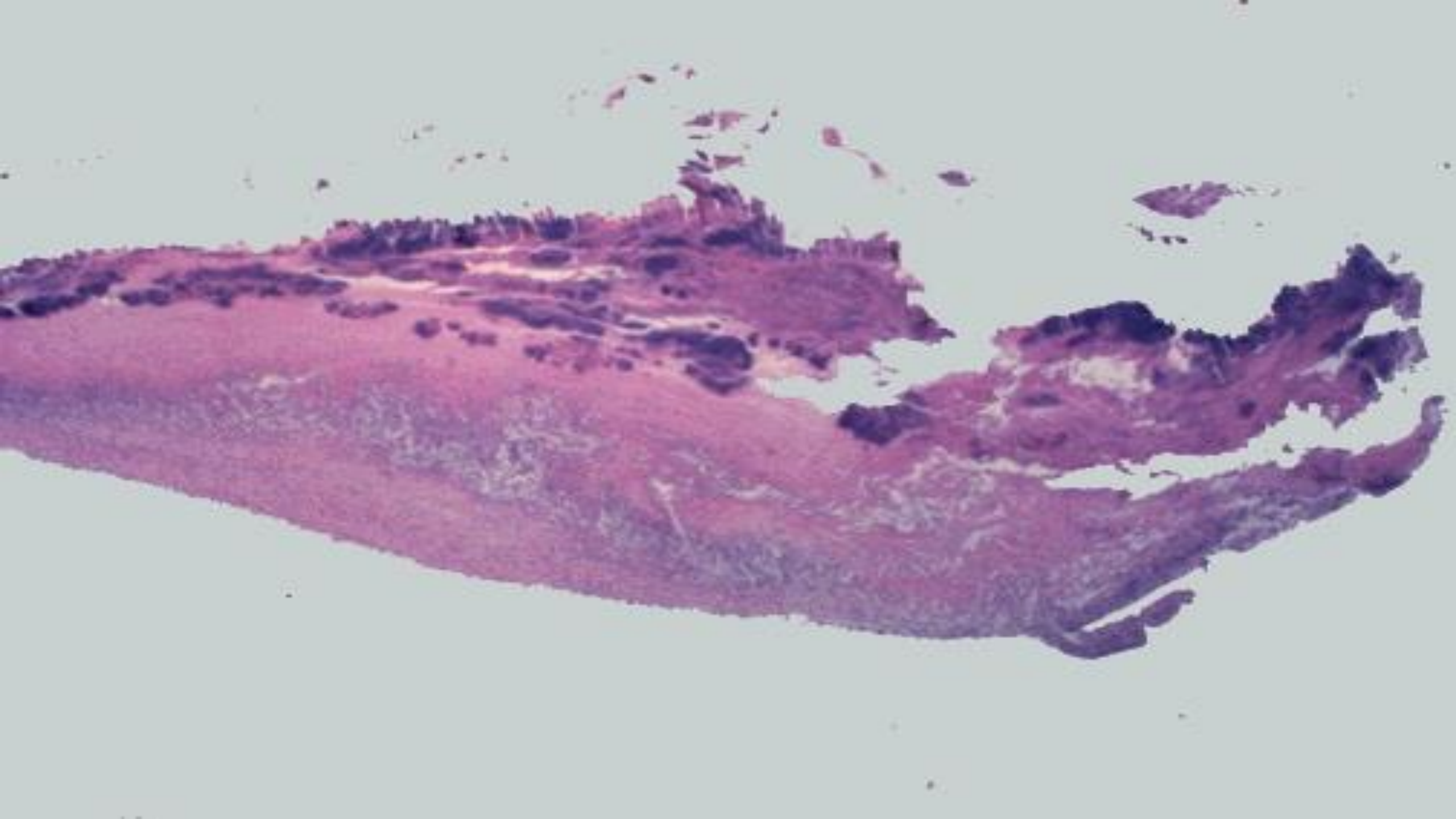


Figure 12.23 Comparison of the four major forms of vegetative endocarditis. The rheumatic fever phase of rheumatic heart disease *(RHD)* is marked by small, warty vegetations along the lines of closure of the valve leaflets. Infective endocarditis *(IE)* is characterized by large, irregular masses on the valve cusps that can extend onto the chordae (see Fig. 12.24A). Nonbacterial thrombotic endocarditis *(NBTE)* typically exhibits small, bland vegetations, usually attached at the line of closure. One or many may be present (see Fig. 12.25). Libman-Sacks endocarditis *(LSE)* has small- or medium-sized vegetations on either or both sides of the valve leaflets.

- Friable, bulky vegetation containing fibrin, inflammatory cells, and microbes
- Aortic and mitral valves involved most commonly.
- Right side valve involvement in iv drug users.





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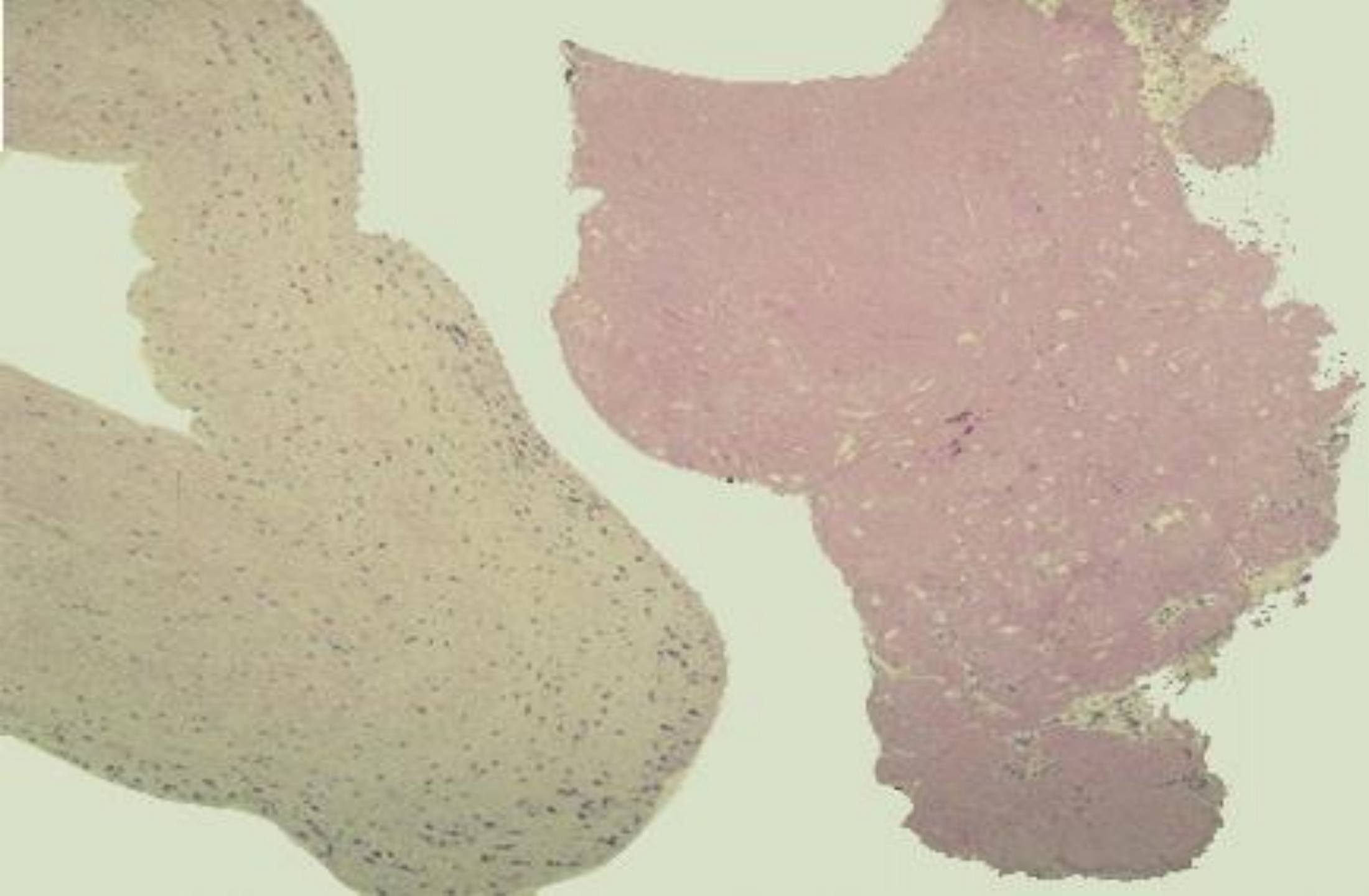
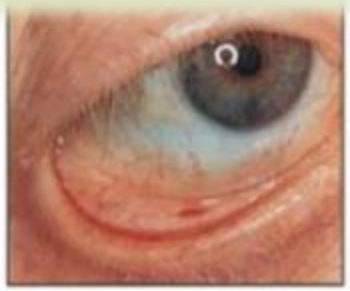
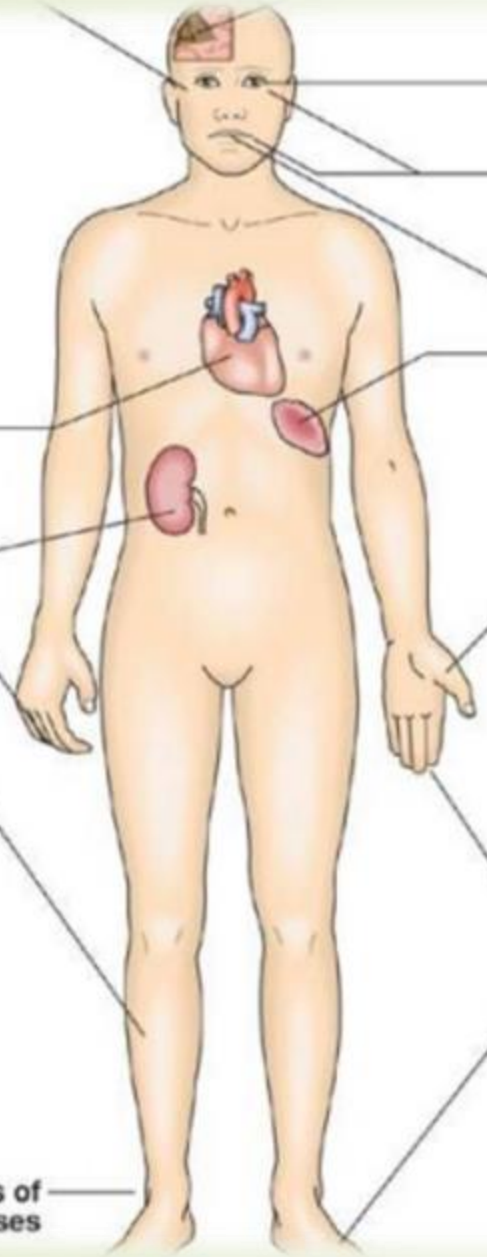
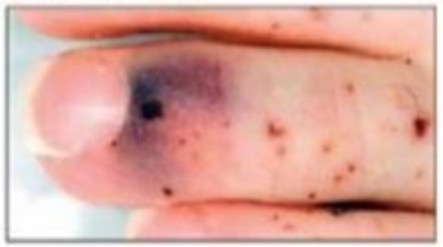


