PATHOLOGY OF THE CARDIOVASCULAR SYSTEM

BLOOD VESSEL DISEASES
Blood vessels have a primary function of nourishing various organs and tissues of the body by supplying them with blood. Vascular diseases are manifested clinically through three mechanisms that are reflected through the diseased vessel(s) as
1. Progressive narrowing of the lumen associated with progressive ischemia of the relevant tissues.
2. Thrombosis associated with partial or complete luminal obstruction and/or embolism.
3. Aneurysmal dilatation that may eventuate in rupture with ischemic and destructive consequences.
4. ARTERIOSCLEROSIS
This generic term refers to a group of disorders having in common thickening and loss of elasticity of arterial walls and thus leading to sclerosis i.e. hardening of the wall.
Under this heading come three distinctive morphological variants, namely
   1. Atherosclerosis (the most frequent and important type)
   2. Medial calcific sclerosis
   3. Arteriolosclerosis

ATHEROSCLEROSIS
This disease is responsible for more deaths and serious complications than any other disorder. This is because its prime targets are vital arteries, namely the coronaries, cerebral arteries, & the aorta.
Accordingly the major consequences are
   1. Myocardial infarction
   2. Cerebral infarction
   3. Aortic aneurysm
Myocardial infarction alone is responsible for about 25% of all deaths. By definition atherosclerosis is “a disease primarily of large elastic arteries and medium sized muscular arteries. Its basic lesion is the atheroma (fibro-fatty plaque), which is a raised patch within the intima having a core of lipid (mainly cholesterol and its esters) and a cap of fibrous tissue”. Examples of large elastic arteries are aorta, carotid, and the iliac arteries, & examples of medium-sized muscular arteries are the coronaries and popliteal arteries.
Risk factors of atherosclerosis
Risk factors of atherosclerosis are expressed largely in terms of the incidence of deaths caused by ischemic heart disease (IHD). This is because atherosclerosis does not by itself produce signs and symptoms but its prevalence is detected by its effects on the most commonly involved arteries, namely the coronaries.
Risk factors that predispose to atherosclerosis and the resultant IHD can be divided into two main groups
   Major
      A. Potentially modifiable (controllable)
         1. Diet and hyperlipidemia
         2. Hypertension
         3. Cigarette smoking
4. Diabetes mellitus

**B. Nonmodifiable**
1. Increasing age
2. Male gender
3. Family history
4. Genetic abnormalities

**Minor (uncertain risks)**
1. Obesity
2. Physical inactivity
3. Stress (type A personality)
4. High carbohydrate intake
5. Lipoprotein (a)
6. Hardened unsaturated fat intake
7. Chlamydia pneumonia
8. Hyperhomocysteinemia

**Diet and Hyperlipidemia**

Hyperlipidemia (particularly hypercholesterolemia) and other abnormalities in lipid metabolism are major risk factors in atherosclerosis. *The evidences linking hypercholesterolemia to atherosclerosis include the following*

1. Atherosclerotic plaques are rich in cholesterol and its esters. These are largely derived from lipoproteins of the blood.
2. Atherosclerotic lesions can be induced in experimental animals by feeding them diets that raise their plasma cholesterol levels.
3. Genetic disorders that cause severe hypercholesterolemia lead to premature atherosclerosis, often fatal in childhood.
4. Acquired diseases associated with hypercholesterolemia (as part of their manifestations) for e.g. nephrotic syndrome and hypothyroidism, are associated with increasing risk of atherosclerosis
5. Populations having relatively high levels of serum cholesterol show higher mortality from IHD. This is reflected by the marked geographical variations in the incidence of atherosclerosis-related IHD, for e.g. the mortality rate from IHD is six times higher in the USA than that in Japan. This is probably related to differences in the life style and dietary customs.

High dietary intake of cholesterol and saturated fats, e.g. those present in egg yolk, animal fats, and butter, raises plasma cholesterol level. The higher the level of serum cholesterol the higher the risk particularly, with levels exceeding 200 mg/dl. The most striking association is with elevated levels of low-density lipoprotein (LDL). This is the lipoprotein moiety richest in cholesterol. In fact the major component of the total serum cholesterol associated with increased risk is LDL. Hypertriglyceridemia also appears to increase the risk. In contrast, serum levels of high-density lipoprotein (HDL) are inversely related to the risk. It is believed that HDL mobilizes cholesterol from developing atheromas and transports it to the liver to be eventually excreted into the bile. Exercise also raises the HDL level, whereas obesity and smoking lower it.
**Hypertension** is a major risk factor at all ages. Elevated blood pressure accelerates the process of atherosclerosis and increases the incidence of IHD and cerebrovascular diseases. Men over the age of 45 years with a blood pressure exceeding 170/95 mm Hg have more than five-fold greater risk of IHD than normotensives. Antihypertensive therapy reduces the incidence of atherosclerosis-related diseases, particularly IHD and CVA (cerebrovascular accidents; strokes).

**Cigarette smoking** is a well-established risk factor. It is the most important avoidable cause of IHD. Cigarette smoking is the main cause responsible for the relatively recent increase in the incidence and severity of atherosclerosis in women. In the context of IHD, two facts are related to smoking
a. It increases the incidence of sudden death among those with IHD
b. Cessation of smoking in high-risk individuals is followed within a few years by a reduction in the risk of dying from IHD.

**Diabetes mellitus**: diabetics are more susceptible, compared with nondiabetics to atherosclerosis-related diseases and in particular IHD, cerebrovascular accidents (CVA) and gangrene of lower extremities. This is probably related to
1. Hyperlipidemia, which is seen in up to 50% of diabetics
2. Increased platelets adhesiveness; predisposing to thrombotic episodes.
3. Some diabetics tend to be obese and hypertensive; thus have increased tendency to develop severe atherosclerosis.

All diabetics who have had the disease for at least ten years, irrespective of the age of onset, are likely to develop clinically significant atherosclerosis.

**Nonmodifiable risk factor**
- **Age**: death rates from IHD rise with each decade of life.
- **Male gender**: since myocardial infarction is particularly uncommon in premenopausal women.
- **Certain genetic defects**: certain families suffer increased frequency of heart attacks at an early age. This familial predisposition appears to be related to hyperlipidemia (due for e.g. to genetic defects in lipoprotein metabolism), hypertension, and diabetes mellitus.

**Pathology of atherosclerosis**

**Gross features**
- The basic lesion in atherosclerosis is a focal intimal thickening termed atheromatous plaque or fibro-fatty plaque.
- Each plaque is white to whitish yellow elevation up to 1.5 cm in diameter; adjacent plaques, however, may fuse to form larger plaques. (Fig. 1-4)
- The superficial portion of these lesions (i.e. facing the lumen) tends to be firm and white; this is the fibrous cap, whereas the deep portion is yellow and soft and represents the lipid component. It is from this yellow soft debris, the term atheroma is derived (Greek word for gruel).
- The most heavily involved arteries by atherosclerosis and in descending order are
  1. Abdominal aorta
  2. Coronaries
  3. Popliteal arteries
  4. Descending thoracic aorta
  5. Internal carotid arteries
  6. Arteries forming the circle of Willis at the base of the brain.
Atheromatous plaques are patchy in distribution and may involve the arterial wall in asymmetrical fashion i.e. involve one portion of the wall circumference more severely than elsewhere and as such produce eccentric lesions.

**Microscopic features (Fig. 1-5)**
- The superficial cap is composed of smooth muscle cells and relatively dense collagen fibers.
- Just beneath and to the sides of the cap there is a cellular area made of variable mixture of macrophages, smooth muscle cells and T-lymphocytes.
- Deep to the cellular area is a necrotic core; consisting of lipid material, cholesterol clefts, cellular debris and lipid-laden foam cells.
- Finally, especially around the edges of the lesion there are proliferating small, thin-walled blood vessels.
- The above mentioned components may occur in varying proportions in different plaques, for e.g. some plaques may be composed mostly of smooth muscle cells and fibrous tissue (fibrous plaques).

**The complicated atheroma**
The advanced atheromas are susceptible to the following changes that have clinical significance
1. **Focal rupture, ulceration, or erosion of the luminal surface.** This results in exposure of highly thrombogenic substances that induce thrombus formation. Alternatively, the fatty debris present within the core may be discharged into the blood stream producing microemboli (atheroemboli or cholesterol emboli). (Fig. 1-6)
2. **Hemorrhage in to the plaque** which is especially seen in the coronaries, either from rupture of the fibrous cap or rupture of the thin-walled capillaries that vascularise the atheroma. The atheroma, as a result, expands. This will worsen the already present stenosis. (Fig. 1-7)
3. **Superimposed thrombosis** is the most serious complication that usually occurs on disrupted lesions (ruptured, ulcerated, eroded lesions or those with intralesional hemorrhage). Thrombi may partially or completely occlude the lumen. They may become incorporated into the atheromatous plaque, enlarging it by subsequent organization. (Fig. 1-6)
4. **Aneurysmal dilatation;** in severe cases, particularly in large arteries such as the aorta, the underlying media undergoes pressure or ischemic atrophy with loss of elastic fibers. This may cause sufficient weakness that allows for aneurysmal dilatation (see under aneurysms)
5. **Calcification,** this may be patchy or massive. (Fig. 1-8)

**Pathogenesis of atherosclerosis**
The most widely accepted theory of pathogenesis is called the **response to injury hypothesis.**
This theory states that
- Lesions of atherosclerosis are initiated as a response to some form of repeated chronic injury to arterial endothelium.
- This injury increases endothelial permeability to plasma lipids as well as permitting blood monocytes and platelets to adhere to the endothelium.
- Monocytes subsequently enter the intima, transform into macrophages and accumulate lipids to become foam cells.
- Factors released from both platelets and macrophages cause migration of smooth muscle cells from the media into the intima with eventual synthesis and accumulation of collagen.
- Hyperlipidemia, hypertension and smoking may be responsible for the endothelial injury.
Macrophages produce, among other substances, toxic free oxygen radicals (ROS) that oxidize (modify) LDL in the lesions. This oxidized LDL is considered atherogenic, as it is:
- Chemotactic to blood monocytes
- Inhibits macrophage motility thus preventing them from leaving the atheroma.
- Cytotoxic to endothelial cells increasing their permeability

This suggests that antioxidants e.g. vitamin E and β-carotene may be effective in preventing atherosclerosis by reducing LDL oxidation.

Infection and Atherosclerosis
Seroepidemiologic studies have suggested that some infectious agents may contribute to atherosclerosis. Chlamydia pneumoniae and cytomegalovirus have been the most studied, although there is also interest in Helicobacter pylori, herpesvirus, and other organisms. Genomic sequences of these agents have been found in human atherosclerotic lesions, but whether they are causally associated or simply enter the diseased artery wall is not known.

Clinical significance of atherosclerosis
Atherosclerosis cause clinical disease through the following:
1. Slow, progressive narrowing of the arterial lumen that result in chronic ischemia of the relevant tissues.
2. Sudden occlusion of the lumen by superimposed thrombosis or hemorrhage into the atheroma.
   This may produce severe ischemia that if prolonged may terminate in infarction. (Fig. 1-7) & (Fig. 1-9)
3. Providing a site for thrombosis and then embolism.
4. Weakening of the wall of an artery, causing aneurysmal dilatation with subsequent rupture.

In large arteries such as the aorta the main complications are
1. Development of large mural thrombi over the plaques that may dislodge leading to peripheral emboli.
2. Aneurysmal dilatation of the wall due to weakness of the media.
3. Rupture of the atheroma leading to the development of cholesterol emboli.

