RHEUMATIC HEART DISEASE

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INFLAMMATORY DISEASES OF THE HEART may involve any or all of the anatomic layers of the heart and may produce severe deformity of one or more of the heart valves. Chronic valvular disease may become the most important clinical feature of inflammatory heart disease.

A. **Rheumatic heart disease** is the most important manifestation of acute rheumatic fever because it alone can cause severe parenchymal injury or death. Rheumatic fever is a systemic, nonsuppurative inflammatory complication of untreated pharyngeal infection with group A β-hemolytic streptococci, which is characterized by inflammatory lesions primarily involving the heart, joints, and subcutaneous tissue. Acute rheumatic carditis develops in 40% to 50% of patients with a first attack of acute rheumatic fever.

1. **Epidemiology.** Overall, less than 1% of untreated cases of group A streptococcal pharyngitis develops into acute rheumatic fever. Patients who do develop rheumatic fever are susceptible to recurrent attacks and risk greater cardiac effects with each attack.

a] Rheumatic fever typically occurs in children between the ages of 5 and 15 years, however, any age-group may be affected. Males and females are equally susceptible.

b] Worldwide in distribution, rheumatic fever most frequently occurs in developing countries and in lower socioeconomic groups; it is believed to be the cause of 25% to 40% of all cardiovascular disease in the Third World.

2. **Etiopathogenesis**. After a long controversy, the etiologic role of preceding throat infection with β-haemolytic streptococci of group A in RF is now generally accepted. However, the mechanism of lesions in the heart, joints and other tissues is not by direct infection but by induction of hypersensitivity or autoimmunity. Thus, there are 2 types of evidence in the etiology and pathogenesis of RF and RHD: the epidemiologic evidence and the immunologic evidence.

3. **Pathologic changes.**

RF is generally regarded as an autoimmune focal inflammatory disorder of the connective tissues throughout the body. The cardiac lesions of RF in the form of pancarditis, particularly the valvular lesions, are its major manifestations. However, supportive connective tissues at other sites like the synovial membrane, periarticular tissue, skin and subcutaneous tissue, arterial wall, lungs, pleura and the CNS are all affected (extracardiac lesions).

A. **Cardiac Lesions**

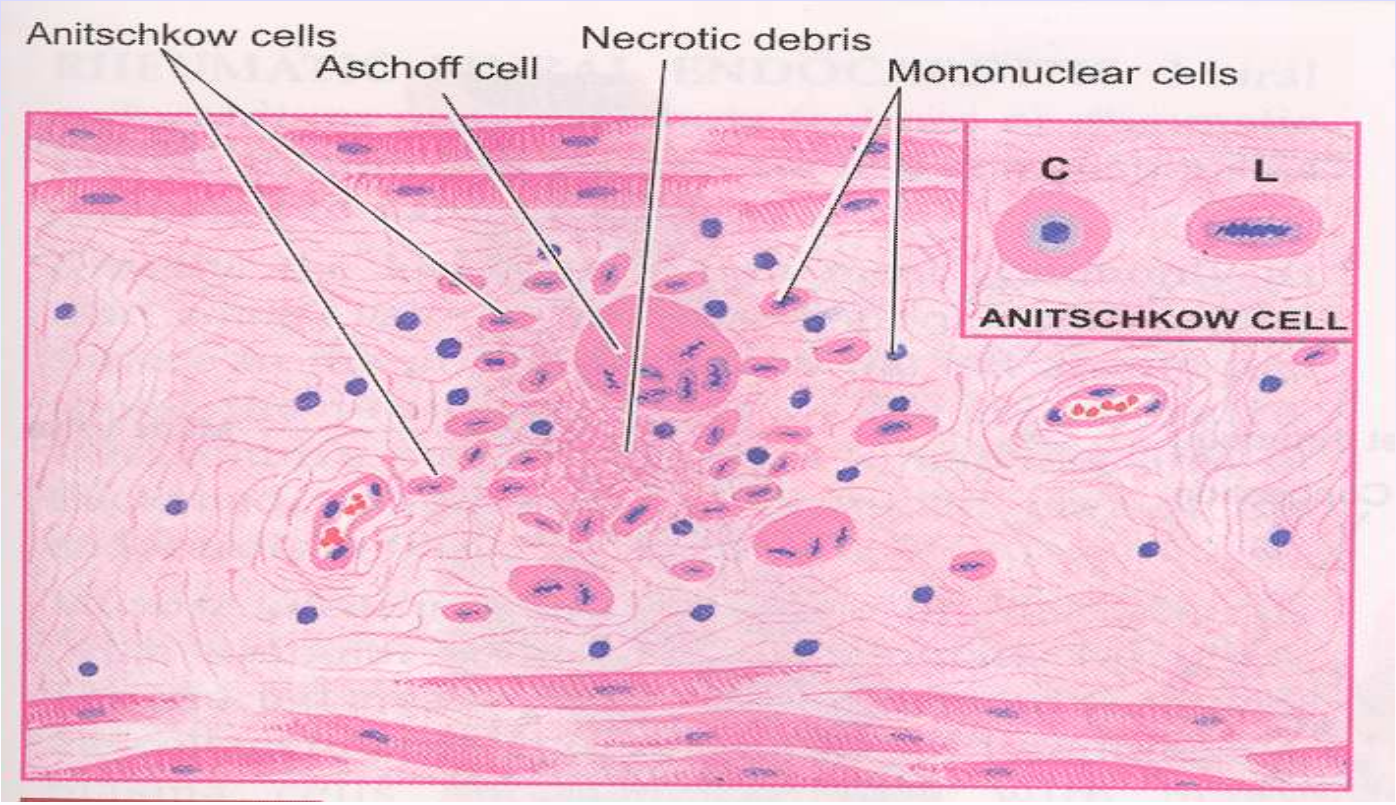
The cardiac manifestations of RF are in the form of focal inflammatory involvement of the interstitial tissue of all the three layers of the heart, the so-called pancarditis. The pathognomonic feature of pancarditis in RF is the presence of distinctive Aschoff nodules or Aschoff bodies.