Sub-acute Endocarditis







- Persistent fever
- Constitutional symptoms
- New signs of valve dysfunction
- Heart failure

- Embolic Stroke
- Peripheral arterial embolism

- Other features

Modified Duke's criteria

Definite IE

Pathological criteria

- Microorganisms demonstrated by culture or on histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
- Pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis

Clinical criteria

- 2 major criteria; or
- 1 major criterion and 3 minor criteria; or
- 5 minor criteria

Possible IE

- 1 major criterion and 1 minor criterion; or
- 3 minor criteria

Rejected IE

- Firm alternate diagnosis; or
- Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days; or
- No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or
- Does not meet criteria for possible IE, as above

CARDIOMYOPATHIES

1-Dilated Cardiomyopathy

- characterized by *progressive cardiac dilation and contractile (systolic) dysfunction,* usually with concurrent hypertrophy; regardless of cause, the clinicopathologic patterns are similar.

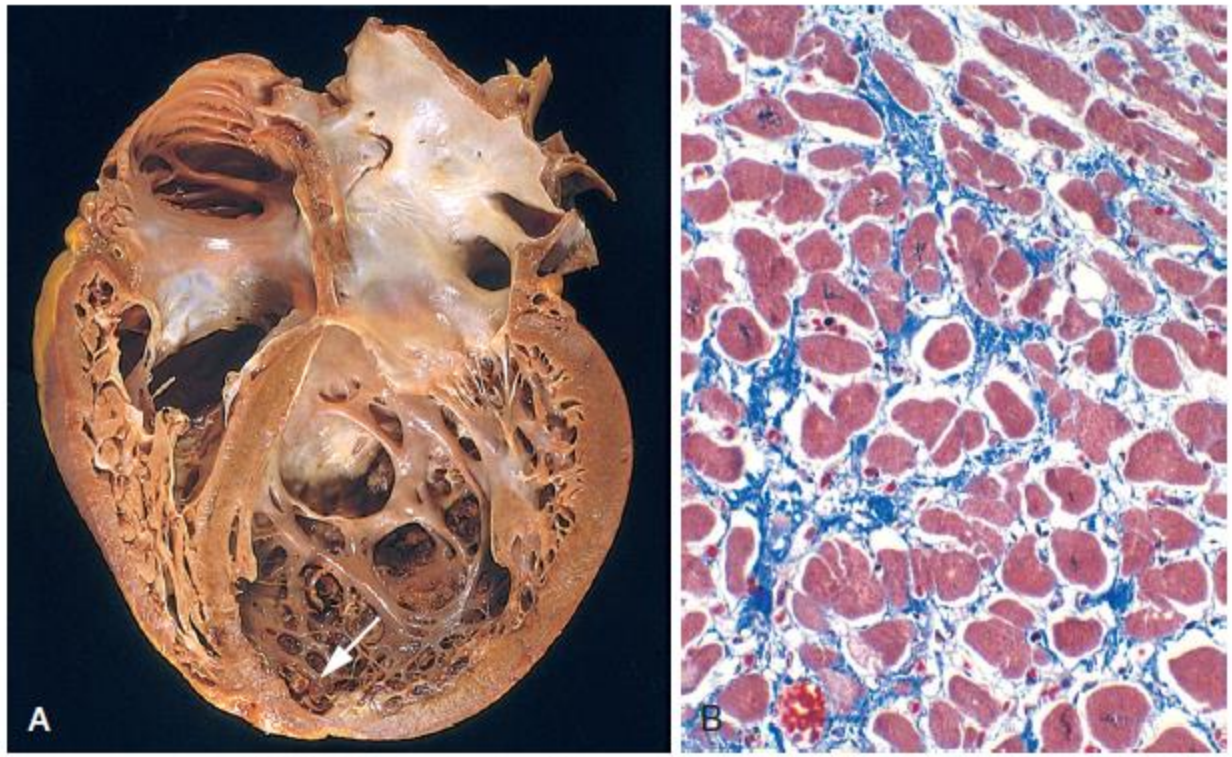


Figure 10–26 Dilated cardiomyopathy (DCM). **A,** Four-chamber dilation and hypertrophy are evident. A small mural thrombus can be seen at the apex of the left ventricle (*arrow*). **B,** The nonspecific histologic picture in typical DCM, with myocyte hypertrophy and interstitial fibrosis (collagen is blue in this Masson trichrome–stained preparation).

Arrhythmogenic Right Ventricular Cardiomyopathy

- Is an autosomal dominant disorder of cardiac muscle with variable penetrance.
- It classically manifests with right sided heart failure and rhythm disturbances that can cause sudden cardiac death.
- Morphologically, the right ventricular wall is severely thinned owing to myocyte replacement by massive fatty infiltration and lesser amounts of fibrosis.
- Many of the mutations involve genes encoding

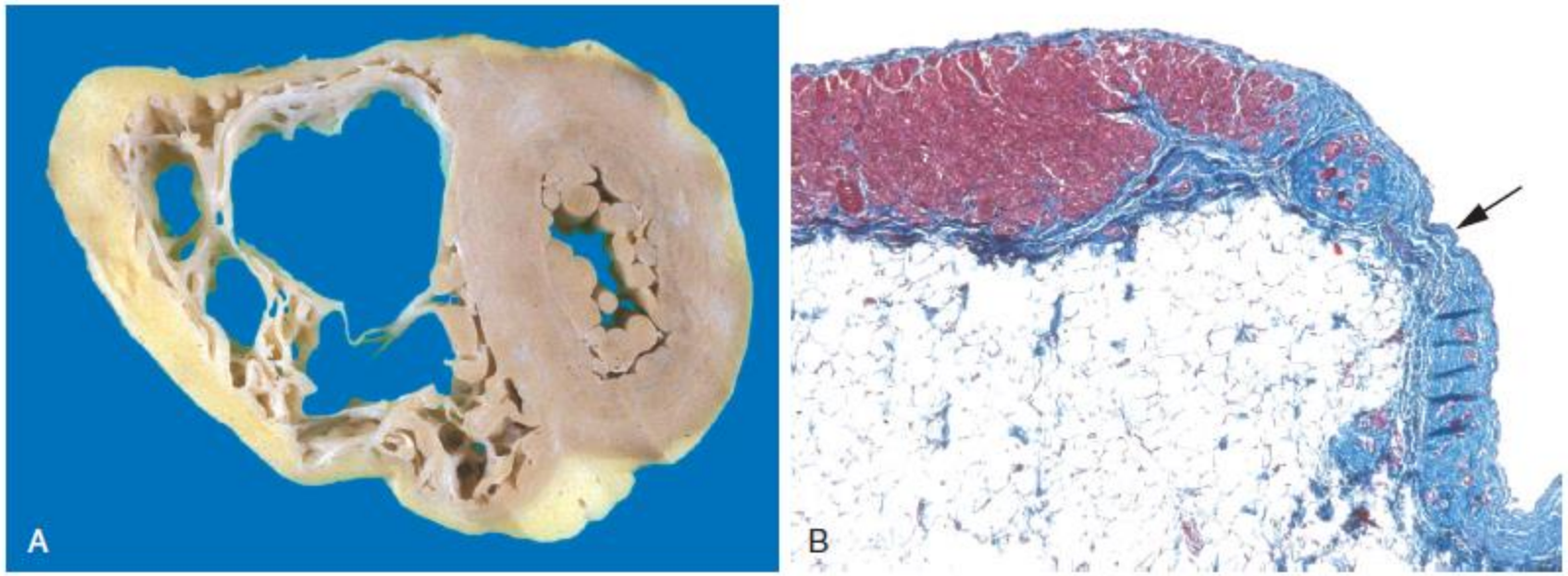


Figure 10–27 Arrhythmogenic right ventricular cardiomyopathy. **A,** The right ventricle is markedly dilated with focal, almost transmural replacement of the free wall by adipose tissue and fibrosis. The left ventricle has a grossly normal appearance in this heart; it can be involved (albeit to a lesser extent) in some instances. **B,** The right ventricular myocardium *(red)* is focally replaced by fibrous connective tissue (*blue, arrow*) and fat (Masson trichrome stain).

Hypertrophic cardiomyopathy (HCM)

- Characterized by *myocardial hypertrophy, defective diastolic filling,* and—in a third of cases—*ventricular outflow obstruction.*
- The heart is thick-walled, heavy, and hypercontractile.
- Systolic function usually is preserved in HCM, but the myocardium does not relax and therefore exhibits primary diastolic dysfunction.
- HCM needs to be distinguished clinically from disorders causing ventricular stiffness (e.g., amyloid deposition) and ventricular hypertrophy (e.g., aortic stenosis and hypertension).
- **HCM is fundamentally a disorder of sarcomeric proteins. Of these, β-myosin heavy chain is most frequently affected**.

