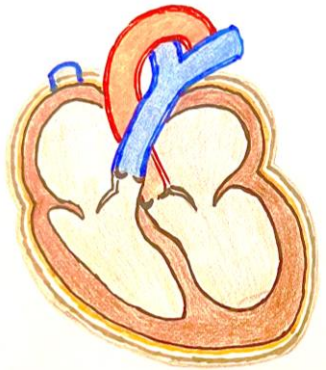
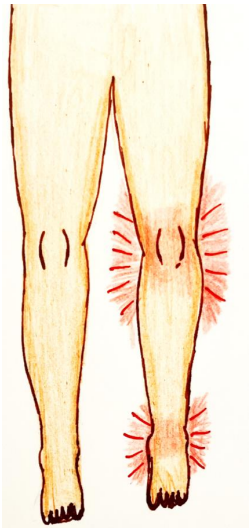


RHEUMATIC FEVER

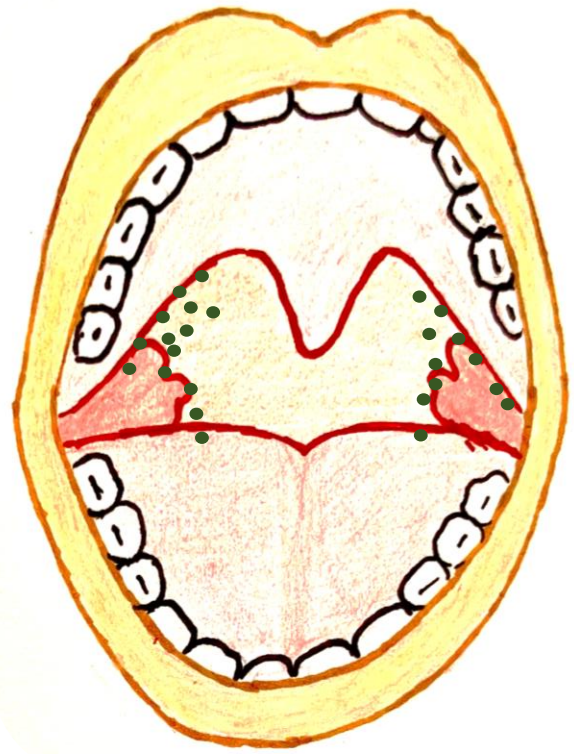
LICKS THE JOINTS AND BITES THE HEART



Dr.V.Shanthi
Professor, Pathology
Sri Venkateswara Institute of Medical Sciences, Tirupathi

RHEUMATIC FEVER

- Rheumatic fever (RF) is an acute, immunologically mediated, multisystem inflammatory disease classically occurring a few weeks after group A streptococcal pharyngitis
- Acute RF typically appears 10 days to 6 weeks after a group A streptococcal infection in about 3% of patients
- Mortality by RF and RHD is reduced due to improved sanitation, and rapid diagnosis and treatment of streptococcal pharyngitis



RHEUMATIC FEVER

Risk factors

- Age
  - ARF is common in children aged 5 to 15 years
  - Recurrent episodes often affect slightly older children, adolescents or young adults
  - Though RHD occurs in children its prevalence peaks in adulthood
- Sex
  - ARF is equally common in males and females
  - However RHD shows slight female predominance with M:F ratio of 1:1.6 to 2.0
- Environmental factors
  - Poverty
  - Overcrowding
  - Undernutrition

GROUP A BETA HEMOLYTIC STREPTOCOCCI

Extracellular substances

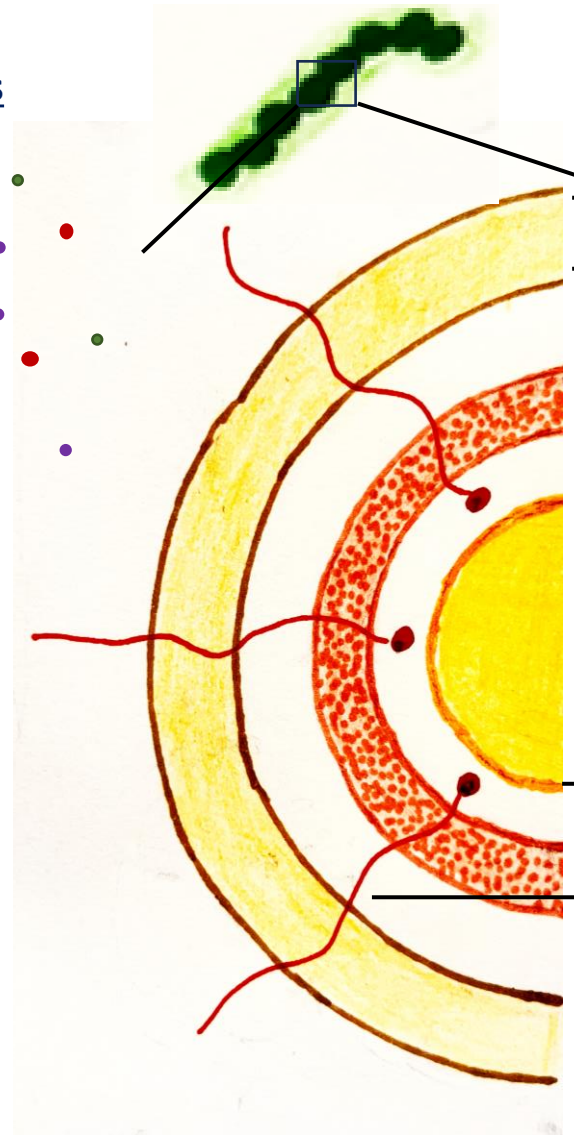
Streptolysins
- Streptolysin O
- Streptolysin S

Hyaluronidase

DNA ase

Streptokinase

Pyogenic exotoxins



Capsule (hyaluronic acid)

Peptidoglycan (cell wall) – group A carbohydrate antigen, rhamnose, N-acetyl glucosamine

Cell membrane

Pili with M-protein type antigen, lipotechioc acid, R and T proteins

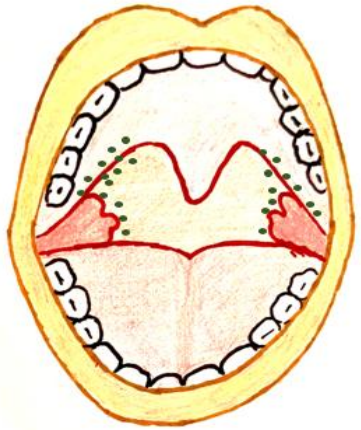
ANTIGENIC COMPONENT

α-helical protein structures found in streptococcal M protein shares a close resemblance with cardiac myosin, keratin, laminin and vimentin and leads to cross reactivity with antibodies that react to M protein, group A carbohydrate antigen and N-acetyl glucosamine

Pharyngeal cultures for streptococci are negative by the time the illness begins, antibodies to one or more streptococcal enzymes, such as streptolysin O and DNA ase B, can be detected in the sera of most patients with RF

RHEUMATIC FEVER
Pathogenesis

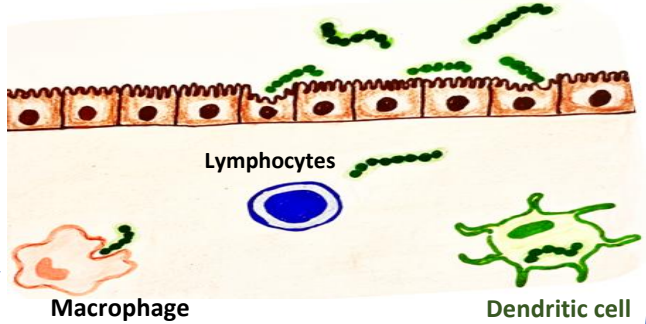
Throat infection (also from skin and mucosal infection)



