

# Valvular Heart Disease

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- **Stenosis** is the failure of a valve to open completely, which impedes forward flow.
- **Insufficiency/ regurgitation** results from failure of a valve to close completely, thereby allowing reversed flow
- **Functional regurgitation** is used to describe the incompetence of a valve stemming from an abnormality in one of its support structures, as opposed to a primary valve defect.

- Valvular abnormalities can be congenital or acquired.
- Acquired valvular stenosis has relatively few causes; it is almost always a consequence of a remote or **chronic** injury of the valve **cusps** that declares itself clinically only after many years
- In contrast, acquired valvular insufficiency can result from intrinsic disease of the valve **cusps** or damage to or distortion of the **supporting structures**, may appear **acutely or chronically**

- The most frequent causes of the major functional valvular lesions are:
  - **Aortic stenosis:** calcification and sclerosis of anatomically normal or congenitally bicuspid aortic valves due to aging. The most common valvular abnormality.
  - **Aortic insufficiency:** dilation of the ascending aorta, often secondary to hypertension and/or aging.
  - **Mitral stenosis:** rheumatic heart disease.
  - **Mitral insufficiency:** myxomatous degeneration (mitral valve prolapse).

## Mitral Valve Disease

### Mitral Stenosis

Postinflammatory scarring (rheumatic heart disease)

### Mitral Regurgitation

#### *Abnormalities of Leaflets and Commissures*

Postinflammatory scarring  
Infective endocarditis  
Mitral valve prolapse  
Drugs (e.g., fen-phen)

#### *Abnormalities of Tensor Apparatus*

Rupture of papillary muscle  
Papillary muscle dysfunction (fibrosis)  
Rupture of chordae tendineae

## Aortic Valve Disease

### Aortic Stenosis

Postinflammatory scarring (rheumatic heart disease)  
Senile calcific aortic stenosis  
Calcification of congenitally deformed valve

### Aortic Regurgitation

Postinflammatory scarring (rheumatic heart disease)

Degenerative aortic dilatation  
Syphilitic aortitis  
Ankylosing spondylitis  
Rheumatoid arthritis  
Marfan syndrome

# Rheumatic Fever and Rheumatic Heart Disease

- **Rheumatic fever** (RF) is an acute, immunologically mediated, multisystem inflammatory disease classically occurring a few weeks after an episode of group A streptococcal pharyngitis; occasionally, RF can follow streptococcal infections at other sites, such as the skin
- Acute rheumatic carditis is a common manifestation of active RF and may progress over time to chronic **rheumatic heart disease** (RHD), mainly manifesting as valvular abnormalities

- RHD is characterized principally by deforming fibrotic valvular disease, particularly involving the mitral valve; indeed, RHD is virtually the only cause of mitral stenosis

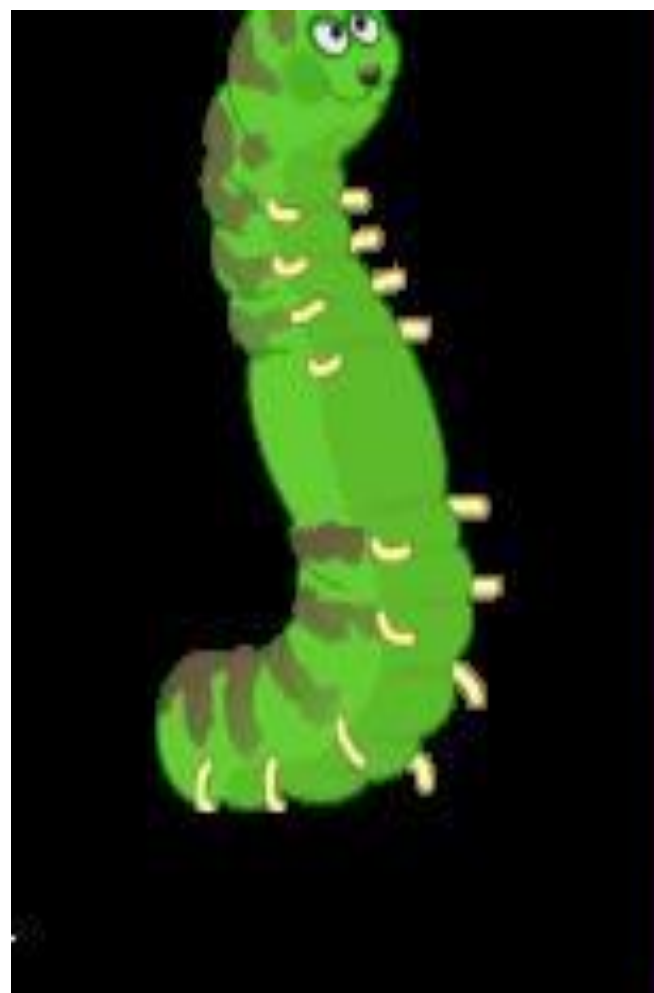
- Pathogenesis:

Acute rheumatic fever results from host immune responses to group A streptococcal antigens that cross-react with host proteins. In particular, antibodies and CD4+ T cells directed against **streptococcal M proteins** can also in some cases recognize cardiac self-antigens. Damage to heart tissue may thus be caused by a combination of antibody- and T cell-mediated reactions



- MORPHOLOGY:

During acute RF, focal inflammatory lesions are found in **various tissues**. Distinctive lesions occur in the heart, called ***Aschoff bodies***, consisting of foci of T lymphocytes, occasional plasma cells, and plump activated macrophages called ***Anitschkow cells/ caterpillar cells*** (pathognomonic for RF).

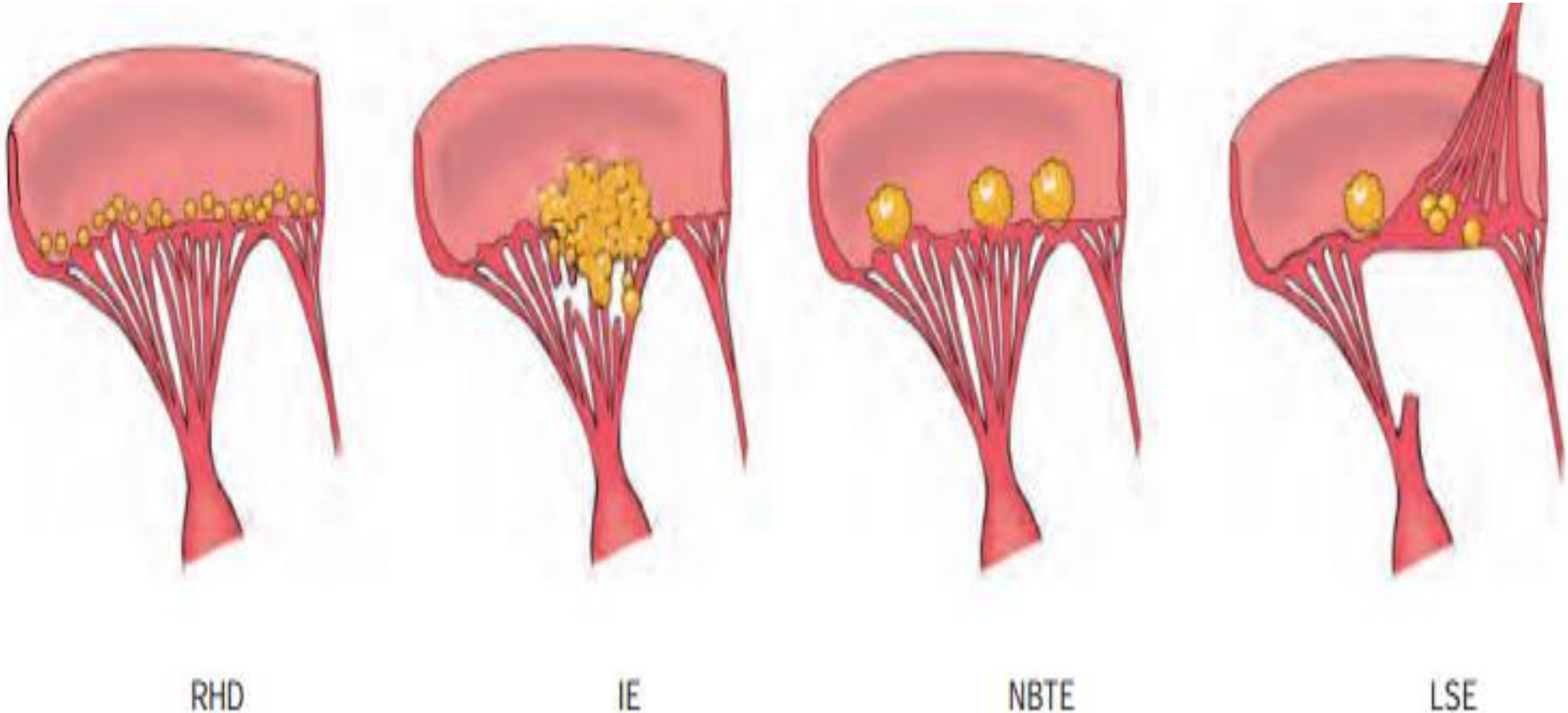


Anitschkow cell - The caterpillar chromatin pattern of the nucleus in longitudinal section

- During acute RF, diffuse inflammation and Aschoff bodies may be found in any of the three layers of the heart, resulting in pericarditis, myocarditis, or endocarditis (*pancarditis*)

- Inflammation of the **endocardium** and the left-sided valves typically results in fibrinoid necrosis within the cusps or tendinous cords. Overlying these necrotic foci and along the lines of closure are small (1 to 2 mm) ***vegetations***, called verrucae.

# vegetative valve disease



RHD

IE

NBTE

LSE

Figure 12-24 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. 12-25A). Nonbacterial thrombotic endocarditis (NBTE) typically exhibits small, bland vegetations, usually attached at the line of closure. One or many may be present (see Figure 12-26). Libman-Sacks endocarditis (LSE) has small or medium-sized vegetations on either or both sides of the valve leaflets.

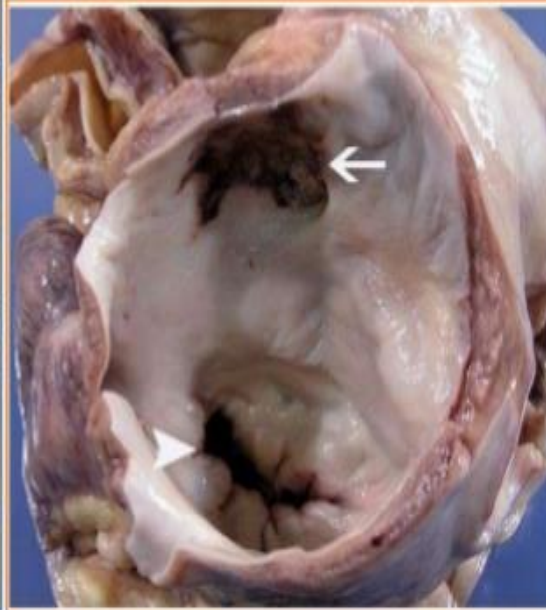