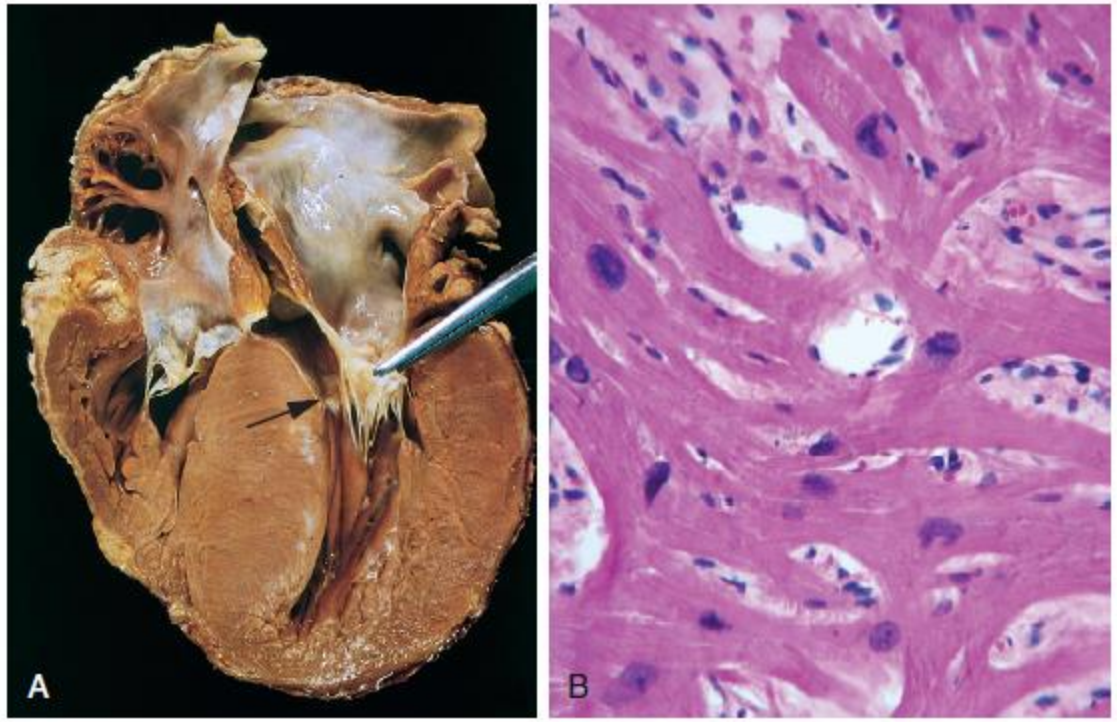


Figure 10–28 Hypertrophic cardiomyopathy with asymmetric septal hypertrophy. **A,** The septal muscle bulges into the left ventricular outflow tract, giving rise to a "banana-shaped" ventricular lumen, and the left atrium is enlarged. The anterior mitral leaflet has been moved away from the septum to reveal a fibrous endocardial plaque (*arrow*) (see text). **B,** Histologic appearance demonstrating disarray, extreme hypertrophy, and characteristic branching of myocytes, as well as interstitial fibrosis.

Table 10–6 Cardiomyopathies: Functional Patterns, Causes

Functional Pattern	Left Ventricular Ejection Fraction*	Mechanisms of Heart Failure	Causes	Secondary Myocardial Dysfunction (Mimicking Cardiomyopathy)
Dilated	<40%	Impairment of contractility (systolic dysfunction)	Genetic; alcohol; peripartum; myocarditis; hemochromatosis; chronic anemia; doxorubicin (Adriamycin); sarcoidosis; idiopathic	Ischemic heart disease; valvular heart diseases; hypertensive heart disease; congenital heart disease
Hypertrophic	50–80%	Impairment of compliance (diastolic dysfunction)	Genetic; Friedreich ataxia; storage diseases; infants of diabetic mothers	Hypertensive heart disease; aortic stenosis
Restrictive	45–90%	Impairment of compliance (diastolic dysfunction)	Amyloidosis; radiation-induced fibrosis; idiopathic	Pericardial constriction

*Range of normal values is approximately 50%–65%.

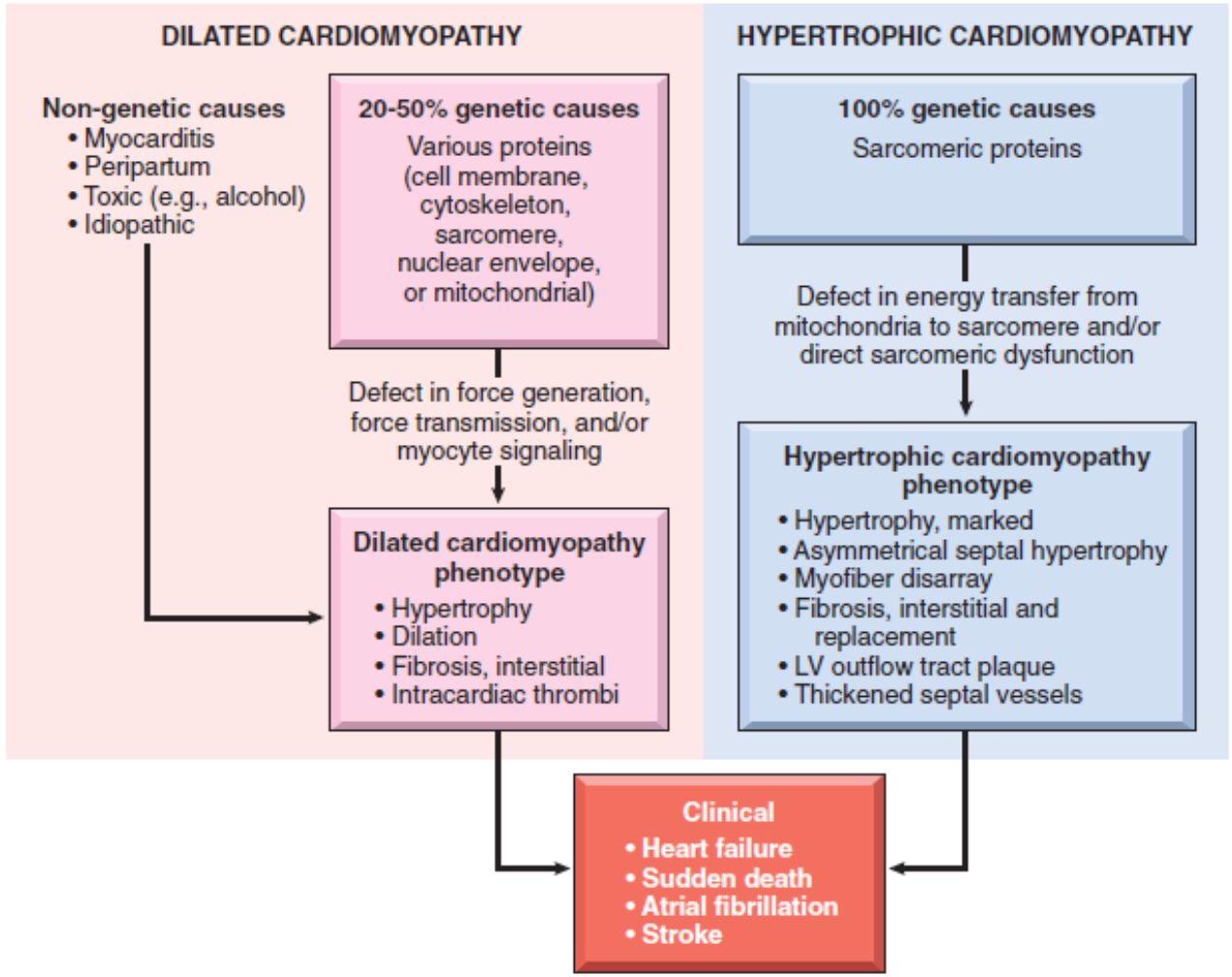


Figure 10–25 Causes and consequences of dilated and hypertrophic cardiomyopathy. A significant fraction of dilated cardiomyopathies—and virtually all hypertrophic cardiomyopathies—have a genetic origin. Dilated cardiomyopathies can be caused by mutations in cytoskeletal, sarcomeric, nuclear envelope, or mitochondrial proteins; hypertrophic cardiomyopathies typically are caused by sarcomeric protein mutations. Although the two forms of cardiomyopathy differ in cause and morphology, they have common clinical end points. LV, left ventricle.

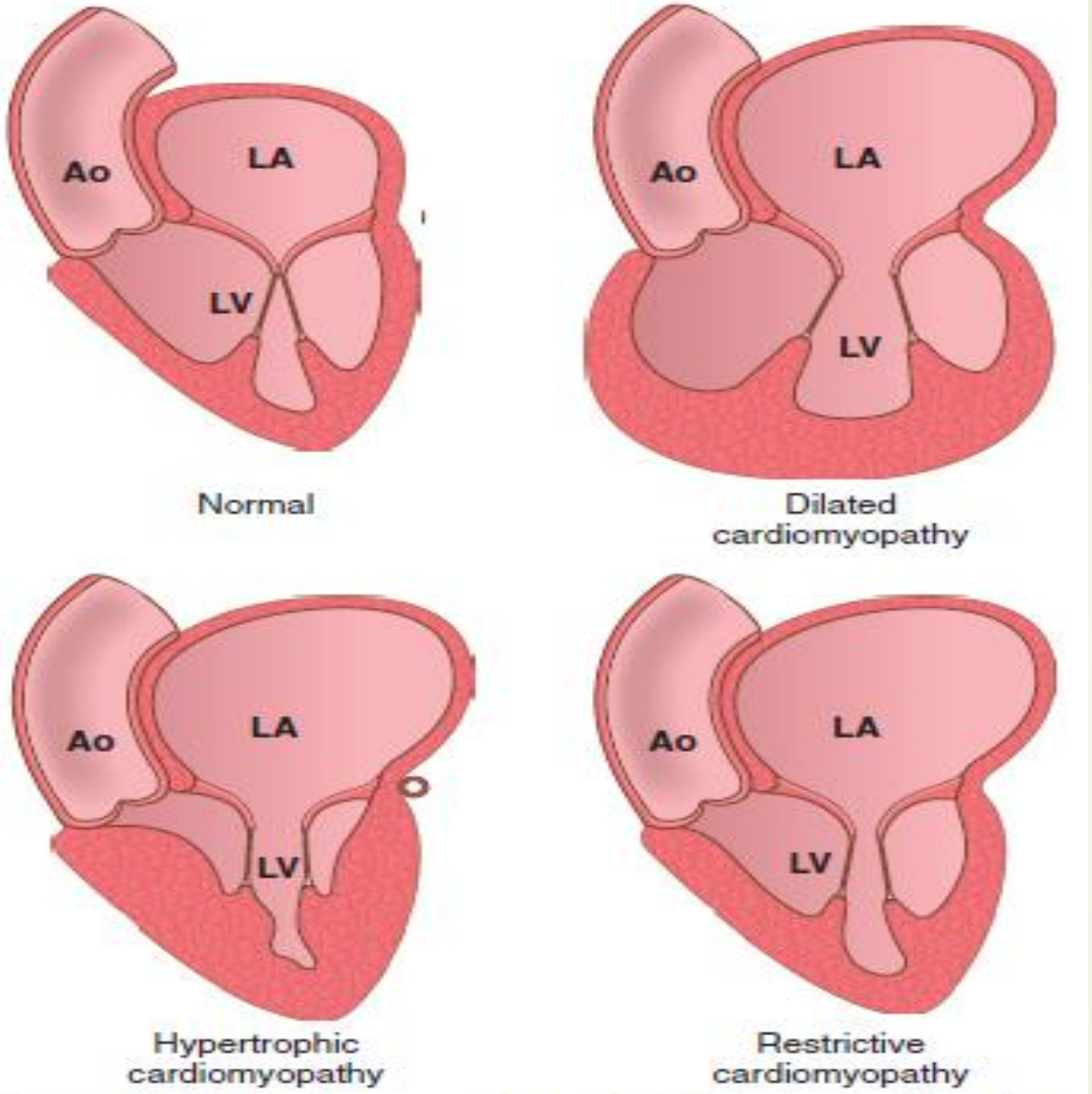


Figure 10–24 The three major forms of cardiomyopathy. Dilated cardiomyopathy leads primarily to systolic dysfunction, whereas restrictive and hypertrophic cardiomyopathies result in diastolic dysfunction. Note the changes in atrial and/or ventricular dilation and in ventricular wall thickness. Ao, aorta; LA, left atrium; LV, left ventricle.