The Aschoff nodules or bodies: The Aschoff nodules or the Aschoff bodies are spheroidal or fusiform distinct tiny structures, 1-2 mm in size, occurring in the interstitium of the heart in RF and may be visible to naked eye. They are especially found in the vicinity of small blood vessels in the myocardium and endocardium and occasionally in the pericardium and the adventitia of the proximal part of the aorta. Lesions similar to the Aschoff nodules may be found in the extracardiac tissues.

Evolution of fully-developed Aschoff bodies involves 3 stages all of which may found in the same heart at different stages of development. These are as follows:

1. **Early (Exudative or degenerative) stage.** The earliest sign of injury in the heart in RF is apparent by about 4th week of illness. Initially, there is oedema of the connective tissue and increase in acid mucopolysaccharide in the ground substance. This results in separation of the collagen fibres by accumulating ground substance. Eventually, the collagen fibres are fragmented and disintegrated and the affected focus takes the appearance and staining characteristic of fibrin. This change is referred to as fibrinoid degeneration.

2. **Intermediate (Proliferative or granulomatous) stage** is this stage of the Aschoff body which is pathognomonic of rheumatic conditions (See figure below)



This stage is apparent in 4th to 13th week of illness. The early stage of fibrinoid change is followed by proliferation of cells that includes infiltration by lymphocytes (mostly T cells), plasma cells, a few neutrophils and the characteristic cardiac histiocytes (Anitschkow cells) at the margin of the lesion. Cardiac histiocytes or Anitschkow cells are present in small numbers in normal heart but their number is increased in the Aschoff bodies; therefore they are not characteristic of RHD. These are large mononuclear cells having central round nuclei and contain moderate amount of amphophilic cytoplasm. The nuclei are vesicular and contain prominent central chromatin mass which is longitudinal section appears serrated or caterpillar-like, while in cross-section the chromatin mass appears as a small rounded body in the centre of the vesicular nucleus, just like an owl's eye (See in above figure). Some of these modified cardiac histiocytes become multinucleate cells containing 1 to 4 nuclei and are called Aschoff cells and are pathognomonic of RHD.

3. **Late (healing or fibrous) stage.** The stage of healing by fibrosis of the Aschoff nodule occurs in about 12 to 16 weeks after the illness. The nodule becomes oval or fusiform in shape, about 200 μm wide and 600 μm long. The Anitschkow cells in the nodule become spindle-shaped with diminished cytoplasm and the nuclei stain solidly rather than showing vesicular character. These cells tend to be arranged in a palisaded manner. With passage of months and years, the Aschoff body becomes less cellular and the collagenous tissue is increased.