- Subendocardial lesions, perhaps exacerbated by regurgitant jets (mitral valve incompetence) and can induce irregular thickenings/fibrosis called ***MacCallum plaques***, usually in the **left atrium above the mitral valve**

- The cardinal anatomic changes of the mitral valve in chronic RHD are leaflet thickening, commissural fusion and shortening, and thickening and fusion of the tendinous cords
- In chronic disease the ***mitral valve is virtually always involved***. The mitral valve is affected in isolation in roughly two thirds of RHD, and along with the aortic valve in another 25% of cases. Tricuspid valve involvement is infrequent, and the pulmonary valve is only rarely affected

- In rheumatic mitral stenosis, calcification and fibrous bridging across the valvular commissures create “***fish mouth***” or “***buttonhole***” stenoses.
- With tight mitral stenosis, the left atrium progressively dilates and may harbor mural thrombi that can embolize.
- Long-standing congestive changes in the lungs may induce pulmonary vascular and parenchymal changes; over time, these can lead to right ventricular hypertrophy.
- The left ventricle is largely unaffected by isolated pure mitral stenosis



## Morphology



- Fibrous bridging across the valves and calcification create **“fishmouth”** or **“buttonhole”** stenoses

- Microscopically, valves show organization of the acute inflammation, with post-inflammatory neovascularization and transmural fibrosis that obliterate the leaflet architecture. ***Aschoff bodies are rarely seen in surgical specimens or autopsy tissue from patients with chronic RHD***, as a result of the long intervals between the initial insult and the development of the chronic deformity.