Group A streptococcal infection

Activates humoral immune response

Activates innate immune response

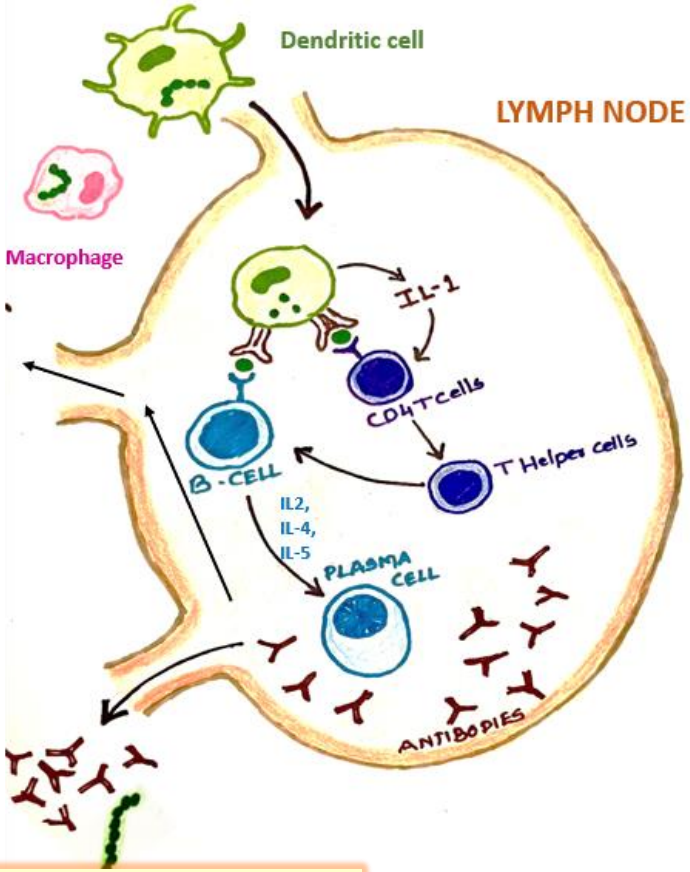


Fibrosis ← Angiotensin II

Produce inflammatory mediators
IL-2, IL-6, IL-8, IL-12, TNF-α and IFN-γ

Facilitate phagocytosis → Eliminate organisms

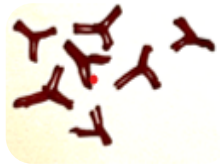
Promotes differentiation of B and T cells



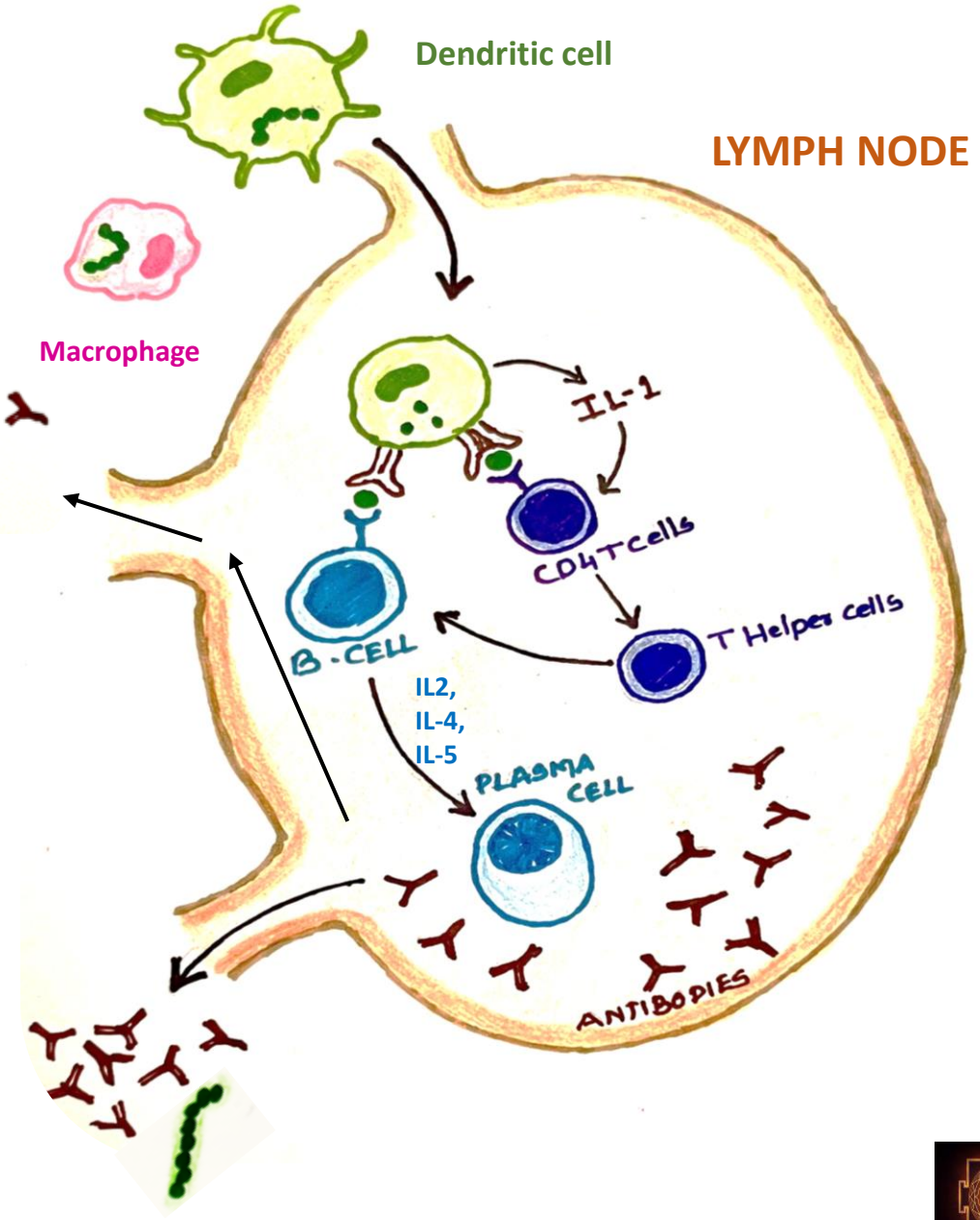
Antibody formation

RHEUMATIC FEVER
Pathogenesis

Due to Molecular mimicry antibodies against M protein of streptococci cross react with



- **Skin**
  - keratin
- **Heart**
  - Laminin
  - Tropomyosin
  - Troponin
  - Actin
  - Myosin
- **Brain**
  - Gangliosides in lentate nucleus, caudate nucleus and subthalamus
- **Joints**
  - Vimentin
- **Endothelial cells**
  - Vimentin
  - Laminin