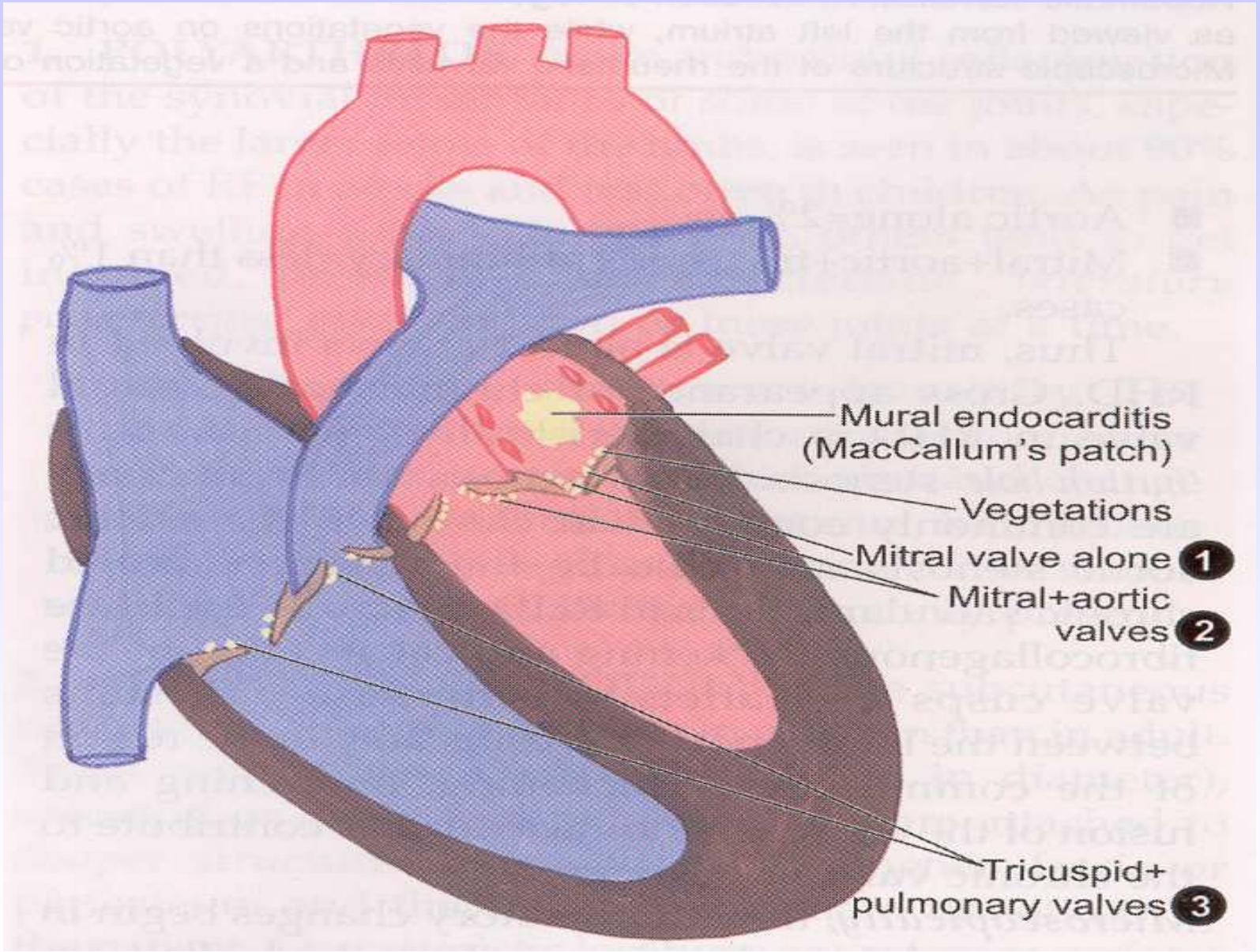
   Eventually, it is replaced by a small fibrocollagenous scar with little cellularity, frequently located perivascularly.

Rheumatic pancarditis: Although all the three layers of the heart are affected in RF, the intensity of their involvement is variable.