In smaller arteries such as the coronary, cerebral, popliteal, renal and mesenteric arteries, the main effect is narrowing of the lumen leading to chronic ischemia. However, if this is complicated by superadded thrombosis or hemorrhage in to the plaque, occlusion of the vessel lumen occurs with subsequent catastrophic events such as myocardial infarction, cerebral infarction, gangrene of lower limbs, renal or intestinal infarctions.

MEDIAL CALCIFIC SCLEROSIS (Monckeberg’s arteriosclerosis)
This variant of arteriosclerosis is of undetermined etiology & is characterized by ring-like calcifications within the media of medium sized to small muscular arteries. The calcification does not narrow the lumen and thus the condition is of little clinical significance. It may coexist with atherosclerosis in the same artery. The arteries most commonly affected are those of the extremities (femoral, tibial, radial and ulnar), and those of the genital tract in both sexes. The condition can be demonstrated in individuals over the age of 50 years. (Fig. 1-10)

ARTERIOLOSCLEROSIS (Hypertensive vascular disease)
Hypertension is the most important cause of this group of vascular diseases. Hypertension has the following effects on blood vessels:
1. It accelerates the process of atherosclerosis.
2. Causes structural changes in the blood vessel wall that predisposes to
   a. Aortic dissection.
   b. Cerebrovascular hemorrhage.
3. Induce changes in arterioles referred to as arteriolosclerosis.
   There are two forms of arteriolosclerosis; hyaline & hyperplastic.

**Hyaline arteriolosclerosis**
This condition is encountered in the
1. Elderly whether normotensive or hypertensive.
2. Hypertensive individuals where it is more severe and more generalized.
3. Diabetics as part of the characteristic diabetic microangiopathy.

**Microscopic features**
- The vascular lesion consists of a *homogeneous, pink, hyaline thickening* of the arteriolar wall with loss of the native structural details
- This is associated with *narrowing of the lumen*. (Fig. 1-11)
The hyaline change in arteriolar wall is believed to be due to leakage of plasma proteins into the wall through a leaking endothelium. Hyaline arteriosclerosis is a major pathologic change in benign nephrosclerosis. In this condition the arteriolar narrowing leads to diffuse symmetric shrinkage and fine granularity of the kidneys. This is due to diffuse bilateral impairment of renal blood supply that results in loss of nephrons. (Fig. 1-12)

**Hyperplastic arteriolosclerosis**
In contrast to hyaline arteriolosclerosis, hyperplastic arteriolosclerosis is related to more acute or severe elevations of blood pressure and is therefore characteristic of malignant hypertension (defined as diastolic pressure usually over 120 mm Hg).

**Microscopic features** (Fig. 1-13)
- It is characterized by an onion-skin concentric, laminated thickening of the arteriolar wall with progressive narrowing of the lumen.
- The changes are due to reduplication of smooth muscle cells with thickening and reduplication of the basement membranes.
- Frequently these changes are associated with fibrinoid necrosis of arteriolar wall (necrotizing arteriolitis).
- Arterioles in all tissues may be affected, but main sites are the renal and intestinal arterioles.

**INFLAMMATORY DISEASE OF BLOOD VESSELS (The vasculitides)**
Vasculitis refers to inflammation, often with necrosis of blood vessels. This is encountered in diverse clinical setting. The terms arteritis, vasculitis and angiitis are used interchangeably because in addition to arteries and arterioles, veins and capillaries may be involved in some of the conditions.

**Mechanisms of vascular injury**
1. Infectious
2. Immunologically mediated
3. Unknown
The two most common mechanisms of injury are
1. Direct invasion of the vascular walls by microorganisms e.g. bacteria, fungi or viruses.
2. Immune-mediated inflammation.
a. Immune complex-mediated as in Henoch-Schönlein purpura and SLE, rheumatoid arthritis, drug induced, Hepatitis B and C virus)
b. Direct antibody attack-mediated as in Goodpasture’s syndrome and Kawasaki disease.
c. Cell-mediated as in organ transplant rejection
d. Antineutrophil cytoplastic autoantibody-mediated (ANCA-mediated) as in microscopic polyarteritis

Infections, in addition of causing direct damage to blood vessels, can indirectly induce immune-mediated damage through, either the formation of immune complexes or triggering cross reactivity. Distinction between direct infectious and immunologic mechanisms is important. This is because immunosuppressive therapy is the appropriate treatment for the latter whereas the same treatment would be potentially harmful for infectious vasculitis (suppressing immunity may flare up the infection). Finally, the mechanism of vasculitis may be unknown as in polyarteritis nodosa (PAN)

Classification of vasculitides
This depends on the size of the vessel involved, its anatomic site, histological features and the clinical manifestations. **Categories include**
1. Large vessel Vasculitis e.g. giant cell (temporal, cranial) arteritis.
2. Medium-sized vessel Vasculitis e.g. polyarteritis nodosa and Kawasaki disease.
3. Small vessel Vasculitis e.g. Henoch-Schonlein purpura and cutaneous leukoclastic Vasculitis.

**Giant cell (temporal) arteritis** is a relatively common disease. It is an acute and chronic, often granulomatous inflammation of large to small arteries. Evidences point to a T-cell –mediated immune response possibly to a vessel-wall antigen. It principally involves cranial vessels especially the temporal arteries in patients over 50 years. Other arteries may also be involved including vertebral and ophthalmic arteries. In some cases the aortic arch has been involved (giant cell aortitis).

Classical manifestations include severe throbbing pain and tenderness over the involved temporal artery, which is associated with swelling and redness of the overlying skin. There is often claudication of the jaw and visual manifestations such as blurring of vision, diplopia or sudden blindness. The ESR is often markedly elevated (over 100 mm/hr). *Biopsy of the temporal artery may be diagnostic and is required to confirm the clinical diagnosis.* (Fig. 1-14 A & B)

**Takayasu Arteritis**
This is another granulomatous vasculitis that classically involves the aortic arch. In half the cases, it affects also the pulmonary arteries. It is characterized principally by ocular disturbances and marked weakening of the pulses in the upper extremities (*pulseless disease*). It is seen predominantly in females younger than age 40. Autoimmune mechanisms are suspected. When the aortic arch is involved, the orifices of the major arteries to the upper portion of the body may be markedly narrowed or even obliterated by intimal thickening. Microscopically, there is chronic inflammation of the adventitia and the media, sometimes with granulomatous inflammation. Thus, the disease may be indistinguishable from giant cell (temporal) arteritis. In fact, distinctions among giant cell lesions of the aorta are based largely on the age of the patient, and most giant cell lesions of the aorta in young patients are Takayasu arteritis. Involvement of the root of the aorta may cause dilation of the aortic valve ring, producing aortic valve insufficiency. Narrowing of the coronary ostia may lead to myocardial infarction.

**Poly arteritis nodosa group of vasculitides (PAN)**
This group is characterized by systemic vasculitis and includes

1. **The classical (macroscopic)** PAN is characterized by necrotizing inflammation of small and medium-sized muscular arteries (but not arterioles, capillaries, or venules). The principal targets are the main visceral arteries such as renal, coronary, hepatic and mesenteric arteries. The pulmonary circulation is characteristically spared.

**Pathological features (Fig. 1-15)**

**Gross features**
- There is a sharply localized segmental involvement of the artery with aneurysmal dilatation.
- The latter can be demonstrated angiographically as nodularity along the course of the affected vessel; hence the term nodosa.

**Microscopic features:** the acute lesions are characterized by
- Fibrinoid necrosis of the arterial wall, which is often localized to a portion of the circumference.
- An intense infiltration of the arterial wall and peri-arterial region by inflammatory cells including neutrophils and eosinophils.
- The consequences of arteritis include
  1. Superadded thrombosis
  2. Weakening of the wall or aneurysmal dilatation may eventuate in rupture of the artery at that point.

As the result of the above changes there is ischemic damage to the tissues supplied by the involved artery e.g. renal, myocardial or intestinal infarction.

The diagnosis can be established by the demonstration of necrotizing arteritis with the above microscopic features in tissue biopsy specimen such as those of the kidney or nodular skin lesions.

2. **Microscopic polyarteritis (allergic or leucocytoclastic vasculitis)**

*(Clastic: broken into pieces; this refers to the fragmented nature of the WBC nuclei present in the lesion)*. This is a systemic necrotizing vasculitis that differs from classic PAN by

a. it affects arterioles, capillaries and venules (small vessel vasculitis)

b. necrotizing glomerulonephritis and pulmonary capillaritis are particularly common.

The main clinical features are hemoptysis, hematuria and proteinuria, bowel bleeding and skin purpura (Fig. 1-16). ANCA*s (anti-neutrophilic cytoplasmic antibodies) are present in 80% of the cases. In many cases the condition is precipitated by an immunological reaction to an antigen such as 1. Drugs e.g. penicillin 2. Microorganisms e.g. streptococci 3. Tumor antigens e.g. in malignancies 4. Heterologous protein

**Kawasaki disease (Mucocutaneous lymph node syndrome)**

This is an acute systemic disorder of infancy and childhood characterized by

1. Skin rash
2. Erythema of the conjunctiva, oral mucosa, palms and feet. (Fig. 1-17)
4. Vasculitis, which is PAN-like and characteristically involves the coronaries.

Death occurs in 2% of the cases due to coronary arteritis with superimposed thrombosis or rupture of coronary artery aneurysm. The cause is uncertain but a viral etiology is suspected.

**Henoch-Schonlein purpura** is a small vessel vasculitis most commonly seen in children. It is characterized by abdominal pain, acute arthritis, glomerulonephritis and nonthrombocytopenic
purpura that is distributed over the extensor aspects of the limbs and buttocks. **(Fig. 1-18)** These skin lesions consist of subepidermal necrotizing vasculitis involving small blood vessels. Deposition of IgA is present in the glomeuli and affected small blood vessels.

**Thromboangiitis obliterans (Buerger’s disease)** is a distinctive disease characterized by segmental vasculitis with thrombosis of medium sized and small arteries and sometimes veins of the extremities. The disease had occurred almost exclusively men who were heavy cigarette smokers. However, it has been increasingly reported in women, probably reflecting the increase in smoking habit by women in the past several decades. The relationship to cigarette smoking is a consistent features of this disease. It is postulated that there is initially an endothelial injury either directly or through hypersensitivity to some tobacco products. To begin with there are features of vascular insufficiency e.g. pain on exercise and intermittent claudication. Eventually gangrene of the extremities occurs that necessitates amputation. Remission and relapses correlate with cessation and resumption of smoking.

**Wegener Granulomatosis** is characterized by a triad of
1. Acute necrotizing granulomas of the upper &/or lower respiratory tracts
2. Necrotizing or granulomatous vasculitis most prominent in the lungs and upper airways
3. Focal necrotizing glomerulonephritis.

**Allergic granulomatosis and angitis (Churg-Strauss syndrome)** is a related entity distinguished by a strong association with allergic rhinitis, bronchial asthma, and peripheral eosinophilia.

**Raynaud’s disease and Raynaud’s phenomenon**
**Raynaud’s disease** refers to attacks of pallor or cyanosis of the fingers or toes. It is caused by intense vasospasm of local small arteries or arterioles. This disease is seen principally in otherwise healthy young females. The arterial and arteriolar walls are devoid of structural changes. The cause is unknown but is probably a reflection of exaggerated normal vasomotor responses to cold or emotion.

**Raynaud’s phenomenon** is clinically similar to the above but it is secondary to arterial narrowing induced by such diseases as SLE, systemic sclerosis, atherosclerosis or Buerger’s disease.