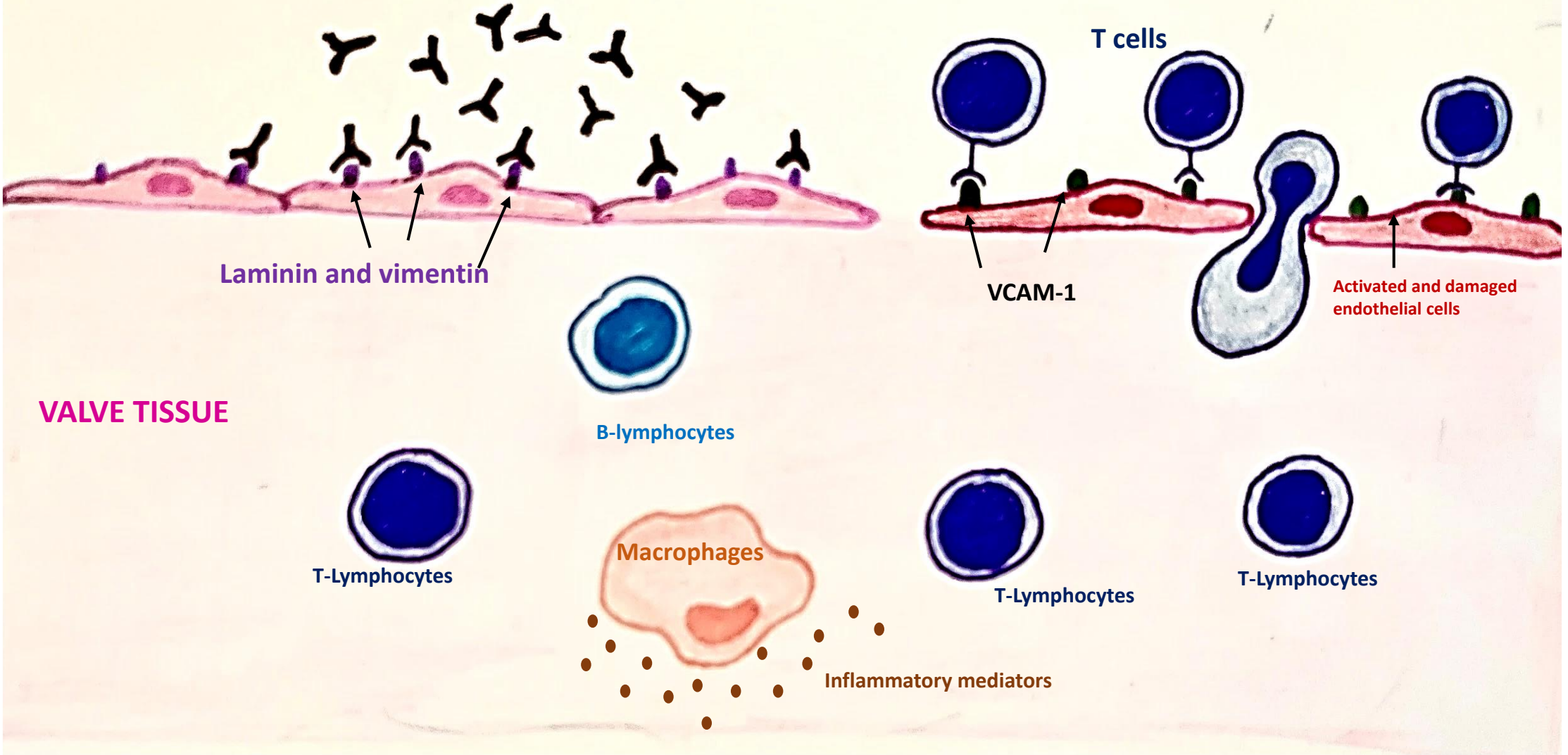


Small minority of infected patients develop rheumatic fever (estimated at 3%) due to genetic susceptibility which influence the development of the cross-reactive immune responses

RHEUMATIC FEVER - PATHOGENESIS

IgG antibodies cross react with laminin and vimentin of the endothelial cells causing damage to endothelial cells

Damaged endothelial cells express vascular cell adhesion molecule-1 (VCAM-1) which promotes infiltration of T cells through the activated endothelial cells into the valve



Both CD4+ and CD8+ T cells infiltrate and only autoreactive T cells survive and are continuously activated by antigens (valve protein)

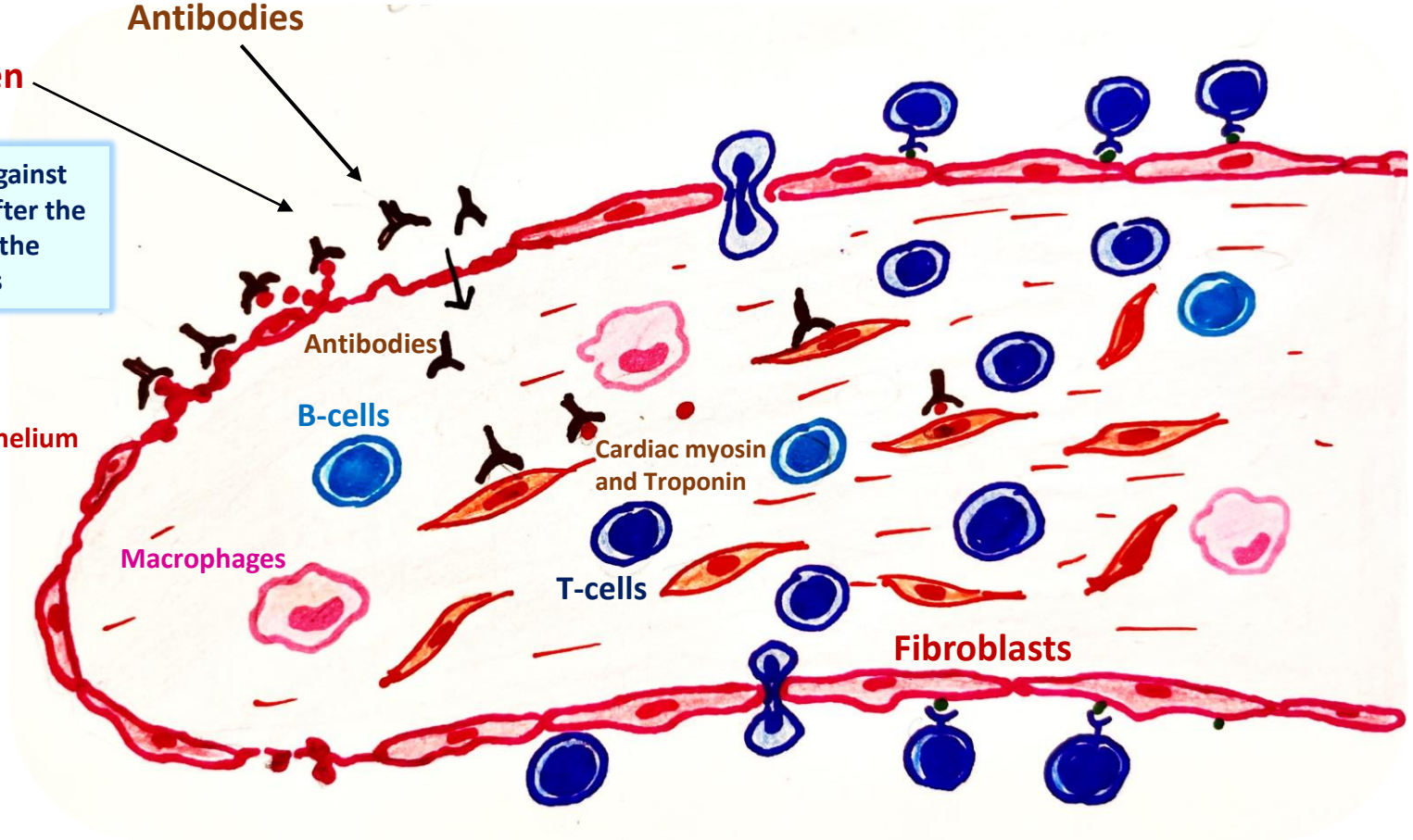
RHEUMATIC FEVER

Pathogenesis

Endothelial cell activation also involves loss of normal endothelial cell arrangement and modification of valvular collagen

Molecular mimicry against cardiac myosin and the Troponin causes damage to cardiac tissue leading to exposure of the immune system to collagen

Antibodies are produced against aggregated wesdscollagen after the release of collagen from the damaged heart valves