1. **Rheumatic Endocarditis.** Endocardial lesions of RF may involve the valvular and mural endocardium, causing rheumatic valvulitis and mural endocarditis, respectively. Rheumatic valvulitis is chiefly responsible for the major cardiac manifestations is chronic RHD.

Rheumatic Valvulitis. Grossly, the valves in acute RF show thickening and loss of translucency of the valve leaflets or cusps. This is followed by the formation of characteristic, small (1 to 3 mm in diameter), multiple, warty vegetations or verrucae, chiefly along the line of closure of the leaflets and cusps. These tiny vegetations are almost continuous so that the free margin of the cusps or leaft3ets appears as a rough and irregular ridge. The vegetations in RF appear grey-brown, transuuent and are firmly attached so that they are not likely to get detached to form emboli, unlike the friable vegetations of infective endocarditis.

Through all the four heart valves are affected, their frequency and severity of involvement varies: mitral valve alone being most common site, followed in decreasing order of frequency, by combined mitral and aortic valve (See below figure). The tricuspid and pulmonary valves usually show frequent and slight involvement. The higher incidence of vegetations on left side of heart is possibly because of the greater mechanical stresses on the valves of the left heart, especially along the line of closure of the valve cusps. The occurrence of vegetations on the atrial surface of the atrioventricular valves (mitral and tricuspid) and on the ventricular surface of the semilunar valves (aortic and pulmonary) further lends support to the role of mechanical pressure on the valves in the pathogenesis of vegetations.


Mural endocarditis
(MacCallum's patch)
Vegetations
Mitral valve alone 1
Mitral+aortic
valves 2
Tricuspid+
pulmonary valves 3

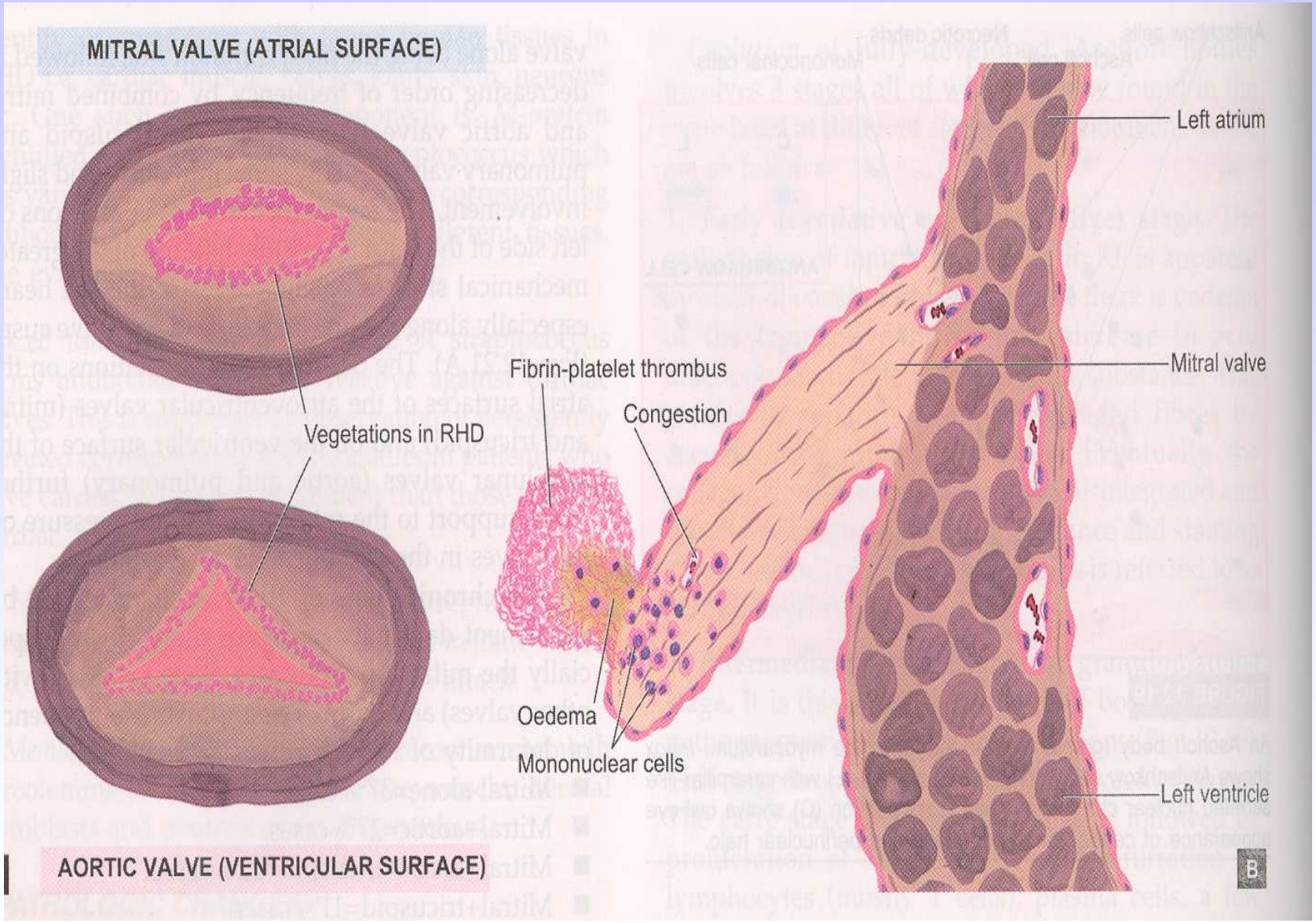
The chronic stage of RHD is characterized by permanent deformity of one or more valve, especially the mitral (in 98% cases alone or along with other valves) and aortic. The approximate frequency of deformity of various valves is as under:

- Mitral alone = 37% cases.
- Mitral+aortic = 27% cases.
- Mitral + aortic + tricuspid = 22% cases.
- Mitral+ tricuspid = 11% cases.
- Aortic alone = 2%
- Mitral+aortic+tricuspid+pulmonary7= less than 1% cases

Thus, mitral valve is almost always involved in RHD. Gross appearance of chronic healed mitral valve in RHD is characteristically 'fish mouth' or 'button hole' stenosis. Mitral stenosis and insufficiency are commonly combined in chronic RHD; calcific aortic stenosis may also be found. These healed chronic valvular lesions in RHD occur due to diffuse fibrocollagenous thickening and calcification of the valve cusps or leaflets which cause adhesions between the lateral portions, especially in the region of the commissures. Thickening, shortening and fusion of the chordae tendineae further contribute to the chronic valvular lesions.

Microscopically, the inflammatory changes begin in the region of the valve rings (where the leaflets are attached to the fibrous annulus) and then extend throughout the entire leaflet, whereas vegetations are usually located on the free margin of the leaflets and cusps.

i. In the **early (acute) stage,** the histological changes are oedema of the valve leaflet, presence of increased number of capillaries and infiltration with lymphocytes, plasma cells, histiocytes with many Anitschkow cells and a few polymorphs. Occasionally, Aschoff bodies with central foci of fibrinoid necrosis and surrounded by palisade of cardiac histiocytes are seen, but more often the cellular infiltration is diffuse in acute stage of RF. Vegetations present at the free margins of cusps appear as eosinophilic, tiny structures mainly consisting of fibrin with superimposed platelet thrombi and do not contain bacteria.


MITRAL VALVE (ATRIAL SURFACE)
Vegetations in RHD
AORTIC VALVE (VENTRICULAR SURFACE)
Fibrin-platelet thrombus
Congestion
Oedema
Mononuclear cells
Left atrium
Mitral valve
Left ventricle
B

ii. In the **healed (chronic) stage,** the vegetations have undergone organization. The valves show diffuse thickening as a result of fibrous tissue with hyalinization, and often calcification. Vascularisation of the valve cusps may still be evident in the form of thick-walled blood vessels with narrowed lumina. Typically Aschoff bodies are rarely seen in the valves at this stage.

Rheumatic Mural Endocarditis. Mural endocardium may also show features of rheumatic carditis though the changes are less conspicuous as compared to valvular changes.

Grossly, the lesions are seen most commonly as MacCallum's patch which is region of endocardial surface in the posterior wall of the left atrium just above the posterior leaflet of the mitral valve. MacCallum's patch appears as a map-like area of thickened, roughened and wrinkled part of the endocardium.

Microscopically, the appearance of MacCallum's patch is similar to that seen in rheumatic valvulitis. The affected area shows oedema, fibrinoid change in the collagen, and cellular infiltrate of lymphocytes, plasma cells and macrophages with many Anitschkow cells. Typical Aschoff bodies may sometimes be found.