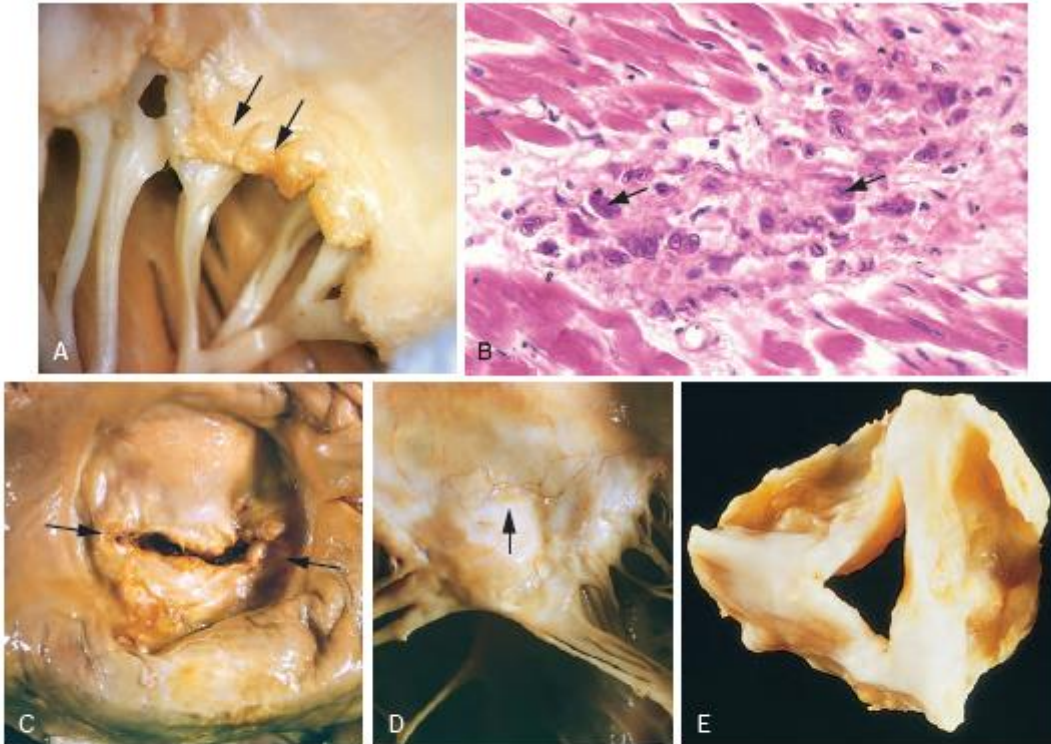


Figure 12-23 Acute and chronic rheumatic heart disease. **A**, Acute rheumatic mitral valvulitis superimposed on chronic rheumatic heart disease. Small vegetations (verrucae) are visible along the line of closure of the mitral valve leaflet (arrows). Previous episodes of rheumatic valvulitis have caused 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 neovascularization of 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, 1987.)

# Clinical Features

- Acute RF typically appears 10 days to 6 weeks after a group A streptococcal infection in about 3% of patients.
- It occurs most often in children between ages 5 and 15, but first attacks can occur in middle to later life.
- Although pharyngeal cultures for streptococci are negative by the time the illness begins, antibodies to one or more streptococcal enzymes, such as streptolysin O and DNase B, can be detected in the sera of most patients with RF

- RF is characterized by a constellation of findings:
  - (1) migratory polyarthrititis of the large joints,
  - (2) Pancarditis
  - (3) subcutaneous nodules
  - (4) erythema marginatum of the skin
  - (5) Sydenham chorea, a neurologic disorder with involuntary rapid, purposeless movements.