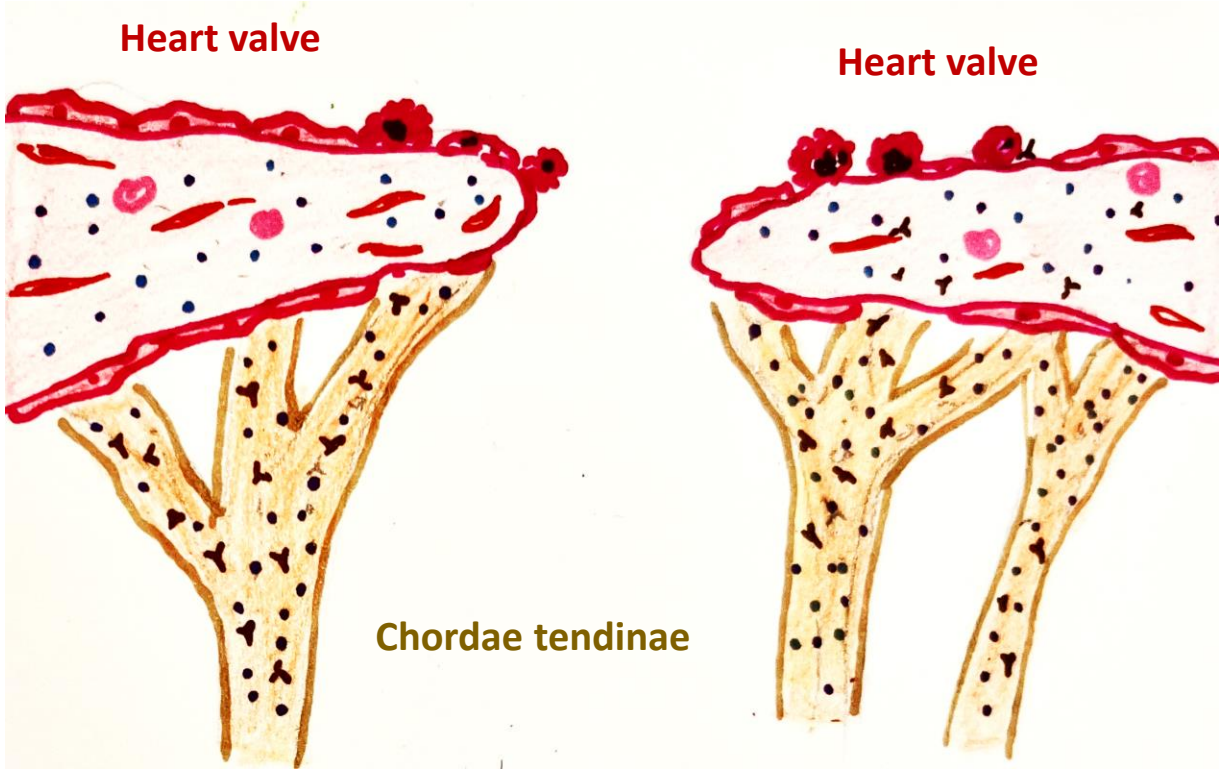
CD4+ T cells activated by streptococcal antigens also cross react with

cardiac antigens

RHEUMATIC FEVER

Pathogenesis

- Inflammatory infiltrate further extends into papillary muscle that contains myosin with in its cardiomyocytes
- eventually leads to damage to the valve tissue, chordae tendinae and myocardium
- Excessive production of autoantibodies upregulate inflammatory mediators leading to granulomatous inflammation producing Aschoff bodies



RHEUMATIC FEVER

Pathogenesis

Angiotensin II released from macrophages

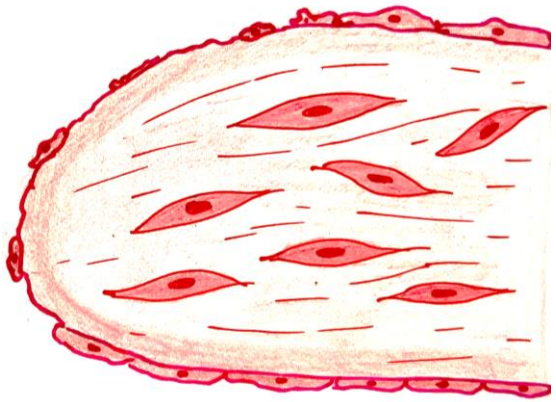
Stimulates ST2 deoxy receptor

Increased phosphorylation in the mitogen – activated protein kinase pathway

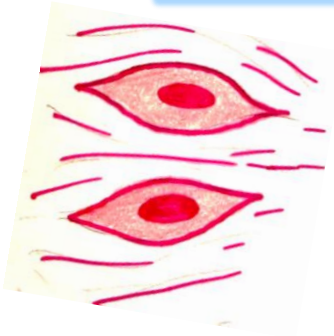
Cell proliferation, growth, differentiation, altered metabolism and gene expression