Myocarditis

Myocarditis encompasses a diverse group of clinical entities in which infectious agents and/or inflammatory processes primarily target the myocardium.

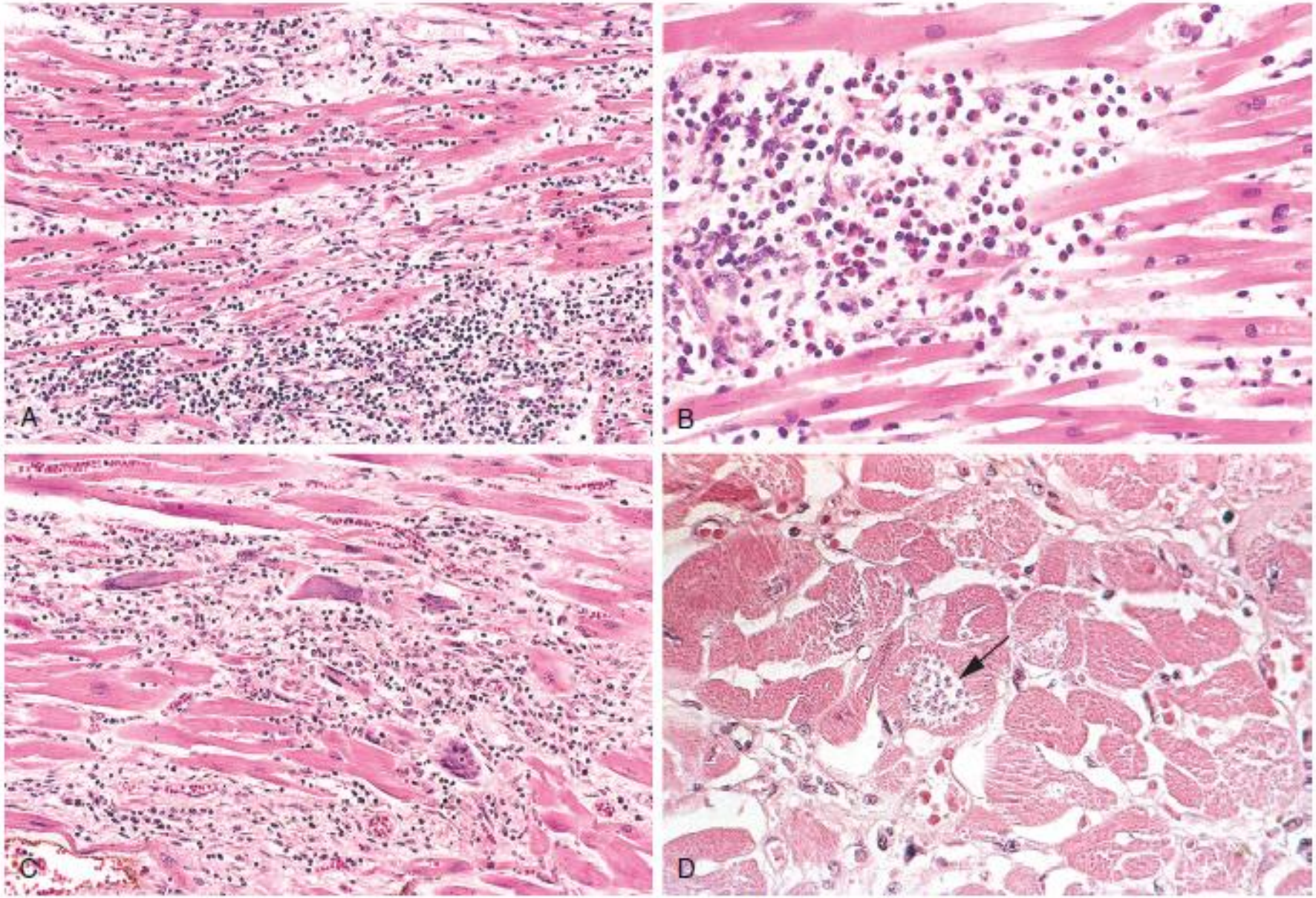


Figure 10–29 Myocarditis. **A,** Lymphocytic myocarditis, with edema and associated myocyte injury. **B,** Hypersensitivity myocarditis, characterized by perivascular eosinophil-rich inflammatory infiltrates. **C,** Giant cell myocarditis, with lymphocyte and macrophage infiltrates, extensive myocyte damage, and multinucleate giant cells. **D,** Chagas myocarditis. A myofiber distended with trypanosomes (*arrow*) is present, along with mononuclear inflammation and myofiber necrosis.

PERICARDIAL DISEASE

MORPHOLOGY

Tuberculous pericarditis:

Exhibits areas of caseation

Acute viral pericarditis or uremia:

The exudate typically is fibrinous, imparting an irregular, shaggy appearance to the pericardial surface (so-called "bread and butter" pericarditis).

Pericarditis due to malignancy

Associated with an exuberant, shaggy fibrinous exudate and a bloody effusion.

Acute bacterial pericarditis:

The exudate is fibrinopurulent (suppurative), often with areas of frank pus .

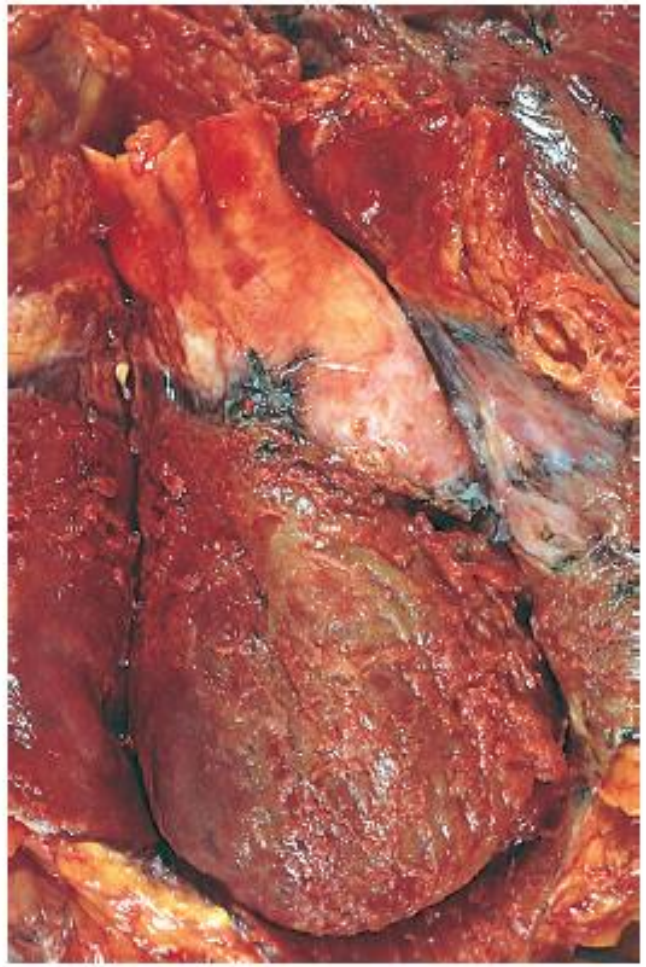


Figure 10–30 Acute suppurative (purulent, exudative) pericarditis, caused by extension from a pneumonia.

2-Pericardial Effusions

- Normally, the pericardial sac contains at most 30 to 50 mL of clear, serous fluid.

1. Serous and/or fibrinous effusions in excess of this amount occur most commonly in the setting of pericardial inflammation.
2. Serous: congestive heart failure, hypoalbuminemia of any cause
3. Serosanguineous: blunt chest trauma, malignancy, ruptured MI or aortic dissection
4. Chylous: mediastinal lymphatic obstruction

- The consequences of pericardial accumulations depend on the volume of fluid and the ability of the parietal pericardium to stretch.

- slowly accumulating effusions—even as large as 1000 mL—can be welltolerated

rapidly developing collections of as little as 250 mL can so restrict diastolic cardiac filling as to produce potentially fatal cardiac tamponade.