The diagnosis is established by the so-called ***Jones criteria***: evidence of a preceding group A streptococcal infection, with the presence of two of the major manifestations listed earlier or one major and two minor manifestations (nonspecific signs and symptoms that include fever, arthralgia, or elevated blood levels of acute phase reactants).

- The predominant clinical manifestations are carditis and arthritis, the latter more common in adults than in children.
- Arthritis typically begins with **migratory polyarthritis** (accompanied by fever) in which one large joint after another becomes painful and swollen for a period of days and then subsides spontaneously, ***leaving no residual disability.***
- Clinical features related to acute carditis include pericardial friction rubs, tachycardia, and arrhythmias.
- Myocarditis can cause cardiac dilation that may culminate in functional mitral valve insufficiency or even heart failure.
- Approximately 1% of affected individuals die of fulminant RF.

- After an initial attack there is increased vulnerability to reactivation of the disease with subsequent pharyngeal infections, and the same manifestations are likely to appear with each recurrent attack.
- Damage to the valves is cumulative. Turbulence induced by ongoing valvular deformities leads to additional fibrosis.
- Clinical manifestations appear years or even decades after the initial episode of RF and depend on which cardiac valves are involved.

- Complications:

cardiac murmurs, cardiac hypertrophy and dilation, heart failure, individuals with chronic RHD may suffer from arrhythmias (particularly atrial fibrillation in the setting of mitral stenosis), thromboembolic complications, and infective endocarditis.



# prognosis

- The long-term prognosis is highly variable. Surgical repair or prosthetic replacement of diseased valves has greatly improved the outlook for persons with RHD.

# Infective Endocarditis

- Infective endocarditis (IE) is a microbial infection of the heart **valves** or the mural endocardium that leads to the formation of vegetations composed of thrombotic debris and organisms, often associated with destruction of the underlying cardiac tissues.
- The **aorta**, **aneurysms**, other blood vessels, and **prosthetic devices** can also become infected. Although fungi and other classes of microorganisms can be responsible, most infections are bacterial (bacterial endocarditis).

- Traditionally, IE has been classified on clinical grounds into acute and subacute forms.

**Acute infective endocarditis** is typically caused by infection of a previously **normal** heart valve by a highly **virulent** organism (e.g., *Staphylococcus aureus*) that rapidly produces necrotizing and destructive lesions. These infections may be **difficult to cure** with antibiotics alone, and usually require surgery. Despite appropriate treatment, death can ensue within days to weeks.

**Subacute IE** is characterized by organisms with **lower virulence** (e.g., viridans streptococci) that cause insidious infections of **deformed** valves with overall less destruction. In such cases the disease may pursue a protracted course of weeks to months, and cures can be achieved with antibiotics.