**ANEURYSMS AND DISSECTION**
An aneurysm by definition is a localized abnormal dilatation of any vessel including the heart. The aorta is the most commonly involved vessel. Left ventricular aneurysm may complicate myocardial infarction. Aneurysms are either true or false. A **true aneurysm** is bounded by the components of the blood vessel wall i.e. the blood is still within the confines of the circulatory system. In contrast, a **false aneurysm** (**pseudoaneurysm, pulsating hematoma**) is an extra-vascular collection of blood that communicates with the intravascular space. Its wall is derived from the outer layers of the arterial wall or peri-arterial tissue. False aneurysm is seen for e.g. as a result of a post-myocardial infarction rupture contained by pericardial adhesions or a leak at the anastomosis of a vascular graft. **Arterial dissection**, usually of the aorta (dissecting aneurysm), arises when blood enters the wall of the artery, dissecting between its layers and creating a blood-filled cavity within the wall itself.
Classifications of aneurysms

Aneurysms are classified either morphologically (according to their gross appearance or etiologically (the underlying mechanism responsible for their development).

Morphological classification (Fig. 1-19)

This is based on the macroscopic shape and size

1. **Berry aneurysm** is a small, spherical dilatation usually up to 1.5 cm in diameter. It is most frequently seen within the circle of Willis at the base of the brain. *Berry: any small globular or ovoid juicy fruit, not having a stone*

2. **Saccular aneurysm** is a spherical bulge from a portion of the vessel wall that varies in size from 5 to 20 cm in diameter i.e. a giant berry aneurysm.

3. **Fusiform aneurysm** results from gradual, progressive dilatation of the whole circumference of a segment of the vessel and may reach up to 20 cm in diameter.

Etiological classification

1. Atherosclerosis
2. Cystic medial necrosis or degeneration
3. Syphilis
4. Vasculitides e.g. PAN and Kawasaki disease
5. Trauma leading to arterio-venous aneurysm
6. Congenital defects such as that producing berry aneurysms in the brain
7. Mycotic aneurysm produced as a result of infection of the arterial wall.

The most important causes of aortic aneurysms are atherosclerosis and cystic medial degeneration.

Atherosclerotic aneurysm

Atherosclerosis is the most frequent etiology of aneurysms. It causes arterial wall thinning through medial destruction secondary to intimal plaques. Atherosclerosis is a major cause of abdominal aneurysms.

Pathologic features (Fig. 1-20 A & B)

- It usually occurs in the abdominal aorta, mostly between the levels of renal arteries and the iliac bifurcation. They may also be seen in the common iliac arteries, the aortic arch, and descending portions of thoracic aorta.
- It is usually fusiform, contains atheromatous ulcers covered by mural thrombi. The latter may be a source of emboli that may lodge in renal vessels or those to the lower limbs.

Two Abdominal Aortic Aneurysms (AAA) variants merit special mention:

a. **Inflammatory AAA** is characterized by dense periaortic fibrosis with lymphoplasmacytic infiltrate.

b. **Mycotic AAA** is an infected atherosclerotic aneurysm by circulating microorganisms in the wall, particularly in the setting of bacteremia from a primary Salmonella gastroenteritis. In such cases, suppuration further destroys the media, potentiating rapid dilation and rupture.

The clinical effects of aortic aneurysm include

1. Rupture into the peritoneal cavity or retroperitoneum with massive or fatal hemorrhage.
2. Pressure on adjacent structures leading for e.g. obstruction of a ureter or erosion of vertebrae.
3. Occlusion of a vessel either by direct pressure or through intramural thrombus formation e.g. vertebral branches supplying spinal cord.
4. Embolism from the atheroma or mural thrombus.
5. Creation of abdominal mass that may be confused on physical examination with a tumor.

Prosthetic grafts should replace large aneurysms (> 5 cm in diameter) to avoid the possibility of rupture.

**Aortic dissection (dissecting aneurysm)**

This is characterized by dissection of blood along the plane of aortic media, with the formation of blood-filled channel within the aortic wall that often ruptures, causing massive hemorrhage. The dissection may or may not be associated with significant dilatation of the aorta; it is for this reason the older term dissecting aneurysm is discouraged. This dissection of the aorta occur principally in two groups of patients:

1. Hypertensive men (90% of the cases)
2. In those with a systemic or localized abnormality of connective tissues that affects the aorta (e.g. Marfans syndrome) (10% of the cases), the patients are usually younger than the above group.

**Conditions associated with aortic dissection are**

1. Hypertension (80% of the cases)
2. Cystic medial necrosis or degeneration of the aortic wall
3. Previous surgery to the aorta e.g. coronary bypass or aortic valve replacement
4. Pregnancy usually third trimester

**Gross features (Fig. 1-21 A)**

- A tear in the aortic intima causes the dissection. This is usually transverse and located within the ascending portion of thoracic aorta.
- This tear exposes the diseased media to the blood at intra-aortic pressure. The media is cleaved into two layers, creating a false lumen in addition to the existing true lumen.

**Microscopic features**

- The blood dissects into the media of the wall creating a vessel with a double lumen. (Fig. 1-21 B)
- In most patients with aortic dissection no specific underlying causative pathology is seen in the aortic wall.
- The most frequent histologically detectable abnormality is called **cystic medial degeneration** (CMD); this is presumably responsible weakening of the wall. The degenerative changes range from mild fragmentation of elastic fibers to focal separation of both elastic and fibro-muscular fibers by small clefts or cystic spaces (cystic medial degeneration).

**Aortic dissection may have the following consequences**

1. Rupture into any of the three body cavities i.e. pericardial, pleural or peritoneal. This is the most common cause of death.
2. Extension of the dissection into the great arteries of the neck, coronaries, renal, mesenteric, or iliac arteries. This leads to their obstruction with subsequent ischemic damage to the relevant organs e.g. myocardial infarction, renal infarction, and spinal cord ischemic injury (due to involvement of spinal arteries). (Fig. 1-22)
3. Retrograde dissection into the aortic root that leads to disruption of the valvular apparatus with consequent aortic valve insufficiency.
4. Rupture in the lumen of the aorta through a second distal tear. This is thought to prevent a fatal extra-aortic hemorrhage.

**Syphilitic (Luetic) aneurysm**
This is a recognized complication of tertiary syphilis. With the decline in the incidence of tertiary syphilis, these types of aneurysms have become uncommon. The dilatation is confined to the thoracic aorta and usually involves the arch. To begin with, there is inflammation of the vasa vasorum within the aortic adventitia that eventuates in their luminal obliteration. The inflamed small vessels (vasa) are surrounded by an infiltrate rich in plasma cells. This leads to ischemic injury of the media that terminates in medial scarring and hence weakening and aneurysmal dilatation. Contraction of the scarred media leads to intimal redundancy with subsequent wrinkling referred to as ‘tree barking’. Syphilitic aneurysm may also cause aortic valve ring dilatation resulting in aortic insufficiency. This is due to circumferential stretching of the cusps and widening of the commissures between the cusps. On the long run the Lt ventricular wall undergoes volume overload hypertrophy with subsequent dilatation. The resultant markedly cardiomegaly has been likened to a cow’s heart (cor bovinum). The thoracic location of syphilitic aneurysm distinguishes it from typical atherosclerotic aneurysm, which rarely affects the aortic arch and never involves the root of the aorta.

**Mycotic aneurysm**
This refers to a dilatation of an artery as a result of weakness of its wall secondary to infection. Thrombosis and rupture are possible complications. The infection reaches the artery through one of three routes
1. Lodgment of septic embolus in the artery, usually complicating infective endocarditis.
2. Extension of an adjacent Suppurative precesses.
3. Circulating microorganisms (bacteremia, septicemia) that directly infect the arterial wall.
Mycotic aneurysm may involve, among others, the aorta, cerebral vessels or the popliteal artery.

**Berry aneurysm (saccular aneurysm-Congenital aneurysm)**
This is the most frequent type of intracranial aneurysms and the one most frequently responsible for subarachnoid hemorrhage. It has an incidence of about 2% in the general population. An unruptured berry aneurysm is a thin-walled bright red out-pouching at arterial branch points along the circle of Willis or major vessels just beyond. *(Fig. 1-24)* The pathogenesis is thought to be due to congenital defect of the media especially at bifurcations. Ruptured berry aneurysm with clinically significant subarachnoid hemorrhage is most frequent in the age group of 40-50 years.

**DISEASES OF VEINS AND LYMPHATICS**
Varicose veins and phlebothrombosis/thrombophlebitis together constitute about 90% of venous diseases.

**Varicose veins**
These are abnormally dilated, tortuous veins produced by prolonged increase in intraluminal venous pressure. The superficial veins of the legs are the usual sites of involvement. Much less common, but more significant are involvement of veins in the lower esophagus (esophageal varices) due to portal hypertension for e.g. secondary to liver cirrhosis. Hemorrhoids are another example of varicose veins. **Varicose veins of leg superficial veins**
**Predisposing factors**
1. Conditions associated with elevation of venous pressure in these veins
   a. Pregnancy; this explains the higher incidence in females
   b. Obesity
   c. Occupations requiring long periods of standing
2. Weakening of the walls of veins
   a. Defective development of the vein wall; this possibly explains the familial tendency of varicose veins.
   b. Age; the condition is much more common over the age of 50 years.
The affected veins, which are visible through the skin of legs, are dilated, tortuous, elongated and scarred. (Fig. 1-25) There is variation in the thickness of the wall. The above changes lead to deformity and incompetence of the vein valves. This aggravates the situation and a vicious circle is thus created.
Varicose veins lead to local venous stasis, congestion, edema and thrombosis. Embolism is very rare (superficial veins).

**Disabling complications include**
1. Persistent edema
2. Stasis dermatitis (due to stasis of blood and liberation of hemosiderine)
3. Varicose ulcers.

**Thrombophlebitis and phlebothrombosis**
These are two designations for inflammation and venous thrombosis.

**Predisposing factors include**
1. Cardiac failure
2. Neoplasia
3. Pregnancy
4. Obesity
5. Postoperative states
6. Prolonged bed rest and immobilization

**Site of occurrence include**
1. The deep veins of the leg are the most common sites of venous thrombosis.
2. Additional sites for deep vein thrombosis (DVT) include periprostatic plexus of veins in males and the pelvic veins in females.
3. Dural sinuses and skull veins in bacterial meningitis and otitis media.
4. Portal vein thrombosis may complicate intra-abdominal sepsis.

**Two special variants of phlebothrombosis**
1. **Phlegmasia Alba Dolens (painful white leg):** this is an ileo-femoral venous thrombosis that occurs usually in pregnant females, in the third trimester or immediately following delivery. It is manifested by severely painful swelling of the lower limb. The predisposition to thrombosis is attributed to stasis of blood caused by the pressure of gravid uterus on the pelvic veins compounded by the hypercoagulable state during pregnancy.
2. **Migratory thrombophlebitis:** this refers to the occurrence of venous thrombi, often multiple that classically disappears at one site to reappear elsewhere. It is usually encountered in patients with visceral malignancies especially those of the pancreas, lung and colon.
VASCULAR TUMORS
This is a heterogeneous group of neoplasms and tumor-like conditions. It is best divided according to their biological behavior into the following three groups

I. Benign: e.g. hemangiomas, pyogenic granulomas, glomus tumor, and vascular ectasias.

II. Intermediate: locally aggressive tumors that rarely metastasize e.g. hemangioendothelioma and Kaposi’s sarcoma

III. Malignant: e.g. angiosarcoma, hemangiopericytoma.

I. Benign vascular tumors & tumor-like lesions

- Hemangiomas are very common tumors, constituting more than 5% of all benign tumors. They are most common in infants and children. They are subdivided into

  Capillary hemangiomas, which represent focal proliferation of capillary-sized blood vessels. They usually occur in the skin, subcutaneous tissues, lips, and oral mucous membranes. Strawberry type of capillary hemangioma is seen in the skin of newborns, but it usually regresses and disappears in the majority of the cases.