CARDIAC TUMORS

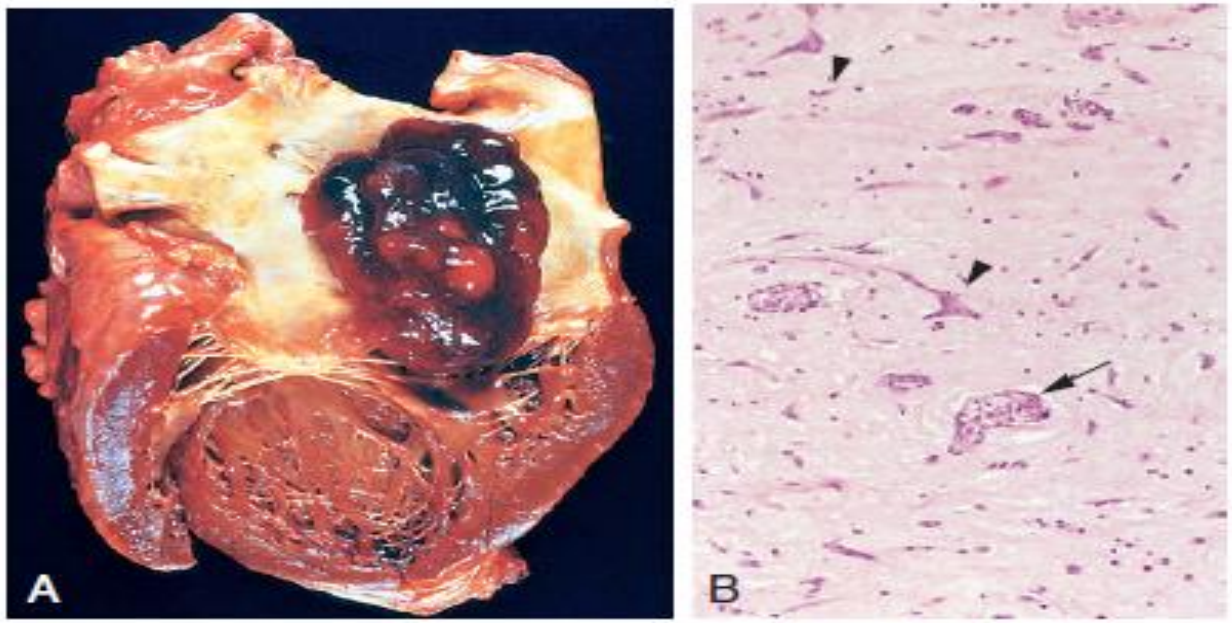


Figure 10–31 Atrial myxoma. **A,** A large pedunculated lesion arises from the region of the fossa ovalis and extends into the mitral valve orifice. **B,** Abundant amorphous extracellular matrix contains scattered multinucleate myxoma cells (*arrowheads*) in various groupings, including abnormal vascular formations (*arrow*).

HYPERTENSIVE HEART DISEASE

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Table 1: AHA/ACC[a] Guideline Recommendations by Blood Pressure Category

BP[b] Category	Pressure Ranges	Recommendations
Normal BP	<120/<80 mmHg	Promote healthy lifestyle; reassess BP annually.
Elevated BP	120-129/<80 mmHg	Start with nonpharmacologic therapy, reassess BP in 3-6 months.
Stage1 Hypertension	130-139/80-89 mmHg	**ASCVD[c] or 10-year CVD[d] risk ≥10%:** Start with both nonpharmacologic and pharmacologic therapy. Reassess BP in 1 month. If at goal, reassess every 3-6 months. If not at goal, assess for adherence and consider intensification of therapy.
		No ASCVD and 10-year CVD risk <10%: Start with nonpharmacologic therapy, reassess BP in 3-6 months. If not at goal, consider initiation of pharmacologic therapy.
Stage 2 Hypertension	≥140/≥90 mmHg	Start with both nonpharmacologic and pharmacologic therapy. Reassess BP in 1 month. If at goal, reassess every 3-6 months. If not at goal, assess for adherence and consider intensification of therapy.

a: AHA/ACC, American Heart Association, American College of Cardiology.
b: BP, blood pressure.
c: ASCVD, atherosclerotic cardiovascular disease.
d: CVD, cardiovascular disease

https://www.acc.org/latest-in-cardiology/articles/2021/06/21/13/05/new-guidance-on-bp-management-in-low-risk-adults-with-stage-1-htn

TYPES

1. **(95%) are idiopathic (essential hypertension).**

This form is compatible with long life unless a myocardial infarction, stroke, or another complication supervenes.

2.(5%) **(secondary hypertension)** .

1-Hyaline arteriolosclerosis

- is associated with benign hypertension.
- It is marked by homogeneous, pink hyaline thickening of the arteriolar walls, with loss of underlying structural detail, and luminal narrowing.

2- Hyperplastic arteriolosclerosis

- Is more typical of severe hypertension.
- Vessels exhibit "onionskin," concentric, laminated thickening of arteriolar walls and luminal narrowing.
- The laminations consist of smooth muscle cells and thickened, reduplicated basement membrane.

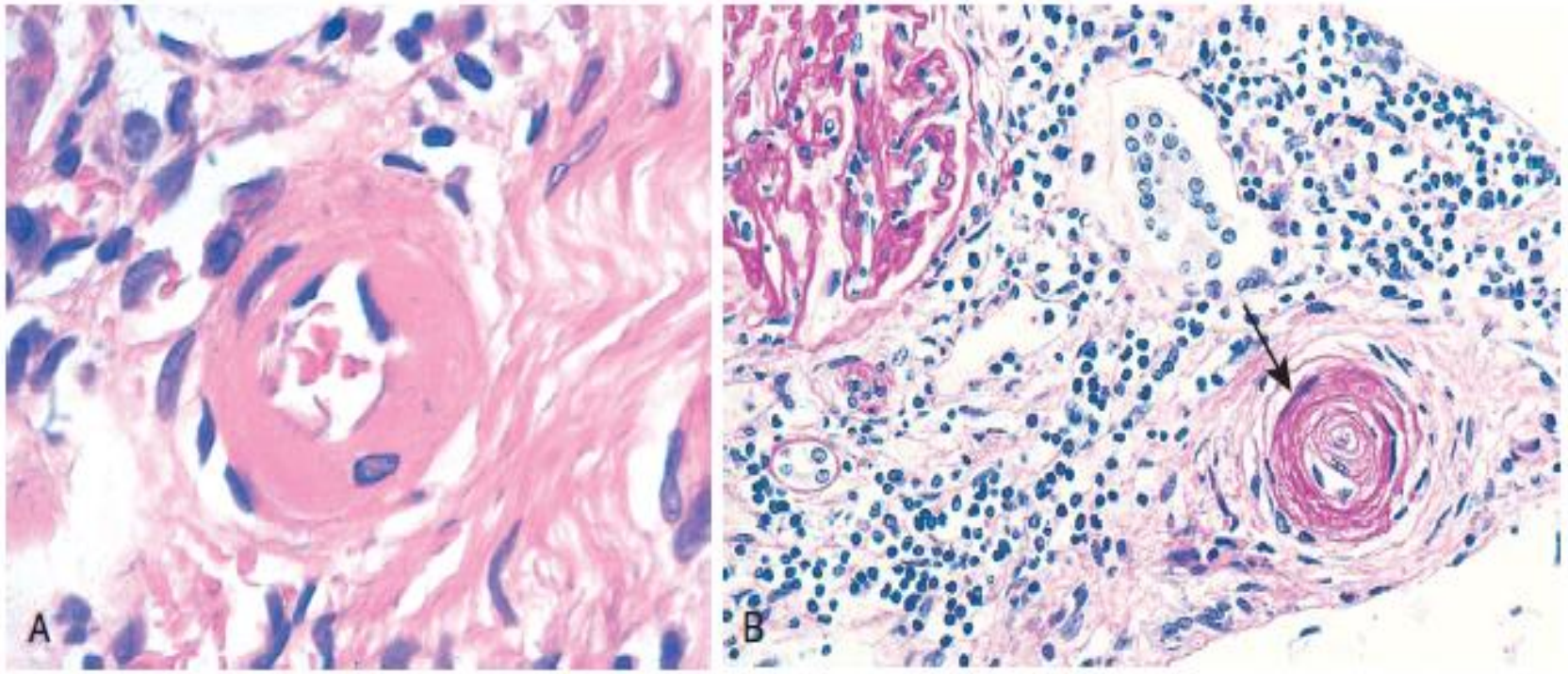


Figure 9–5 Hypertensive vascular disease. **A,** Hyaline arteriolosclerosis. The arteriolar wall is thickened with the deposition of amorphous proteinaceous material (hyalinized), and the lumen is markedly narrowed. **B,** Hyperplastic arteriolosclerosis ("onion-skinning") (*arrow*) causing luminal obliteration (periodic acid–Schiff stain).

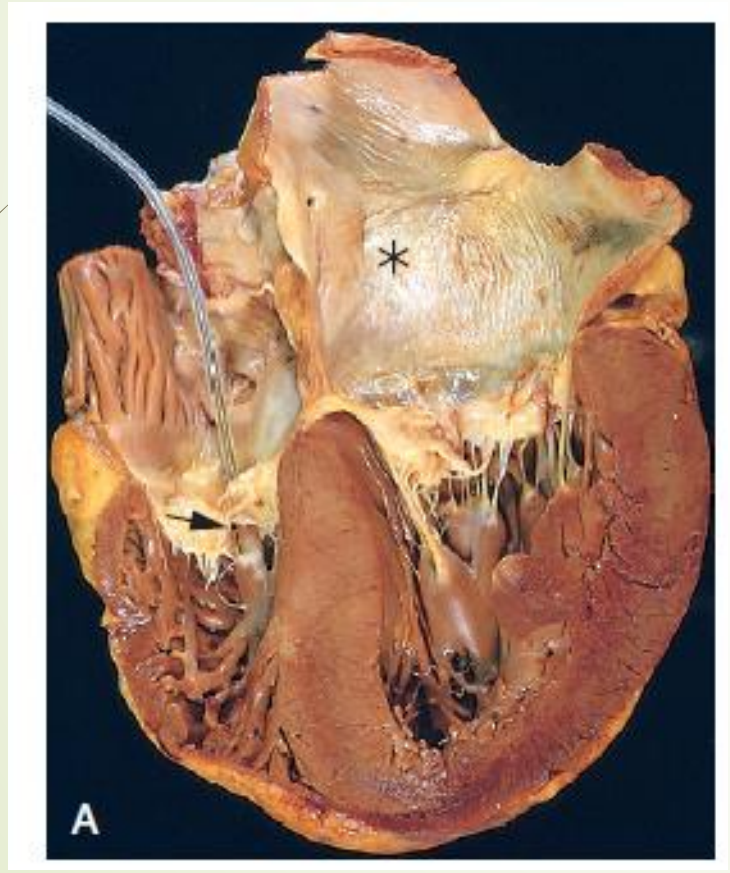
(Courtesy of Helmut Rennke, MD, Brigham and Women's Hospital, Boston, Massachusetts.)

HYPERTENSIVE HEART DISEASE

- Hypertensive heart disease (HHD) is a consequence of the increased demands placed on the heart by hypertension, causing pressure overload and ventricular hypertrophy.