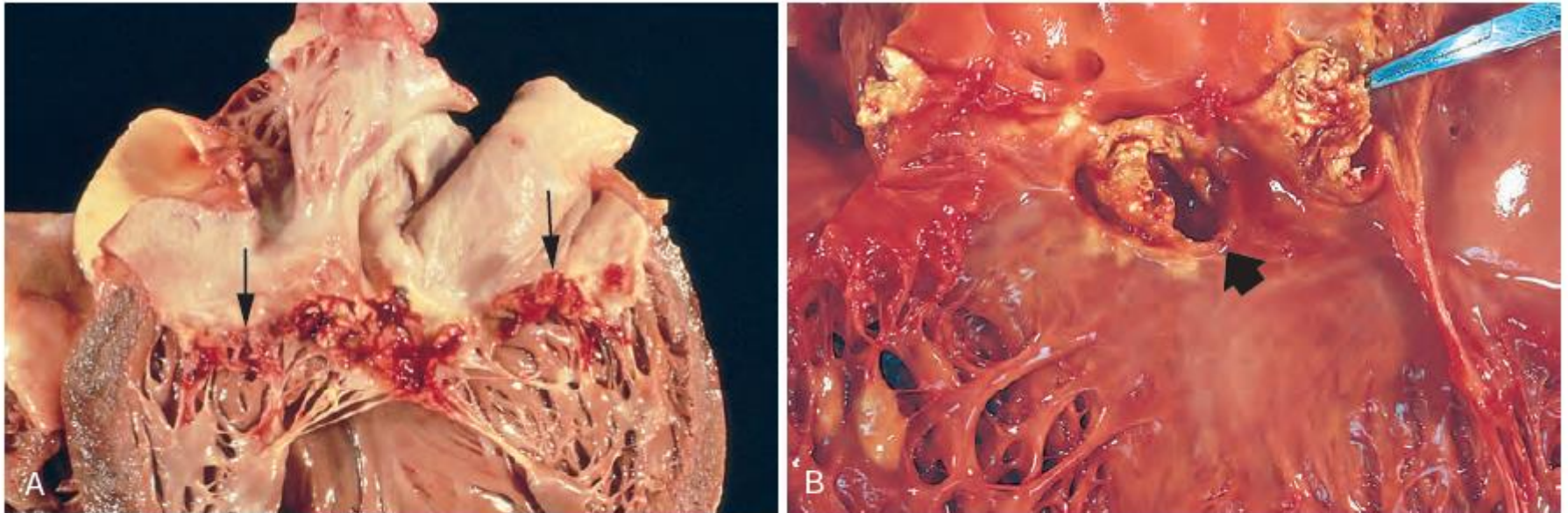
- **Pathogenesis:** Although highly virulent organisms can infect previously normal valves, a variety of **cardiac and vascular abnormalities increase the risk of developing IE** (e.g RHD, artificial (prosthetic) valves).
- The causal organisms differ among the major high-risk groups:
  - Endocarditis of native but previously damaged or otherwise **abnormal valves** is caused most commonly (50% to 60% of cases) by **Streptococcus viridans**, a normal component of the oral cavity flora.
  - More virulent **S. aureus** organisms commonly found on the skin can infect either **healthy** or deformed valves and are responsible for 20% to 30% of cases overall; notably, S. aureus is the major offender in IE among **intravenous drug abusers**.
  - Other bacterial causes include enterococci and the so-called **HACEK group** (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella), all commensals in the oral cavity.
  - **Prosthetic valve** endocarditis is caused most commonly by coagulase-negative staphylococci (e.g., **S. epidermidis**).
  - Other agents causing endocarditis include gram-negative bacilli and fungi.
  - In about 10% of all cases of endocarditis, no organism can be isolated from the blood ("**culturenegative**" **endocarditis**); reasons include prior antibiotic therapy, difficulties in isolating the offending agent, or because deeply embedded organisms within the enlarging vegetation are not released into the blood.

Foremost among the factors predisposing to endocarditis are those that cause microorganism seeding into the blood stream (**bacteremia or fungemia**). The source may be an obvious infection elsewhere, a dental or surgical procedure, a contaminated needle shared by intravenous drug users, or seemingly trivial breaks in the epithelial barriers of the gut, oral cavity, or skin. In patients with valve abnormalities, or with known bacteremia, IE risk can be lowered by antibiotic prophylaxis.

- MORPHOLOGY:

**Vegetations** on heart valves are the classic hallmark of IE; these are friable, bulky, potentially **destructive** lesions containing fibrin, inflammatory cells, and bacteria or other organisms. The **aortic and mitral valves** are the most common sites of infection, although the **valves of the right heart may also be involved, particularly in intravenous drug abusers.**

Vegetations can be **single or multiple** and may involve **more than one valve**; they can occasionally erode into the underlying myocardium and produce an abscess (**ring abscess**). Vegetations are prone to embolization; because the embolic fragments often contain virulent organisms, abscesses frequently develop where they lodge, leading to sequelae such as **septic infarcts or mycotic aneurysms.**



**Figure 12-25** Infective (bacterial) endocarditis. **A**, Endocarditis of mitral valve (subacute, caused by *Streptococcus viridans*). The large, friable vegetations are denoted by *arrows*. **B**, Acute endocarditis of congenitally bicuspid aortic valve (caused by *Staphylococcus aureus*) with extensive cuspal destruction and ring abscess (*arrow*).