2. **Rheumatic Myocarditis. Grossly,** in the early (acute) stage, the myocardium, especially of the left ventricle, is soft and flabby. In the intermediate stage, the interstitial tissue of the myocardium shows small foci of necrosis. Later, tiny pale foci of the Aschoff bodies may be visible throughout the myocardium.

Microscopically, the most characteristic feature of rheumatic myocarditis is the presence of distinctive Aschoff bodies. These diagnostic nodules are scattered throughout the interstitial tissue of the myocardium and are most frequent in the interventricular septum, left ventricle and left atrium. Derangements of the conduction system may, thus, be present. The Aschoff bodies are best identified in the intermediate stage when they appear as granulomas with central fibrinoid necrosis and are surrounded by palisade of Anitschkow cells and multinucleate Aschoff cells. There is infiltration by lymphocytes, plasma cells and some neutrophils. In the late stage, the Aschoff bodies are gradually replaced by small fibrous scars in the vicinity of blood vessels and the inflammatory infiltrate subsides. Presence of active Aschoff bodies along with old healed lesions is indicative of rheumatic activity.

3. **Rheumatic pericarditis.** Inflammatory involvement of the pericardium commonly accompanies RHD.

Grossly, the usual findings is fibrinous pericarditis in which there is loss of normal shiny pericardial surface due to deposition of fibrin on its surface and accumulation of slight amount of fibrinous exudate in the pericardial sac. If the parietal pericardium is pulled off from the visceral pericardium, the two separated surfaces are shaggy due to thick fibrin covering them. This appearance is often likened to 'bread and butter appearance' i.e. resembling the buttered surfaces of two slices in a sandwich when they are gently pulled apart. If fibrinous pericarditis fails to resolve and, instead, undergoes organization, the two layers of the pericardium form fibrous adhesions resulting in chronic adhesive pericarditis.

Microscopically, fibrin is identified on the surfaces. The subserosal connective tissue is infiltrated by lymphocytes, plasma cells, histiocytes and a few neutrophils. Characteristic Aschoff bodies may be seen which later undergo organization and fibrosis. Organization of the exudate causes fibrous adhesions between the visceral and parietal surfaces of the pericardial sac and obliterates the pericardial cavity.

B. Extracardiac Lesion

Patients of the syndrome of acute rheumatism develop lesions in connective tissue elsewhere in the body, chiefly the joint, subcutaneous tissue, arteries, brain and lungs.

1. **Polyarthritis.** Acute and painful inflammation of the synovial membranes of some of the joints, especially the larger joints of the limbs, is seen in about 90% cases of RF in adults and less often in children. As pain and swelling subside in one joint, others tend to get involved, producing the characteristic 'migratory polyarthritis' involving two or more joints at a time.

Histologically, the changes are transitory. The synovial membrane and the periarticular connective tissue shows hyperaemia, oedema, fibrinoid change and neutrophilic infiltration. Sometimes, focal lesions resembling Aschoff bodies are observed. A serous effusion into the joint cavity is commonly present.

2. **Subcutaneous nodules.** The subcutaneous nodules of RF occur more often in children than in adult. These nodules are small (0.5 to 2 cm in diameter), spherical or ovoid and painless. They are attached to deeper structures like tendons, ligaments, fascia or periosteum and therefore often remain unnoticed by the patient. Characteristic locations are extensor surface of the wrists, elbows, ankles and knees.

Histologically, the subcutaneous nodules of RF are representative of giant Aschoff bodies of the heart. They consist of 3 distinct zones: a central area with fibrinoid changes, surrounded by a zone of histiocytes and fibroblasts forming a palisade arrangement, and the outermost zone of connective tissue which is infiltrated by non-specific chronic inflammatory cells and proliferating blood vessels.

It may be mentioned here that histologically similar but clinically different subcutaneous lesions appear in rheumatoid arthritis; they are larger, painful and tender and persist for months to years.

3. **Erythema marginatum.** This non-pruritic erythematous rash is characteristic of RF. The lesions occur mainly on the trunk and proximal parts of the extremities. The erythematous area develops central clearing and has slightly elevated red margins. The erythema is transient and migratory.
4. **Rheumatic Arteritis.** Arteritis in RF involves not only the coronary arteries and aorta but also occurs in arteries of various other organs such as renal, mesenteric and cerebral arteries. The lesions in the coronaries are seen mainly in the small intramyocardial branches.