  Cavernous hemangiomas are characterized by focal proliferation of large (venous-sized) vascular channels. They are seen most often in the skin, lips, and tongue but also encountered in the liver, spleen, and pancreas. (Fig. 1-26) In most cases, the tumors are of little clinical significance; however,

    1. There can be a cosmetic disturbance. (Fig. 1-27)
    2. Visceral hemangiomas detected by imaging studies may need to be distinguished from more ominous malignant tumors.
    3. Brain hemangiomas can cause pressure symptoms or rupture.
    4. Cavernous hemangiomas are component of von Hippel-Lindau disease; they involve the cerebellum or brain stem and eye grounds, along with similar lesions in the pancreas and liver.

- Pyogenic Granuloma (see GIT; mouth)

  This form of capillary hemangioma is a rapidly growing red nodule on the skin, gingival, or oral mucosa; it bleeds easily and is often ulcerated. Roughly a third of lesions develop after trauma. The proliferating capillaries are accompanied by edema and an acute and chronic inflammatory infiltrate, an appearance with striking similarity to exuberant granulation tissue. Pregnancy tumor (granuloma gravidarum) is a pyogenic granuloma that occurs in the gingiva of 1% of pregnant women. These lesions can spontaneously regress (especially after pregnancy) or undergo fibrosis.

- Lymphangioma

  1. Simple (Capillary) Lymphangioma are slightly elevated or pedunculated, small lesions are composed of small lymphatic channels. They are mainly seen in the head, neck, and axillary subcutaneous tissues.

  2. Cavernous Lymphangioma (Cystic Hygroma) are typically found in the neck or axilla of children. These lesions can occasionally be enormous (up to 15 cm in diameter) and may fill the axilla or produce gross deformities about the neck. Tumors are composed of massively dilated endothelial-lined lymphatic spaces separated by intervening connective tissue stroma containing lymphoid aggregates.

- Glomangioma (glomus tumor) is a tumor that originates from glomus bodies (which normally control skin blood flow and temperature), especially in fingers and toes. It is seen as a very tender, bluish nodule, near the end of a finger or toe. It consists of vascular spaces surrounded by rounded cuboidal cells of smooth muscle derivation.
Vascular Ectasias are common lesions characterized by local dilation of preexisting vessels; they are not true neoplasms; they include
1. Nevus Flammeus
2. Spider Telangiectasia
3. Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Bacillary Angiomatosis is an opportunistic infection in immunocompromised persons (e.g. AIDS patients) that manifests as vascular proliferations involving skin, bone, brain, etc. It is caused by infection with gram-negative bacilli of the Bartonella genus.

II. Intermediate-Grade (Low-Grade Malignant) Tumors
A. Kaposi Sarcoma is used to be fairly common in patients with AIDS prior to the advent of effective antiretroviral therapy, and its presence is used as a criterion for diagnosing AIDS. Four forms of the disease are recognized, all of these share the same underlying viral pathogenesis:
1. Chronic KS (classic KS) characteristically occurs in older men. It is not associated with HIV. There multiple red to purple skin plaques or nodules, usually in the distal lower extremities.
2. Lymphadenopathic KS (African, endemic KS) is particularly prevalent among South African Bantu children; it is also not associated with HIV. Skin lesions are sparse, and patients present instead with lymphadenopathy due to KS involvement; the tumor occasionally involves the viscera and is extremely aggressive.
3. Transplant-associated KS occurs in the setting of solid-organ transplantation with its attendant long-term immunosuppression. It tends to be aggressive (even fatal) with nodal, mucosal, and visceral involvement; cutaneous lesions may be absent.
4. AIDS-associated KS (epidemic KS) was found in a third of AIDS patients, particularly male homosexuals. However, with current regimens of intensive antiretroviral therapy, KS incidence is now less than 1% (although it is still the most prevalent malignancy in AIDS patients in the United States). AIDS-associated KS can involve lymph nodes and viscera, with wide dissemination early in the course of disease. Most patients eventually die of opportunistic infectious rather than from KS.

Pathogenesis
Regardless of the clinical subtype (described above), 95% of KS lesions have been shown to be due to human herpesvirus 8 [HHV-8] infection. The virus is transmitted sexually and by poorly understood nonsexual routes.

Pathological features (Fig. 1-27 A & B)
- Three stages are recognized: patch, plaque, and nodular.
- Patches are solitary or multiple pink, red, or purple macules, typically confined to the distal lower extremities. They are difficult to distinguish from granulation tissue.
- With time, lesions spread proximally and convert into larger, violaceous, raised plaques composed of dermal accumulations of dilated, jagged vascular channels lined by plump spindle cells and perivascular aggregates of similar spindled cells. Scattered between the vascular channels are red blood cells, hemosiderin-laden macrophages, lymphocytes, and plasma cells.
- At a still later stage, lesions become nodular. These lesions are more sarcomatous than the above. The nodular stage is often accompanied by nodal and visceral involvement, particularly in the African and AIDS-associated variants.
B. **Hemangioendotheliomas** are vascular neoplasms with histology and clinical behaviors intermediate between benign hemangiomas and frankly anaplastic angiosarcomas.

III. **Malignant Tumors**

A. **Angiosarcomas** are malignant endothelial neoplasms with histology varying from highly differentiated tumors that resemble hemangiomas to anaplastic lesions. Older adults are commonly affected. They occur at any site but most often involve skin, soft tissue, breast, and liver. **Hepatic angiosarcomas** are associated with carcinogenic exposures, including arsenic (arsenical pesticides), Thorotrast (a radioactive contrast agent formerly used for radiologic imaging), and polyvinyl chloride (PVC; a widely used plastic). The increased frequency of angiosarcomas among PVC workers is one of the truly well-documented instances of human chemical carcinogenesis. Angiosarcomas can also arise in the setting of lymphedema, classically in the ipsilateral upper extremity several years after radical mastectomy for breast cancer; the tumor presumably arises from lymphatic vessels (lymphangiosarcoma). Angiosarcomas can also be induced by radiation. Clinically, angiosarcomas are locally invasive and can metastasize readily. The current 5-year survival rates approach 30%.

B. **Hemangiopericytomas** are rare tumors derived from pericytes-myofibroblast-like cells that are normally arranged around capillaries and venules. They are most common on the lower extremities (especially the thigh) and in the retroperitoneum. They consist of numerous branching capillary channels and gaping sinusoidal spaces enclosed within nests of spindle-shaped to round cells. The tumors may recur after excision, and roughly half metastasize, usually hematogenously to lungs, bone, or liver.
THE HEART

The Normal heart
The average weight of the heart in females is 250 to 300 g whereas in males it is slightly heavier (300 to 350 g). The normal thickness of the Rt. ventricular wall is 0.3 to 0.5 cm whereas that of the Lt ventricle is thicker (1.2 to 1.5 cm). Higher weight or ventricular thickness signifies hypertrophy; below normal weight signifies atrophy; and below normal thickness of the ventricular wall implies dilatation. A normal ventricular thickness may be found in a markedly heavy (hypertrophied) heart indicating ventricular dilatation.

The three major epicardial coronary arteries are
1. The left anterior descending (LAD) artery
2. The left circumflex (LCX) arteries
3. The right coronary artery (RCA).

Both the LAD & LCX arise from the stem of the left coronary artery.

Knowledge of the areas of the ventricles supplied by each of the three major coronary arteries helps predicting the location of infarcts that result from occlusion of any of these arteries.

The left main coronary artery bifurcates within 1 cm of its origin into the LAD and LCX coronary arteries. The LCX supplies the lateral wall of the left ventricle (Fig. 11-2). The LAD coronary artery provides blood to the
1. Anterior left ventricle
2. Adjacent anterior right ventricle, and
3. Anterior half-to-two thirds of the interventricular septum.

In the apical region, the LAD artery supplies the ventricles circumferentially (see Fig. 11-2). The RCA nourishes the bulk of the right ventricle and posteroseptal left ventricle (see Fig. 11-2), including the posterior third-to-half of the interventricular septum at the base of the heart. The epicardial coronary arteries are usually arranged in a so-called right coronary-dominant distribution. The pattern of dominance is determined by the coronary artery that contributes most of the blood to the posterior descending coronary artery. Ten percent of human hearts display a left-dominant pattern, with the left circumflex coronary artery supplying the posterior descending coronary artery.

Thus, occlusions of the right as well as the left coronary artery can cause left ventricular damage.

HEART FAILURE (CONGESTIVE HEART FAILURE) (CHF)
CHF is a common condition with a poor prognosis; it represents the end point of many cardiac diseases. The failing heart is unable to pump sufficient blood to meet the requirements of the body. Excluded from this definition are conditions in which inadequate cardiac output (COP) is not due to cardiac abnormality e.g. shock states including blood loss or conditions that impairs blood return to the heart (e.g. thrombosis of inferior vena cava). Inadequate cardiac output (forward failure) means that the failing ventricle can no longer pump the whole blood delivered to it by the venous circulation. Thus, there is an associated increase in venous pressure & congestion of the venous circulation (backward failure). In CHF, other organs are eventually affected by some combination of forward and backward failure.

Cardiac hypertrophy
This is an adaptive response to increased mechanical load on the heart in which there is an increase in the rate of protein (myofilaments) synthesis within each cell. As a result there is an increase in cell size (hypertrophy). Causes of hypertrophy include
1. Pressure overload
a. systemic or pulmonary hypertension  
  b. aortic or pulmonary stenosis  

2. Volume overload  
  a. aortic or pulmonary regurgitation  
  b. abnormal communications between the two sides of the heart, congenital or acquired  

3. Excessive stimulation as of β-adrenergic receptors e.g. in hyperthyroidism leading to an increase in heart rate.  

The severity of hypertrophy depends on the underlying causes  
1. Mild hypertrophy (up to 2X normal weight) as in ischemic heart disease  
2. Moderate hypertrophy (>2X to 3X normal) as in systemic hypertension & aortic stenosis  
3. Marked hypertrophy (> 3X normal; up to 1000 gm heart weight) as in aortic regurgitation and hypertrophic cardiomyopathy.  

The pattern of hypertrophy reflects the nature of the underlying cause, for e.g. in pressure-overload hypertrophy there is concentric hypertrophy of the left ventricle. This hypertrophy may reduce the cavity diameter i.e. restrict diastolic filling. (Fig. 1-29) In contrast, in volume-overload hypertrophy there is also dilation that increases the size of the ventricular cavity. Owing to the dilation, wall thickness of a heart in which both hypertrophy and dilation have occurred is not necessarily increased, and it may be normal or even less than normal i.e. the dilation masks hypertrophy (Fig. 1-30). Thus, wall thickness is not by itself an adequate measure of volume-overload hypertrophy. Hypertrophied heart shows increased oxygen consumption due to increased metabolic requirements and thus, hypertrophy constitutes a breakable balance of the adaptation-related changes (e.g. new myofilaments synthesis) versus those related to the injurious agent e.g. decrease in capillary density due to the pressure effect of the enlarged myocyte and this stimulates deposition of fibrous tissue. Thus sustained cardiac hypertrophy often progresses to cardiac failure. In contrast to the pathologic hypertrophy, physiologic hypertrophy that is induced by regular tough exercise is rather an extension of normal growth and has minimal or no harmful effect.  