1. Systemic (Left-Sided) Hypertensive Heart Disease.
2. Pulmonary Hypertensive Heart Disease—Cor Pulmonale.

- Systemic (left-sided) hypertensive heart disease. There is marked concentric thickening of the left ventricular wall causing reduction in lumen size. The left ventricle and left atrium are on the right in this four-chamber view of the heart. A pacemaker is present incidentally in the right ventricle (arrow). Note also the left atrial dilation (asterisk) due to stiffening of the left ventricle and impaired diastolic relaxation, leading to atrial volume overload.



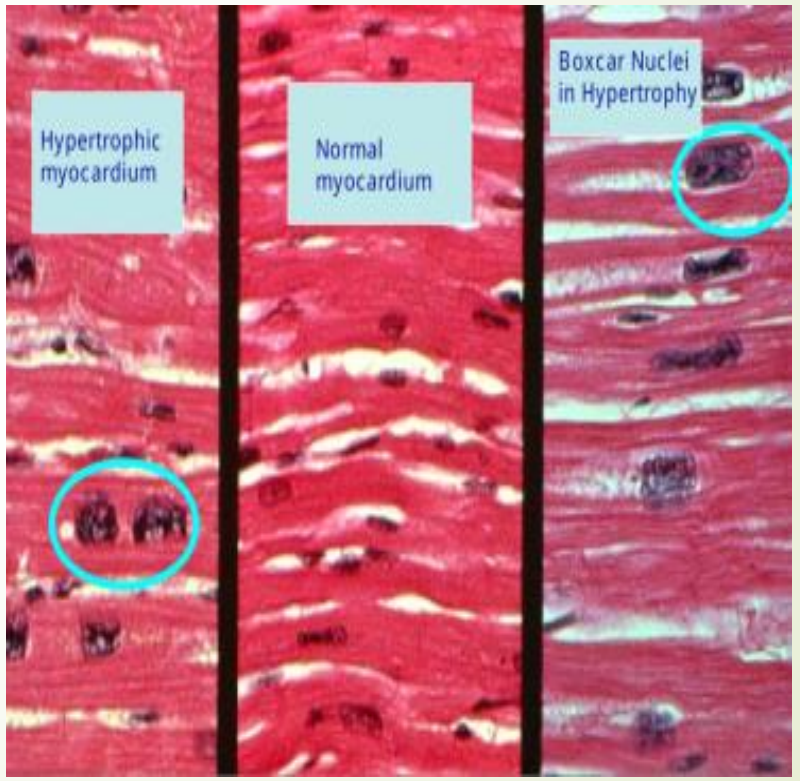


Table 10–4 Disorders Predisposing to Cor Pulmonale

Diseases of the Pulmonary Parenchyma
Chronic obstructive pulmonary disease
Diffuse pulmonary interstitial fibrosis
Pneumoconiosis
Cystic fibrosis
Bronchiectasis
Diseases of the Pulmonary Vessels
Recurrent pulmonary thromboembolism
Primary pulmonary hypertension
Extensive pulmonary arteritis (e.g., Wegener granulomatosis)
Drug-, toxin-, or radiation-induced vascular obstruction
Extensive pulmonary tumor microembolism
Disorders Affecting Chest Movement
Kyphoscoliosis
Marked obesity (pickwickian syndrome)
Neuromuscular diseases
Disorders Inducing Pulmonary Arterial Constriction
Metabolic acidosis
Hypoxemia
Obstruction to major airways
Idiopathic alveolar hypoventilation

MORPHOLOGY

- ✓ **In acute cor pulmonale**, the right ventricle usually shows only dilation; if an embolism causes sudden death, the heart may even be of normal size.
- ✓ **Chronic cor pulmonale** is characterized by right ventricular (and often right atrial) hypertrophy.

- When ventricular failure develops, the right ventricle and atrium often are dilated.
- Because chronic cor pulmonale occurs in the setting of pulmonary hypertension, the pulmonary arteries often contain atheromatous plaques and other lesions, reflecting longstanding pressure elevations.

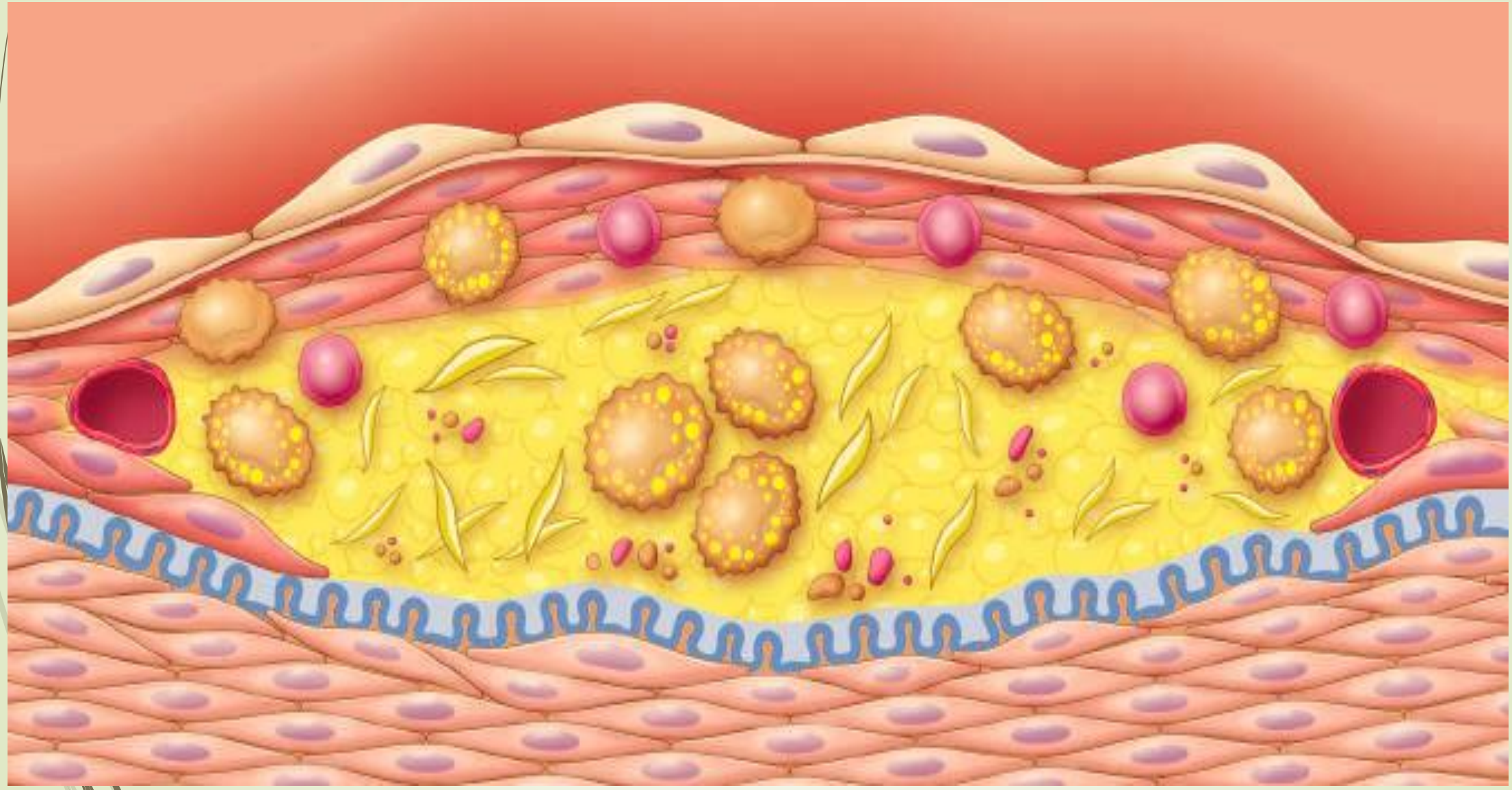
Chronic cor pulmonale. The right ventricle (shown on the left side of this picture) is markedly dilated and hypertrophied with a thickened free wall and hypertrophied trabeculae. The shape and volume of the left ventricle have been distorted by the enlarged right ventricle.

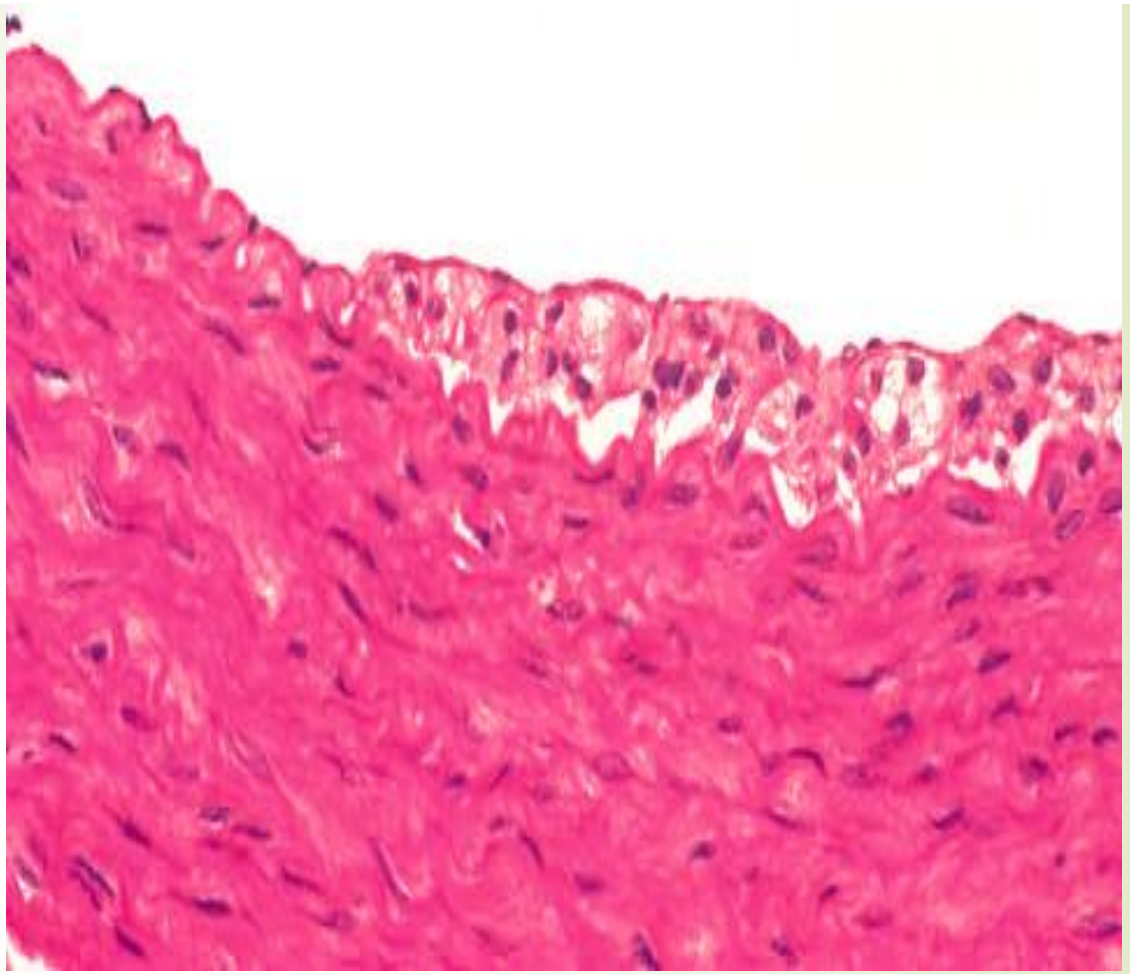
Arteriosclerosis

Literally, "hardening of the arterie"; A generic term for thickening and loss of elasticity of arterial walls. Four patterns of arteriosclerosis are recognized:

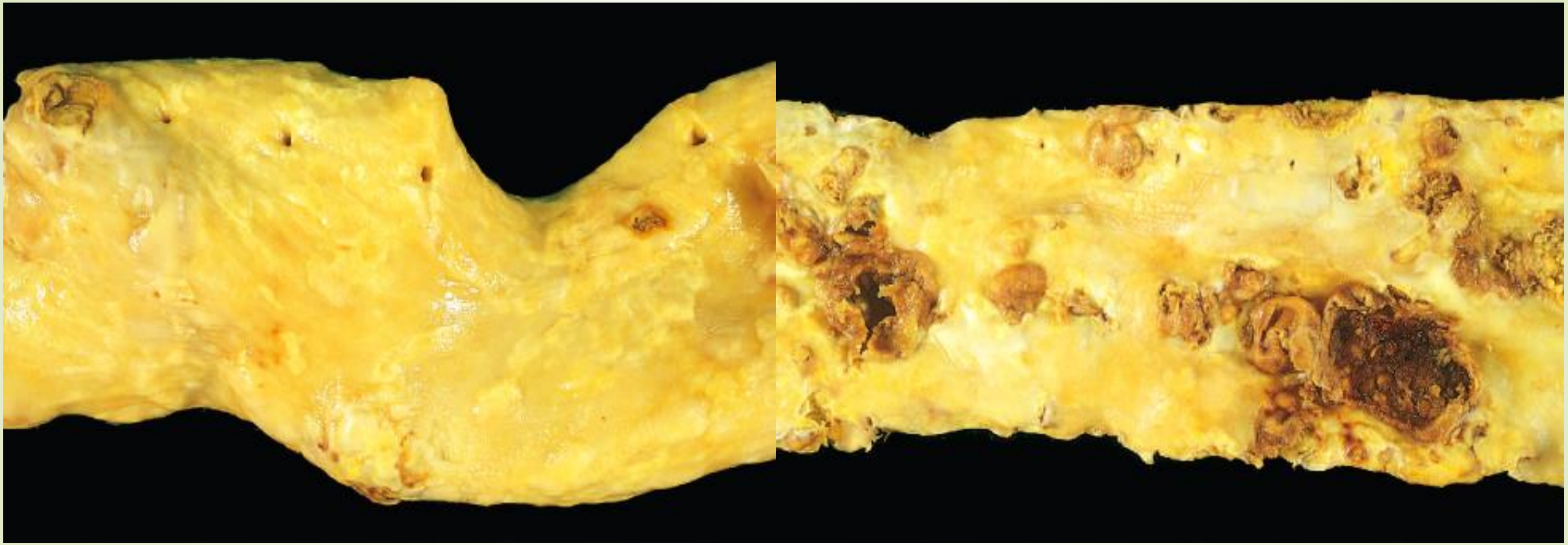
1. Arteriolosclerosis: Small arteries & arterioles, may cause ischemic:
    a. hyaline type
    b. hyperplastic type.
2. Monckberg medial calcification.
3. Fibromuscular intimal hyperplasia: thickened vascular wall with luminal narrowing.
4. Atherosclerosis..

Structure of an atheromatous plaque

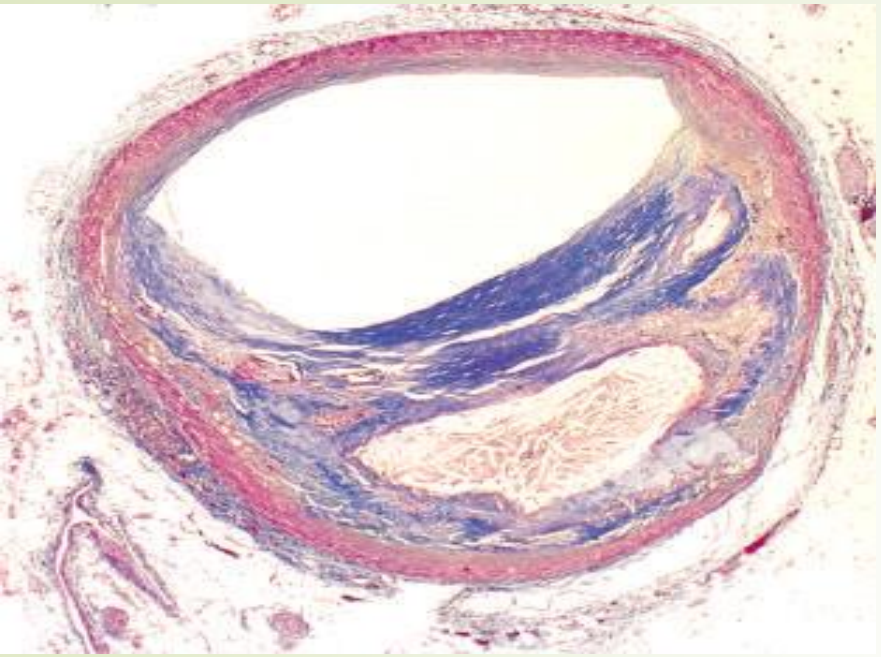


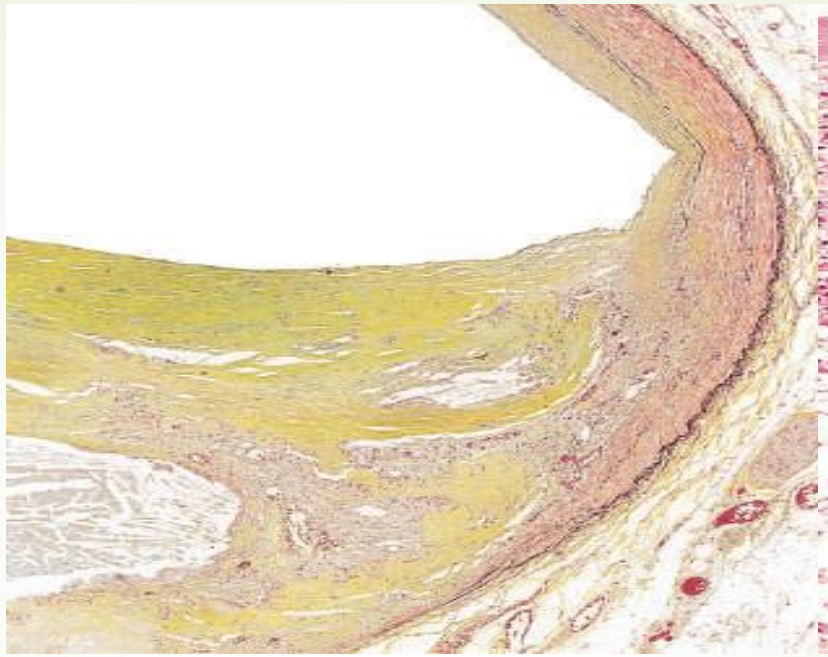


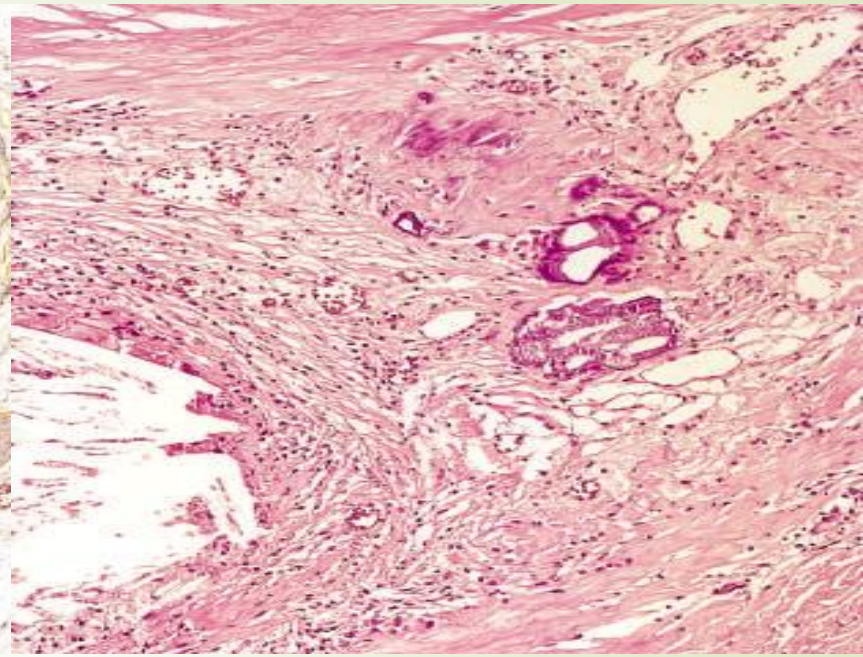
Fatty streaks: minute yellow, flat macules → coalesce into elongated lesions,> 1 cm. Composed of lipid-filled foamy macrophages. No flow disturbance. Aortas of infants can exhibit them, & present in all adolescents, regardless of genetic, clinical, or dietary risk factors. Not all fatty streaks progress to atherosclerotic plaques.