Fibroblast activation and proliferation

Stimulates TGF-β



Thickened and fibrotic valve tissue

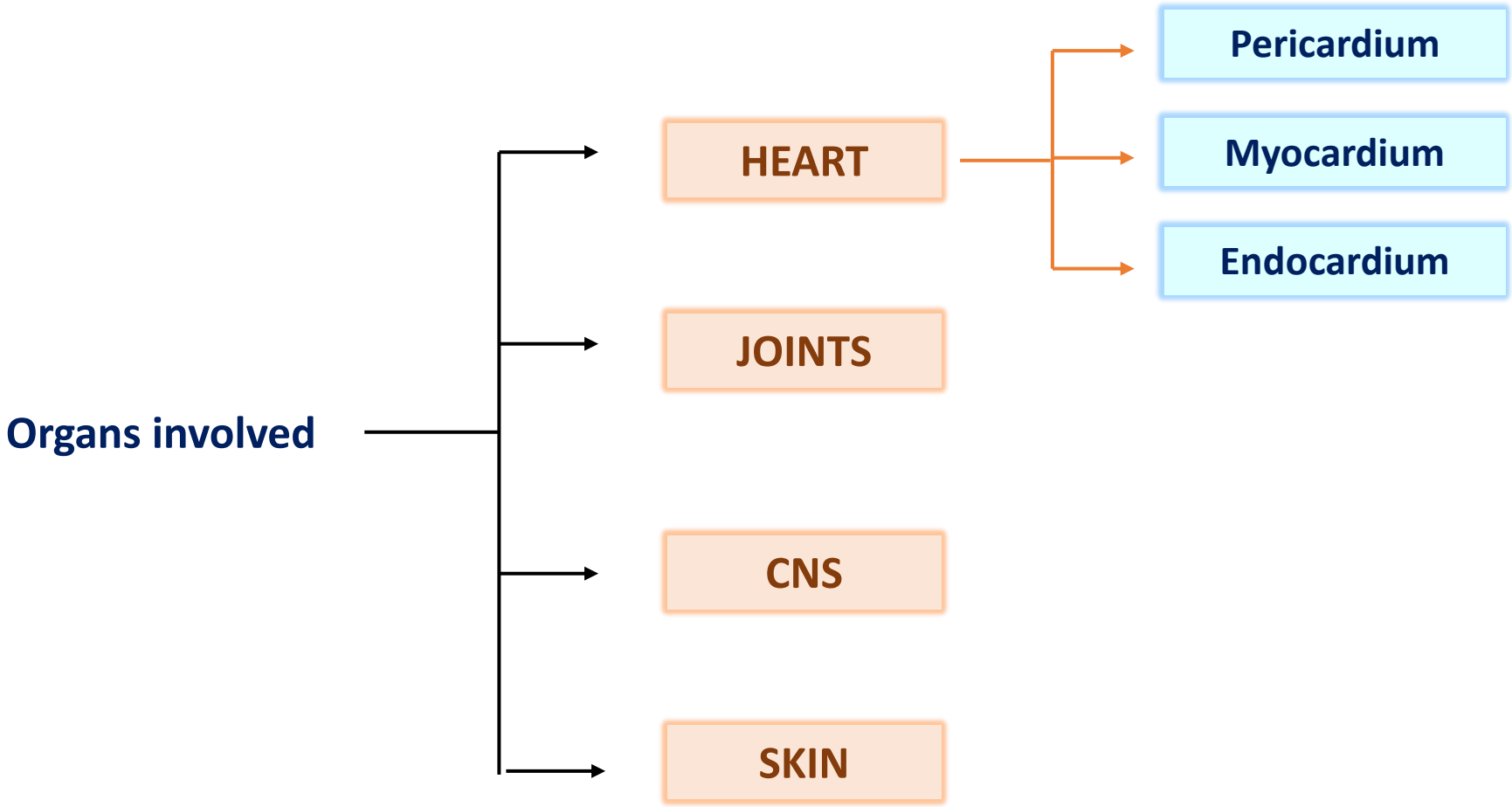


Activated fibroblast

Normal fibroblasts

RHEUMATIC FEVER

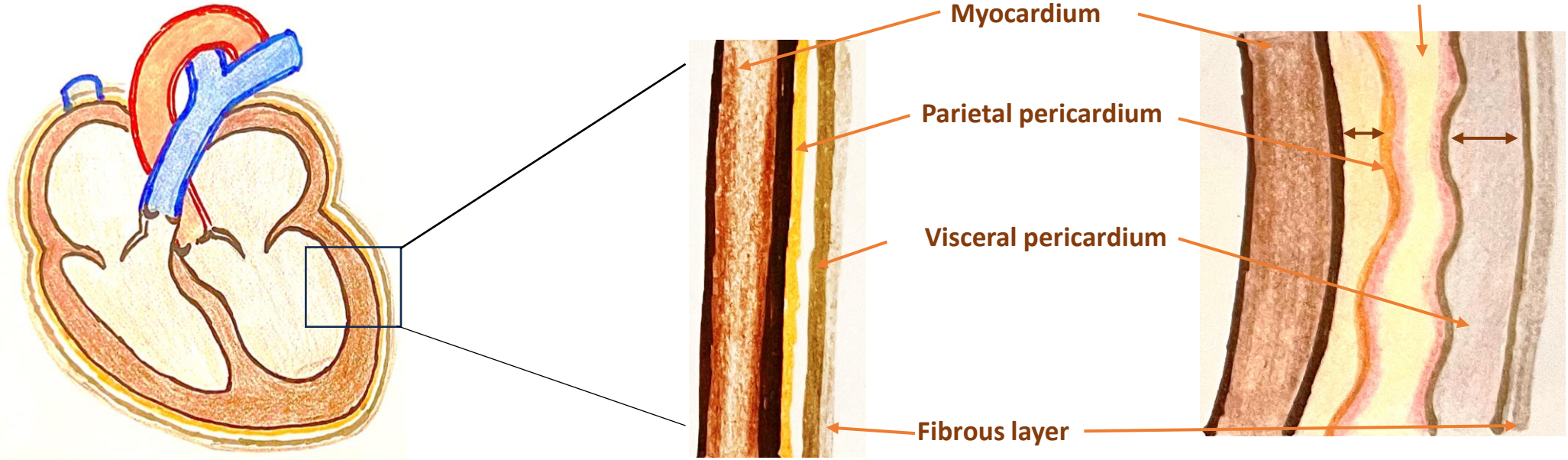
Morphology



RHEUMATIC FEVER- MORPHOLOGY

HEART– Pericardium changes

- Rheumatic pericarditis is autoimmune (not infective), and proposed to be involving pericardial antigen
- It primarily involves T cell mediated reaction
- Both layers of pericardium are irregulary thickened and covered by a shaggy fibrinous exudate
- Pericardial surface becomes opaque and granular and resembles two pieces of buttered bread pressed together than pulled apart – "Bread and butter pericarditis"
- Microscopy – shows deposition of fibrin material and leukocytic exudate



Produces pain and friction rub

RHEUMATIC FEVER- MORPHOLOGY

HEART– Myocardium changes

Myocardium

Myocarditis

- Fibrinoid necrosis
- Aschoff bodies

Decreased contractility

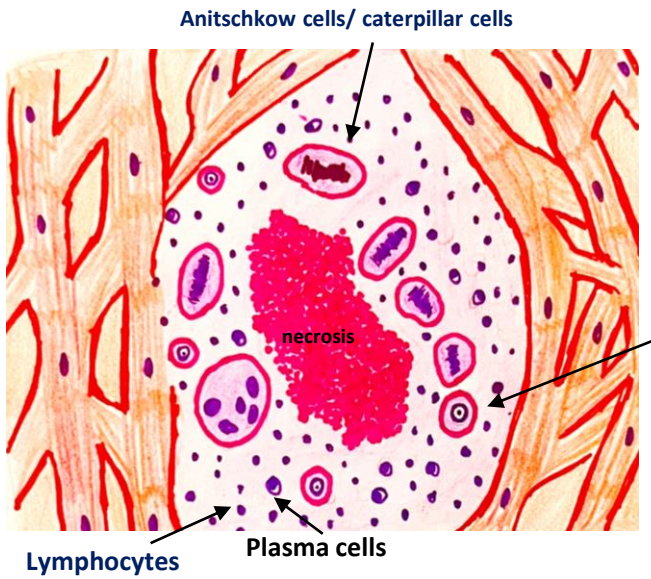
Decreased cardiac output

CHF

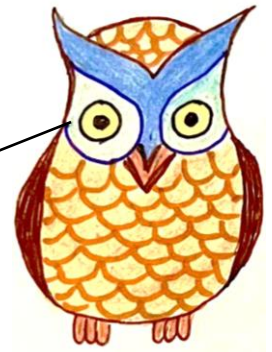
Aschoff bodies

- composed of foci of T lymphocytes, occasional plasma cells, and plump activated macrophages called Anitschkow cells
- These macrophages have abundant cytoplasm and central round to ovoid nuclei (occasionally binucleate) in which the chromatin condenses into a central, slender, wavy ribbon (hence the designation "caterpillar cells")

ASCHOFF BODY



Owl eyed appearance of cells



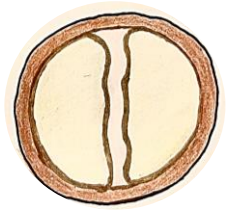
RHEUMATIC FEVER- MORPHOLOGY

HEART– Endocardium – valve changes

HEART – VALVULAR TISSUE

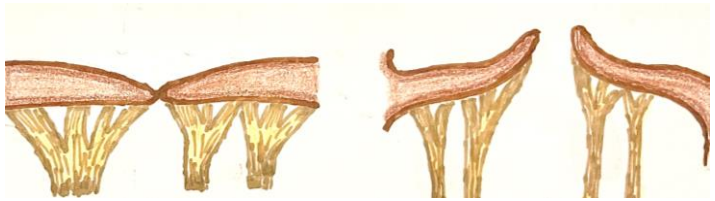
Dilation of valve annular-ring that surrounds the valve and that helps close leaflets during systole

Normal valves with annular ring



Dilated annular ring

Elongation of chordae tendine which connect leaflets of the mitral and tricuspid valves to the left and right ventricles



Normal valves

Elongated chordae tendine

Inflammation leads to fibrinous vegetation in the rough zone of the anterior leaflet

Vegetations on valve

Scarring of leaflet

Inadequate coaptation of valve leaflets, which inturn cause
VALVULAR REGURGITATION

valve becomes narrowed, and cannot fully open
VALVULAR STENOSIS

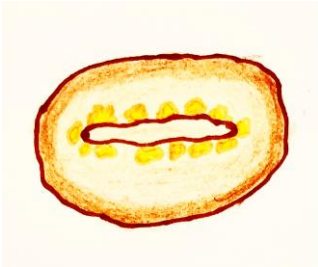
RHEUMATIC FEVER

Morphology

HEART – VALVULAR TISSUE

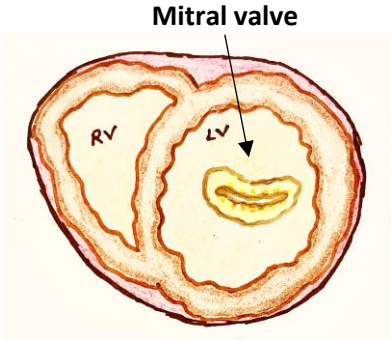
Verrucous vegetations

Overlying the necrotic foci and along the lines of closure, small (1 to 2 mm) vegetations, called verrucae which are grey white translucent are formed