Heart failure is a common eventual outcome of many forms of heart disease.  
Heart failure can affect predominantly the left side or the right side, or both sides of the heart. Left-sided and right-sided failure can occur independently. Nevertheless, because the CVS is a closed circuit, failure of one side (particularly the left side) often produces excessive strain on the other side, terminating in global heart failure.  

Causes of left-sided cardiac failure include  
1. IHD (the most common)  
2. Systemic hypertension (the next most common)  
3. Mitral or aortic valve disease  
4. Primary diseases of the myocardium (cardiomyopathies)  

Causes of right-sided heart failure include  
1. Left ventricular failure (the most common); it is due to its associated pulmonary congestion with elevation of pulmonary arterial pressure.  
2. Intrinsic diseases of the lung parenchyma&/or pulmonary vasculature (cor pulmonale)  
3. Right sided valve diseases  
4. Congenital heart diseases, associated with left-to-right shunts  

Left-sided heart failure  
The clinical effects of left-sided CHF primarily result from  
1. Progressive damming of blood within the pulmonary circulation (venous congestion)
2. The consequences of diminished cardiac output i.e. multi-organ ischemia.

The morphological changes in left-sided heart failure are divided into cardiac & extracardiac.

**Cardiac changes**: in addition to the causative agent (e.g. myocardial infarction, valvular deformity, etc.), the left ventricle is usually hypertrophied and often dilated. The latter often leads to secondary enlargement of the left atrium with resultant atrial fibrillation that may lead to
1. Further reduction of the stroke volume
2. Blood stasis with possible thrombus formation (particularly in the atrial appendage). Dislodgement of such a thrombus (or part of it) carries a risk of embolism e.g. CVA.

**Extracardiac changes** are manifested most prominently in the lungs, although the kidneys and brain may also be affected.

**Lungs**
The Pressure in the pulmonary veins increases and is ultimately transmitted retrograde to the capillaries and arteries. The result is pulmonary congestion and edema, with heavy, wet lungs. The pulmonary changes include, in sequence (Fig. 1-31)
1. Progressive edematous widening of alveolar septa
2. Accumulation of edema fluid in the alveolar spaces
3. RBCs, which leak from congested capillaries, are phagocytosed by macrophages, where their hemoglobin is converted to hemosiderin. Hemosiderin-containing macrophages accumulate in the alveoli (heart failure cells).

These anatomic changes are associated clinically at first with dyspnea (breathlessness) that progresses to orthopnea (dyspnea on lying down) that progresses to paroxysmal nocturnal dyspnea (attacks of extreme dyspnea, usually occurring at night).

**Kidneys**
Decreased cardiac output causes a reduction in renal perfusion, which activates the renin-angiotensin-aldosterone system, inducing retention of salt and water with consequent expansion of the interstitial fluid and blood volumes. This can contribute to the pulmonary edema in left-sided heart failure. If the perfusion deficit of the kidney becomes sufficiently severe, impaired excretion of nitrogenous products may cause azotemia (elevated levels of urea or other nitrogenous waste products in the blood)

**Brain**
In far-advanced Lt sided failure, cerebral hypoxia may give rise to hypoxic encephalopathy (irritability, restlessness, which may progress to coma).

**Right-sided heart failure (RHF)**
Any increase of pressure within the pulmonary circulation secondary to left-sided heart failure (backward failure) leads to an increased burden on the right side of the heart. The causes of right-sided heart failure must then include all those that induce left-sided heart failure. Pure right-sided heart failure most often occurs with chronic severe pulmonary hypertension, which puts a pressure overload on the right ventricle. In such cases hypertrophy and dilation are generally confined to the right ventricle and atrium. The major morphologic and clinical effects of pure right-sided heart failure differ from those of left-sided heart failure in that
1. Pulmonary congestion is minimal
2. Engorgement of the systemic and portal venous systems is prominent.

**Morphological changes of RHF**
In addition to the cardiac changes (see above), the extracardiac organs principally affected by Rt. Sided heart failure include

**Liver**
The liver is usually increased in size and weight (congestive hepatomegaly), and a cut section displays prominent passive congestion. Congested red centers of the liver lobules are surrounded by paler, sometimes fatty, peripheral regions (nutmeg liver) (Fig. 1-32). In some instances, especially when left-sided heart failure is also present, the severe central hypoxia produces centrilobular necrosis along with the sinusoidal congestion (central hemorrhagic necrosis). With long-standing severe right-sided heart failure, the central areas can become fibrotic, creating cardiac fibrosis.

**The Portal System (spleen, bowel and peritoneal cavity)**
RHF also leads to increased pressure in the portal vein and its tributaries (portal hypertension) due to backward reflection of the increased pressure within the inferior vena cava. Congestion produces a tense, enlarged spleen (congestive splenomegaly). Chronic edema of the bowel wall can occur and may interfere with absorption of nutrients. In addition, accumulations of transudate in the peritoneal cavity may give rise to ascites (Fig. 1-33).

**Kidneys:** congestion of the kidneys is more marked with RHF than with LHF, leading to greater fluid retention, peripheral edema, and more pronounced azotemia.

**Brain:** venous congestion and hypoxia of the central nervous system are associated with symptoms essentially identical to those described in LHF.

**Pleural and Pericardial Spaces:** accumulation of fluid (effusion) in the pleural space (particularly right) and pericardial space may appear. Thus, while pulmonary edema indicates left-sided heart failure, pleural effusions accompany right-sided heart failure. Pleural effusions can cause partial collapse of the corresponding lung.

**Subcutaneous Tissues:** peripheral edema of the dependent portions, especially ankle and pretibial soft tissues, is a hallmark of RHF (Fig. 1-34). In chronically bedridden patients, the edema may be primarily presacral. Generalized massive edema (anasarca) may also occur in severe, advanced cases.

**HEART DISEASES**
Heart disease, especially ischemic, is the predominant cause of disability and death. It accounts for about 40% of all postnatal deaths; this is twice the number of deaths caused by all forms of cancer combined.

**Five categories of disease account for nearly all cardiac mortality**
1. Congenital heart disease
2. Ischemic heart disease (IHD) (coronary heart disease)
3. Hypertensive heart disease (systemic and pulmonary)
4. Valvular heart disease (Rheumatic, etc.)
5. Cardiomyopathies (non-ischemic-primary myocardial disease)

**ISCHEMIC HEART DISEASE (IHD)**
IHD covers four closely related syndromes resulting from inadequacy of oxygenated blood supply to the heart to meet its physiologic demands.
1. Angina pectoris
2. Myocardial infarction
3. Chronic ischemic heart disease
4. Sudden cardiac death, which may be superimposed on any of the above three.
The occurrence of any of the above depends on the rate of development of arterial narrowing(s) and its ultimate severity; this in turn is a reflection of the relative contributions of four events, namely

a. Stenosis  b. platelet aggregation  c. thrombosis  d. coronary artery spasm

**Pathogenesis of ischemic heart disease**

The heart may suffer a deficiency of oxygen supply with the following circumstances

1. **Reduction in coronary blood flow** (90% of the cases) due to one or more of the following
   a. Atherosclerosis (the main cause)
   b. Coronary artery spasm
   c. Hemodynamic derangements leading to hypoperfusion (e.g. shock states and heart failure)
   d. Nonatherosclerotic coronary diseases (e.g. arteritis)

2. **Increased demand** *(as in tachycardia, ventricular hypertrophy)*

3. **Reduced oxygen carrying capacity of the blood** *as occurs in*
   a. Anemia
   b. Cigarette smoking
   c. Advanced lung diseases
   d. Cyanotic congenital heart diseases
   e. Carbon monoxide poisoning

**A. The role of coronary atherosclerosis:** over 90% of patients with one of the ischemic syndromes have advanced coronary atherosclerosis. This is defined as having *one or more* stenotic lesions causing at least 75% reduction of the luminal cross sectional area of at least one of the major (epicardial) coronary arteries. The stenosing plaques tend to occur within the first 2 cm of the LAD and LCX & proximal and distal thirds of the RC.

**B. The role of platelets:** rupture of an atheromatous plaque exposes the subendothelial collagen, which is thrombogenic and thus leading to platelet adherence, activation, and a chain of release reaction. These changes eventuate in the production of a large pool of activated platelets within the coronary system. The aggregated platelets may lead to

1. Occlusive thrombosis
2. Micro-emboli that aggravate the perfusion deficit
3. Liberation of vasoactive products released by the activated platelets that include thromboxane A2, histamine, and serotonin, which contribute to a possible coronary vasospasm.

*Two agents have been found to significantly reduce* the incidence of mortality from IHD

1. *The long-term use of small doses of aspirin,* which interferes with the synthesis of thromboxane A2. The latter is a potent aggregator of platelets and a vasoconstrictor.
2. *The eating of diets rich in fish* with their polyunsaturated omega-3 fatty acids, which tend to inhibit platelet aggregation.

**C. The role of vasospasm:** vasospasm of atheromatous epicardial arteries has been documented angiographically in some patients with angina or MI. This spasm may contribute to rupture or fissuring of plaques with subsequent platelet aggregation & thrombosis. Activation of aggregated platelets could aggravate the spasm through their products. Thus vasospasm could initiate platelet aggregation & aggregated platelets could worsen the vasospasm. In rare cases, coronary artery spasm has been associated with acute MI in patients having no atheromatous coronary narrowing.
D. The role of nonatheromatous lesions of the coronaries

The following disorders, when involving the coronaries, have been associated with one or more of the IHD syndromes:
1. Emboli to the coronaries
2. Arteritis (e.g., Takayasu's disease, SLE, Kawasaki's syndrome, PAN and others)
3. Cocaine abuse through triggering arrhythmias and vasospasm
4. Trauma to the coronaries.

E. The role of hemodynamic disturbances

1. Shock may be associated with significant fall in blood pressure thus severely reducing coronary perfusion, particularly in vessels already narrowed by atherosclerosis.
2. Left-sided heart failure is associated with a decrease in cardiac output that in turn reduces perfusion of the coronary system.

The above two in addition to conditions interfering with oxygen-carrying capacity of the blood (listed above) could aggravate the already present ischemia.

The acute ischemic coronary syndromes (Fig. 1-39): this term encompasses the following
1. Unstable angina
2. Acute MI (transmural or subendocardial)
3. Sudden cardiac death
4. Percutaneous coronary interventions

The above four reflect rapid progression in the severity of coronary artery stenosis; generally initiated by a rapid (acute) conversion of a stable atherosclerotic plaque to unstable one, usually with superimposed thrombosis. The acute conversion involves the one of two events
1. Erosion, ulceration, fissuring or rupture; these are complicated by superimposed thrombosis.
2. Hemorrhage into the plaque, expanding its volume and thus aggravates the already present stenosis.

Slowly developing stenoses may stimulate collateral vessels over time, which protect against myocardial ischemia and infarction even with an eventual severe narrowing of the lumina.
Although only a single major coronary artery may be affected by the stenosis, two or all three coronaries (LAD, LCX, and RCA) are often involved. Disruption of the atheromatous plaque is decisive to the pathogenesis of the acute coronary syndromes. In acute transmural MI, the usual event is a thrombus superimposed on a disrupted but partially stenotic plaque. This converts the stenosis into a total occlusion. In contrast, with unstable angina, acute subendocardial infarction, or sudden cardiac death, the luminal obstruction by thrombosis is usually incomplete. Sudden cardiac death can be the result of regional myocardial ischemia that induces a fatal ventricular arrhythmia (e.g. ventricular fibrillation).