- **Clinical Features.** Acute endocarditis has a stormy onset with rapidly developing **fever**, chills, weakness, and lassitude. **Murmurs** are present in 90% of patients with left-sided IE, either from a new valvular defect or from a preexisting abnormality.

# Modified Duke criteria

**Table 12-9** Diagnostic Criteria for Infective Endocarditis\*

Pathologic Criteria
Microorganisms, demonstrated by culture or histologic examination, in a vegetation, embolus from a vegetation, or intracardiac abscess
Histologic confirmation of active endocarditis in vegetation or intracardiac abscess
Clinical Criteria
Major
Blood culture(s) positive for a characteristic organism or persistently positive for an unusual organism
Echocardiographic identification of a valve-related or implant-related mass or abscess, or partial separation of artificial valve
New valvular regurgitation
Minor
Predisposing heart lesion or intravenous drug use
Fever
Vascular lesions, including arterial petechiae, subungual/splinter hemorrhages, emboli, septic infarcts, mycotic aneurysm, intracranial hemorrhage, Janeway lesions <sup>†</sup>
Immunological phenomena, including glomerulonephritis, Osler nodes, <sup>‡</sup> Roth spots, <sup>§</sup> rheumatoid factor
Microbiologic evidence, including a single culture positive for an unusual organism
Echocardiographic findings consistent with but not diagnostic of endocarditis, including worsening or changing of a preexistent murmur

\*Diagnosis by these guidelines, often called the Duke Criteria, requires either pathologic or clinical criteria; if clinical criteria are used, 2 major, 1 major + 3 minor, or 5 minor criteria are required for diagnosis.

<sup>†</sup>Janeway lesions are small erythematous or hemorrhagic, macular, nontender lesions on the palms and soles and are the consequence of septic embolic events.

<sup>‡</sup>Osler nodes are small, tender subcutaneous nodules that develop in the pulp of the digits or occasionally more proximally in the fingers and persist for hours to several days.

<sup>§</sup>Roth spots are oval retinal hemorrhages with pale centers.

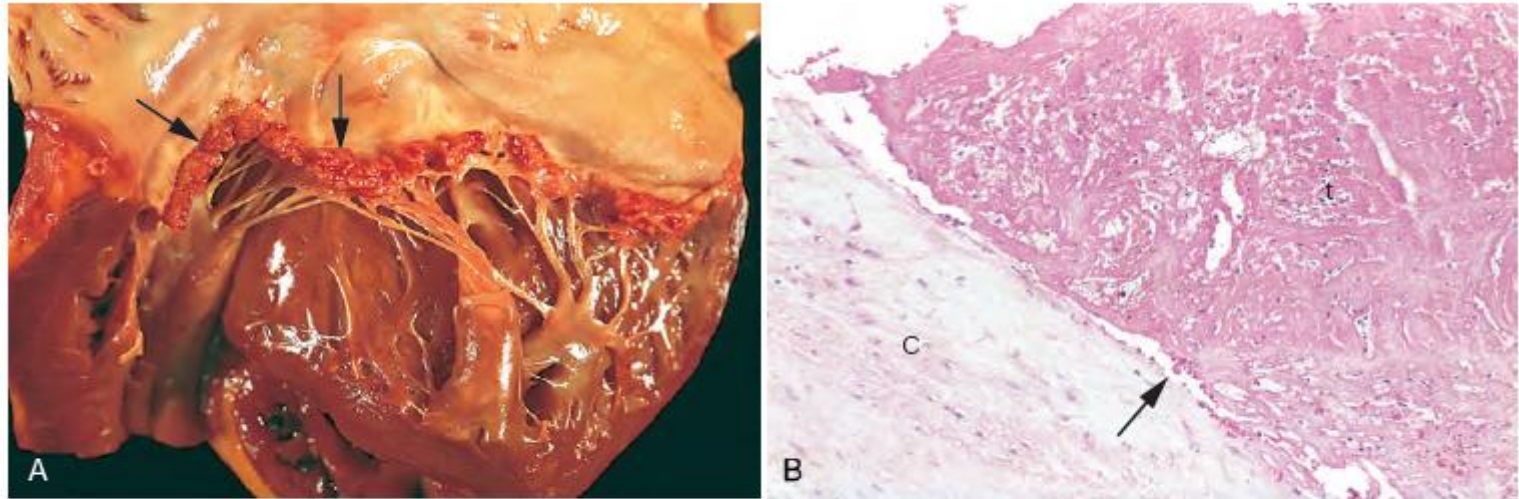
Modified from Durack DT, et al: New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. *Am J Med*, 96:200, 1994, and Karchmer AW: Infective Endocarditis. In Braunwald E, Zipes DP, Libby P (eds): *Heart Disease. A Textbook of*