Mitral stenosis

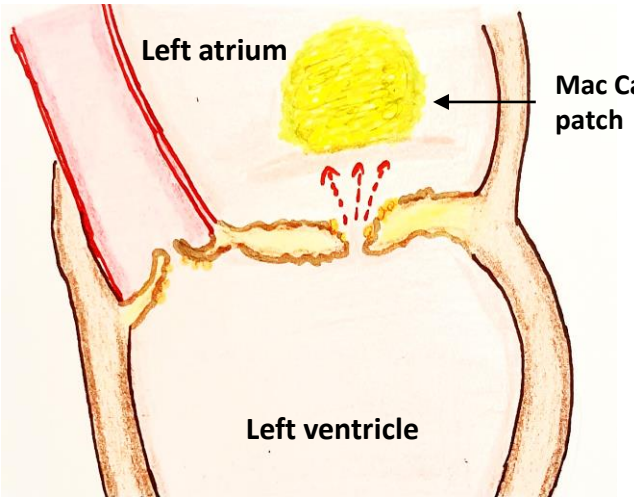
Calcification and fibrous bridging across the valvular commissures create "fish mouth" stenoses



Fish mouth appearance

MacCallum plaques

Subendocardial lesions, due to regurgitant jets, can induce irregular thickenings of endocardium called MacCallum plaques, usually in the left atrium



Regurgitation due to vegetations, calcifications and commissural fusion

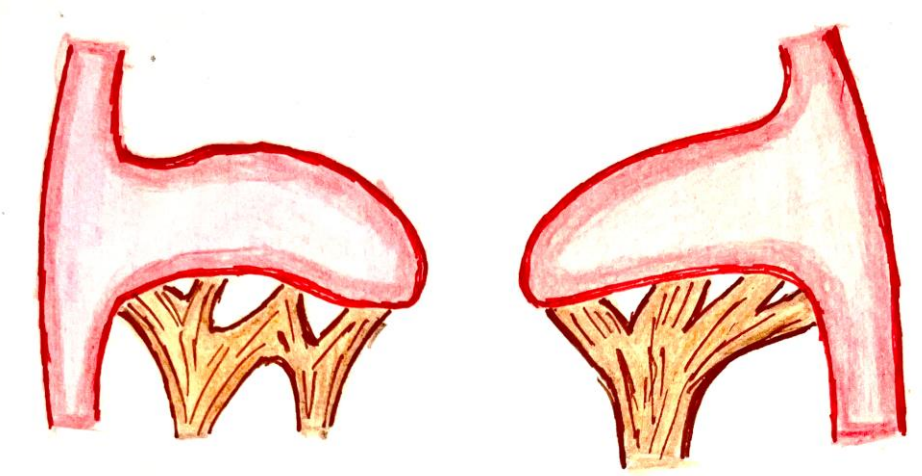
Left atrium progressively dilates and may harbor mural thrombi that can embolize

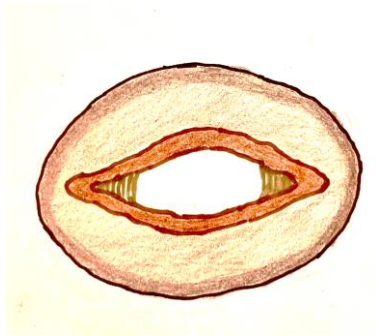
RHEUMATIC FEVER

Morphology

Mitral valve changes in chronic RHD

- **Leaflet thickening**
- **Shortening, thickening and fusion of the tendinous cords**
- **Commissural fusion**

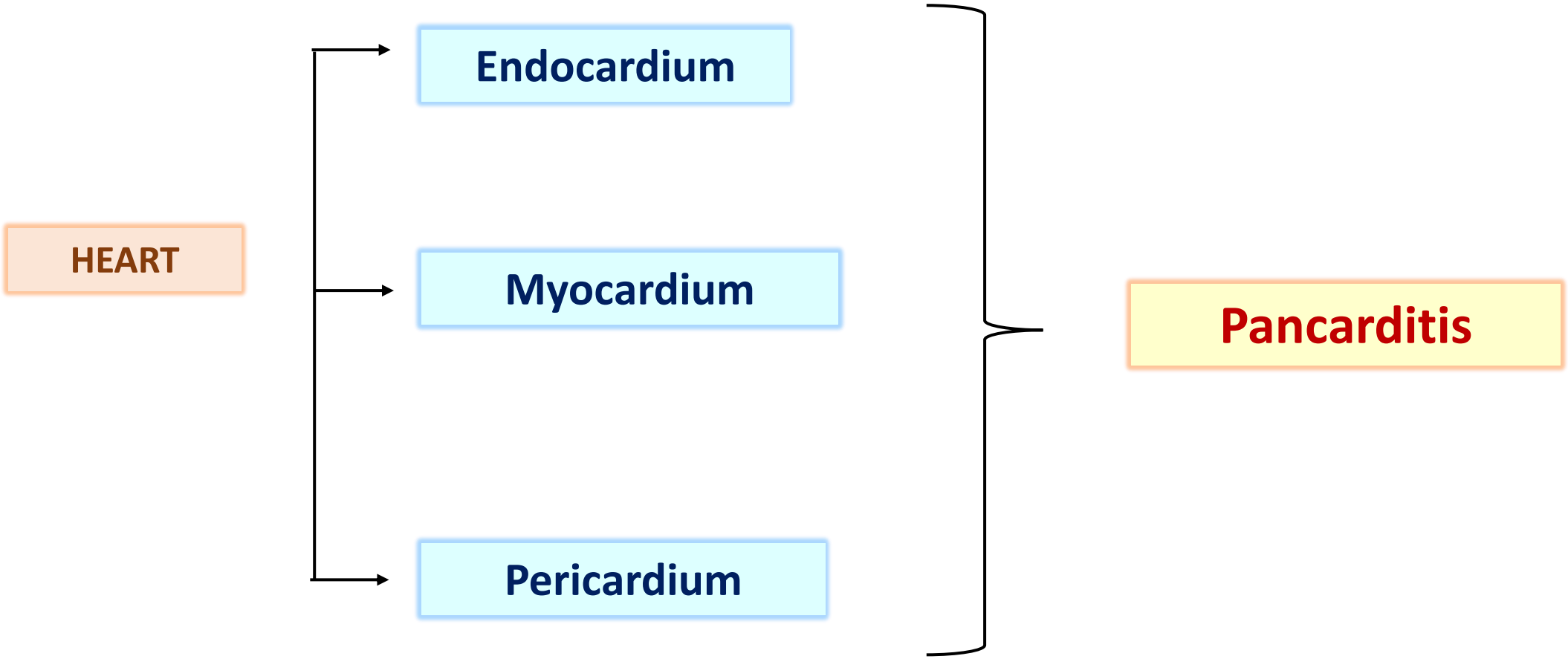




Mitral valve is affected in isolation in roughly two-thirds of cases, and along with the aortic valve in another 25%