ANGINA PECTORIS is characterized by sudden, usually recurrent attacks of substernal or precordial chest discomfort or pain caused by transient myocardial ischemia. This ischemia is not sufficient enough to cause infarction. There are three overlapping patterns of angina
1. Stable angina
2. Prinzmetal (variant) angina
3. Unstable (crescendo angina) (preinfarction angina).

They are caused by varying combinations of increased myocardial demand and decreased myocardial perfusion.

Stable (typical) angina is the most common form that is caused by reduction of coronary perfusion to a critical level by chronic fixed stenosing atherosclerosis of 75% or greater of the
original lumen. This generally causes symptomatic ischemia whenever there is increased cardiac workload, such as that produced by physical activity, emotional excitement, etc. It is usually relieved by rest or nitroglycerin. The latter is a strong vasodilator.

**Prinzmetal (variant) angina** is uncommon form that occurs at rest and is due to episodic occlusive coronary artery spasm of normal or minimally diseased coronary artery.

**Unstable angina** is one of the acute coronary syndromes and characterized by progressively increased frequency and more prolonged attacks of angina. It is induced by disruption of an atherosclerotic plaque with superimposed thrombosis and possibly embolization to a more distal vessels and/or vasospasm. These changes generally cause a severe reduction of the arterial lumen by 90%. Unstable angina lies intermediate between stable angina on the one hand and MI on the other.

**MYOCARDIAL INFARCTION** is the most important form of IHD and is the leading cause of death in many countries. Over 50% of these fatalities occur in the first hour, before the patient reaches the hospital, mainly due to the onset of fatal arrhythmias such as ventricular fibrillation.

Morphologically MI are divided into two types; these have differing significance

1. **Transmural infarct**, which is the most common and more serious.
2. **Subendocardial (nontransmural) infarct**.

**Pathogenesis of MI**

**Transmural infarction:** the vast majority of these (90%) are caused by an occlusive coronary thrombus overlying an ulcerated or fissured stenotic atheroma. Increased myocardial demand, as with tachycardia or hemodynamic disturbances, may constitute the final blow in an already unstable situation.

It seems that behind every acute MI a dynamic interaction has occurred among several or all of the following:

1. severe coronary atherosclerosis
2. acute atheromatous change (fissuring, ulceration, etc.)
3. Platelet aggregation & activation
4. superimposed thrombosis
5. vasospasm

**Subendocardial myocardial infarction**

The subendocardium is most vulnerable region to any reduction in coronary blood flow. Almost always there is advanced, but often not severe, coronary atherosclerosis. Thrombosis has been demonstrated in only 25% of the cases and **total occlusion of a major coronary artery or branch is uncommon** (autopsy studies). There is a suspicion that a thrombus often initiates the process, but is then spontaneously lysed. In support of this hypothesis is the beneficial effect of **fibrinolytic treatment** of patients with recently developed subendocardial infarcts. It has been proposed that diffuse atherosclerosis with global reduction of coronary flow (increased demand, vasospasm, or platelet aggregation) transform the situation into critical insufficiency that eventuates in this form of infarction.

**Gross features of MI**

**Transmural infarcts**

Virtually all transmural infarcts involve the Lt ventricle (including the interventricular septum). When they affect the posterior free wall and posterior portion of interventricular septum, they extend into the adjacent Rt ventricular wall in up to 30% of the cases. Isolated infraction of the Rt ventricle is distinctly uncommon (1-3%). The transmural infarct is usually 4 to 10 cm in the
longest dimension, but may involve the entire circumference of the Lt Ventricle (Fig. 1-40). Severe stenosing coronary atheroma is generally present with an occlusive thrombus. The efficiency of the collaterals may modify the extent and distribution of the infarct. Depending on the length of patient's survival, the area of necrosis undergoes a progressive sequence of gross changes.

- Myocardial infarcts less than 12 hours old are usually invisible on gross examination.
- After that the lesion displays pallor or red-blue cyanotic discoloration (due to stagnated, trapped blood)
- After 24 hours from onset, the infarct becomes progressively a more sharply defined, yellow, softened area
- By the end of the first week it is rimmed by a hyperemic, narrow zone of highly vascularized connective tissue (line of demarcation)
- Over the succeeding weeks, the necrotic muscles are progressively replaced by the ingrowth of granulation tissue.
- In most instances, scarring is well advanced by the end of six weeks, but the time required for total replacement depends on the size of the original infarct.

The anterior or posterior papillary muscles may be involved by the infarction. The resultant loss of contraction may induce acute mitral valve incompetence that may persist with fibrous healing of the infarct. Even worse, the acutely infarcted papillary muscle may rupture transversely to cause catastrophic gross incompetence. (Fig. 1-41)

A fibrinous or fibrino-hemorrhagic pericarditis usually develops about the 2nd or 3rd day. It usually resolves with the healing of the infarct.

Involvement of the ventricular endocardium often results in mural thrombosis, which produces a risk of peripheral embolism. Later the thrombus organizes to be eventually represented by dense fibrous thickening.

Rupture of the infarct (5% of cases) may occur in the free wall of the Lt Ventricle (resulting in cardiac tamponade) or less often, the inter-ventricular septum (resulting in L→R shunting of blood). The rupture occurs usually about the 4th or 5th day from the onset of infarction; at which time the necrotic focus is maximally soft (myomalacia cordis). (Fig. 1-42)

With large infarcts, the necrotic area may balloon out; this is called infarct expansion. Mural thrombosis is common in such areas. Eventual fibrosis of the infracted area leads to ventricular aneurysm. (Fig. 1-43)

**Subendocardial infarct**

The morphology of the subendocardial infarct is analogous qualitatively to the of transmural infarct. By definition, however, it is limited to the inner third of the LV wall. The lesion may be multifocal, cover an arc of the circumference of the LV, or sometimes totally encircle it. Although mural thrombi may complicate the picture, pericarditis, ventricular aneurysms, and rupture are rare complication. (Fig. 1-44)

**Microscopic features** (Fig. 1-45)

- Typically the myocardial cells show coagulative necrosis. This is not detectable for the first 4 to 8 hours.
- The necrotic area is invaded by acute inflammatory cells & later by macrophages.
- Gradual replacement of the infarct by granulation tissues from the line of demarcation occurs.
The eventual event is healing by fibrosis. Once an MI is completely healed, it is impossible to distinguish its age (i.e., the dense fibrous scars of 8-week-old and 10-year-old lesions look similar).

**Infarct Modification by Reperfusion (reperfusion injury)**
The most effective way to rescue ischemic myocardium threatened by infarction is to restore tissue perfusion quickly by restoration of coronary flow (reperfusion). This could be established through one of the following
1. Thrombolysis
2. Balloon angioplasty
3. Coronary arterial bypass graft (CABG).

However, this *reperfusion induces a set of complications that include*
1. Reperfusion-induced arrhythmias
2. Myocardial hemorrhage
3. Apoptotic and necrotic cell damage
4. Microvascular injury
5. Prolonged ischemic dysfunction (myocardial stunning).

Thus, despite the possible beneficial outcomes of reperfusion some small amount of new cellular damage may occur. Reperfusion injury is mediated by the generation of oxygen free radicals from infiltrating leukocytes during reperfusion. Apoptosis may be prominent; thus, prevention of apoptosis may be a potential therapeutic target to limit reperfusion injury. Reperfusion-induced microvascular injury causes not only hemorrhage, but also endothelial swelling that occludes capillaries and may prevent local reperfusion to areas of critically injured myocardium (no reflow).

**Complications of Myocardial Infarction**

75% of patients with acute infarcts sustain one or more of the following complications

1. **Pump (heart) failure**, which is proportional to the size of the infarct.
   a. Some degree of *left ventricular failure* with hypotension is often present. This is complicated by pulmonary vascular congestion, which may progress to pulmonary edema.
   b. *Cardiogenic shock* complicating severe "pump failure". This is particularly seen in patients with extensive infarcts of the left ventricle (greater than 40% of the left ventricle muscle mass). *The mortality rate is 70% (two thirds of in-hospital deaths).*
2. **Arrhythmias**; the result of conduction disturbances and myocardial irritability following MI. They are the usual cause of the over 50% of deaths that occur within the first hour of onset of MI; these individuals never reach the hospital.
3. **Myocardial rupture** the result of mechanical weakening of the necrotic and subsequently inflamed myocardium and include
   a. Rupture of the ventricular free wall, with hemopericardium and cardiac tamponade; this is usually fatal.
   b. Rupture of the ventricular septum, leading to a L→R shunt
   c. Rupture of the papillary muscles, resulting in acute severe mitral regurgitation.
4. **Pericarditis**: a fibrinous or fibrohemorrhagic pericarditis is usual but resolves over time.
5. **Right ventricular infarction**; this is often accompanies ischemic injury of the adjacent posterior left ventricle and ventricular septum. A right ventricular infarct can yield serious functional impairment.
6. **Infarct extension**: new necrosis may occur adjacent to an existing infarct.
8. **Infarct expansion**: owing to the weakening of necrotic muscle, there may be disproportionate stretching, thinning, and dilation of the infarct region (especially with anteroseptal infarcts), which is often associated with mural thrombus.

9. **Mural thrombus**: this occurs due to the combination of
   a. Locally deficient contractility (causing stasis)
   b. Endocardial damage that exposes the subendocardial thrombogenic zone with eventual thrombus formation that could act as a potential embolus.

10. **Ventricular aneurysm** of the ventricular wall that is bounded by a healed fibrotic myocardium, which paradoxically bulges during systole. Complications of ventricular aneurysms include mural thrombosis, arrhythmias, and heart failure. *Rupture of the fibrotic wall, however, does not occur. (Fig. 1-23)*

11. **Mitral regurgitation (insufficiency)** complicating MI may occur as an early or late event. The early onset insufficiency is either due to ischemic dysfunction of a papillary muscle and underlying myocardium or rupture of a necrotic papillary muscle. Whereas the late onset insufficiency is due to papillary muscle fibrosis and shortening &/or ventricular dilation

12. **Progressive late heart failure** (see chronic IHD).

**CHRONIC ISCHEMIC HEART DISEASE (CIHD) (ISCHEMIC CARDIOMYOPATHY)**

By definition this is a *"progressive heart failure that complicates ischemic myocardial damage"*. CIHD usually represents a post-infarction cardiac decompensation due to exhaustion of the compensatory hypertrophy of the viable myocardium. However, in other cases severe CIHD may be present without acute or healed infarction but with diffuse myocardial dysfunction. CIHD is characterized by the development of severe, progressive heart failure, sometimes punctuated by episodes of angina or MI. Arrhythmias are common. The diagnosis rests largely on the exclusion of other forms of cardiac diseases. Such patients make up nearly 50% of cardiac transplant recipients.

**SUDDEN CARDIAC DEATH (SCD)** is defined as *"unexpected death from cardiac causes within 1 hour after symptom onset or without the onset of symptoms"*. In many adults, SCD is a complication and often the first clinical manifestation of IHD. With decreasing age of the victim, the following nonatherosclerotic causes of SCD become increasingly probable:

1. Congenital structural coronary arterial abnormalities
2. Aortic valve stenosis
3. Mitral valve prolapse
4. Myocarditis and Cardiomyopathy

**HYPERTENSIVE HEART DISEASE (HHD)**

This refers to the *adaptive response on the part of the heart to the increased pressure overload induced by hypertension*. HHD is of two types; left-sided due to systemic hypertension and right-sided HHD (cor pulmonale) due to pulmonary hypertension.