- **Complications** of IE generally begin within the first few weeks of onset, and can include glomerular antigenantibody complex deposition causing **glomerulonephritis** .
- Earlier diagnosis and effective treatment has nearly eliminated some previously common clinical manifestations of long-standing IE—for example, microthromboemboli (manifest as splinter or subungual hemorrhages).

# Nonbacterial Thrombotic Endocarditis

- Nonbacterial thrombotic endocarditis (NBTE) is characterized by the deposition of small **sterile thrombi** on the leaflets of the cardiac valves.
- The lesions are 1 to 5 mm in size, and occur as single or multiple, **loosely attached** to the underlying valve; the vegetations are **not invasive**, although the local effect of the vegetations is usually trivial, they can be the **source of systemic emboli** that produce significant infarcts in the brain, heart, or elsewhere.
- vegetations **along the line of closure** of the leaflets or cusps.
- Pathogenesis: It frequently occurs concomitantly with deep venous thromboses, pulmonary emboli, or other findings suggesting an underlying **systemic hypercoagulable state**. Indeed, there is a striking association with mucinous adenocarcinomas, potentially relating to **the procoagulant effects of tumor-derived mucin or tissue**. **Endocardial trauma, as from an indwelling catheter**, is another well-recognized predisposing condition.



**Figure 12-26** Nonbacterial thrombotic endocarditis (NBTE). **A**, Nearly complete row of thrombotic vegetations along the line of closure of the mitral valve leaflets (*arrows*). **B**, Photomicrograph of NBTE, showing bland thrombus, with virtually no inflammation in the valve cusp (*c*) or the thrombotic deposit (*t*). The thrombus is only loosely attached to the cusp (*arrow*).

# Endocarditis of Systemic Lupus Erythematosus (Libman-Sacks Disease)

- **Mitral and tricuspid** valvulitis with small, **sterile vegetations**, called Libman-Sacks endocarditis, is occasionally encountered in systemic lupus erythematosus.
- The lesions are small (1 to 4 mm in diameter), single or multiple, sterile, pink vegetations with a warty (verrucous) appearance. **They may be located on the undersurfaces of the atrioventricular valves, on the valvular endocardium, on the chords, or on the mural endocardium of atria or ventricles.**
- Due to the use of steroids, the incidence of this complication has been greatly reduced.

# Carcinoid Heart Disease

- The **carcinoid syndrome** refers to a systemic disorder marked by flushing, diarrhea, dermatitis, and bronchoconstriction that is caused by bioactive compounds such as serotonin released by carcinoid tumors .
- **Carcinoid heart disease** refers to the cardiac manifestations caused by the bioactive compounds and occurs in roughly half of the patients in whom the systemic syndrome develops. Cardiac lesions do not typically occur until there is a massive hepatic metastatic burden, since the liver normally catabolizes circulating mediators before they can affect the heart. Classically, **endocardium and valves of the right heart** are primarily affected since they are the first cardiac tissues bathed by the mediators released by gastrointestinal carcinoid tumors. **Typical findings are tricuspid insufficiency and pulmonary stenosis.** The left side of the heart is afforded some measure of protection because the pulmonary vascular bed degrades the mediators. However, left heart carcinoid lesions can occur in the setting of atrial or septal defects and right-to-left flow, or can be elicited by primary pulmonary carcinoid tumors.