Atherosclerotic Plaque: Intimal thickening and lipid accumulation plaques are white to yellow **raised** lesions; range from 0.3 to 1.5 cm in diameter, can coalesce to form larger masses. Thrombus superimposed on ulcerated plaques imparts a red-brown color







Plaques: (1)A superficial **Fibrous cap** composed of SMCs and relatively dense collagen. Where the cap meets the vessel wall (shoulder) is a more cellular area (macrophages, T cells, & SMCs)

Deep to the fibrous cap is (2) a necrotic **core**, containing lipid, necrotic debris, foam cells, fibrin, variably organized thrombus, & other plasma proteins.

the internal and external elastic membranes are attenuated, & the media of the artery is thinned under the most advanced plaque

Plaques progressively enlarge over time through cell death & degeneration, synthesis & degradation of ECM (remodeling), & thrombus organization. Atheromas also often undergo calcification and neovascularization

Acute Plaque Change

Plaque erosion or rupture typically triggers thrombosis, leading to partial or complete vascular obstruction & often tissue infarction; three general categories:

- **Rupture/fissuring,** exposing highly thrombogenic plaque constituents.
- **Erosion/ulceration,** exposing the thrombogenic subendothelial basement membrane to blood.
- **Hemorrhage into the atheroma,** expanding its volume.

It is now recognized that plaques responsible for myocardial infarctions & other acute coronary syndromes often are asymptomatic before the acute event. The worrisome conclusion is that large numbers of asymptomatic individuals are at risk for a catastrophic coronary event.

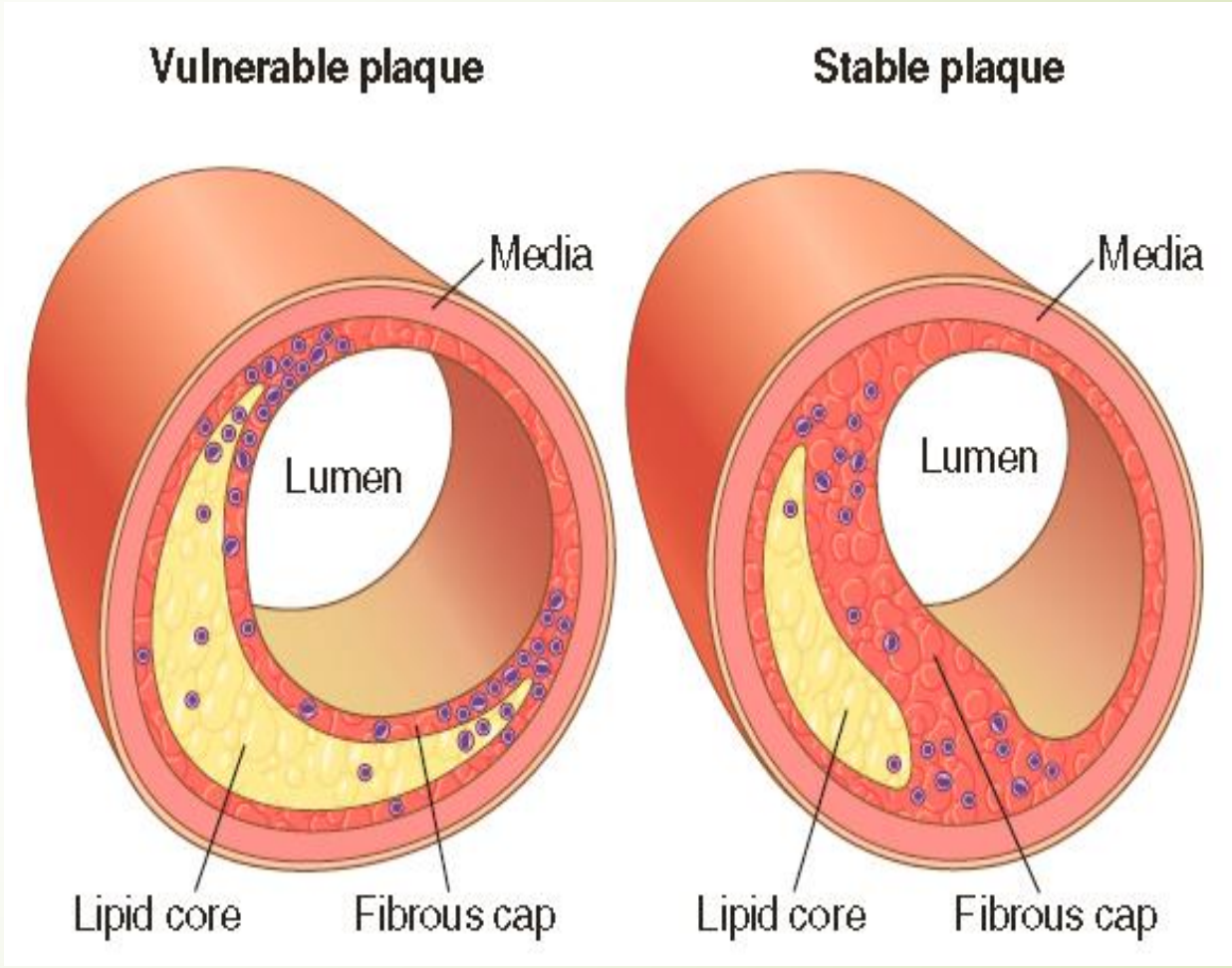
Causes of acute plaque changes

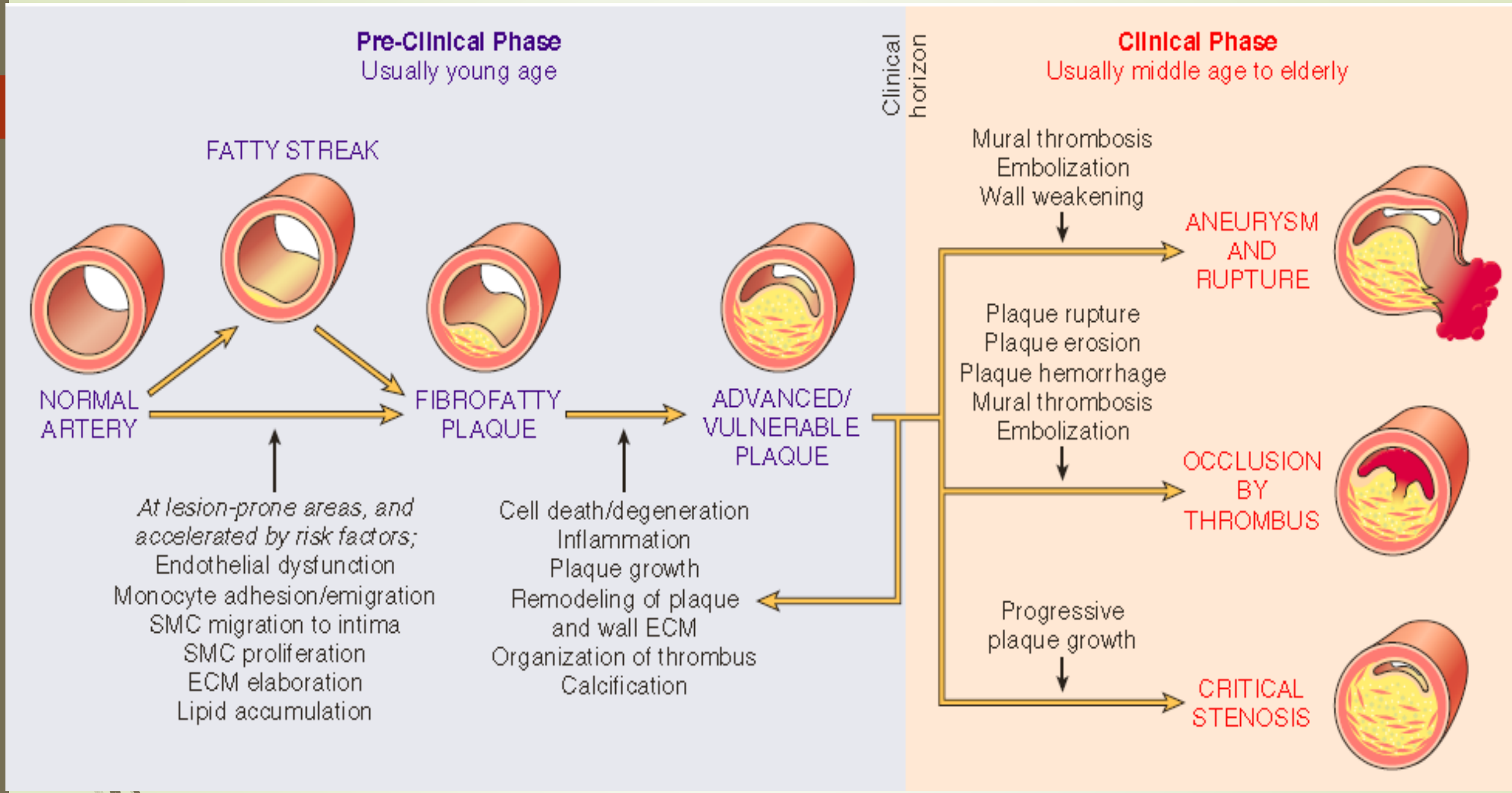
- **Complex but could be divided:**
- **Intrinsic factors:**

Vulnerable plaques: Plaques at high risk for rupture, they contain **large** numbers of **foam cells** & **abundant extracellular lipid**, have **thin fibrous caps** containing **few SMCs**, and contain **clusters of inflammatory cells.**

- **Extrinsic factors:**

Adrenergic stimulation (as with intense emotions) can increase systemic blood pressure or induce local **vasoconstriction**, thereby increasing the mechanical stress on a given plaque.




Pre-Clinical Phase
Usually young age
Clinical horizon
Clinical Phase
Usually middle age to elderly
FATTY STREAK
NORMAL ARTERY
FIBROFATTY PLAQUE
ADVANCED/ VULNERABLE PLAQUE
At lesion-prone areas, and accelerated by risk factors;
Endothelial dysfunction
Monocyte adhesion/emigration
SMC migration to intima
SMC proliferation
ECM elaboration
Lipid accumulation
Cell death/degeneration
Inflammation
Plaque growth
Remodeling of plaque and wall ECM
Organization of thrombus
Calcification
Mural thrombosis
Embolization
Wall weakening
ANEURYSM AND RUPTURE
Plaque rupture
Plaque erosion
Plaque hemorrhage
Mural thrombosis
Embolization
OCCLUSION BY THROMBUS
Progressive plaque growth
CRITICAL STENOSIS