**The left-sided (Systemic) HHD**

In systemic hypertension, hypertrophy of the heart can lead to cardiac dilation, heart failure or sudden death.

**The minimal criteria for the diagnosis of systemic HHD are**

1. Left ventricular hypertrophy
2. A history or pathologic evidence of hypertension.
3. Exclusion of other cardiovascular pathology that might have induced the hypertrophy
Even mild hypertension (slightly above 140/90 mm Hg), if sufficiently prolonged, induces left
ventricular hypertrophy. The hypertrophy is concentric (symmetrical). In time, the increased
thickness of the left ventricular wall leads to a stiffness that impairs diastolic filling. The clinical
manifestations of systemic HHD are indirect; either through the onset of atrial fibrillation (owing
to left atrial enlargement) (Fig. 1-46) and/or Lt. sided heart failure with cardiac dilation.
Effective control of hypertension can prevent or lead to regression of cardiac hypertrophy and its
associated risks.

**Right-sided (pulmonary) HHD (Cor pulmonale)**
The pulmonary hypertension leads to RVH, dilation and eventually Rt sided heart failure.
Pulmonary hypertension is caused by disorders of the lungs or pulmonary vasculature. *Not
included under this heading is right ventricular hypertrophy & dilation secondary to diseases of
the left side of the heart or congenital heart diseases.* Cor pulmonale may be acute or chronic,
depending on the speed of development of the pulmonary hypertension. *Acute cor pulmonale*
can follow massive pulmonary embolism. *Chronic cor pulmonale* usually implies right
ventricular hypertrophy (and dilatation) secondary to prolonged pressure overload caused by
obstruction of the pulmonary arteries or arterioles or compression or obliteration of septal
capillaries (e.g., owing to primary pulmonary hypertension or emphysema). In acute cor
pulmonale, there is marked dilation of the right ventricle without hypertrophy. In chronic cor
pulmonale, the right ventricular wall thickens, sometimes up to 1.0 cm or more (N: 0.3 to 0.5
cm), and may even come to approximate that of the left ventricle. (Fig. 1-47)

**VALVULAR HEART DISEASE**
This is defined as "cardiac diseases due primarily to valvular abnormalities namely stenosis,
regurgitation (insufficiency or incompetence), or both". Stenosis is failure of a valve to open
completely, thus interfering with forward flow. Regurgitation, in contrast, results from failure of
a valve to close completely, thus allowing reversed flow. Stenosis and regurgitation may occur in
isolation or in combination.

*Functional regurgitation* (no structural abnormality of the valve) occurs in association with
1. **Dilatation of mitral or tricuspid valves**; this occurs secondary to ventricular dilation, which
causes the papillary muscles of the relevant valve to be pulled down and outward, thus
preventing the cusps of the intact valves to come together closely during systole.
2. **Dilatation of aortic or pulmonary valves** secondary to dilation of the relevant valve ring,
thus pulling the valve commissures apart preventing full closure of the valve cusps.
Valvular dysfunction can vary in degree from slight and physiologically unimportant to severe
and rapidly fatal. For example, sudden destruction of an aortic valve cusp by infective
endocarditis may cause rapidly fatal cardiac failure owing to massive regurgitation. In contrast,
rheumatic mitral stenosis usually develops over years and its clinical effects are remarkably well
tolerated. Valvular abnormalities may be either congenital or acquired; most frequent of these are stenoses
of the aortic and mitral valves.

**Valvular Degenerations**
1. **Valvular degenerations caused by calcification**
The heart valves are subjected to repetitive mechanical stresses; these normally delicate structures suffer cumulative damage that is complicated by dystrophic calcification, which may lead to clinically important disease. The most frequent calcific valvular diseases are
1. Calcific aortic stenosis
2. Calcification of a congenitally bicuspid aortic valve
3. Mitral annular calcification

**Calcific Aortic Stenosis** is the consequence of calcification owing to progressive and advanced age-associated "wear and tear" of either previously anatomically normal (tricuspid) aortic valve or congenitally bicuspid valve. It usually manifests in the sixth to seventh decades of life with congenitally bicuspid valves but not until the eighth and ninth decades with previously normal valves; hence the term se

**Mitral Annular Calcification**

Degenerative calcific deposits can develop in the fibrous ring (annulus) of the mitral valve as irregular, stony hard nodules that lie behind the leaflets. The process generally does not affect valvular function.

2. **Myxomatous degeneration of the mitral valve (mitral valve prolapse; floppy mitral valve)** (Fig. 1-49): in this condition one or both mitral leaflets are "floppy" and prolapse or balloon back into the left atrium during systole. Mitral valve prolapse affects 3% or more of adults, most often young women & is one of the most common forms of valvular heart disease in the industrialized world. The affected leaflets are often enlarged, redundant, thick, and rubbery. The tendinous cords are elongated, thinned, and occasionally ruptured. Annular dilation is characteristic. The essential histological change is reduction of the fibrosa layer of the valve, on which the structural integrity of the eaflet depends, accompanied by focally marked thickening of the spongiosa layer with deposition of mucoid (myxomatous) material. A favored pathogenetic mechanism is the proposal that there is an underlying developmental defect of connective tissue, possibly systemic. This is supported by the common occurrence of this condition in Marfan syndrome. Although the great majority of patients have no troublesome effects, approximately 3% develop one of five serious complications:
   1. Infective endocarditis
   2. Mitral regurgitation
   3. Embolism resulting from leaflet thrombi
   4. Arrhythmias
   5. Sudden death

**RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE**

Rheumatic fever (RF) is an acute inflammatory, immunologically mediated, systemic disease occurring a few weeks after an episode of group A streptococcal pharyngitis. The most important consequences of RF are chronic deformities of cardiac valves (particularly mitral stenosis) due to damage and fibrosis. These produce permanent dysfunction and severe cardiac problems decades later. The incidence of RF has declined remarkably in many parts of the world over the past 40 years. During acute RF, focal inflammatory lesions are found in various tissues of the body but most distinctively within the heart, where they are called **Aschoff bodies**. Aschoff bodies consist of foci of swollen collagen surrounded by lymphocytes, some plasma cells, and distinctive
plump macrophages called *Anitschkow cells* (pathognomonic for RF). Anitschkow cells have abundant cytoplasm and central round-to-ovoid nuclei in which the chromatin is disposed in a central, slender, wavy ribbon (hence the designation "caterpillar cells"). Some of these macrophages become multinucleated to form *Aschoff giant cells* (Fig. 1-50). During acute RF, diffuse inflammation and Aschoff bodies may be found in any of the three layers of the heart-pericardium, myocardium, or endocardium—hence the designation *rheumatic pancarditis*. In the pericardium, the inflammation is accompanied by a fibrinous or serofibrinous pericardial exudate, described as a "bread-and-butter" pericarditis (Fig. 1-51). The myocarditis takes the form of scattered Aschoff bodies within the interstitial connective tissue, often perivascularly. Concomitant involvement of the endocardium and the left-sided valves by inflammatory foci typically results in fibrinoid necrosis within the cusps (and along the tendinous cords) on which sit small (1- to 2-mm) vegetations (verrucae) along the lines of closure (Fig. 1-52). These irregular, warty projections probably arise from the precipitation of fibrin at sites of erosion, related to underlying inflammation and collagen degeneration, and cause little disturbance in cardiac function. Subendocardial lesions, perhaps exacerbated by regurgitant jets, may induce irregular thickenings called *MacCallum patches*, usually in the left atrium.

**Chronic RHD** is the result of organization of the acute inflammation and subsequent fibrosis. In particular, the valvular leaflets become thickened and retracted, causing permanent deformity. The cardinal anatomic changes of the mitral valve are

1. Leaflet thickening
2. Commissural fusion
3. Shortening, thickening and fusion of the tendinous cords. *In chronic disease, the mitral valve is virtually always abnormal;* alone (70% of the cases) or together with the aortic valve (25%). *RHD is the most frequent cause of mitral stenosis (99% of cases).* Microscopically there is diffuse fibrosis often with invasion by new blood vessels; these changes obliterate the originally layered and avascular leaflet architecture. The diagnostic Aschoff bodies are rarely seen being replaced by fibrosis. Fibrous bridging across the valvular commissures and calcification create "fish mouth" or "buttonhole" stenoses (Fig. 1-53). With tight mitral stenosis, the left atrium progressively dilates and may harbor mural thrombus. Long-standing congestive changes in the lungs may induce pulmonary vascular and parenchymal changes and in time lead to right ventricular hypertrophy. The left ventricle is generally normal with isolated pure mitral stenosis.

**Pathogenesis of RF & RHD** (Fig. 1-54)

It is assumed that RF is due to a hypersensitivity reaction induced by group A streptococci. It is thought that *antibodies that are originally developed and directed against the M protein of the offending streptococci also cross-react with glycoprotein antigens in the heart, joints, and other tissues*. In support of this is the absence of the bacteria in RF lesions of various tissues. A *genetic predisposition* to the disease appears operating as well, because only a minority of infected patients (3%) develop RF. The chronic sequelae result from progressive fibrosis due to both healing of the acute inflammatory lesions and the turbulence of blood flow induced by the valvular deformities. Acute RF appears most often in children between ages 5 and 15 years. 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*, are present and can be detected in the sera of most patients. After an initial attack, there is an increased tendency of having further insults of the disease with subsequent pharyngeal infections. Hazards associated with RHD include

1. An increased tendency of having further new attacks of RF. Carditis is likely to worsen with each recurrence, and damage is cumulative.
2. Embolization primarily from atrial thrombi
3. Infective endocarditis superimposed on deformed valves.

The manifestations of chronic rheumatic carditis usually occur years or even decades after the initial episode of acute RF.

**INFECTIVE ENDOCARDITIS (IE)**

This serious condition signifies "colonization of the heart valves (or the endocardium) by microbes with eventual formation of bulky, friable vegetations that is often results in destruction of the underlying cardiac structures". Bacteria are the most common offenders (bacterial endocarditis) but other microorganisms are occasionally the causative agents e.g. fungi, rickettsiae of Q fever, and chlamydiae. IE has been classified on clinical grounds into acute and subacute forms.

**Acute endocarditis** signifies an infection that is
- Destructive
- Involving frequently a normal heart valve
- Caused by virulent microorganism
- Associated with a rapid course leading to death within days to weeks of more than 50% of the patients despite treatment; the disease is difficult to cure by antibiotics and usually require surgery.

In contrast **subacute endocarditis** signifies an infection that is
- A less destructive
- Involving a previously abnormal heart, particularly deformed valves
- Caused by organisms of low virulence
- Associated with insidious and protracted course (weeks to months). Subacute IE recovers after appropriate antibiotic therapy

**Etiology and Pathogenesis**

Two sets of factors predispose to IE

1. **Structural abnormalities of the heart valves**; IE may develop on previously normal valves, but the presence of cardiac and vascular abnormalities predispose to this form of infection. These include
   a. Rheumatic heart disease
   b. Myxomatous (floppy) mitral valve
   c. Degenerative calcific aortic stenosis
   d. Bicuspid aortic valve (calcified or not)
   e. Artificial (prosthetic) valves

2. **Host factors** particularly those that interfere with defenses; such as
   a. neutropenia
   b. immunodeficiency e.g. associated with malignancy & therapeutic immunosuppression.
   c. diabetes mellitus
   d. alcohol
   e. intravenous drug abuse

Endocarditis of previously damaged or abnormal valves is caused most commonly (60% of cases) by *Streptococcus viridans*. In contrast, the more virulent *Staph. aureus* can attack either healthy or deformed valves; they are responsible for 10% to 20% of cases overall. Staph. aureus is also a major offender in intravenous drug abusers. Prosthetic valve endocarditis is caused most commonly by coagulase-negative staphylococci (e.g., Staph. epidermidis). **In about 10% of all**
cases of endocarditis, no organism can be isolated from the blood (culture-negative" endocarditis). The primary event in the development of endocarditis is seeding of the blood with microbes. The portal of entry of the agent into the bloodstream may be
a. Obvious or occult focus of infection
b. Dental or surgical procedure that cause transient bacteremia
c. Injection of contaminated material into the bloodstream by IV drug users

Gross features (Fig. 1-55)
- Friable, bulky, and potentially destructive vegetations are formed in both the subacute and acute forms of the disease.
- 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.
- The vegetations may be single or multiple and may involve more than one valve.
- Vegetations sometimes erode into the underlying myocardium to produce an abscess cavity (ring abscess).
- The vegetations of subacute endocarditis are associated with less valvular destruction than those of acute form, although the distinction between the two forms may be difficult.