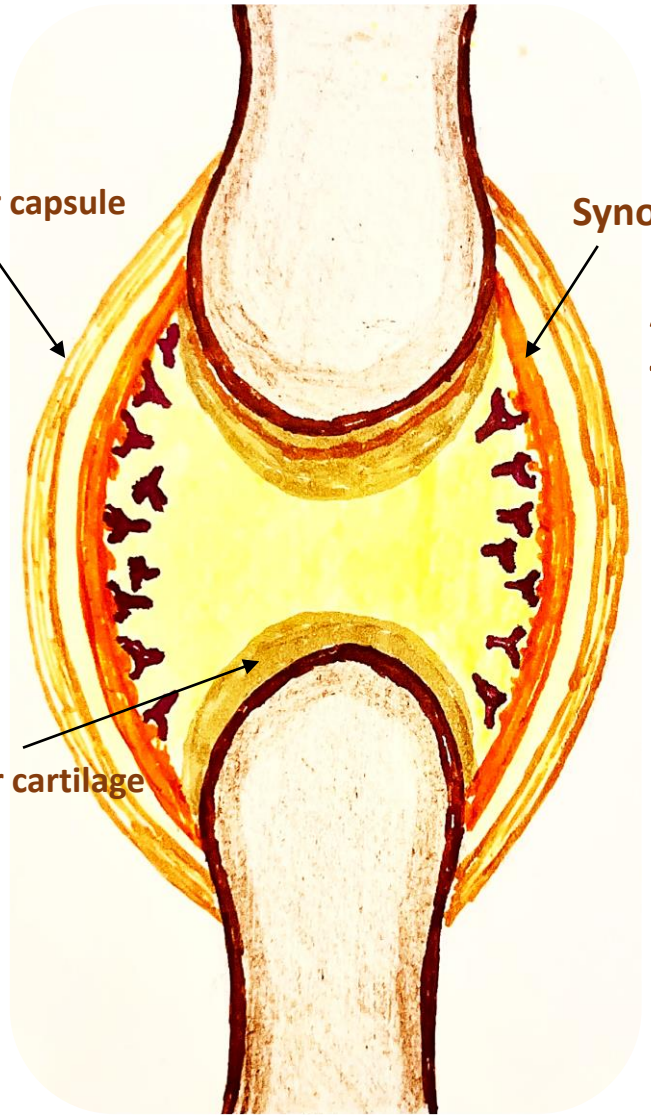
RHEUMATIC FEVER

Morphology



RHEUMATIC FEVER- MORPHOLOGY

JOINTS



Antibodies against the vimentin and collagen in joints

↓

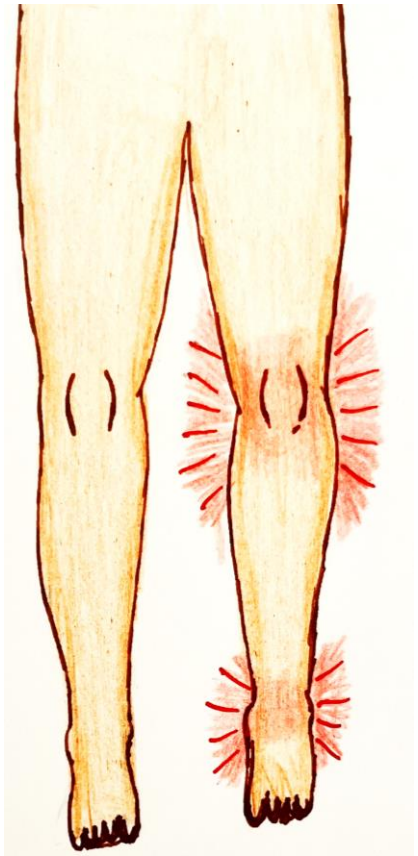
Formation of immune complexes

↓

Recruitment of inflammatory cells

↓

Arthritis



Type of arthritis

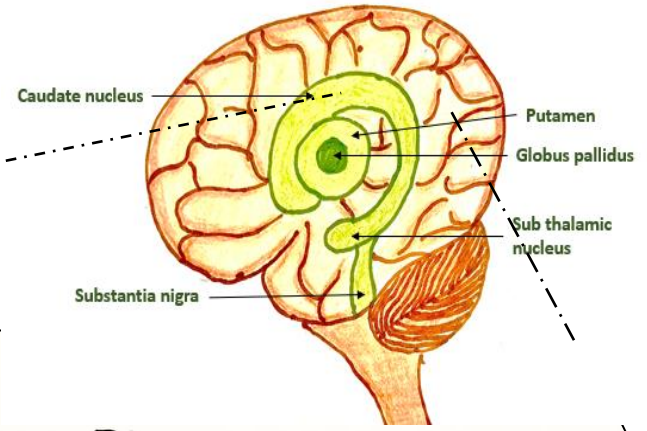
Migratory Polyarthritis

one large joint after another becomes painful and swollen for a period of days and then subsides spontaneously, leaving no residual disability