Histologically, the lesions may be like those of hypersensitivity angiitis, or sometimes may resemble polyarteritis nodosa. Occasionally, foci of fibrinoid necrosis or ill-formed Aschoff bodies may be present close to the vessel wall.

5. **Chorea Minor.** Chorea minor or Sydenham's chorea or Saint Vitus' dance is a delayed manifestation of RF as a result of involvement of the central nervous system. The condition is characterized by disordered and involuntary jerk movements of the trunk and the extremities accompanied by some degree of emotional instability. The condition occurs more often in younger age, particularly in girls.

Histologically, the lesions are located in the cerebral hemispheres, brainstem and the basal ganglia. They consist of small haemorrhages, oedema and perivascular infiltration of lymphocytes. There may be endarteritis obliterans and thrombosis of cortical and meningeal vessels.

6. **Rheumatic pneumonitis and pleuritis.** Involvement of the lungs and pleura occurs rarely in RF. Pleuritis is often accompanied with serofibrinous pleural effusion but definite Aschoff bodies are not present. In rheumatic pneumonitis, the lungs are large, firm and rubbery.

Histologically, the changes are oedema, capillary haemorrhages and focal areas of fibrinous exudate in the alveoli. Aschoff bodies are generally not found.

- **Clinical Features**
- The first attack of acute RF generally appears 2 to 3 weeks after streptococcal pharyngitis, most often in children between the age of 5 to 15 years. With subsequent streptococcal pharyngitis, there is reactivation of the disease and similar clinical manifestations appear with each recurrent attack. The disease generally presents with migratory polyarthritis and fever. However, RF has widespread systemic involvement and no single specific laboratory diagnostic test is available. Therefore, for diagnosis, the following set of guidelines called revised Jones' criteria are followed:

A. Major criteria are:

1. Carditis
2. Polyarthritis.
3. Chorea (Sydenham's chorea)
4. Erythema marginatum
5. Subcutaneous nodules

B. Minor criteria are:

1. Fever
2. Arthralgia
3. Previous history of RF
4. Laboratory findings of elevated ESR, raised C-reactive protein, and leucocytosis.
5.. ECG finding of prolonged PR interval.

C. **Supportive evidence** of preceding group A streptococcal infection: positive throat culture for group (antispreptolysin O and S, antistreptokinase, antistreptohyaluronidase and anti DNAase B).

Clinical diagnosis of RF is made in a case with antecedent laboratory evidence of streptococcal throat infection in the presence of : any tow of the major criteria, or occurrence of one major and two minor criteria.

In the heart is spared in a case of acute RF, the patient may have complete recovery without any sequelae. However, once the heart is involved, it is often associated with reactivation and recurrences of the disease. Myocarditis, in particular, is the most life-threatening due to involvement of the conduction system of the heart and results in serious arrhythmias. The long term sequelae or stigmata are the chronic valvular deformities, especially the mitral stenosis, as already explained. Initially, a stage of compensation occurs, while later decompensation of the heard leads to full-blown cardiac failure. Currently, surgical replacement of the damaged valves can alter the clinical course of the disease.

The major **causes of death** in RHD are cardiac failure, bacterial endocarditis and embolism:

1. Cardiac failure is the most common cause of death from RHD. In young patients, cardiac failure occurs due to the chronic valvular deformities, while in older patients coronary artery disease may be superimposed on old RHD.
2. Bacterial endocarditis of both acute and subacute type may supervene due to inadequate use of antibiotics.
3. Embolism in RHD originates most commonly from mural thrombi in the left atrium and its appendages, in association with mitral stenosis. The organs most frequently affected are the brain, kidneys, spleen and lungs.
4. Sudden death may occur in RHD as a result of ball thrombus in the left atrium or due to acute coronary insufficiency in association with aortic stenosis.

a] **Acute rheumatic carditis** is a **pancarditis** (i.e. all heart layers are affected); typically, the myocardium is most severely involved. The gross appearance of the heart is relatively unremarkable, with only modest dilatation and mural softening. Characteristic microscopic features of the carditis are as follows:

(1) **Myocarditis.** The presence of well-developed Aschoff bodies is the pathognomonic feature of acute rheumatic carditis, although a diffuse nonspecific myocarditis associated with a variable amount of myocyte necrosis and chronic inflammation often is present as well. Although classically found in the interstitial fibrous regions of the heart, Aschoff bodies also may be identified in the joints, tendons, and other connective tissues. They may be found in the heart long after the clinical signs of disease have resolved. There are three histologic phases in the development of Aschoff bodies.

a] The **early phase** (exudative stage) occurs within 4 weeks after the onset of carditis and is characterized by a focus of swollen, eosinophilic, perivascular collagen fibers (fibrinoid necrosis) associated with an inflammatory infiltrate of neutrophils (primarily) and chronic inflammatory cells (to a lesser degree).

b] In the **intermediate phase** (proliferative or granulomatous stage), which extends from 4 to13 weeks after the onset of carditis, the central focus of fibrinoid necrosis is surrounded by chronic inflammatory cells and fibroblasts. The cellular zone also contains large mesenchymal cells known as Anitschkow cells, which may be multinucleate (Aschoff giant cells) and are believed to be derived from fibroblasts. Anitschkow cells are identified by their characteristic nuclei, which have a "caterpillar" appearance when cut longitudinally and an "owl-eye" appearance when cut transversely. The intermediate phase is the only pathognomonic phase for acute rheumatic fever.

c] In the **late phase** (healed or fibrous stage) which extends from 3 to 4 months after the onset of carditis, the Aschoff body appears as a non-specific hyalinized scar.

- (2) **Endocarditis** is the most characteristic and potentially damaging effect of rheumatic fever. Typically, the valvular endothelium demonstrates numerous small (1 to 2 mm), rubbery verrucae (i.e., warty vegetations) composed of fibrinoid material along the lines of leaflet closure. These vegetations arise over foci of ulcerated endocardium, which may demonstrate mesenchymal proliferation similar to that of an Aschoff body.

(3) **Pericarditis**. A prominent fibrinous pericarditis often is present, which may lead to fibrous organization that is of little significance.

b] **Chronic rheumatic heart disease** refers to the late valvular effects (i.e., stenosis, insufficiency or both) of rheumatic fever (Figure 2). About half of the cases involve only the mitral valve. The remaining cases involve (in decreasing order of frequency) the mitral and aortic valves; the aortic valve only; the mitral, aortic, and tricuspid valves; the tricuspid valve only; and the pulmonic valve.

(1) **Valvular effects.** The valve leaflets become quite thickened and deformed by fibrosis, the commissures often are fused, and valvular calcification frequently is noted (see Figure 3). Neovascularization is often present. The chordae tendineae become thickened, shortened, and fused. The atrial surface of the mitral valve may acquire a "fish-mouth" appearance. Focal fibrotic thickenings of the left atrial mural endocardium located just above the mitral valve, termed MacCallum's plaques, represent jet lesions related to mitral regurgitation.

(2) **Secondary effects.**

a] Marked left atrial dilatation may result from severe mitral stenosis or insufficiency. In about 40% of cases, this condition is complicated by the formation of mural thrombi, which most often are found in the left auricular appendage.

b] Cor pulmonale may develop as a consequence of secondary pulmonary hypertension induced by severe mitral valve disease.

(4) **Clinical features and diagnosis**. Diagnosis of the initial attack of rheumatic fever is based on the modified Jones criteria and requires the presence of at least two major or one major and two minor clinical manifestations as well as supportive evidence of prior streptococcal infection (Table 2). Individuals with a history of rheumatic fever are at high risk for recurrence when reinfected with group A streptococci.

(5) **Course and diagnosis**.

a] Although death during the acute phase of rheumatic fever (usually due to intractable myocarditis) is quite rare, the long-term sequelae of chronic valvular disease (i.e. congestive heart failure, bacterial endocarditis, peripheral embolism) remain important causes of morbility and mortality in these patients. Valve replacement may become necessary. An increased risk for developing chronic valvular disease is seen in those patients who demonstrate clinical evidence of carditis during the acute attack of rheumatic fever and in those who suffer recurrent attacks.

b] Primary prevention consists of antibiotic treatment of streptococcal pharyngitis, however, rheumatic fever arises after clinically inapparent infections in about one-third of cases.