Microscopic features
- The vegetations in general contain fibrin, inflammatory cells, and bacteria (or other organisms)
- The vegetations of typical subacute IE often have granulation tissue at their bases (suggesting chronicity).
- With the passage of time, fibrosis, calcification, and a chronic inflammatory infiltrate may develop.
- Subacute endocarditis is typically associated with less valvular destruction than is the acute form.

Complications of IE (whether acute or subacute)
A. Cardiac
1. Valvular destruction leading to dysfunction (insufficiency or stenosis) that eventuates in heart failure
2. Myocardial abscesses that eventuates in perforation of IV septum or free wall
3. Suppurative pericarditis
4. Artificial valve dehiscence
B. Embolic with infarctions
1. Lt sided: brain, spleen, kidneys, etc.
2. Rt sided: lungs
C. Metastatic infections (including septic infarcts) especially with acute e.g. brain and renal abscesses, meningitis, etc.
D. Renal complications
1. Embolic infarction that may be multiple and septic
2. Immunologically mediated glomerulonephritis; owing to trapping of antigen-antibody complexes, which can cause hematuria, albuminuria, or renal failure.

NON-INFECTED VEGETATIONS
1. Nonbacterial thrombotic endocarditis (NBTE); this is characterized by the deposition of small sterile vegetations (fibrin, platelets, etc.) on the leaflets of the cardiac valves (Fig. 1-56).
They may be a source of emboli and results in infarcts of the brain, heart, etc. Because of its frequent association with venous thromboses (and pulmonary embolism), a common origin of the two has been suggested i.e. a hypercoagulable state with systemic activation of the coagulation system (a situation analogous to that occurring in DIC). Conditions associated with NBTE include

A. Conditions that promote hypercoagulability
1. Cancer (especially, mucinous adenocarcinomas of the pancreas)
2. Hyperestrogenic states
3. Extensive burns
4. Sepsis

B. Endocardial trauma, as from an indwelling catheter.

2. Endocarditis of SLE (Libman-Sacks endocarditis)
In some SLE patients, there is mitral and tricuspid valvulitis complicated by presence of small, sterile vegetations. Subsequent fibrosis can lead to serious valvular deformities that resemble chronic Rheumatic heart disease. (Fig. 1-57)

CARCINOID HEART DISEASE
This is one of the major features of the carcinoid syndrome as it is seen in about half of the patients. The syndrome itself is seen in about 10% of patients with GI carcinoids with hepatic metastses. The cardiac involvement is characterized by fibrous thickening of the endocardium that is seen mainly on the outflow tract of the Rt ventricle. The pathogenesis of the changes is uncertain, but probably attributed to the elevated blood levels of serotonin or bradykinins.

MYOCARDITIS
This is defined as "inflammation of the heart muscles and characterized by a leukocytic infiltration and necrosis or degeneration of the myocytes".

Major causes include
1. Viruses eg. Coxackie, ECHO, influenza, polio
2. Chlamydia and Rickettsia
3. Bacteria e.g Corynebacterium (diphtheria), TB, salmonella
4. Fungi and parasites e.g. aspergillus, monilia and echinococcus.
5. Immune mediated e.g. poststreptococcal (Rheumatic fever), SLE, drugs e.g. methyldopa (aldomet), transplant rejection
6. Others as radiation, heat stroke, sarcoidosis, giant cell myocarditis and Kawasaki disease

During the active phase the heart is enlarged with dilatation of all its chambers. The ventricular myocardium is flabby and mottled by pale or hemorrhagic foci. The endocardium and valves are unaffected. After the acute phase has passed the heart may appear normal. Microscopy is influenced by the etiologic agent. The involvement may be patchy and thus cardiac biopsy may give false negative results. Isolated myofiberlysis or patchy foci of necrosis are accompanied by an inflammatory cell infiltration. With viral myocarditis the infiltrate is usually mononuclear while pyogenic bacteria produce suppurative inflammation sometimes with microabscesses.

CARDIOMYOPATHIES (CMP)
By definition this is a "non-inflammatory heart muscle disease of unknown cause". Cardiomyopathies are divided in to three pathological categories
1. Dilated (congestive)
2. Hypertrophic
3. Restrictive

**Dilated (congestive) CMP**

In this condition there is gradual development of heart failure associated with dilatation of all the four chambers of the heart. The valves are normal and there is no significant coronary atheroma (Fig. 1-58). The etiology is uncertain but the following are suspected

1. Alcohol toxicity
2. Nutritional deficiency related to pregnancy
3. Genetic defect
4. Post-viral myocarditis

The patients usually die within 5 years due to progressive heart failure or embolism (complicating chamber thrombosis due to poor contraction and blood stasis or arrhythmia)

**Hypertrophic CMP** (Fig. 1-59)

This occurs most often in young adults, and is characterized by cardiac enlargement with myocardial hypertrophy. The hypertrophy is often asymmetrical in that the Lt ventricle is usually more involved than the Rt. On cross section, the ventricular cavity loses its usual round to ovoid shape and may become compressed into a banana-like by the thickened IV septum that protrudes into the lumen. This may interfere with the outflow of blood through the aorta (obstructive hypertrophic CMP). Sudden death is common. The most distinctive microscopic feature is the disorganization and disarray of the hypertrophied muscle fibers. Evidences suggest a genetic basis for the disease.

**Restrictive/infiltrative CMP**

There is restriction of ventricular filling due to infiltration of the myocardium by one of the following

1. Amyloidosis
2. Sarcoidosis
3. Edocardial fibroelastosis
4. Endomyocardial fibrosis
5. Loefer’s endocarditis

**Cardiac amyloidosis:** may be part of systemic amyloidosis or may affect only the heart, particularly in the aged.

**PROSTHETIC CARDIAC VALVES;** the introduction of these has changed the prognosis of patients with valve disease significantly. Two types of prosthetic valves are currently used

1. Mechanical: usually tilting disk devices made of pyrolytic carbon. They require chronic anticoagulation. Those of aortic valves can cause significant hemolysis due to the traumatic effect of the valve on RBCs.
2. Bioprosthetic: are bovine tissues, or cryopreserved human valves. These do not require anticoagulation but can fail because of matrix deterioration or stiffening. This may be associated with stenosis. Calcification of the leaflets is common and can contribute to the stenosis. They can perforate or tear, resulting in valvular insufficiency. Prosthetic valves are also subject to infective endocarditis that typically involves the suture line and adjacent perivalvular tissue and may cause the valve to detach.

**PERICARDITIS**

Primary pericarditis is uncommon; in most cases it is caused by infection, usually by viruses; this may be associated with myocarditis. *In most cases pericarditis is secondary* and due to

1. Acute MI
2. Cardiac surgery
3. Mediastial irradiation
4. Pneumonia or pleuritis
5. Uremia (the most common systemic disorder associated with pericarditis)
6. Other less frequent cause e.g. rheumatic fever, SLE, and metastatic cancers.

Pericarditis may resolve without sequele but the process can progress to chronic fibrosis. However, it may cause immediate hemodynamic complications if a significant effusion is present (see below).

**Pathological features**

- In patients with viral, uremic or rheumatic pericarditis, the exudate is typically fibrinous, imparting a shaggy appearance to the surface (bread-and-butter pericarditis) ([Fig. 1-51]).
- In acute bacterial pericarditis the exudate is fibrinopurulent (suppurative), often with areas of frank pus ([Fig. 1-60]). Tuberculous pericarditis can show areas of caseation.
- Pericarditis due to malignancy is often associated with shaggy fibrinous exudate and a bloody effusion ([Fig. 1-61]); metastases can be grossly evident as irregular excrescences or may be relatively inapparent (as in leukemia).
- Acute fibrinous or fibrinopurulent pericarditis usually resolves without any sequelae. However, when there is extensive suppuration or caseation, healing can result in chronic pericarditis with fibrosis. Chronic pericarditis displays delicate adhesions or dense, fibrotic scars that obliterate the pericardial space. In extreme cases the heart is so completely encased by dense fibrosis that it cannot expand normally during diastole (constrictive pericarditis).

**PERICARDIAL EFFUSIONS**

Normally, there is about 30 to 50 ml of thin, clear, straw-colored serous fluid in the pericardial sac. Pericardial effusions in excess of this amount occur in a number of settings, in addition to the inflammatory states described above. The major types and some of their more common causes include:

- **Serous**: CHF, hypoalbuminemia
- **Serosanguinous**: chest trauma, malignancy, ruptured MI or aortic dissection
- **Chylous**: mediastinal lymphatic obstruction

The consequences of pericardial effusions depend on the amount of fluid and the rate of its accumulation. Slowly accumulating effusions—even as large as 1000 ml—can be tolerated without clinical manifestation. In contrast, rapidly developing collections of as little as 250 ml can restrict diastolic cardiac filling to produce fatal cardiac tamponade.

**HEMOPERICARDIUM** is the presence of pure blood within the pericardial sac. This may complicate penetrating injuries to the heart, ruptured MI or ruptured aortic dissection (at the root of the aorta).

**CARDIAC TUMORS**

**Metastatic Neoplasms**
The most common tumor of the heart is a metastatic one; tumor metastases to the heart occur in about 5% of patients dying of cancer. *In descending order cancers metastatic to the heart are*

1. Lung carcinoma
2. Lymphoma
3. Breast carcinoma
4. Leukemia
5. Melanoma
6. Others e.g. carcinomas of the liver, and colon

**Primary Neoplasms**
These are uncommon & mostly benign. The five most common (account for 80% to 90% of all primary heart tumors), in descending order of frequency (adults)

1. Myxomas  
2. Fibromas  
3. Lipomas  
4. Papillary fibroelastomas  
5. Rhabdomyomas  
6. Angiosarcomas (malignant)

Myxoma is the most common primary tumor of adult hearts. The vast majority (90%) are located in the atria, mostly the left and at the region of fossa ovalis. They may reach a large size (10 cm), and are spherical, hard or soft, translucent lesions with a gelatinous appearance. Pedunculated forms are often mobile causing intermittent obstruction of the mitral valve during systole. Sometimes, this is associated with damage to the valve (wrecking-ball effect). (Fig. 1-62)

Rhabdomyoma is the most common primary tumor of infants/children hearts, and frequently discovered because of an obstruction of a valvular orifice or cardiac chamber. These tumors occur with high frequency in patients with tuberous sclerosis. They are considered as hamartomas rather than true neoplasms and may be caused by defective apoptosis during developmental remodeling. They are generally small, gray-white myocardial masses up to several centimeters in diameter that protrude into the ventricular chambers (Fig. 1-63).