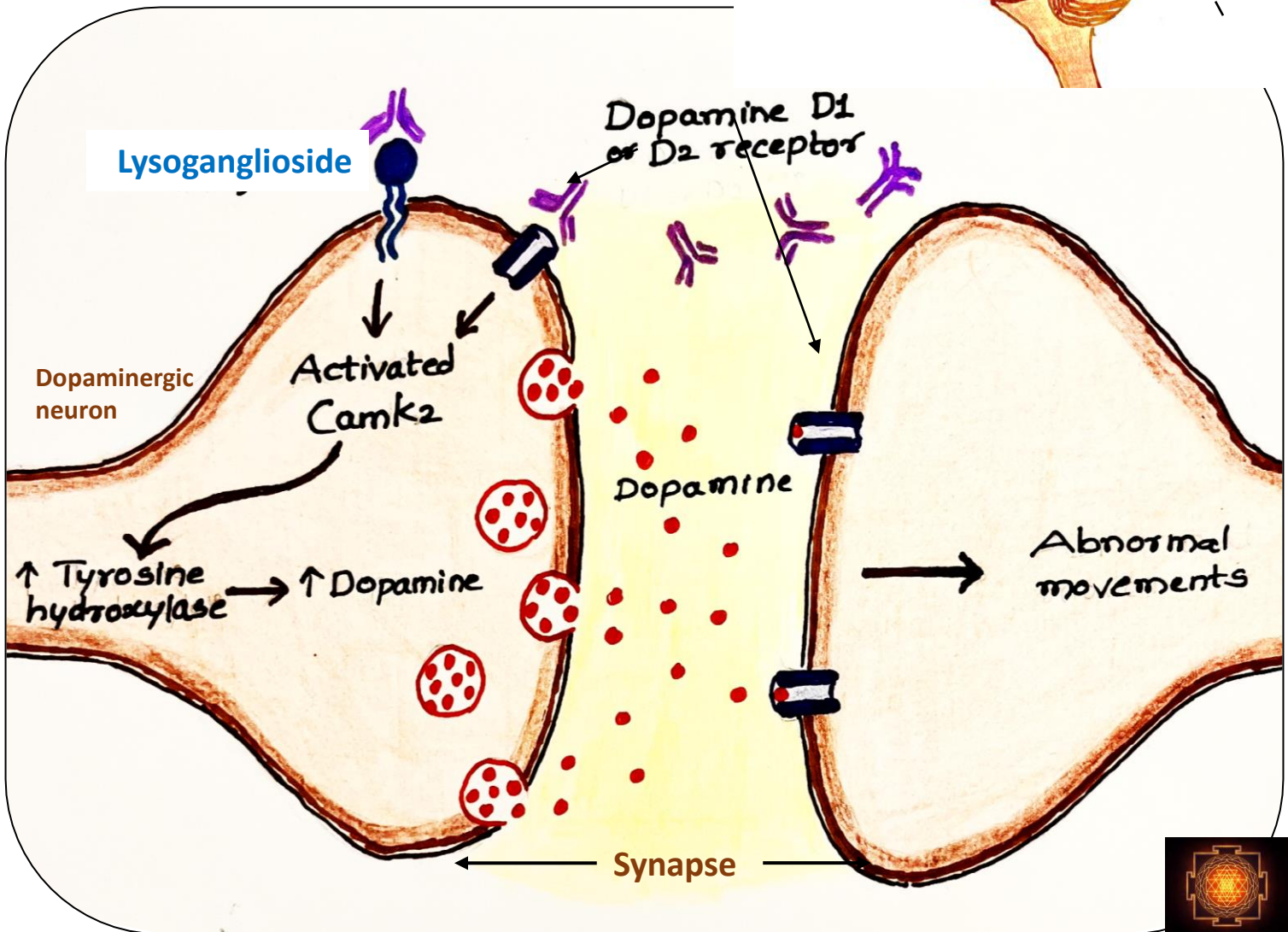
Large joints are involved

RHEUMATIC FEVER- MORPHOLOGY

CNS INVOLVEMENT

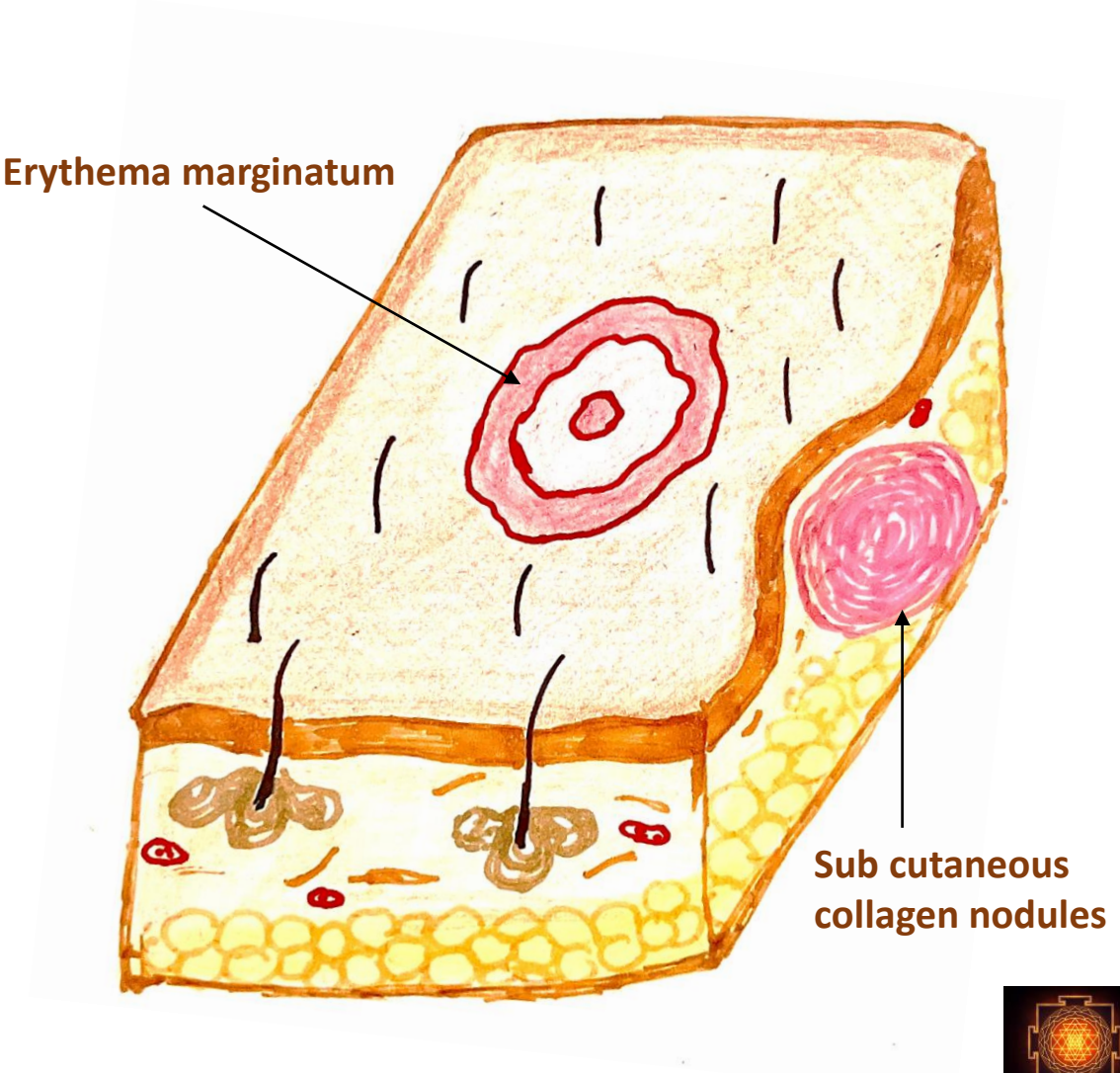


- Antibodies attack neurons in basal ganglia
- Antibodies react against D1 and D2 dopamine receptors, lysoganglioside and tubulin
- This causes signaling through activation of calcium/calmodulin – dependent protein kinase type II (CAMK2), which leads to an increase in tyrosine hydroxylase and dopamine release
- Produces Sydenhams chorea – characterized by uncontrolled and rapid movements of
  - Extremities
  - Face
  - tongue



RHEUMATIC FEVER- MORPHOLOGY
SKIN INVOLVEMENT

- **Erythema marginatum**
  - might be due to antibodies cross reacting to keratin
  - Type of lesion with pale centre and slightly raised red border
- **Subcutanous nodules**
  - might be caused by delayed hypersensitivity against group A streptococcal antigens and due to deposition of collagen
  - These painless nodules are found on joints like back of the wrist, elbow, knees, ankles and knuckles



RHEUMATIC FEVER

JONES CRITERIA

MAJOR CRITERIA

JONES FACE P

- **J** — Migratory polyarthritis of the large joints
- **♥** — Pancarditis (myocarditis, pericarditis, or endocarditis)
- **N** — Subcutaneous nodules (typically on extensor surfaces of extremities)
- **E** — Erythema marginatum, an irregular circinate skin rash
- **S** — Sydenham chorea, a neurologic disorder with involuntary rapid movements

MINOR CRITERIA

- **F** • Fever
- **A** • Monoarthralgia
- **C** • Elevated blood levels of acute-phase reactants (C reactive protein ≥ 3.0mg/dl)
- **E** • Raised ESR (≥ 60 mm of Hg)
- **P** • Prolonged PR interval

DIAGNOSTIC CRITERIA

Evidence of antecedent streptococcal infection

- Throat swab culture or rapid antigen test
- Elevated or increased streptolysin O titres in serum

+

2 MAJOR CRITERIA

OR

ONE MAJOR AND TWO MINOR CRITERIA

RHEUMATIC FEVER

Clinical features

CARDITIS

Pericardial involvement

- Pericardial friction rub

Myocardium

- Cardiac dilation and hypertrophy
- Valve insufficiency
- Heart failure

Valve tissue

- Thickened valve, commissural fusion and vegetations on valve
- Valve stenosis
- Regurgitations and cardiac murmurs

JOINTS

- Migratory polyarthritis

SKIN

- Erythema marginatum
- Subcutaneous nodules

Chronic RHD

- Arrhythmias
- Thromboembolic complications, and infective endocarditis

Approximately 1% of affected individuals die of fulminant RF involvement of the heart

RHEUMATIC FEVER

Complications

- **Adhesive pericarditis - adhesions develop after fibrinous pericarditis**
- **Infective endocarditis – damaged valves are the sites for deposition and growth of bacteria**
- **Mural thrombi in atrial and ventricular chambers**
- **Thromboemboli – mural thrombi may develop lead to emboli and infarction of various organs**
- **Congestive heart failure**
- **Arrhythmias**

RHEUMATIC FEVER

TREATMENT

- Primarily with antibiotics like Pencillin to control infection with Group A beta hemolytic streptococci
- Complications
  - medical treatment for CHF and with anticoagulants
  - Surgical repair and replacement of diseased valves

Summary

RHEUMATIC FEVER

Definition : is an acute, immunologically mediated, multisystem inflammatory disease classically occurring a 10 days to 6 weeks after group A streptococcal pharyngitis

Age : ARF more commn in - childhood; RHD in adulthood

Pathogenesis : cross reactivity of Ab's against M protein with cardiac myosin, keratin, laminin, vimentin and ganglioside

Organs involved

Heart → Pancarditis

- **Pericardium** — Fibrinous pericarditis
- **Myocardium** — Myocarditis with Ascoff bodies
- **Endocardium** — Mainly involve valvular tissue

- Thickening and elongation of valves
- Vegetations on valve
- Elongation of chorde tendinae
- Fish mouth stenosis
- Later Shortening and thickening of thickening cords
- Mac callums plaque

Joints	Migratory polyarthritis- due to Abs to vimentin and collagen in synovial tissue
CNS	Ab's against ganglioside, D1 and D2 receptor leads to Sydenhams chorea
Skin	Erythema marginatum and subcutaneous collagen nodules

Complications – P E T C A T

Diagnostic criteria

JONES CRITERIA
- Major criteria
- Minor criteria

Evidence of preceding streptococcal infection + (2 MAJOR CRITERIA or ONE MAJOR AND TWO MINOR CRITERIA)

JONES FACE P

THANK YOU